DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/11/2023-09/15/2023 FEI NUMBER 3013345425

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
Mr. Tu Yongjun, President

TO: FIRM NAME	STREET ADDRESS
Linhai Tianyu Pharmaceutical Co., Ltd.	No. 15 Donghai 5th Ave., Zhejiang Provincial Chemical and Medical Raw Materials Base Linhai Zone
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Taizhou, Zhejiang 317016 China	Active Pharmaceutical Ingredient and Intermediate Manufacturer

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 WE OBSERVED:

OBSERVATION 1

Written procedures are deficient for the cleaning and maintenance of equipment used in the manufacturing, processing, packing, or holding of a drug substance. Specifically,

Your firm's clean hold time study and evaluation report (Confirmation report on the validity of the clean retention time of the crude (b) (4) production equipment GP-EV-PR-3-211203; Evaluation Report on Reasonableness of CHT of (b) (4) Area Equipment GR-EV-PR-3-220805) that are applicable for drug substances and intermediates, including (b) (4) conclude a (b) (4) clean hold time in (b) (4) following a (b) (4) clean. Your firm's Equipment Cleaning Management Procedure SMP-PR-011 requires a (b) (4) clean for (b) (4) beyond this (b) (4) hold time that is valid for (b) (4) Your firm's Cleaning Management Procedure (SMP-PR-011) and clean hold time study and evaluation (GP-EV-PR-3-211203, GR-EV-PR-3-220805) are deficient because they do not include adequate scientific justification for the (b) (4) clean hold time following a (b) (4) clean after (b) (4) clean. For example, we reviewed Equipment Operational Logbooks FOM-GDL-035-01 for 2022.05.09~2022.08.10 and 2022.08.18~2022.08.28 for (b) (4) (b) (4) 215 in Workshop (b) (4) On July 4, 2022, your firm completed a (b) (4) clean after a production campaign of (b) (4) (b) (4) later, your firm completed a (b) (4) clean on (b) (4) per your firm's Cleaning Management Procedure (SMP-PR-011). On August 16, 2022, your firm began a (b) (4) batch production campaign for (b) (4) an intermediate used in the manufacturing of drug substance (b) (4) for the China and Europe market. Your firm has no scientific

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Arsen Karapetyan Anders W Evenson	Arsen Karapetyan, Investigator, DDC Anders W. Evenson, Investigator	09/15/2023

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/11/2023-09/15/2023 FEI NUMBER 3013345425

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
Mr. Tu Yongjun, President	
TO: FIRM NAME Linhai Tianyu Pharmaceutical Co., Ltd.	STREET ADDRESS No. 15 Donghai 5th Ave., Zhejiang Provincial Chemical and Medical Raw Materials Base Linhai Zone
CITY, STATE, ZIP CODE, COUNTRY Taizhou, Zhejiang 317016 China	TYPE ESTABLISHMENT INSPECTED Active Pharmaceutical Ingredient and Intermediate Manufacturer

justification that confirms a [(b) (4)] clean following a [(b) (4)] clean hold time is sufficient on [(b) (4)] equipment used between production campaigns of [(b) (4)] different products.

OBSERVATION 2

Facilities and equipment used in the manufacturing of drug substances are not adequately maintained. Specifically,

During our facility walk-through on 9/11/2023, we observed the following conditions in Workshops [(b) (4)] and [(b) (4)] that are used for drug substance manufacturing of [(b) (4)] and other drug substances and intermediates intended for the U.S. market:

- Workshop [(b) (4)]
  - [(b) (4)] 315 with three ~2 feet segments of broken pipe insulation laying near utility pipes that connect to the [(b) (4)] station and [(b) (4)] tank
  - [(b) (4)] 318 with multiple reddish/brown areas on the ground and a puddle of water under the utility pipes that connect to the [(b) (4)] station and the [(b) (4)] tank
  - [(b) (4)] 322 with reddish/brown areas surrounding utility pipes that run through the floor and connect to the [(b) (4)] station and [(b) (4)] tank
  - Area between [(b) (4)] 214 and [(b) (4)] 215 with 1) a [(b) (4)] ~3-feet by 2-feet by 2-inch pan-like item placed under the utility pipes that connect to the [(b) (4)] station and [(b) (4)] tanks 2) a ~2 feet by 1 foot reddish/brown area of peeling floor under utility pipes that connect to the [(b) (4)] station 3) a drooping clear coil with reddish/brown residue that connects to utility pipes that connect to the [(b) (4)] station
  - [(b) (4)] 217 with a drooping clear coil with reddish/brown residue that carries [(b) (4)] to utility pipes that connect to the [(b) (4)] station and [(b) (4)] tank

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	CEK AWE	Arsen Karapetyan, Investigator, DDC Anders W. Evenson, Investigator	09/15/2023

  - [redacted] with a detached floor area of ~1 foot by 1 foot with reddish/brown residue directly next to the [redacted] tank with a pipe running through it
- Workshop [redacted]
  - [redacted] 416 with [redacted] insulation on the outside of the [redacted] station while production of [redacted] batch [redacted] was occurring

Your firm uses Equipment Maintenance Management Procedure SMP-EN-003 that requires [redacted] patrol and documentation of facilities and equipment used in the production of drug substances in Workshops [redacted] and other workshops. Your firm did not adequately document [redacted] patrols nor the inadequate status of equipment and pipelines in Workshop [redacted] within the Equipment Inspection Record FOM-SMP-EN-003-03.03 for Workshop [redacted] that is required per the Equipment Maintenance Management Procedure SMP-EN-003.

OBSERVATION 3

Written records of investigation into unexplained discrepancies and the failure of a batch or any of its components to meet specification do not always include the conclusions and follow-up. Specifically,

Investigations initiated and performed by your Quality Unit in response to Out of Specification results, laboratory events, and market complaints related to intermediates and API manufactured by your firm are not always scientifically sound or comprehensive with respect to root cause determination. Additionally, Corrective Action/Preventive Action (CAPAs) as a result of investigations are not always comprehensive to address root causes documented to have been performed. For Example:

A. -On or around 01/14/2021, OOS-205301-21001 was initiated for intermediate [redacted] batch number [redacted] (intermediate for [redacted] drug substance) for other single impurity with results as [redacted]% and [redacted]% versus specification of NMT [redacted]%. Your firm's

investigation determined the root cause to be "the tester did not change gloves after testing the (b) (4) solution and directly prepared the (b) (4) sample solution, resulting in contamination".

-On or around 01/21/2021, OOS-10501-21001 was initiated for drug substance (b) (4) (b) (4) batch number (b) (4) for (b) (4) impurity (b) (4) with result as (b) (4) ppb versus specification of LOD (b) (4) ppb. Your firm's investigation determined the root cause to be "the tester did not wear gloves when weighing back, returning the control and transferring the test solution, resulting in contamination of the test solution".

-On or around 06/08/2021, OOS-10501-21003 was initiated for intermediate (b) (4) (intermediate for (b) (4) drug substance), batch number (b) (4) for test item (b) (4) standard with result as (b) (4) ppm versus specification of NMT (b) (4) ppm. Your firm's investigation determined the root cause to be "the inspector did not change his gloves when testing (b) (4) resulting in some bottle caps being contaminated with (b) (4)

-On or around 01/01/2022, OOS-10501-22001 was initiated for drug substance (b) (4) (b) (4) batch number (b) (4) 6-month accelerated stability test for (b) (4) (b) (4) impurity (b) (4) with result as (b) (4) ppb versus a specification of LOD (b) (4) ppb. Your firm's investigation determined the root cause to be "the bottle cap used for the test did not differentiate between the use of samples and controls, and the tester got the (b) (4) contaminated bottle cap, resulting in the test solution being contaminated with (b) (4)

For all OOS investigations performed by your firm, the assignable root cause was determined without performing hypothesis studies and without scientific justification.

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/11/2023-09/15/2023 FEI NUMBER 3013345425

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
Mr. Tu Yongjun, President	
TO: FIRM NAME Linhai Tianyu Pharmaceutical Co., Ltd.	STREET ADDRESS No. 15 Donghai 5th Ave., Zhejiang Provincial Chemical and Medical Raw Materials Base Linhai Zone
CITY, STATE, ZIP CODE, COUNTRY Taizhou, Zhejiang 317016 China	TYPE ESTABLISHMENT INSPECTED Active Pharmaceutical Ingredient and Intermediate Manufacturer

B. Starting from 04/01/2021 to 07/07/2022, your firm has initiated 2 OOT and 7 OOS investigations for 11 batches with respect to intermediate product (b) (4) for test specifications for any individual impurity (NMT (b) (4) and/or total impurities (NMT (b) (4) %). All batches involved were said to be destroyed as a result. Subsequent investigations performed by your firm's QC and R&D units have resulted in the identification of a root cause for formation of the impurity, however no adequate CAPA has been implemented to address this root cause. Per your firm's personnel, current action plan, should another OOS occur, is to destroy the batch.

C. During our review of your Empower 3 chromatography software, interrupted sequences were observed, which generated "Data Incomplete" chromatographic data. Your firm documented these interrupted injections due to a power outage via investigation no. DR-3-22003R, dated 02/27/2022, showing that no chromatograms had been generated for (b) (4) drug substance batch numbers (b) (4) However, during the investigation, the interrupted sample injections were not adequately documented and/or investigated, in that your firm did not verify the incomplete data to evaluate if the interrupted sequence chromatogram for abnormalities.

D. Complaint No. CH-3-23004, dated 02/20/2023 was initiated due to customer complaint (b) (4) OOS results for 7 batches of (b) (4) intermediate shipped to your customer. This intermediate is used for the manufacture of (b) (4) API, potentially intended for the U.S. Market. Based on your firm's investigation, no issues were found, and the complaint was not justified. After your firm communicated the results of your findings to your customer, your customer replied that their quality unit had released these batches for use to manufacture. There was no adequate follow up by your firm to determine why these batches were released, specifically what the root cause of your customers investigation revealed. During our inspection, your firm re-initiated communication with your customer to determine your customers investigation results.

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
SEE REVERSE OF THIS PAGE	AK AWE	Arsen Karapetyan, Investigator, DDC Anders W. Evenson, Investigator	09/15/2023

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/11/2023-09/15/2023 FEI NUMBER 3013345425

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
Mr. Tu Yongjun, President	
TO: FIRM NAME Linhai Tianyu Pharmaceutical Co., Ltd.	STREET ADDRESS No. 15 Donghai 5th Ave., Zhejiang Provincial Chemical and Medical Raw Materials Base Linhai Zone
CITY, STATE, ZIP CODE, COUNTRY Taizhou, Zhejiang 317016 China	TYPE ESTABLISHMENT INSPECTED Active Pharmaceutical Ingredient and Intermediate Manufacturer

E. On or around 03/07/2019, 7 OOS investigations for 7 batches were initiated for intermediate [(b) (4)] for OOS results with respect to specification other individual impurity NMT [(b) (4)]%. Your firm's investigations resulted in root cause determination as a damaged [(b) (4)] Your firm's CAPA included replacing the damaged [(b) (4)] with a new [(b) (4)] and retesting. No consideration was given to the establishment of [(b) (4)] management and maintenance procedure as part of your investigation and CAPA.

OBSERVATION 4

Laboratory records are not completed contemporaneously and do not include complete data derived from all tests to assure compliance with established specifications and standards. Specifically,

A. Electronic and physical laboratory records data review are not completed contemporaneously by your QC reviewers. During our walkthrough of your QC laboratory data review room on 09/11/23, I observed your QC analyst/reviewer checking off boxes on a form titled "Checklist of Electronic Data" for approximately 5 analytical batch records for [(b) (4)] testing of [(b) (4)] API via Ion Chromatography test, one after another, without any software opened for review. In all, we counted approximately 18 analytical test records for six batches which the analyst confirmed to have performed during the observed review process from above. Your analyst stated that they had reviewed the electronic data on the software in another room approximately one hour before.

B. Microbiology laboratory records and usage logbooks are not completed contemporaneously by your analysts. During our walkthrough of your microbiology laboratory, we observed a QC analyst filling out a form titled "Preparation and Use Records of Control Medium" for preparation of [(b) (4)] controlled media used for system suitability reference for testing of [(b) (4)] water. Items observed in the process of being filled out included, but not limited to, reagents used, quantity of reference media and [(b) (4)] water used, stirring to dissolve operations, dispensing into a bottle operation, and

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	AK AWE	Arsen Karapetyan, Investigator, DDC Anders W. Evenson, Investigator	09/15/2023

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/11/2023-09/15/2023 FEI NUMBER 3013345425

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
Mr. Tu Yongjun, President	
TO: FIRM NAME Linhai Tianyu Pharmaceutical Co., Ltd.	STREET ADDRESS No. 15 Donghai 5th Ave., Zhejiang Provincial Chemical and Medical Raw Materials Base Linhai Zone
CITY, STATE, ZIP CODE, COUNTRY Taizhou, Zhejiang 317016 China	TYPE ESTABLISHMENT INSPECTED Active Pharmaceutical Ingredient and Intermediate Manufacturer

(b) (4) operations. Per your analyst, they had finished preparation of the (b) (4) controlled media prior to my arrival to the room.

OBSERVATION 5

There is no written testing program designed to assess the stability characteristics of drug substances and intermediates.

Specifically, the assay and related substance test methods for intermediate (b) (4) used for stability testing are not stability indicating, where they can detect the change with time in chemical, physical or microbiological properties of the intermediate drug substance so that the content of active ingredients and degradation products can be accurately measured without interference. As a result, the validity of the stability of the process cannot be verified, in that your firm is not able to monitor results during stability studies in order to assure safety, efficacy and quality for your intermediate drug substance.

OBSERVATION 6

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

GMP related computerized systems and equipment have not been validated/qualified to demonstrate the suitability of computer hardware and software to perform assigned tasks. Your firm appears to have performed Performance Verification and data integrity assessments for Empower 3 software, however the verification and assessments do 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" chromatographic data. Your firm has not demonstrated full understanding of the different types of

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
SEE REVERSE OF THIS PAGE	AM AWE	Arsen Karapetyan, Investigator, DDC Anders W. Evenson, Investigator	09/15/2023

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/11/2023-09/15/2023 FEI NUMBER 3013345425

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
Mr. Tu Yongjun, President	
TO: FIRM NAME Linhai Tianyu Pharmaceutical Co., Ltd.	STREET ADDRESS No. 15 Donghai 5th Ave., Zhejiang Provincial Chemical and Medical Raw Materials Base Linhai Zone
CITY, STATE, ZIP CODE, COUNTRY Taizhou, Zhejiang 317016 China	TYPE ESTABLISHMENT INSPECTED Active Pharmaceutical Ingredient and Intermediate Manufacturer

communication errors and circumstances which may lead to a "Data incomplete" or Bad Checksum/Data Missing chromatography considering the relationship between the Empower application and database server, Empower RDS servers, internet connection, Empower LAC/Es, and the instruments connected to LAC/Es. This discrepancy in your firm's ability to review, document, and investigate all electronic data is a gap in your Data Integrity Program.

OBSERVATION 7

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed. Specifically,

Supervisory oversight over the laboratory electronic systems and data is deficient. Per your firm's data review procedure, Quality Control (QC) personnel perform review electronic test data for all analytical batch records using an approved review procedure and checklist for HPLC/GC network equipment. This review process does not appear to be adequate, in that all potential data generated during that specific review period for that product are not reviewed. For example, your firm utilizes up to five different software's for testing of intermediate and API products on HPLC and GC equipment, which include, Empower 3, Openlab CDS, LabSolutions, MassHunter. There is no software dedicated to testing of a particular intermediate or API, as the analyst may use whichever software is available at the time of the test. There is no adequate reconciliation of all generated electronic test data during the review process for HPLC/GC network equipment.

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
SEE REVERSE OF THIS PAGE	AWE	Arsen Karapetyan, Investigator, DDC Anders W. Evenson, Investigator	09/15/2023

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/11/2023-09/15/2023 FEI NUMBER 3013345425

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
Mr. Tu Yongjun, President

TO: FIRM NAME	STREET ADDRESS
Linhai Tianyu Pharmaceutical Co., Ltd.	No. 15 Donghai 5th Ave., Zhejiang Provincial Chemical and Medical Raw Materials Base Linhai Zone
CITY, STATE, ZIP CODE, COUNTRY Taizhou, Zhejiang 317016 China	TYPE ESTABLISHMENT INSPECTED Active Pharmaceutical Ingredient and Intermediate Manufacturer

***DATES OF INSPECTION**
09/11/23 (Mon), 09/12/23 (Tue), 09/13/23 (Wed), 09/14/23 (Thu) and 09/15/23 (Fri)

APPEARS THIS WAY ON ORIGINAL

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
SEE REVERSE OF THIS PAGE	Arsen Karapetyan Anders W Evenson	Arsen Karapetyan, Investigator, DDC Anders W. Evenson, Investigator	09/15/2023