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SUMMARY (HMM)

The current directed and comprehensive Establishment Inspection (EI) was conducted per issuance of CDER/OTS/OSIS/DNDSI, PDUFA, Routine, Surveillance Inspection, eNSpect assignment ID 272103 and CDER/OSIS assignment memo dated 3/8/2024 (Attachment 1) and CBER/OCBQ/DIS/BM, PDUFA, Routine, Surveillance assignment memo dated 9/1/2024 (Attachment 2). The EI was the initial for the inspected firm and was conducted in accordance with CP 7348.808, entitled, “Good Laboratory Practice (Nonclinical Laboratories)”. The

current inspection covered the conduct and oversight of various GLP studies, including the following: Protocol (b) (4): (b) (4) ; Protocol (b) (4): (b) (4) " and Protocol (b) (4) (CBER). The EI also covered the firm's compliance with the applicable compliance program and regulations (21 CFR 58). The inspection team included Hugh M. McClure III, National Expert (OII), Andrew R. Wasko II, Biologist (CDER/OTS/OSIS/DNDSI), and Mark J. Seaton, Sr. Pharmacokineticist, (CDER/OTS/OSIS/DNDSI).

At the conclusion of the current EI, a closeout meeting was held with firm management. During this meeting, a two item Form FDA 483 (Attachment 3), Inspectional Observations was issued to the firm citing regulatory deviations as follows:

- The testing facility does not have written standard operating procedures setting forth nonclinical laboratory study methods that management is satisfied are adequate to ensure the quality and integrity of the data generated in the course of a study.
- Reserve samples of test article for studies of more than 4 weeks duration were not retained for the period of time provided by 58.195.

Firm management promised a written response to the FDA-483 with corrective actions within fifteen business days. The firm's response to the 483 was received and is attached as Attachment 4.

No refusals were met, and no samples were collected during the current EI. At the conclusion of the EI, firm management was reminded of the requirement to adhere to all applicable regulations. Management stated understanding.

ADMINISTRATIVE DATA (HMM)

Inspected firm:	InnoStar Bio-Tech Nantong Company, Ltd.
Location:	Building A18, 100 Dongtinghu Road Linjiang Town, Haimen District Nantong City, Jiangsu Province, China
Phone:	8651380180668
FAX:	8651308180188
Mailing address:	InnoStar Bio-Tech Nantong Company, Ltd. Building A18, 100 Dongtinghu Road Nantong City, Jiangsu Province, China

Email address: ychang@innostar.cn
Dates of inspection: 10/28-11/1/2024
Days in the facility: 5
Participants: **Hugh M McClure III, National Expert, (OII)**
Andrew R. Wasko II, Biologist (CDER/OTS/OSIS/DNDSI)
Mark J. Seaton, Sr. Pharmacokineticist (CDER/OTS/OSIS/DNDSI)

On 10/28/2024, the inspection team arrived at the Building A18, 100 Dongtinghu Road, Nantong City, China. We presented our credentials to Dr. Yan Chang, who serves as the General Manager for InnoStar Bio-Tech Company, Ltd. I informed Dr. Chang that we were conducting a GLP routine, surveillance inspection of the facility to include data audits for nonclinical laboratory studies conducted at the facility. This EIR was written by Hugh M. McClure III, BIMO National Expert, (OII), Andrew R. Wasko II, Biologist (CDER/OTS/OSIS/DNDSI), and Mark J. Seaton, Sr. Pharmacokineticist (CDER/OTS/OSIS/DNDSI).

HISTORY (HMM)

The testing facility provided an overview of their facility, organizational chart, and capabilities (**Exhibit 1**). Shanghai InnoStar Bio-Tech Company, Ltd. (InnoStar) was established in 2010 in Shanghai, China and is a subsidiary of China National Pharmaceutical Industrial Research Co. Ltd., China National Pharmaceutical Group. InnoStar operates facilities in Nantong, China (InnoStar Nantong) established in 2018; Huangshan, China (InnoStar Huangshan) established in 2021; and Shenzhen, China (InnoStar Shenzhen) established in 2022. The current inspection was conducted at the InnoStar Bio-Tech Co. Nantong facility (IBN). The overall scope of work performed at IBN includes Nonclinical Pharmacodynamics, Nonclinical Pharmacokinetics, Nonclinical Safety Evaluation (GLP), and Clinical Sample Bioanalysis (GCLP). IBN started its GLP operation in 6/2018, was licensed for the use of laboratory animals by the Chinese National Medical Products Administration (NMPA) in 7/2018 and was certified by the NMPA for GLP in 1/2020. IBN was inspected by OECD member Hungary and received OECD certification for GLP in 9/2024. IBN has been inspected by NMPA annually on 12/2019, 11/2020, 10/2021, 2/2023 and 8/2024. IBN was also AAALAC certified 11/2019 and was recertified 3/2023. IBN employs approximately (b) (4) individuals including (b) (4) study directors (SD), (b) (4) uality assurance unit (QAU) auditors, (b) (4) pathologists (b) (4) scientists including Analytical, Bioanalytical, and Clinical Pathology, (b) (4) Study Coordinators, Analysts & Technicians, three veterinarians, and (b) (4) animal husbandry staff. The main facility comprises four buildings (B3, B5, A18 and A19) totaling (b) (4) m^2 with (b) (4) m^2 of laboratory space, (b) (4) m2 of animal housing, and (b) (4) m^2 of support area.

The firm performs studies in nonhuman primates, beagles, rabbits, minipigs, and rodents. Study directors are assigned to a given study by testing facility management (TFM), Dr. Hua Li. As of this inspection, the testing facility has (b) (4) qualified SDs. The QAU includes (b) (4) QAU auditors, who report to Mr. Yong Wang, Associate Director, QAU.

INTERSTATE (I.S.) COMMERCE/ JURISDICTION (HMM)

IBN is a nonclinical laboratory which conducts safety studies of FDA regulated products in support of applications for research or marketing permits. The study information for the reviewed studies which are regulated under the FD&C Act are as follows:

1. Application/File Type and Number: IND-(b) (4)
Submission Status: Original
Product(s) Name: (b) (4)
Protocol/Study Number and Title/Name:
Protocol (b) (4): (b) (4)
Sponsor: (b) (4)

2. Application/File Type and Number: IND-(b) (4)
Submission Status: Original
Product(s) Name: (b) (4)
Protocol/Study Number and Title/Name: Protocol (b) (4): " (b) (4)
Sponsor: (b) (4)

3. Application/File Type and Number: IND-(b) (4)
Submission Status: IND Hold
Product(s) Name: (b) (4) - (b) (4)
Protocol/Study Number and Title/Name: Protocol (b) (4): (b) (4)
Sponsor: (b) (4)

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED (HMM)

Hua Li, Ph.D., DCST, TFM: Dr. Li is the most responsible individual at IBN and reports to Dr. Yan Chang, CEO and General Manager. He provided oversight of all studies conducted at the site. Dr. Li has over 20 years of experience in toxicology research with over twelve years of experience as a study director (SD). Dr. Li is also responsible for appointing SDs to a given GLP study performed at the testing facility. Dr. Li facilitated the current EI ensuring the FDA inspection team was provided all documents and information as requested.

Yong Wang, M.S., RQAP-GLP, QAU Management, Associate Director: Mr. Wang is responsible for the Quality Assurance Unit (QAU) at IBN. He provided oversight of inspection of various quality systems at IBN. Dr. Wang oversees all of the QAU functions at IBN

including auditing and testing of the quality systems at the IBN. He provides direction and oversight to twenty-three QAU staff and ensures effective execution of QAU responsibilities at IBN. Mr. Wang accompanied the inspection team throughout the inspection and provided information requested by the team. Mr. Wang reports to Dr. Hua Li, TFM.

Yan Chen, Senior Director of Laboratory Technology Department and Animal Management Department: is responsible for and has oversight of the vivaria at IBN. He is responsible for the care and husbandry of the study animals housed at IBN. He has over than 18 years of working experience in animal laboratories including extensive experience in animal experimentation technology and management. Mr. Chen facilitated the tours and observation of the animal facilities and provided oversight of staff during the current EI, to ensure all questions were answered, and the FDA inspection team was provided all documents and information as requested. Mr. Chen reports to Dr. Hua Li, TFM.

(b) (6)**, Expert Sr. Manager of Pathology, Master**: Dr. (b) (6) has 10 years working experience as a pathologist at nonclinical laboratories and is responsible for the daily operation and management of the pathology department. Dr. (b) (6) supervises fourteen study pathologists and associated staff including anatomists and technicians. He assisted with providing information on the processes within the pathology department including necropsy through slide processing and reading by study pathologists. Dr. (b) (6) reports Dr. Hua Li, TFM.

Liping Wei, Associate Director of Toxicology, Master of Health Toxicology: Ms. is responsible for the oversight of toxicology studies conducted at IBN. Dr. Li has been engaged in nonclinical safety evaluation research, toxicology research, and safety evaluation of new drugs for over 12 years. During the current EI, Ms. Wei provided information and answered questions related to the conduct of toxicology studies at IBN. Ms. Wei reports to Dr. Hua Li, TFM.

(b) (6)**, B.S., Archivist**: Ms. (b) (6) is responsible for the oversight of the archive department at IBN. Ms. (b) (6) has overall responsibility for the archive department and staff charged with the intake and maintenance of study documentation, reports, and specimens for nonclinical laboratory studies conducted at IBN. She provided information and answers to questions related to the archiving of study records, reports, and specimens as well as the retrieval process. Mr. (b) (6) reports to Linhua Cheng, B.S., Sr. Director of Operations Department.

Min Lu, M.S., Study Director: Ms. Lu served as the study director for studies (b) (4) and (b) (4). She was available to answer questions about these studies and her responsibilities as a study director. She also facilitated document requests for study (b) (4). Ms. Lu reports to Yan Wang, Ph.D., DCST, Sr. Manager of Toxicology.

Honggang Tu, M.S., DCST, Study Director: Mr. Tu served as the study director for study (b) (4), "(b) (4)". He was available to answer questions about this study and his responsibilities as a study director. He

also facilitated document requests for study (b) (4). Mr. Tu reports to Yan Wang, Ph.D., DCST, Sr. Manager of Toxicology.

In addition to those mentioned above, information requested during this EI was also provide by the following MPR staff members:

- Feng Miao, Director, Test Article Management
- (b) (6), Sr. Manager of Clinical Pathology
- (b) (6), Clinical Pathology
- (b) (6), Clinical Pathology
- (b) (6), Clinical Pathology
- Bohua Xu, Associate Director, Radioactive Imaging Evaluation Department
- (b) (6), Laboratory Technology
- (b) (6), Laboratory Technology
- (b) (6), Laboratory Technology
- (b) (6) Laboratory Technology
- (b) (6), Laboratory Technology
- (b) (6), Laboratory Technology
- (b) (6), Laboratory Technology
- (b) (6), Laboratory Technology
- (b) (6), Laboratory Technology
- (b) (6) Laboratory Technology
- (b) (6), Laboratory Technology
- (b) (6), Monitoring Department
- (b) (6) Test Article Management
- (b) (6), Dose Formulation Analysis
- (b) (6) Small Molecule Bioanalysis
- (b) (6), Quantitative PCR Analysis
- (b) (6), Monitoring Room
- (b) (6), Archive
- (b) (6), Archive
- (b) (6), Test article control
- (b) (6) Test article control

FIRM'S TRAINING PROGRAM (HMM)

Training records are maintained for all employees at IBN by the training administrator. Employee training begins when employees are first onboarded and consists of an initial GLP training program, animal welfare training, general and safety policy training including zoonotic disease training. All employees involved in the conduct and support of nonclinical studies performed at the testing facility also receive periodic refresher training on the principles of GLP as well as animal welfare and safety. Employees also receive job specific training, which includes on-the-

job training in procedures relevant to their position as well as training on the pertinent SOPs. Professional development and continuing education are also supported for study related positions including SDs, QA Auditors, veterinarians, IACUC members, pathologists, and scientists. The testing facility maintains an SOP for employee training as well as specific job and task related SOPs. We ensured that training was adequate prior to task performance and involvement in the reviewed studies. During the review of the testing facility's training, we reviewed the individual training records for several members of management and staff. Training files for various staff members were reviewed to include archive staff, quality assurance, management, in life research associates, study directors, study pathologists, and the attending veterinarian. Training files included current position descriptions and curricula vitae. We also reviewed the training process with members of management, that were utilized to assess specific task performance and competency. No deviations were noted during the review of the testing facility's training program and employee training records.

ORGANIZATION AND PERSONNEL (HMM)

We collected the IBN organizational chart (see **Exhibit 2**) and determined that a chain of command is in place at IBN. The most responsible person/TFM at IBN is Dr. Hua Li, TFM.

IBN maintains personnel records on each employee that includes their required training records, position description and curriculum vitae. We reviewed training records for employees involved in the audited studies. These individuals were noted to have performed significant roles during the studies, and we found that they were properly qualified to perform these functions through both training and education. Practices and SOPs were in place to ensure that employees take necessary health precautions and wear appropriate clothing. We observed that employees wore the required personal protective equipment (PPE) while in the vivarium and support laboratories; PPE was removed as necessary when exiting these areas. FDA team members also observed the testing facility's PPE requirements when conducting the facility inspection.

Testing Facility Management (TFM) (HMM)

An SOP exists for assigning and replacing of study directors. TFM, Dr. Hua Li, has the authority to assign and replace study directors and to establish and support the QAU which reports to Dr. Li. We verified that TFM assured the investigational drugs were properly tested/characterized, and we were informed that this was always the responsibility of the study sponsor. We also determined that TFM is responsible for authorizing and approving testing facility SOPs including new and revisions to existing SOPs.

Personnel (HMM)

IBN maintains personnel records on each employee that includes their required training records. We reviewed training records for employees involved in the audited studies including the SDs and technical staff. These individuals were noted to have performed significant roles during the studies, and we found that they were properly qualified to perform these study related tasks through both training and education. Practices and SOPs are in place to ensure that employees take necessary health precautions and wear appropriate clothing. I observed that employees wore the required PPE while in the vivarium and supporting laboratories. PPE was removed as necessary when exiting these areas.

Computerized Operations (HMM)

The testing facility uses both paper records and electronic data capture to record, analyze, report and store study related data. In-life study data, including animal dosing, clinical observations, body weights, food consumption, etc. as well anatomical and clinical pathology data are captured electronically by (b) (4). The clinical pathology laboratory included instrumentation used for urinalysis, coagulation, serum chemistry, and hematology and instruments and all instruments are interfaced with Provantis. The animal facilities HVAC is monitored and controlled by the Siemens Environmental Monitoring System (EMS), WinCC version 7.5.2.0. Other software application systems used at the testing facility include those for Analytical and Bioanalytical, e.g., Analyst software, Document Management System/Electronic Notebook, e.g. DMS (SOPs, training, and archives), Toxicology/Physiology, e.g., (b) (4), and Data Backup, e.g., Symantec Backup Exec. A comprehensive listing of software applications used at this testing facility including current version numbers is attached as **Exhibit 3.**

Study Director (HMM)

The testing facility has (b) (4) SDs all of whom are appointed to a given study by the TFM, Dr. Hua Li. Dr. Li is also responsible for replacing a SD, if necessary, during a study. The study director's duties and responsibilities are detailed in a facility SOP which was reviewed and found to be adequate.

For the studies audited during this inspection, we verified the SD's active participation through review of the study records and interviews with each. The protocol and amendments used in the studies audited were signed by the SD prior to the initiation of the study and protocol amendments were approved and signed by the SD before being implemented. Our review revealed that the personnel were familiar with and adhered to the study protocol and that the SD assured that study data and specimens were transferred to the archives at the close of the study which was required to be done after the SD's signing of the final report (FR). The SDs for the three studies audited do appear to have fulfilled their responsibilities.

QUALITY ASSURANCE UNIT (QAU) (HMM)
The QAU at IBN is currently headed by Yong Wang, M.S. and (b) (4) QAU auditors, report to him. QAU functions include study critical phase inspections, facility inspections,

process inspections, final report audits, protocol, and SOP reviews for compliance with GLP regulations. The QAU also maintains copies of protocols for all GLP studies. The QAU conducts critical phase audits for on-going studies for compliance with the protocol, SOPs, and GLP regulations and audits all draft FRs for GLP studies conducted at IBN.

The IBN QAU maintains a copy of the master schedule for all GLP studies conducted at the testing facility as well all study protocols/amendments for which it is responsible. A copy of the current IBN master schedule covering approximately the past five years is attached as **Exhibit 4.** All QAU findings noted during inspections (critical phase, facility, and process) and audits are reported to TFM, and the SDs. The QAU performs periodic facility inspections and maintains written and signed records of these inspections. The QAU also periodically reviews laboratory SOPs for compliance with actual procedures being performed and recommends SOP revisions when necessary. The QAU also performs inspections/quality assessments of contracted vendors. Finally, the QAU provides GLP training for staff and assists TFM in strategizing, implementing, and improving the IBN quality systems. Mr. Wang reports directly to Dr. Li. We found that the QAU is independent from those personnel involved in study direction and conduct of studies at IBN. QAU SOPs are in place defining roles and responsibilities of the QAU and were found to be adequate.

FACILITIES (HMM, MJS, ARW)

Evaluation of the testing facility and compliance with the GLP regulations was accomplished through a comprehensive inspection of the vivaria and support laboratories. The areas covered include animal receiving and housing; equipment storage; feed and bedding storage; and autoclaving and storage; test article receipt, storage, and formulation; necropsy, archive, and the HVAC system. Due to the size and number of buildings comprising the IBN campus and the time constraints, it was decided that each inspection team member would cover a separate building. The IBN campus is comprised of four buildings, A18, A19, B3, and B5. I (HMM) covered Building B5, Mr. Wasko covered B3, and Dr. Seaton covered A19. Building A18 was covered jointly. The facilities were found to be of adequate design and construction to facilitate the conduct of nonclinical studies and were found to be adequately cleaned/sanitized in all cases. Floor plans of the buildings comprising the testing facility were provided in the testing facility's introductory presentation that is attached as **Exhibit 1.**

In the archive room, I (MJS) interviewed the assistant archivist about temporary storage of documents submitted to archive. I noted that the date that the documents are received in the archive is not recorded in the electronic Document Management System (eDMS). The date that the SD approved the digital archive form and the date that the archivist inventories the documents is recorded. Per SOP, there may be up to 5 days between submission and inventory. The firm revised the procedure so that the eDMS captures the date that materials are submitted to the archive so that a complete chain of custody is formed.

While covering Building A19, I (MJS) inspected Test Article Control, Clinical Pathology, and Histology. I visited the Gene and Cell Therapy Assay area, where a robot is used to automate

assay steps. I also visited the glassware cleaning area and the facility monitoring room.

In the Test Article Control area, I watched test article formulation activities for study number (b) (4) No issues were noted.

In the Clinical Pathology laboratory, I reviewed the use and maintenance log for the urine analyzer. From my review of the form, it seemed that technicians might be using the form to document activities that they plan to perform, rather than to document the activities that were completed. During the inspection the firm revised this form and others so that they clearly demonstrate what activities were performed, when, and by whom.

In the Histology labs, I inspected trimming, embedding, processing, microtomy, and slide preparation areas. In the processing (dehydration) area I asked to see the SOP for the Leica ASP300S. The technician pulled up the SOP on an iPad. The SOP states that after 4 runs have been completed, the reagents need to be changed. The Unit #1 processor did not accurately reflect the use of reagents, as the instrument use log screen showed one run had been completed since the previous reagent change but the instrument screen indicated that only formalin (and not the other reagents, such as ethanol) was used on that one run. All the other reagents showed 0 runs since the previous reagent change. I was told that the hardcopy use log, and not the instrument screen, is used to capture runs, and to signal when 4 runs have been completed and the reagents need to be changed. During the inspection the firm contacted the vendor who came and installed a software update on the instrument.

I observed microtomy and slide staining activities. No issues were noted.

No issues were noted in the glassware and facility monitoring rooms.

During my inspection of Building 3 on Oct 29, 2024, I (ARW) started with the isotope and large animal facility on the first floor. We were provided a radiation and safety protection training prior to entering the isotope laboratory. Bohua Xu, Associate Director, Radioactive Imaging Evaluation Department, escorted an interpreter and me throughout the isotope laboratory. We donned a dosimeter, lab coat, mask, and shoe covers to enter the isotope laboratory. At the entrance of the laboratory area, the real-time radiation levels of each room were displayed. Rooms examined included the isotope labeling lab (3103A), preparation room (3105), balance room (3106), sample processing (3107), clinical pathology (3108), animal receiving (3133) and quarantine room (3133A), necropsy room (3139), cleaning room (3129), clean staging area (3127), specific pathogen free (SPF) animal holding room (3123), and conventional anteroom (3136).

Next, I (ARW) inspected the fourth floor of Building 3, which included an SPF barrier system. (b) (6), Department Head of Laboratory Technology, escorted us through this area. Rooms inspected included the clean staging area (3408), feed temporary storage (3407), inhalation laboratory (3428), feed storage (3437), necropsy rooms (3434 and 3434B), washroom (3433), as well as several rodent anterooms and respective holding rooms (3411,

3412, 3421, 3422, 3423, 3425, 3426, 3427).

On Oct 30, 2024, I continued with the inspection of the third floor of Building 3, which also included a SPF barrier system. I inspected clean storage (3312), cleaning room (3340), cleaning/sterilization (3344), bedding storage (3342), and rodent rooms (3313, 3320, 3336).

In rodent room 3313, I (ARW) observed oral dosing of rats for GLP study (b) (4), "(b) (4) [redacted]" Stickers were used to color code the doses to be administered (Group 1 – white, Group 2 – yellow, Group 3 – green, and Group 4 – red). One animal in the vehicle dose group, 1141, had a microchip, which was not responsive. The research associates notified the study director, Min Lu, of the issue. A new chip number was provided to the study director, who then modified the study protocol in Provantis to update the animal record with the new implant chip number. The new chip was implanted into the rat. Once the chip was scanned, the appropriate animal ID dosing record window was opened in Provantis, and the appropriate dose volume (2.6 mL) was administered via oral gavage. Occasionally, rats would struggle during the oral dosing. The dosing technician would stop dosing, wait a few seconds to reduce stress on the animal before restraining the animal again manually to finish administering the full dose volume. The dosing technician would state "done" when the dosing was complete so that the Provantis operator could document the time of dosing. All of the vehicle control group animals were dosed prior to moving onto the lowest test article formulation. The dose formulation containers were weighed prior to the start of dosing and at the completion of dosing for all animals in each group. The balance used was also verified with a certified weight set prior to use on study and at the end of dosing. All animals appeared to be administered the appropriate dose during the time of observation. I requested and was provided a copy of the Provantis records for the observed dosing of study (b) (4) (**Exhibit 5**).

On Oct 30, 2024, I (ARW) completed the inspection of Building 3 with the second floor. This is a conventional large animal facility. I inspected several anterooms and the respective animal holding rooms housing beagles (3207, 3209, 3210, 3213, 3214, 3217) and swine (3211). In addition, I inspected the quarantine anteroom (3218), feed storage (3216), procedure/storage room (3215), and the water purification room (3212). The automatic drinking water system was installed on Aug 7, 2024; however, the system was not in use at the time of the inspection.

The laboratory areas were clean and well-organized. There were no signs of infestation. Generally, animals were observed to be healthy at the time of inspection or received the appropriate veterinary care. Equipment was labeled with a unique identifiers and calibration statuses.

EQUIPMENT (HMM)

The equipment observed in the testing facility and used in the acquisition, measurement, and

analysis of data was found to be of adequate design and possessed the performance capabilities necessary to execute protocol requirements. Likewise, equipment requiring periodic calibration and maintenance was found to be maintained and calibrated in accordance with the applicable written SOPs. Not all equipment, however, was found to be maintained that would prevent an adverse effect on the test system and, ultimately, the quality and integrity of the nonclinical laboratory studies conducted at IBN. These deficiencies were noted primarily with equipment used to house and water in the testing facility. Specifically, the cage racks containing conduit for the automatic watering system were not drained as part of the cleaning/sanitizing procedure. This deficiency was cited in the FDA 483, Inspectional Observations (Observation #1C.) and is discussed in greater detail under the **Objectionable Conditions and Management's Response** heading of this report.

TESTING FACILITY OPERATIONS (HMM)

At the beginning of this inspection, an index/table of contents of all current facility SOPs was requested (see **Exhibit 6**). The firm has SOPs which cover all relevant aspects of testing facility operations and the conduct of nonclinical laboratory studies. Testing facility SOPs are maintained electronically in the facility's Document Management System (DMS) and are accessible to staff at computer terminals throughout the facility. The testing facility also maintains hardcopies of all current SOPs. Historical SOPs are maintained in the facility archive.

Reagent and Solutions (HMM)

All reagents and solutions observed during this inspection were appropriately labeled and contained an expiration date applied either by the manufacturer or by the facility in accordance with its current SOP. No expired reagents were observed nor was there evidence of expired reagents being used in the testing facility.

Animal Care (HMM)

The primary laboratory animals used in nonclinical studies at this facility include rabbits, miniature pigs, beagles, NHPs (cynomolgus macaque, rhesus monkeys), and rodents.
The facility does have an IACUC which reviews and approves all studies conducted at the facility involving the use of animals. The IACUC chairperson is Liping Wei, M.S. The IACUC's operation is detailed in an IBN SOP. All studies involving the use of animals at the testing facility are required to be approved by the IACUC.

During receipt of animals, a staff veterinarian is available to observe animals for any potential health issues. Animal cages, racks, and accessory equipment were found to be appropriately designed and constructed to facilitate proper animal care and study conduct. However, not all cages, racks, and accessory equipment were found to be maintained in a manner that would prevent an adverse effect on study animals and the potential to affect the quality and integrity of study data and results. Specifically, the cage racks containing conduit for the automatic watering system were not drained as part of the cleaning/sanitizing procedure. This deficiency

was cited in the FDA 483, Inspectional Observations (Observation #1C.) and is discussed in greater detail under the **Objectionable Conditions and Management's Response** heading of this report. Environmental conditions in the animal rooms including temperature and relative humidity, pressure differentials, lighting, noise, and room air changes are monitored in accordance with facility SOPs. Facility documentation associated with each of these environmental parameters was reviewed during this inspection for calendar years 2022 and 2023 and no deficiencies were noted.

Animal drinking water sampling and analysis is currently required to be performed on a quarterly basis includes chemical and microbiological analysis. Additionally, microbiological testing of animal feed and bedding is performed every 6-months. As part of this inspection, water testing records for 2022 and 2023 were reviewed. Quarterly water samples collected in the vivaria are sent to a contract laboratory for analysis.

The animal feeds used at this facility are assigned an expiration date of 6-months from the vendor's manufacture date if an expiration date is not provided by the vendor. No expired feeds were observed and there was no evidence that expired feeds have been used on nonclinical laboratory studies.

TEST AND CONTROL ARTICLES (T/CA) (HMM)

As part of this inspection, we covered the test and control article storage and formulation areas. Access to the test article/control article storage room is limited to the manager and technicians in the test article receipt, storage, and dispensing area. Controlled test articles can only be accessed by the controlled drugs manager and designated staff. Only the manager and technicians have access to the test and control article storage areas including room temperature, refrigerated and frozen storage. All test and control articles are inspected by a technician upon receipt and are entered into a test/control article receiving form. The in transit temperature monitoring device report is uploaded and any excursions are communicated to the sponsor for review and impact assessment. If determined to be acceptable for use, the test and control articles are stored under the conditions specified by the sponsor. There was adequate documentation to verify the shipping, receipt, and storage of the test and control articles. Test and control articles were randomly reviewed in the ambient storage cabinet, refrigerator, and freezer and were found to be properly labeled and stored under the required temperature conditions. We were informed that in all cases, test and control article characterization is performed by the sponsor for GLP studies, and formulation uniformity testing, and concentration analysis is performed by the IBN Analytical Laboratory. The sponsor provides the SD for a given nonclinical laboratory study information regarding test and control article characterization usually in the form of a certificate of analysis for each batch used in the study. The testing facility has SOPs for receipt, handling, formulation, dispensing, and storage of test and control articles as well as reserve samples for GLP studies greater than 4-weeks duration. We found test and control articles were separately stored and the desiccants, where required, were in good condition. The formulation preparation areas were also separate for test and control article formulations.

PROTOCOL AND CONDUCT OF NONCLINICAL LABORATORY STUDIES (HMM)

For the audited studies, there was an original protocol, and all protocol amendments were contained in the study file that were compared with the FRs contained in the inspection background material and no discrepancies were noted. The protocols contained all the required elements. The test and control articles were specified in the protocol and dose formulations were described to include dosing solution uniformity and assay.

The test systems were also described in the protocols to include the required weight range. Receipt, handling, housing, diet, water and bedding were described in study records. The weights and sex of each animal were appropriate for inclusion based on the protocol requirements. Raw data were recorded on paper and electronically (Provantis version 10.5.0.4) and errors were properly corrected.

RECORDS AND REPORTS (HMM)
All raw data, documentation, protocols, final reports, and specimens resulting from nonclinical studies conducted at this facility are maintained in the testing facility archives.

DATA AUDIT (HMM/MJS/ARW)

Protocol (b) (4): (b) (4)

IND-(b) (4)
Test Article: (b) (4)
Study Number: (b) (4)
Study Director: **Min Lu, M.S.**
Sponsor: (b) (4)

Study Initiation Date: Apr 12, 2023
Study Completion Date: Oct 30, 2023 (Final Report Amendment No. 2)

I (ARW) reviewed the (b) (4) study file against the final study report. The original protocol was approved by the study director on Apr 12, 2023. The original final study report GLP Compliance Statement was signed by Min Lu, M.S. on Sep 29, 2023, and claimed compliance to NMPA and US FDA Good Laboratory Practices. Analyses of the test article, vehicle control, the cytokine assay, circulation immune complex, PD marker analysis, and immunohistochemistry were identified as exceptions for GLP compliance (page 2 of **Exhibit 7**). A Quality Assurance Statement was signed by Changxiong Yang, B.S. on Sep 29, 2023, and outlined several study and process inspections performed by the QAU throughout the course of the study (pages 3-5 of **Exhibit 7**).

The pathology report (Appendix XIV) (page 735 of **Exhibit 7**) was signed by the study

pathologist, (b) (6), M.S. on Sep 29, 2023. The study pathologist was changed with protocol amendment number 8 on Sep 25, 2023. (b) (6), B.S. was assigned as the original study pathologist. A Peer Review Statement (page 744 of **Exhibit 7**) was signed by (b) (6), Diplomate of Japanese Society of Toxicologic Pathology (DJSTP), on Aug 11, 2023, and indicated that glass slides, whole slide images, and pictures were assessed for three animals per sex for animals from group 1 (vehicle control) and three animals per sex for animals in group 4 (100mg/kg). The draft pathology report, organ weight data, summary of macroscopic and microscopic observations, clinical observations, clinical pathology results and immune function test results were provided for reference during the peer review process.

The version of the original final report provided by the firm during the inspection had 1,174 pages; however, the version of the final report submitted by the sponsor under IND (b) (4) had 1,173 pages. Page 1008 of the original final report provided by the firm was blank for the original English version (**Exhibit 7**). Page 1008 of the final report submitted by the sponsor is missing the images for Figures 1 and 2 of Appendix XVII "The PD marker analysis report and the relationship between the exposure levels of (b) (4) and ADM after dosing on Day 1 and Day 22" (**Exhibit 8**).

Final Report Amendment No. 001 was issued on Oct 20, 2023, to address errors in the final report text and Appendix IV "The dose site irritation report," Appendix IX "Individual data of cytokine analysis," Appendix XVII "The PD marker analysis report and the relationship between the exposure levels of (b) (4) and ADM after dosing on Day 1 and Day 22," and Appendix XVIII "the immunogenicity report" (**Exhibit 9**). This final report amendment included a GLP compliance statement signed by the study director on Oct 20, 2023. The Quality Assurance Statement was signed by (b) (6), Quality Assurance Auditor, on Oct 20, 2023, and outlined the audit of the contributing scientists' report amendments as well as Final Report Amendment 001. The amendments outlined the individual changes made within each report as well the as the reason for the changes.

Final Report Amendment No. 002 was issued on Oct 30, 2023 to edit the text of the final report summary (pages 14 and 15), Section 5.15 Toxicokinetic Analysis (page 44), and Section 6 Conclusion (page 47) to indicate following intravenous administration at 25, 50 or 100 mg/kg once a week for 4 weeks, no apparent accumulation in the systemic exposure ($AUC_{(0\text{-}t)}$ and C_{max}) of (b) (4) was noted except that exposure of $AUC_{(0\text{-}t)}$ had significant accumulation at 100 mg/kg, the accumulation ratio was 2.06, which was greater than 2.0 (**Exhibit 10**). This final report amendment also included a GLP compliance statement and Quality Assurance Statement signed on Oct 30, 2023. This amendment clearly outlined the changes made to the final report text, indicated the reason for the changes, and indicated that the changes had no impact on the data and conclusions.

I reviewed the archived study (b) (4) paper records. The archived study file was paginated. The hard copy records reviewed included the original final report; study schedules with amendments 001-003; the study protocol and amendments 001 – 008; protocol training records; test and control article certificates of analysis; test and control article receipt records;

test and control article shipment temperature monitoring; test and control article distribution and return records; dose formulation preparation records; dose formulation distribution; stock animal reuse table; animal receipt and quarantine records; animal screening; animal acclimation; pre-study hematology, coagulation, and serum chemistry; abnormal animal reports, laboratory animal treatments; physical examinations; records of parasite egg examination; analgesic/sedation; deviations, records of TB examination, dosing records, TK blood collection records, plasma and serum sample preparation; euthanasia; syringe verification records; electrocardiograms; flow cytometry assay records; clinical pathology smear and stain records; and dose formulation analysis. The paper records documented study activities and met ALCOA (attributable, legible, contemporaneous, original, and accurate) principles.

Electronic raw data were captured within Provantis and included blood and urine sample collection, blood pressure, body temperature, body weight, dosing, dose site and clinical observations, ophthalmology examinations, coagulation, hematology, serum chemistry, urinalysis, gross and histopathology, and organ weights. I verified the raw data for selected animals in datasets against the final study report, and I did not find any discrepancies. Provantis data collected prior to group assignment were collected under Provantis protocol, (b) (4). Audit trails for the Provantis datasets were enabled and reviewed for selected datasets with no objectionable conditions identified.

Records of Dosing Formulation Preparation (Form-HM-SC-TCA-017) included calculations to determine the volume of test article and vehicle required for each dose group formulation, as well as preparation details for each dose group. Dose formulations were documented as performed in a sterile environment protected from light. The firm assigned internal tracking numbers to the test and control article. The test article, (b) (4) lot number (b) (4), was assigned code (b) (4). The control article, (b) (4) Placebo, lot number (b) (4), was assigned code (b) (4). I (ARW) verified that the calculations for the concentration of the test article, (b) (4), were prepared for each formulation as specified in the study protocol (Group 1, 0 mg/mL; Group 2, 5.0 mg/mL; Group 3, 10.0 mg/mL; and Group 4, 20.0 mg/mL), mixed gently, and subsequently filtered through a 0.22 µm filter. Formulations were protected from light and stored at 2 – 8 °C (See pages 39-42 of **Exhibit 11**). Dose formulations were prepared on Apr 18, 2023, Apr 26, 2023, Apr 30, 2023, May 10, 2023, and May 16, 2023, for administration on Apr 20, 2023, Apr 27, 2023, May 4, 2023, May 11, 2023, and May 18, 2023, respectively. Dose formulation analyses on Days 1 and 22 were analyzed under analytical method (b) (4). The mean absorbance of Group 1 was below 30% of the absorbances of the LLOQ. Groups 2 – 4 were well within the 90% - 110% acceptance of the nominal concentrations (page 293 of **Exhibit 7**).

Double syringe pumps were used to administer doses to two different animals simultaneously. Syringe pump volume delivery was verified prior to use. The Animal Dosing Volume Records Table (Form-HM-EO-DOS-049) was used to document the volume of dosing solution loaded into the syringe for each animal as well as the theoretical and actual volumes

of administration (pages 18-19 of **Exhibit 12**). The Body Weight and Dosing Record of Non Rodent (Injection Pump Administration) (Form-HM-EO-DOS-005) documented the animal number, animal identification (implant), body weight, theoretical and actual dose volumes (mL), theoretical and actual injection rates, syringe pump number and channel, injection site, and dose start times (pages 20-23 of **Exhibit 12**).

Using the most recent body weights captured within Provantis on April 18, 2023 and referencing the Study Placement Plan Report (pages 2-8 of **Exhibit 12**), I was able cross reference the pre-study subject numbers/animal identification in Provantis prior to group assignment and confirm that the doses administered on April 20, 2023 (Day 1) to NHPs in Groups 1-4 were dosed at a volume of 5 mL/kg at a rate of 1 mL/min as specified in the study protocol.

I interviewed the (b) (4) study director, Min Lu. She answered several questions regarding SD assignment, study planning, protocol development, notification to update the Master Schedule, review of formulation instructions, SD monitoring throughout the study, documenting and responding to unforeseen circumstances and deviations, data review, responding to QA audit reports, final report compilation, and study archival.

IND-(b) (4)
Protocol/Study Number and Title/Name: Protocol (b) (4)**:** (b) (4)

Test Article: (b) (4)
Study Number: (b) (4)
Study Director: **Yimin Qian, M.S.**
Sponsor: (b) (4)

Study Initiation Date: Mar. 22, 2023
Study Completion Date: Sep. 26, 2023

I (MJS) reviewed hardcopy raw data and study records as well as raw data captured electronic using the Provantis electronic data capture system. The majority of raw data was captured using the Provantis system. A subset of digitally captured data was compared against the final study report and no discrepancies were noted.

Two concerns were noted during the study audit, and these were discussed with relevant study personnel and the Manager of QA:

1. Necropsy

SOP HM-EO-PAT-005 Weighing of Organs (**Exhibit 13**), states "if it is seen that an error with the result the organs will be re-weighed." During my interview of technical staff, I learned that

when organs are re-weighed the original weight is not retained. As a result, no documentation exists for the original organ weight, and actions taken prior to re-weighing the organ, and the reason for re-weighing the organ. I was told that if an organ weight falls outside a pre-determined weight range, Provantis prompts the operator to reject or accept value. Generally the technician will reject the weight and re-weigh the organ, with no documentation. This deficiency was cited in the FDA 483, Inspectional Observations (Observation #1A.)

2. This study included a four-week dosing phase and a four-week recovery phase. Because this study is greater than four weeks duration, a sample of test article must be retained. Due to oversight, a reserve sample was not retained. This deficiency was cited in the FDA 483, Inspectional Observations (Observation #2.)

(b) (4) " (b) (4)

IND (b) (4)
Test Article: (b) (4)
Study Number: (b) (4)
Study Director: **Xinbei Jiang, B.S.**
Sponsor: (b) (4)

Study Initiation Date: Nov 22, 2021
Study Completion Date: Mar 10, 2022

The final report for study (b) (4) was submitted to the U.S. FDA under IND (b) (4). The original final report was finalized in Chinese and translated to English. The English version of the final report submitted to the IND does not contain any content under the header for Table 7 on page 80 of 913 (**Exhibit 14**). This version of the final report includes a translation statement signed by Caiyun Hao and Xinbei Jiang of Innostar on Apr 26, 2022 (page 2 of **Exhibit 14**).

We requested a copy of the English version of the final report (**Exhibit 15**). This version of the report does include tables after the Table 7 header. It should be noted that the translation statement for the English version of the final report includes a translation statement signed by Caiyun Hao and Xinbei Jiang of InnoStar on May 6, 2022 (page 2 of **Exhibit 15**). This version of the translated English report includes a total of 921 pages to account for the additional eight pages under the Table 7 header on page 80.

SOP-HM-SC-STC-023 outlined the requirements for the translation of study reports and amendments and the qualifications of translators.

Study: (b) (4), " (b) (4)"
Study Director: Honggang Tu, M.S., DCST
Sponsor: (b) (4)

Test system: Bama Miniature Pigs
Test article: (b) (4)- Circular RNA encoding Vascular Endothelial Growth Factor (VEGF)-165 (subset of VEGF-A), Lot # (b) (4).
Schedule of Events: Study initiation: 3/2/2024(Study Director Protocol Signature); Study Completion: 7/16/2024 (Study Director Signature Final Report).
Experimental Start (In-Life), Surgery/Dosing 3/11/2024; **Experimental Completion (In-Life):** Day 64, 5/16/2024 (Recovery Necropsies).

The protocol was signed by the study director prior to the initiation of the study. The raw data were recorded on paper records and in Provantis The data were attributable to the person who observed and recorded the data. All changes to original entries were initialed and dated, and did not obscure the original entry, and the reason for change was indicated. Approved SOPs existed during the conduct of this study. The equipment used in this study had documentation of standardization and calibration. There were no significant changes in equipment noted during the conduct of the study. Study methods described in the final report met the requirements of the protocol. Selection of test systems for species, source, weight range, number, age, date ordered, and date received were in keeping with the study protocol. Procedures for receipt, examination, and isolation of newly received animals were documented. Methods for identification, housing and randomization were all documented.

Twenty-three male and twenty-four female Bama Mini Pigs were received at the testing facility on 1/24/2024 from (b) (4). The proper quarantine/acclimation period was observed (minimum 7 days), and the animals were randomized to the high dose, low dose or control groups (15 male and 15 female). Three animals/sex/group were assigned to the main study and 2 animals/sex/group were assigned to the recovery study. The first surgeries/dosing were performed on 3/11/2024 and were completed on 3/15/2024. I interviewed the study director, Honggang Tu, M.S., DCST, about the conduct of the study. I discussed the five animals that expired during the surgery/dosing procedure. Mr. Tu acknowledged that this number of deaths was unusually high, and we discussed the case of each animal that expired during the surgery/dosing in depth. My findings from our review of each case are summarized as follows:

- Animal #113 (Vehicle Control Group)-review of the operative record with the SD revealed that the animal experienced slow heart rate during the procedure as well as decreased oxygen saturation, abnormal QRS wave, and abnormal pupil response. The animal was administered adrenaline for rescue, but the animal did not respond, went into cardiac arrest and expired. The animal was not dosed prior to death. Animal 113 was replaced with animal 113-1.
- Animal 113-1(Vehicle Control Group)-review of the operative record with the SD revealed that during the operative procedure the animal developed air bubbles in its trach tube which caused bubbling and irritation in the trachea. The animal was dosed and approximately one minute after dose administration, the animal expired.
- Animal # 111(Vehicle Control Group, replaced with Animal 111-1)-review of the

operative record with the SD revealed that during the surgical procedure, the animal experienced decreased heart rate, decreased oxygen saturation, and abnormal ECG specifically, abnormal QRS wave. Attempts were made to rescue the animal including administration of 0.6 mL of adrenaline; however, the animal did not respond and expired. The animal was not dosed.

- Animal # 211(Low Dose Group, replaced with Animal 211-1)-review of the operative report with the SD revealed that the animal experienced decreased heart rate, decreased oxygen saturation, and abnormal ECG specifically abnormal QRS wave and the animal became cyanotic. Attempts were made to rescue the animal with an injection of adrenaline, but the animal expired within five minutes of receiving adrenaline. According to the SD, this animal was dosed.
- Animal # 305 (High Dose Group, replaced with Animal 305-1)-review of the operative report with the SD revealed that animal experienced decreased heart rate, decreased oxygen saturation, and abnormal ECG specifically abnormal QRS during dose administration after administration of approximately 1.5 mL of the test article. Rescue attempts were made with the administration of 1 mL of adrenaline; however, the animal expired approximately four minutes after administration of adrenaline.

The surgeon for all study procedures was the same individual according to the SD, Mr. (b) (6) Laboratory Technology, Lead Technician. I interviewed Mr. (b) (6) and was informed that he had received special training in the surgical procedure used in this study and had performed the procedure before this study. Mr. (b) (6) received training in Shanghai on 4/17/2020 at the Shanghai Oriental Hospital. He received specific training in pig myocardial injection surgical training under Dr. (b) (6). I reviewed Mr. (b) (6)'s training record and his training in the study surgical/dosing procedure was well documented to include training in the testing facility's SOP, SOP-HM-EO-DOS-022, v1.0 "Mini Pig Heart Exposed Open Heart Surgery". The SD informed me that an investigation/root cause analysis was performed to determine why the five animals were lost during the surgical/dosing procedure and it was determined that the deaths were not related to the test article, but rather, the surgical procedure itself. The SD informed me that the decision made to repeat the study with a revised protocol that includes significant improvements in the response to the intraoperative symptoms that occurred during the surgical procedures in the current study. This also includes an improved operative report to capture more intraoperative detail related to vital sign data. The Animal Intra-Operative Monitoring reports for the animals that expired during the surgical/dosing procedure are attached as **Exhibit 16**. A copy of the draft, revised protocol was requested and is attached as **Exhibit 17**.

Comparison of the final report that accompanied the inspection assignment with that found in the study records revealed no discrepancies. Statements of the final report were compared with the protocol requirements and raw data. The records reviewed include animal receipt and acclimation/quarantine; physical examinations; test article receipt, storage, preparation, utilization, and disposition; surgery/dosing, body weights, environmental controls; specimen collection (blood and tissue) clinical pathology, toxicokinetics, necropsy, organ weights, and histopathology. There was no evidence of test article and vehicle preparation/formulation

errors nor was there evidence of mis-dosing of any animals during the study. Likewise, there was no evidence of improper blood and tissue specimen collection and analysis (e.g., clinical pathology, toxicokinetics, histopathology). All deviations were properly documented, and no additional deviations/discrepancies were noted. All unused test article formulation and test article was discarded at the testing facility or returned to the sponsor in accordance with the sponsor's directions.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE (HMM/MJS/ARW)
Observations listed on form FDA 483:

Observation 1

The testing facility does not have written standard operating procedures setting forth nonclinical laboratory study methods that management is satisfied are adequate to ensure the quality and integrity of the data generated in the course of a study. Specifically,

A. SOP HM-EO-PAT-005, Version 5.0, "Weighing of Organs", does not require all original experimental data to be accurately recorded.

B. SOP-HM-EO-PAT-004, Version 5.0, "Non-Rodent Necropsy and Routine Tissue Organ Collection" does not include the procedure for placing and holding the harvested tissues in 0.9% normal saline for up to 30 minutes before being placed in the required fixative.

C. SOP-HM-EM-EQB-017, Version 6.0 "Use and Maintenance of the Edstrom Automatic Watering System" does not require the draining of excess water in the conduit attached to cage/racks and storing dry as part of the cage/rack sanitation procedure.

Reference: 21 CFR 58.81(a)

Supporting Evidence and Relevance: **Exhibit 13, SOP HM-EO-PAT-005 "Weighing of Organs" and Attachment 4, InnoStar Bio-Tech Nantong Company, Ltd. written response dated Nov 18, 2024**.

Discussion with Management:

A. SOP HM-EO-PAT-005 Weighing of Organs (**Exhibit 13**), states "if it is seen that an error with the result the organs will be re-weighed." During my interview of technical staff, I (MJS) learned that when organs are re-weighed the original weight is not retained. As a result, no documentation exists for the original organ weight, and actions taken prior to re-weighing the organ, and the reason for re-weighing the organ. I was told that if an organ weight falls outside a pre-determined weight range, Provantis prompts the operator to reject or accept value. Generally, the technician will reject the weight and re-weigh the organ, with no documentation.

B. During my (HMM) inspection of Building B5, I observed a Nonhuman Primate necropsy being performed for study # (b) (4) in Room # 5114B. I observed the excision of the protocol required tissues by the prosectors and noticed that upon the harvesting of each tissue, they were not placed directly into the 10% Neutral Buffered Formalin (10% NBF) for fixation. Instead, the tissues were removed and weighed., if required, then placed on a labeled tray containing 0.9% Normal Saline (10%NS). Upon completion of the necropsy, the prosectors inventoried/accounted for the protocol tissues and placed them individually in the 10% NBF. The tissues remained in the 10% NS until the end of the necropsy. I questioned the pathologist on duty and was informed that the tissues could remain in the 10% NS for up to ½ hour before being placed in the fixative. I asked her if this was in the relevant SOP, SOP-HM-EO-PAT-004, Version 5.0, "Non-Rodent Necropsy and Routine Tissue Organ Collection" and she said that it was not. She informed me that the basis for the ½ hour time in 10% NS before fixing was taken from the relevant literature and that the ½ time in the 10% NS before fixing did not have a deleterious effect on the tissues or the quality of the slides produced for histopathological evaluation. I informed the pathologist that the SOP should include this procedure and that the time between harvesting the tissues and fixation should be documented.

C. During my (HMM) inspection of Building B5, Room 5302, I noted sanitized cage racks ready for use with a significant volume of water in the conduit of the Edstrom automatic watering system. I was informed by management that the cage/rack sanitizing procedure did not include opening the drain valve at the bottom of each rack. I informed management that this should be included in the cage/rack sanitization procedure and the conduit should be stored dry. I went on to say that residual water in the conduit could promote bacterial growth and could have an adverse effect on study animals when in use. Management acknowledged this observation and indicated that this would be added to their SOP for sanitizing cage/racks. The next day, 10/29/2024, I was informed by management that facility staff were instructed to drain the cage/rack automatic watering conduit for all cage/racks that had been sanitized in the testing facility. Management also informed me that the relevant facility SOP SOP-HM-EM-EQB-017, Version 6.0 "Use and Maintenance of the Edstrom Automatic Watering System" had been revised to include draining the conduit during the sanitization of cage/racks. Management also indicated that this observation and associated corrective action would be covered in their written response to the FDA-483 observation (see **Attachment 4**).

Observation 2

Reserve samples of test article for studies of more than 4 weeks duration were not retained for the period of time provided by 58.195. Specifically,

For study number (b) (4), (b) (4) via Oral Gavage in Beagle Dogs Followed by a 4-week Recovery Period, no reserve sample of test article was retained.

Reference: 21 CFR 58.105(d)

Supporting Evidence and Relevance: This study was greater than four weeks duration and therefore, a reserve sample of each lot of test and control article used in the study was required to be retain.

Discussion with Management:

This study included a four-week dosing phase and a four-week recovery phase. Because this study is greater than four weeks duration, a sample of test article must be retained. Due to oversight, a reserve sample was not retained.

REFUSALS (HMM)

No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT (HMM/ARW)

An exit interview was held on 11/1/2024 and in attendance were Hugh M McClure III, National Expert, (OII), Andrew R. Wasko II, Biologist (CDER/OTS/OSIS/DNDSI), Mark J. Seaton, Sr. Pharmacokineticist (CDER/OTS/OSIS/DNDSI) and Dr. Yan Chang, IBN CEO/General Manager who was accompanied by various members of the IBN staff.

An FDA 483, Inspectional Observations was issued to Dr. Yan Chang, CEO/General Manager. The observations were discussed with Dr. Chang who acknowledged each and stated that they would be addressed. She also stated that a response letter would be sent within 15 business days (see **Attachment 4**).

In addition to the observations cited in the FDA-483, additional observations were made during this inspection that were also discussed with Dr. Chang and her staff. These discussion items are as follows:

DISCUSSION ITEMS

1. In building A19, room 9105A, which was used for room temperature storage of dose formulations, no sensor was present to monitor the temperature of the room. A sensor was present in the adjacent room, 9105. We were told that the door was left open to use this sensor to monitor the temperature of room 9105A. The firm moved the sensor from 9105 into 9105A during the inspection.
2. For study (b) (4), Record of Dose Formulation Preparation, pre-typed information lists the TA code as (b) (4) instead of (b) (4) for dose formulations prepared on April 18, 2023, April 26, 2023, April 30, 2023, May 10, 2023, and May 16, 2023. The correct code was also listed on the same record, but the incorrect

code was listed for the amount of test article used in the formulation. I (ARW) reiterated the importance of verifying pre-typed information.

ADDITIONAL INFORMATION (HMM)

A response letter referencing the FDA 483 observations was received from the firm on Nov 18, 2024. The response letter is included as **Attachment 4**.

SAMPLES COLLECTED (HMM)

There were no samples collected during this inspection.

VOLUNTARY CORRECTIONS (HMM)

Dr. Chang acknowledged the observations cited in the FDA-483 and discussion items with a written response promised within 15-business days. As previously indicated in this report, Dr. Chang's written response was received on Nov 18, 2024, and is included as **Attachment 4**.

EXHIBITS COLLECTED (HMM)

1. Testing Facility Overview, 46 pp.
2. IBN Organizational Chart, 17 pp.
3. Listing of Software, 15 pp.
4. IBN Master Schedule, 54 pp.
5. Provantis Records for the Observed Dosing of Study (b) (4), 67 pp.
6. IBN SOP Index, 31 pp.
7. Final Report Study # (b) (4), 1,174 pp.
8. Final Report Study # (b) (4), 1,173 pp.
9. Study # (b) (4) Final Report Amendment, 26 pp.
10. Study # (b) (4) Final Report Amendment 02, 6 pp.
11. Study # (b) (4) Raw Data, 43 pp.
12. Study # (b) (4) Raw Data, 23 pp.
13. SOP-HM-EO-PAT-005, V 4.0, 10 pp.
14. (b) (4) Final Report, IND (b) (4), 913 pp.
15. (b) (4)-RAT-REPORT-FINAL-V 2.0, 921 pp.
16. Animal Intra-Operative Monitoring Reports, 5 pp.
17. Draft, Revised Protocol Study # (b) (4), 29 pp.

ATTACHMENTS (HMM)

1. CDER/OSIS Inspection Assignment Memorandum, dated Mar 8, 2024, 7 pp.
2. CBER/OCBQ Inspection Assignment Memorandum dated Sep 1, 2024, 6 pp.
3. Form FDA 483, Inspectional Observations dated Nov 1, 2024, 3 pp.

4. InnoStar Bio-Tech Nantong Company, Ltd. Written response Dated Nov 18, 2024, 79 pp.

Hugh M. Mcclure Iii -S Digitally signed by Hugh M. Mcclure Iii -S Date: 2024.12.19 16:32:33 -05'00'

Hugh M. McClure III
BIMO National Expert

Mark J. Seaton -S Digitally signed by Mark J. Seaton -S Date: 2024.12.19 15:57:07 -05'00'

Mark J. Seaton, Ph.D.
Sr. Pharmacokineticist

ANDREW R. WASKO -S Digitally signed by ANDREW R. WASKO -S Date: 2024.12.19 16:02:52 -05'00'

Andrew R. Wasko II
Biologist

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
7520 Standish Place (HFD-45) Rockville, MD 20855-277 (301) 594-0020 Fax (301) 594-1204 Industry Information: www.fda.gov/oc/industry	10/28-11/1/2024
	FEI NUMBER 3029550626

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Yan Chang, CEO, General Manager

FIRM NAME	STREET ADDRESS
InnoStar Bio-Tech Nantong Co. Ltd.	Building A18, 100 Dongtinghu Road, Linjiang Town, Haimen Dist
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Nantong City, Jiangsu Province, China	Nonclinical 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 testing facility does not have written standard operating procedures setting forth nonclinical laboratory study methods that management is satisfied are adequate to ensure the quality and integrity of the data generated in the course of a study. Specifically,

A. SOP HM-EO-PAT-005, Version 5.0, "Weighing of Organs", does not require all original experimental data to be accurately recorded.

B. SOP-HM-EO-PAT-004, Version 5.0, "Non-Rodent Necropsy and Routine Tissue Organ Collection" does not include the procedure for placing and holding the harvested tissues in 0.9% normal saline for up to 30 minutes before being placed in the required fixative.

C. SOP-HM-EM-EQB-017, Version 6.0 "Use and Maintenance of the Edstrom Automatic Watering System", does not require the draining of excess water in the conduit attached to cage/racks and storing dry as part of the cage/rack sanitation procedure.

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Hugh M. McClure III Andrew R. Wasko Mark J. Seaton	Hugh M. McClure III, National Expert Andrew R. Wasko, Biologist Mark J. Seaton, Pharmakokineticist	11/1/2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
7520 Standish Place (HFD-45) Rockville, MD 20855-277 (301) 594-0020 Fax (301) 594-1204 Industry Information: www.fda.gov/oc/industry	10/28-11/1/2024
	FEI NUMBER 3029550626

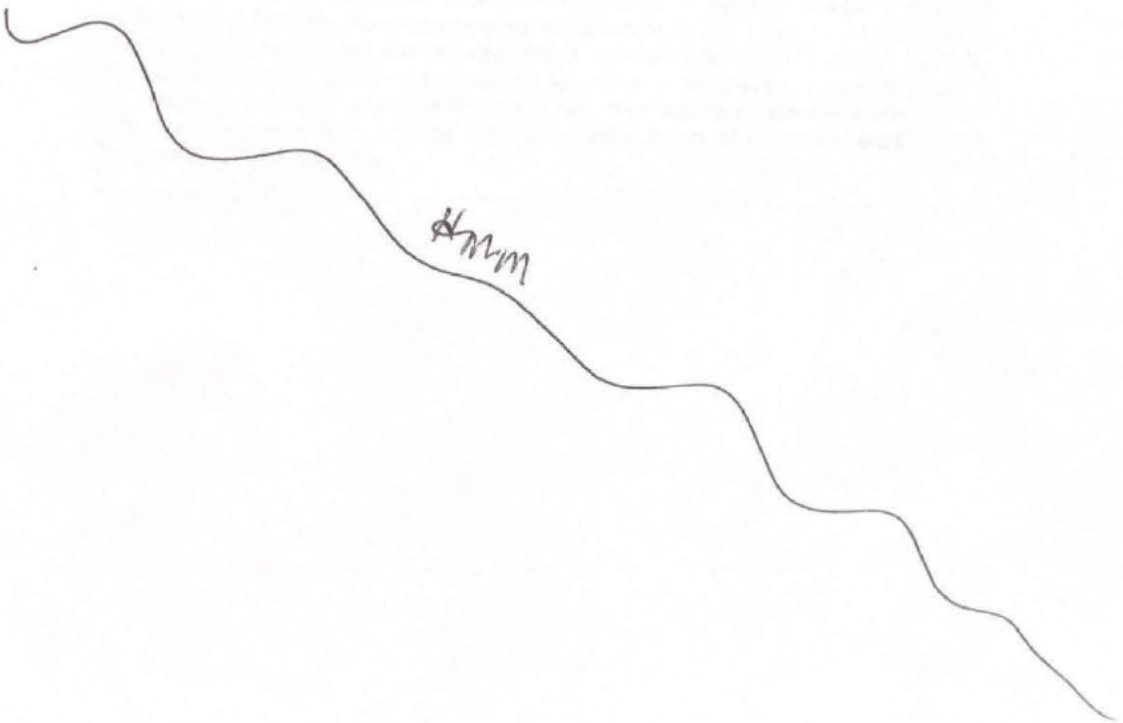
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Yan Chang, CEO, General Manager

FIRM NAME	STREET ADDRESS
InnoStar Bio-Tech Nantong Co. Ltd.	Building A18, 100 Dongtinghu Road, Linjiang Town, Haimen Dist
CITY, STATE AND ZIP CODE Nantong City, Jiangsu Province, China	TYPE OF ESTABLISHMENT INSPECTED Nonclinical Laboratory

2. Reserve samples of test article for studies of more than 4 weeks duration were not retained for the period of time provided by 58.195. Specifically,

For study number (b) (4), (b) (4) via Oral Gavage in Beagle Dogs Followed by a 4-week Recovery Period, no reserve sample of test article was retained.



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SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Hugh M McClure III Andrew R Wasko II Mark J Seaton	Hugh M. McClure III, National Expert Andrew R. Wasko, Biologist Mark J. Seaton, Pharmakokineticist	11/1/2024

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."

A Full Response to FORM FDA 483

Testing Facility:

InnoStar Bio-Tech Nantong Co., Ltd.

SIGNATURE PAGE

Dear Hugh M. McClure III, Andrew R. Wasko, Dr. Mark J. Seaton and OSIS officers,

We sincerely appreciate your inspection conducted from October 28 to November 1, 2024. This presents a valuable opportunity for us to enhance our quality management system. As we have explained during the inspection, we fully acknowledge all items documented in Form FDA 483. In this response document, we have specifically described our actions addressing each issue noted in Form FDA 483. All corrective measures have been implemented in accordance with the suggestions provided by your team.

We look forward to receiving any further comments regarding the post-inspection review that you may provide to our testing facility.

Best regards to you all.

Testing Facility Management: Hua Li, Ph.D., DCST

Signature & Date: NOV. 1st. 2024

OBSERVATIONS AND RESPONSES

Finding No.	1
Finding Description	The testing facility does not have written standard operating procedures setting forth nonclinical laboratory study methods that management is satisfied are adequate to ensure the quality and integrity of the data generated in the course of a study. Specifically. A. SOP-HM-EO-PAT-005, Version 5.0, "Weighing of Organs", does not require all original experimental data to be accurately recorded. B. SOP-HM-EO-PAT-004, Version 5.0, "Non-Rodent Necropsy and Routine Tissue Organ Collection" does not include the procedure for placing and holding the harvested tissues in 0.9% normal saline for up to 30 minutes before being placed in the required fixative. C. SOP-HM-EM-EQB-017, Version 6.0, "Use and Maintenance of the Edstrom Automatic Watering System", does not require the draining of excess water in the conduit attached to cage/racks and storing dry as part of the cage/rack sanitation procedure.
Analysis & Assessment	A: The SOP-HM-EO-PAT-005, Version 5.0, "Weighing of Organs" requires recording the correct data generated from the weighing of organ weights, but does not require all data (even obviously invalid ones) should be recorded. This can be attributed to an incomplete understanding of data integrity. B: The SOP-HM-EO-PAT-004, Version 5.0, "Non-Rodent Necropsy and Routine Tissue Organ Collection" does not explicitly specify the time required from confirming animal death to completing organ fixation. Pathologists have been preserving organs within about 30 minutes based on routine practice. After detailed communication with the FDA inspectors on-site, the inspectors suggested that we could find relatively reasonable time requirements by consulting literature. Specific literatures and corrective actions are detailed in the CAPA actions

	below. C: The SOP-HM-EM-EQB-017, Version 6.0 "Use and Maintenance of the Edstrom Automatic Watering System" requires that the stop valves of the cage branch pipes be closed after disinfection, but it does not explicitly require the draining of excess water from the cage branch pipes. Although we will disinfect the cage branch pipes again before their next use, draining the water can keep them dry during storage, reducing the risk of bacterial growth, and further ensuring that the effectiveness of subsequent disinfection is not compromised. The reasons for the aforementioned issues stem from a lack of comprehensive and in-depth understanding of data integrity and hazard/risk identification. Therefore, in the following CAPA Actions, in addition to revising and improving the three SOPs and Forms, we have also taken further measures.
CAPA Actions	A: SOP-HM-EO-PAT-005, version 6.0, "Weighing of Organs", has been revised (see Annex 1-A-1). The SOP explicitly states that: If the weighing process, results are wrong or the organ weight is out of the range, the original weighing data and the retest results are recorded in necropsy record or the Provantis System. This ensures that all original experimental data (even obviously invalid data) be accurately recorded. Additionally, all pathology personnel have been trained on this SOP (see Annex 1-A-2). B: Based on the relevant literature reviewed (see Annexes 1-B-1 to 1-B-3), it is known that during necropsy, tissues and organs removed from the animal body within 2 hours after death do not undergo autolysis that would affect the evaluation at the optical microscope level (micron level). Based on this conclusion, combined with the experience of our testing facility, and the practices in the field of the industry, we have revised SOP-HM-EO-PAT-002, Version 5.0, "General Rules at Necropsy" (see Annex 1-B-4), which outlines the overall requirements for necropsy of rodents and non-rodents. The SOP explicitly states that:

	After removal, the fixation of tissues/organs must be completed within 2 hours after confirming the death of the animal; The tissues/organs should be infiltrated with normal saline to remain moist; And, we have also revised Form-HM-EO-PAT-009, Version 6.0, "Animal Necropsy Record" (see Annex 1-B-5), to include the necropsy end time, facilitating the control of organ fixation is completed within 2 hours. Training on this SOP (including Form) has been conducted for all personnel involved in necropsy (see Annex 1-B-6). C: The SOP-HM-EM-EQB-017, Version 7.0, "Use and Maintenance of Edstrom Automatic Watering System" (see Annex 1-C-1), has been revised to specify that for cages (including cage branch pipes) not in use for two days, or for newly purchased cage branch pipes, disinfection is required. After disinfection, the water in the cage branch pipes must be drained, and the stop valves should be kept open. Before the next use of the cage branch pipes, they should be disinfected again and the water stop valves must be closed. Additionally, Form-HM-EM-EQB-131, Version 1.0, "Portable Flushing Station Usage Record"(see Annex 1-C-2), has been established. This form requires confirmation of the stop valve's open and closed status after the disinfection of the cage branch pipes, and the relevant information should be documented in the record. Personnel from the Laboratory Animal Service Department have received training on this SOP (including Form) (see Annex 1-C-3). To enhance everyone's comprehensive and in-depth understanding of data integrity and hazard/risk identification, QAU has conducted a training session on GLP data integrity and risk management for all staff. During the training, departments were asked to further review similar issues within the SOP system and to continuously improve and optimize in subsequent SOP revisions. Training records see Annex 1-D.
Status	Completed

Finding No.	2
Finding Description	Reserve samples of test article for studies of more than 4 weeks duration were not retained for the period of time provided by 58.195. Specifically, For study number (b) (4), (b) (4) via Oral Gavage in Beagle Dogs Followed by a 4-week Recovery Period, no reserve sample of test article was retained.
Analysis & Assessment	1. The test article was not retained due to the negligence of the test and control article administrator, which deviated from the requirements of SOP-HM-SC-TCA-001, Version 15.0, "Test and Control Article Management". 2. In the sample retention process of SOP-HM-SC-TCA-001, Version 15.0, "Test and Control Article Management", there is no requirement for the verification of sample retention information. It is necessary to revise this SOP to prevent similar issues from occurring.
CAPA Actions	1. Since other studies of the project were conducted at the parent company, Shanghai InnoStar Bio-tech Co., Ltd. (hereinafter referred to as "Shanghai InnoStar"), we contacted the Test & Control Article Management Department of Shanghai InnoStar to transfer the same batch of the test article to our testing facility's Test Article Management Department, and we conducted sample retention on the day of arrival (see Annex 2-1). After completing the sample retention, confirmation was made with the FDA inspector during on-site inspection. 2. A non-conformance report of SOP deviation was issued (see Annex 2-2), which analyzed the reasons and assessed the impact of not retaining sample, and established corrective and preventive actions. 3. SOP-HM-SC-TCA-001, Version 16.0, "Test and Control Article Management" was revised and in effective, adding a process for a

	second person to check the sample retention information (see Annex 2-3) to prevent similar issues from occurring. 4. The Form-HM-SC-TCA-001, Version 8.0,"TA Receipt Record" and Form-HM-SC-TCA-005, Version 8.0, "CA Receipt Record" were revised to include content for a second person to check the sample retention information (see Annex 2-4). 5. Training on SOP-HM-SC-TCA-001, Version 16.0, "Test and Control Article Management" (including Form) (see Annex 2-5) has been conducted for all personnel involved.
Status	Completed