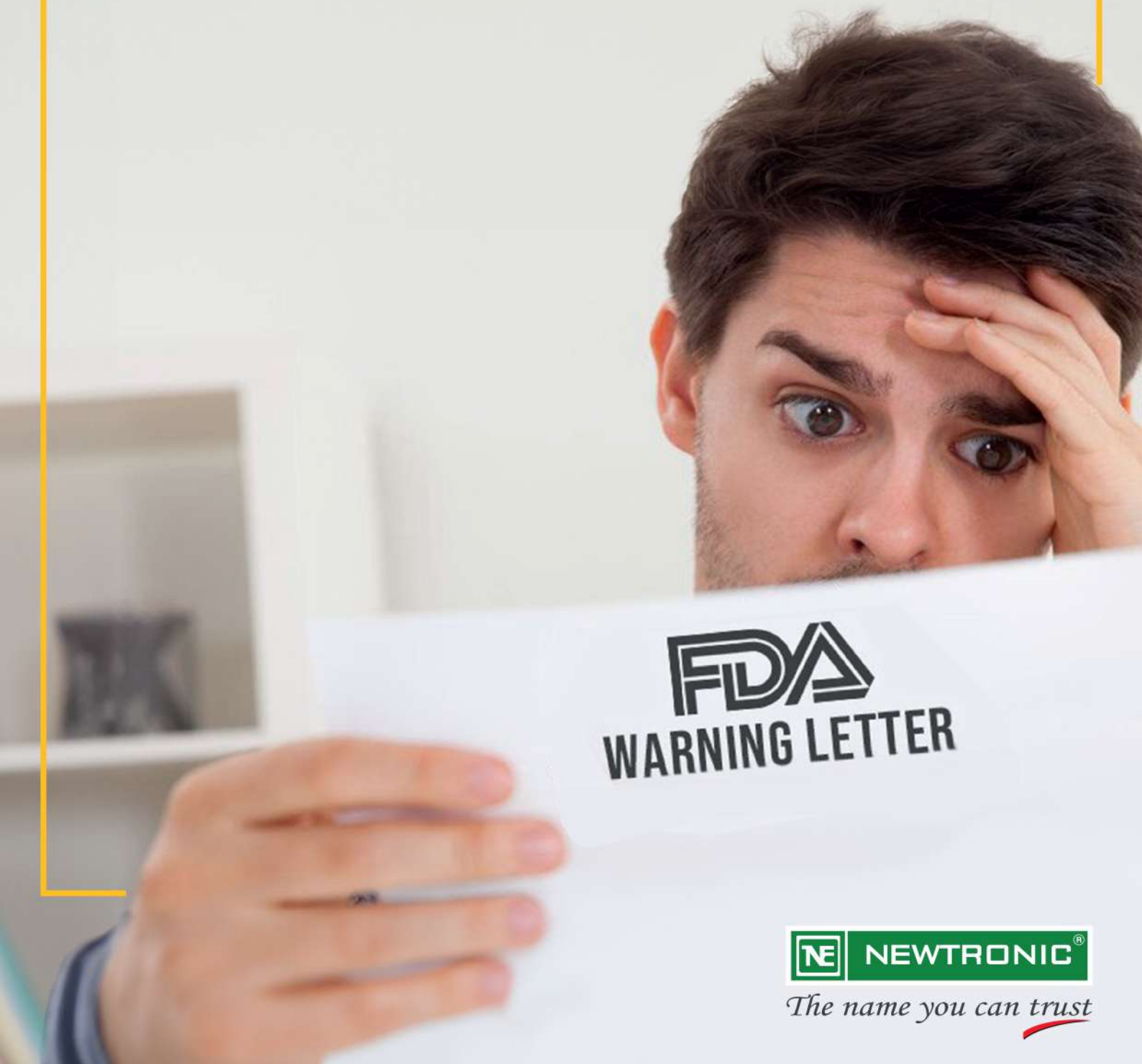
FORM 483s

A Compilation of **USFDA** Observations Specific to Stability Chambers & Related Equipments



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Case Study - 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 CDER-OC-OMQ-International483Response@fda.hhs.gov	11/13/2024-11/19/2024 FEI NUMBER 3005448030

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
FIRM NAME	STREET ADDRESS
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED

several parameters. In addition, you have not defined "like-for-like" including the parameters that must be considered in the assessment in SOP-GLOB-QA-0061, Rev. 10 (*Change Management System*, 09/06/2024 effective date and current version, Ver.12.0). Yet, you have not performed a PV, CV, and placed a batch on stability after replacing the equipment. **See Observation 7A.**

B. On 11/14/2024 during my inspectional walkthrough of (b)(4) Block (b)(4) observed an operator (b)(4) (b)(4) Stage/ Intermediate) into (b)(4) ID #3001388 with exposed hair over the (b)(4) Stage/ Intermediate drum. (b)(4) finished API is a US marketed product.

FACILIITES AND EQUIPMENT SYSTEM
OBSERVATION 4

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Specifically,

A. You did not record actual name of users for traceability in your data acquisition software for stability chambers (Stability Control 1.3 elite). I observed on 11/18/2024 during the review of the software that you issued administration rights and privileges to the user listed below, who is a service engineer which is not traceable in the software.

First Name	Middle Name	Last Name
Thermolab	Sales	Services

In addition, Document #WI-CT002-20-0067 Rev. 2.0 (*Procedure For Administration Activities On Software Stability Control system software, Version-1.3 lite*, 12/30/2022 effective date) does not have any provisions for removal and/or deactivation of users in the software. I observed on 11/18/2024 not all inactive users account in the software have been locked.

B. You have implemented several data acquisition software at your firm and you have not trained your personnel on their operations (i.e. Empower 3.6.1, Stability Control 1.3 elite, and WinCC). They were unable to demonstrate and to perform requested tasks such as creating project audit trail filters for reviewing Empower 3.6.1 projects covering 2023 to date. It took more than an hour (12:41pm – 1:55pm) and (b)(4) of your employees (Including SMEs for Empower) still could not apply the filters and

Case Study - 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	11/8/2022-11/17/2022*
	FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

FIRM NAME	STREET ADDRESS
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B. Your quality unit failed to perform a comprehensive periodic evaluation (i.e., cumulative assessment) of **ANY** alarms, included, but not limited to alarms for Incubators and Cooling Cabinets and the Water for Injection (WFI) System. Furthermore, alarms are not categorized, trend analyses on alarms are not performed, root causes are not determined, no incident investigations are initiated, no corrective and preventive actions (CAPAs) have been initiated, and no impact assessments have been initiated to prevent the reoccurrence alarms and minimize the risk of these alarms.

For example, your firm failed to maintain critical microbiology equipment including **ALL** Incubators (10) and Cooling Cabinets (2) in a state of continuous control to minimize or decrease the occurrence of unreliable microbiological data which is used to support all sterile and aseptic operations at your firm. Your firm had TNTC departures from your established set parameters for all Incubators and Cooling Cabinets and your firm failed to adequately address them. Loss of environmental control can significantly increase contamination risk of drugs intended to be sterile.

For example, from 2019-2022, your firm lacked awareness and failed to acknowledge, define, categorize, investigate, review, trend, and implement appropriate corrective and preventive actions (CAPAs) for [redacted] critical alarms across all [redacted] incubators and [redacted] cooling cabinets used for all microbiological samples, including the following: environmental monitoring (active air, settle plate, and contact plate), personnel monitoring, WFI and purified water, growth promotion, sterility samples of finished products, lysates for bacterial endotoxin (BET) testing and mother balls. Examples of alarm codes include, but are not limited to the following:

- Main temperature sensor failed
- Standby temperature sensor failed

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Saleem A Akhtar, Investigator Kellia N Hicks, Office of Global Policy and Strategy Employee	X Saleem A Akhtar Investigator Signed By: 2001818440 Date Signed: 11-17-2022 14:09:23	11/17/2022

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* Highlighted points shows the observations related to stability studies.
* Company name has been blurred for purpose of confidentiality.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	11/8/2022-11/17/2022*
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

FIRM NAME	STREET ADDRESS
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED

- Temperature Overshoot
- Regular refrigeration system failed
- Standby refrigeration system failed
- Main controlling sensor temperature low alarm
- Temperature low alarm
- Temperature high alarm
- Chamber shutdown
- Temperature safety limit cut-off
- PLC Communication Fail
- UPS power resume (does not say when power failed)

Additionally, your firm failed to perform an evaluation of the impact to temperature conditions under [redacted] which is the lower limit for the incubators, on the growth of microorganisms. Your firm performed study, "Validation Protocol for Impact of Different Temperature Condition on Growth of Microorganism, Effective Date [redacted] which supports the standing that there is no negative impact of temperature on microorganisms incubated from [redacted] and supports a [redacted] hour investigation time limit for excursions. The occurrence of the "Temperature low alarm" and "Temperature safety limit cut-off" alarms occur in this alarm log are TNTC. Your firm lacked knowledge of these alarms and failed to initiate an investigation and determine the impact of the excursion on the microbiological samples stored in this incubator on sterile operations and drug products to determine if the lower temperatures may inhibit the growth of microorganisms.

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	Saleem A Akhtar, Investigator Kellia N Hicks, Office of Global Policy and Strategy Employee X Saleem A Akhtar Investigator Signed By: 2001638440 Date Signed: 11-17-2022 14:09:23	11/17/2022

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FOOD AND DRUG ADMINISTRATION

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A random review of the alarms in Incubator [redacted] revealed on [redacted] the standby refrigeration system failed from [redacted] for a minimum of [redacted] hours. Your firm lacked knowledge of this alarm and failed to initiate and investigation and determine the impact on the microbiological samples stored in this incubator on sterile operations and drug products.

In another example,

Until date, your firm lacked awareness and failed to acknowledge, define, categorize, investigate, review, trend, and implement appropriate corrective and preventive actions (CAPAs) for alarms in your Water for Injection (WFI) system to ensure it was operating in a continuous state of control. Your water system was subject to microbiological contamination and numerous deviations from operating parameters since installation [redacted] No investigations were initiated into **ALL** deviations from set parameters (alarms). We observed the following alarms during the current inspection:

- Distillate High
- 2nd Effect High
- Feedwater Low
- 3rd Effect High

Your firm also firm lacked controls necessary to assure the integrity of quality related electronic data which supports safety, effectiveness, and quality of the drugs you manufacture. Data from this alarm system are not backed up, assured to be exact, complete, and secure from alteration or erasure or loss through the keeping of hardy copy or alternate systems. The HMI for the WFI multi-mill system, which does not have data storage, only maintains on the last [redacted] alarms before

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Case Study - 3

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
12420 Parklawn Drive, Room 2032
Rockville, MD 20857
E-mail: ORAPHARMInternational483responses@fda.hhs.gov

DATE(S) OF INSPECTION
08/11/2022-08/12/2022 08/15-19/2022; 08/26/2022

FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

FIRM NAME

STREET ADDRESS

CITY, STATE, ZIP CODE, COUNTRY

TYPE ESTABLISHMENT INSPECTED

Your firm's quality unit's oversight of your GMP manufacturing and laboratory operations are inadequate.

Specifically,

A. Your oversight of your primary (b) (4) reference standard is inadequate. You utilize USP issued (b) (4) DS as your quality control (QC) primary reference standard for your (b) (4) (b) (4) vials, and (b) (4) vials, intended for release to the US market. You do not know the USP (b) (4) reference standard expiration date. You do not have a written and QA approved stability protocol for the USP standard, which is required once the standard is under the purview of your QA oversight in your manufacturing facility.

B. Your oversight of the (b) (4) analytical assessment procedure is inadequate. Your analytics labs that are responsible for the (b) (4) assessment of multiple proposed (b) (4) drugs, i.e., (b) (4) (b) (4) did not perform a verification of the sample(s)' identity to be tested by the analysts, for any of the (b) (4) assessment analytics. In contrast, your QC labs verifies the analysts' possession of an analytic sample with a two person written verification.

C. Your oversight of critical GMP Q13 sample incubation chambers are inappropriate. Your keys to the Q13 mezzanine 2-8°C stability chambers and 2-8°C retain chamber are stored in an unsecured container, in an unlocked drawer, in the Q13 mezzanine stability facility. (b) (4) individuals have access to the room, along with seven (b) (4) from Engineering & Maintenance.

D. Assurance of the identity of, and discrimination between, (b) (4) DS grades and types, utilized for US market and the rest of world (ROW), are not appropriately controlled. The facility in (3003981475) manufactures multiple (b) (4) DPs intended for different markets. The (b) (4) DS utilized in these DP are manufactured at your (b) (4) (b) (4) facility. The (b) (4) facility manufactures (b) (4) DS with multiple product codes, which indicate the different manufacturing processes and different (b) (4) DS quality. These product codes are the only system used to prevent the (b) (4) DS to be utilized for the ROW and the proposed US marketed (b) (4) vials, (b) (4) (b) (4) and (b) (4) vials, from mix-ups. You do not currently have an analytic performed at your (b) (4) DP manufacturing facility which can discriminate between these different types and grades of (b) (4) DS. Thus, there is no assurance, by the process or by testing, that the correct (b) (4) DS is being used for the (b) (4) drug products to be marketed in the US in accordance with their specific (b) (4)

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE

EMPLOYEE(S) NAME AND TITLE (Print or Type)
Michael R. Shanks, Senior Biologist
Arsen Karapetyan, INV-Dedicated Drug Cadre
Ralph M. Bernstein, Biologist
Zhong Li, Sr. Pharmaceutical Quality Assessor

DATE ISSUED
08/26/2022

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 E-mail: ORAPHARMInternational483responses@fda.hhs.gov	08/11/2022-08/12/2022 08/15-19/2022; 08/26/2022
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for the smaller peaks and consequently underestimates the relative amount of the smaller peaks, *i.e.*, the impurity peaks.

B. The QC standard testing procedure (STP) QC/Q8/SPEC/FP/159-01v003 utilized for the release and stability specification "microscopy test" for (b) (4) DP (b) (4) and (b) (4) (b) (4) DP vial does not describe the procedure that your QC analysts follow. The STP provided to the Agency instructs the analyst to measure the (b) (4) size of each (b) (4) using a micrometer throughout the slide. The analysts follow a procedure that instructs them to identify (b) (4) (b) (4) field with (b) (4) then to capture the field in the microscopy software, and to then measure (b) (4) and to record the (b) (4) shape and range (maximum and minimum length of the (b) (4)

OBSERVATION 8

Your firm has not established adequate procedural controls to protect the electronic data acquisition and/or manufacturing control systems used for DS and DP manufacturing in your Site (b) manufacturing facilities.

Specifically,

A. The computerized system (YOKOGAWA data logger; Model GP10, S/N S5WA12293), used to collect data during the calibration of QC instrument, temperature mapping and thermal validation of critical process equipment, has not been validated to protect original electronic records and relevant metadata (e.g., audit trails).

B. There is a lack of documented evidence that the computerized system, THEMA4 (version W44.3), that controls and collects data from (b) (4) 02 for the (b) (4) filling line in (b) (4) Fill-Finish facility, has been validated for data backup and retrieval. Audit trails enabled in the system are not reviewed for each data set during the batch review process. In addition, there is inadequate segregation of duties in the management of user privileges. The system administrators, responsible for control of the records generated by the system, are also the engineers responsible for the content of the generated records.

C. A system hardware upgrade for the SCADA chromatography system, M2-CS-4, in (b) (4) facility was performed in March of 2021. A revalidation of the software installed on the system, SIMA TIC WinCC Hotfix 2, was not completed prior to the use of the upgraded system for GMP operations in the facility.

OBSERVATION 9

Computer systems used in the testing of a drug product are not of appropriate design to facilitate operations for its intended use.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Michael R. Shanks, Senior Biologist Arsen Karapetyan, INV-Dedicated Drug Cadre Ralph M. Bernstein, Biologist Zhong Li, Sr. Pharmaceutical Quality Assessor	08/26/2022

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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12420 Parklawn Drive, Room 2032 Rockville, MD 20857 E-mail: ORAPHARMInternational483responses@fda.hhs.gov	08/11/2022-08/12/2022 08/15-19/2022; 08/26/2022
	FEI NUMBER

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Specifically,

A. Your firm does not have adequate written procedures for conducting Initial Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). Specifically, qualification activities were performed by your software vendors for networked Empower V3.0 software for HPLC equipment. Your firm appears to have performed Performance Verification for Empower, however this verification is not adequate, in that, it does not evaluate the consistent performance of the software/equipment over a specified period and operating environment. For Example, during our review of your Empower 3 chromatography software, interrupted sequences were observed, which generated "Data Incomplete" and "Bad Check Sum" chromatographic data. Your firm has not demonstrated to understand the different types of communication errors and circumstances which may lead to a "Data incomplete" or " Bad Checksum" chromatography.

B. Your firm maintains SOP S2/BF/QCM/SOP/0076, titled "Procedure For Review of CCTV the CCTV's installed in the microbiology laboratories in (b) (4) and (b) (4) Per this procedure, CCTV usage can be used to support OOS investigations by reviewing footage where "duration of the availability of the footage" is (b) (4) Your firm has not validated the CCTV software Milestone Xprotect Smart Client 2014 to depict that the software functions as purported in a consistent and accurate manner that is secure, reliable, and traceable. In fact, during the inspection, we reviewed two microbiology OOS investigations, OOS No. MM-OOS/M/CS/21/001 (dated 05/13/2021) and OOS No. MM-OOS/M/FP/22/001 (dated 06/07/2022) where CCTV footage was used in support of the root cause analysis which invalidated the OOS; however, all footage was automatically purged after (b) (4) and your does not have a process in place to save footage which was used in support of these investigations.

OBSERVATION 10

GMP Equipment is used outside its validated acceptance criteria for critically controlled material.

Specifically,

Quality Control Stability Chambers, QC-Q13-AI-141 and QC-Q13-AI-142, located in QC Building Q13, are validated for 2 – 8 °C and both have had numerous excursions from their validated temperature over the past two year. Additionally, these excursions have not triggered deviations to be opened.

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
SEE REVERSE OF THIS PAGE		Michael R. Shanks, Senior Biologist Arsen Karapetyan, INV-Dedicated Drug Cadre Ralph M. Bernstein, Biologist Zhong Li, Sr. Pharmaceutical Quality Assessor	08/26/2022

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Case Study - 4

WARNING LETTER

Delivery Method:

VIA UPS

Reference #:

320-20-01

Product:

Drugs

Recipient:

Issuing Office:

Dear Mr. Saldanha:

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your May 10, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

Top ()

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During our inspection, our investigators observed specific violations including, but not limited to, the following.

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether the batch has already been distributed (21 CFR 211.192).

Your firm failed to ensure your investigations identify appropriate root causes and you failed to implement sustainable corrective action and preventive action (CAPA).

a. You failed to thoroughly investigate multiple complaints of grittiness for your topical **(b)(4)** cream USP, **(b)(4)**%. Since November 2017, you rejected 20 batches and received at least 38 complaints about product grittiness. Product grittiness has been an ongoing formulation issue since 2010 and was a deficiency cited in the previous inspection of your facility. You proposed specific remediation for this formulation issue in your response at that time. In your response to the most recent inspection, you stated that the product grittiness issue was remediated during product reformulation in November 2018. Your response is inadequate. You did not provide sufficient data to demonstrate the robustness of the new formulation.

We acknowledge that in July 2019 you recalled all batches within expiry that were manufactured using the original formulation. However, your reformulation and market actions were not performed in a timely manner.

b. You failed to adequately investigate multiple temperature excursions that occurred during shipping of your drug products. Your investigations into the temperature excursions did not include timely actions to prevent their recurrence.

For example, in May 2018, **(b)(4)** cream USP, **(b)(4)**% batches were exposed to temperature excursions up to **(b)(4)**°C and **(b)(4)**°C for **(b)(4)** while in transit to the United States. **(b)(4)** cream should be stored between **(b)(4)**°C. In July 2018, a **(b)(4)**USP, **(b)(4)**% batch was exposed to **(b)(4)**°C for **(b)(4)** while in transit to the United States. **(b)(4)** should be stored between **(b)(4)**°C. These **(b)(4)** batches were distributed to the U.S.

Inadequate investigation into temperature excursions is an ongoing issue and was a deficiency cited during the previous inspection of your facility. Notably, you performed a study to determine the impact of elevated temperature on **(b)(4)** cream USP, **(b)(4)**%. The study showed phase separation of the product at **(b)(4)**°C.

In your response, you stated that you will perform an additional temperature excursion study as well as conduct a long-term stability study. You also stated that you will investigate all confirmed out-of-specification (OOS) results during the temperature excursion studies and will notify the FDA, as appropriate.

Your response is inadequate. You did not provide an adequate risk assessment for marketed batches exposed to temperatures outside the labeled storage conditions. Also, your response mentioned the implementation of new shipping practices to protect your products from thermal excursions, but they were not implemented in a timely manner.

c. You failed to adequately investigate multiple OOS test results for critical product attributes, such as **(b)(4)** For example, in April 2018, **(b)(4)** batch **(b)(4)** failed **(b)(4)** Additionally, in February 2019, **(b)(4)** ointment USP **(b)(4)**% batch **(b)(4)** failed **(b)(4)** These batches were ultimately rejected. However, your investigations into these failures did not determine an appropriate root cause and ensure effective CAPA.

In your response, you indicated that you plan to hire a consultant to enhance the quality of your investigations. Your response is inadequate. You did not assess the potential impact to product quality and the failure to identify potential root causes.

Top ()

Case Study - 5

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301)796-3334 Fax:(301)847-8738	5/8/2017-5/19/2017*
	FEI NUMBER
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
FIRM NAME	STREET ADDRESS
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(b) (4) Tablets USP	(b) (4) ng/ (b) (4) ng	(b) (4)
(b) (4) Tablets USP	(b) (4) ng	

OBSERVATION 4

The batch production and control records are deficient in that they do not include identification of persons performing, supervising and checking each significant step in the operation.

Specifically, there was no identification of the person entering the values from critical process steps in the batch manufacturing records and there was a lack of second person verification of each step. For example,

- Number of bottles went into incubation in each (b) (4) were entered into the batch manufacturing record (Batch# (b) (4) without anyone signing the page during the aseptic process simulation (Media Fill).
- Visual inspection of incubated bottles for the microbial contamination results were entered into the batch manufacturing records by the analysts without anyone checking or verifying.

OBSERVATION 5

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, the qualification of your firm's stability chambers lacks data to fully support the temperature uniformity throughout the chambers.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Tamil Arasu, Investigator TA Darren S. Brown, Investigator DB	5/19/2017

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301)796-3334 Fax:(301)847-8738	5/8/2017-5/19/2017*
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- The temperature mapping of your firm's stability chambers is based on fixed temperature & humidity probes within the stability chambers. According to the mapping diagrams each stability chamber has a total of (b) (4) temperature & humidity probes which have been permanently installed on the (b) (4) panels of the chambers. Each of the (b) (4) probes has data loggers which record temperature and humidity data at its location. As an example, for stability chamber SC-11, which is kept at 25±2 °C/60±5% RH and has a capacity of (b) (4) L, the firm could only provide temperature and humidity data for each of the fixed probes. This stability chamber is used for long-term stability studies for US products. The firm has not provided temperature & humidity data to show that the temperature and humidity in the center of their stability chambers meets the specified conditions.

OBSERVATION 6

Written procedures are not established for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically, your firm does not have a procedure in place to verify if the (b) (4) back-up (b) (4) (b) (4) 01) for the (b) (4) Storage Tank (T-602-1) will work. According to SOP EN2-079-03 section 5.4.18 "Operation of (b) (4) Unit and Distribution Loop," your firm's engineering personnel are to "ensure that tank (b) (4) should be maintained NLT (b) (4) by (b) (4) or (b) (4) , (b) (4) 01 is the back-up (b) (4) for the firm's (b) (4) storage tank (T-602-1) in the event that there is an interruption to the (b) (4) supply. Your firm does not regularly verify that the (b) (4) 01) works as intended. This (b) (4) is used for the regular manufacturing of sterile (b) (4) products such as (b) (4) Solution, (b) (4) % and (b) (4) Solution, (b) (4) %.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Tamil Arasu, Investigator TA Darren S. Brown, Investigator DB	5/19/2017

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Case Study - 6

WARNING LETTER

[redacted]

MARCS-CMS 634233 — OCTOBER 05, 2022

Delivery Method:
VIA Electronic Mail

Product:
Drugs

Recipient:
[redacted]

Issuing Office:
Office of Pharmaceutical Quality Operations, Division II
United States

DATE: 10/5/2022
Case #: 634233

WARNING LETTER

Mr. Hafey:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Sovereign Pharmaceuticals, LLC, FEI 3003229412, at 7590 Sand Street, Fort Worth, from April 13 to 22, 2022.

Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit and to follow written procedures applicable to the quality control unit (21 CFR 211.22(d)).

During the inspection, we observed that your quality unit (QU) was not effectively exercising its responsibilities to oversee the quality of your drug manufacturing operations. In addition, the established procedures applicable to the QU were not properly followed. For example:

A. Your firm's QU failed to provide adequate quality review and approval for your **(b)(4)** tablet validation reports. Specifically, your QU approved validation reports for varying strengths stating no deviations were recorded in the execution of the validation protocols. However, a review of the validation reports showed significant errors and omissions, including but not limited to, drum assay failures and a failure to perform required RSD calculations for drum assay data.

B. Your established procedures require initiation of deviations to investigate and determine the impact of stability chamber excursions greater than **(b)(4)**. This procedure also states to consider alternate storage for excursions expected to exceed **(b)(4)**. However, in multiple instances, your firm did not initiate investigations involving excursions lasting more than **(b)(4)**, and up to 10, days.

Your QU is responsible for fully exercising its authority and responsibilities.

In your response, you stated that a deviation was opened for the excursions cited by our investigators. You committed to initiating **(b)(4)** checks of the stability chambers and to review the entire system to assess improvements in monitoring system devices. You acknowledged the QU's role and responsibilities in deficiently reviewing the validation reports.

Your response is inadequate. You failed to provide sufficient data to show that your stability samples were not negatively impacted by the excursions listed in the observation. In addition, you did not perform a retrospective review for other potential similar excursions to take appropriate CAPAs and product impact evaluations. You also failed to perform a comprehensive review of similarly impacted systems by a deficient QU.

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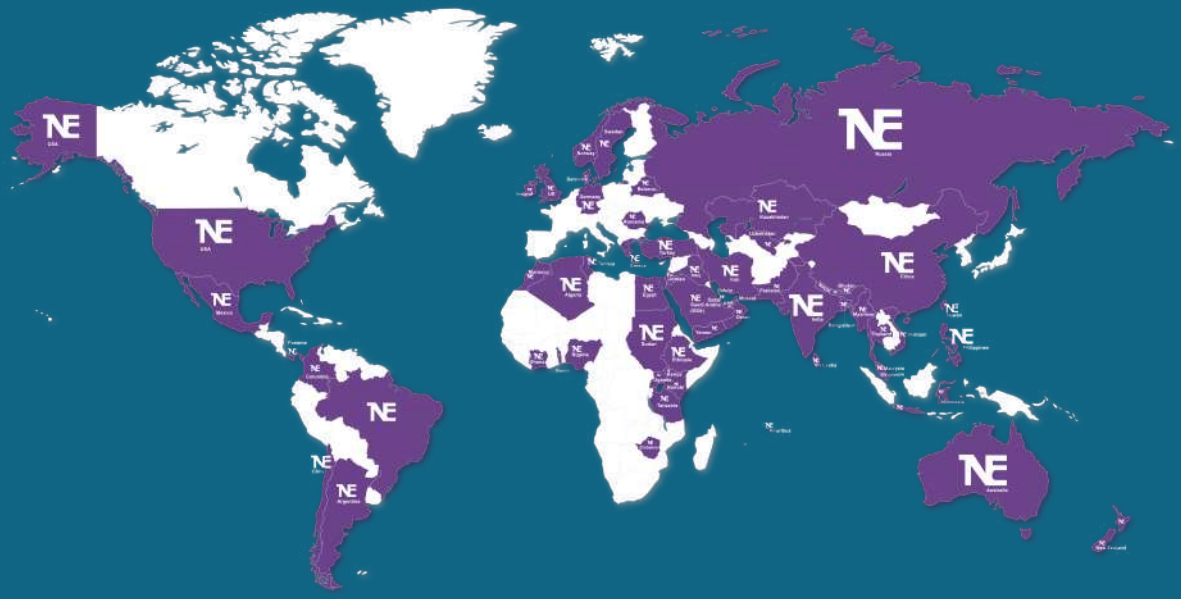

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