DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12225 Wilkins Avenue MPN4, Room #107 Rockville, MD 20852 (240)402-5557 Fax:(301)827-1498	1/20/2020-2/7/2020* FEI NUMBER 3002874838

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Liam Nagle, CEO

FIRM NAME	STREET ADDRESS
Norbrook Laboratories, Ltd.	105 Armagh Road
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Newry, County Down, BT35 6PU United Kingdom	Animal Drug Product 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

The written stability testing program is not followed.

The stability program has not always been followed in that stability time points have been missed, and samples have been placed on stability months late.

Specifically,

A. (b) (4) tablets batch (b) (4) was manufactured August 2017, however the stability study was initiated 22 December 2017. The electronic stability tables generated for the batch do not clearly show dates for each testing timepoint. The timepoint reported as "initial" was measured four months (4) from date of manufacture. SWQC-094 (section 6.6.8) states that stability studies should be initiated within three months of the date of manufacture. Justification must be provided for any samples being placed on stability that are over three months old and recorded on Appendix 1 – Stability Initiation Form.

B. In the MCSR 19-August-2019 A200595 Stability Summary report, (b) (4) mg (resource code (b) (4), batch (b) (4)) and (b) (4) mg (resource code (b) (4), batch (b) (4)) show that hardness out-of-specification (OOS) at the 18 and 24 month time points. These results were investigated under OOS-1926-25 and OOS-1926-27. The reported 24

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month time points were found to have been measured six months late at 30 months. Regression analyses were used to report estimated stabilities at 24 months that barely passed specifications, but with 4-5 data points the curve fit is of a low confidence. This appears to be both missed stability and a data accuracy issue.

C. (b) (4), OOS-1822-40 & 42 investigation reports, dated 22 August 2018, report stability testing out of compliance with SOP SWQC-094-06 for batches (b) (4) and (b) (4). The 24 month stability test point parameters, allowable (b) (4) month, were measured between 26-38 months, (2-14 months late).

D. There were 59 missed stability testing time points for studies in the 2017-2020 stability review period, including the following eleven recent examples in the 2019-2020 period: (b) (4)% batch (b) (4), 9M; (b) (4). Batch (b) (4), 3M; (b) (4) batch (b) (4) and (b) (4), 3M; (b) (4) batches (b) (4) and (b) (4), 12M and 9M; (b) (4) batches (b) (4) 12M; (b) (4) batches (b) (4), 36M; and (b) (4) batch (b) (4), 36M.

E. SOP SWQC-094-08, Quality Processing of a Pharmaceutical Stability Study, effective 27 January 2020 is deficiently written. This procedure enables measured time points to be offset from the stated times of 1, 3, 6, 9, 12, 18, and 24-month that is reported and that is expected to be conducted per product applications. This procedure states in section 6.6.8 that stability studies should be initiated within three (3) months of the date of manufacture. Per management discussion, this three month exception is only supposed to be for products that require additional processing such as (b) (4) sterilization, but that is not specified in the method.

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OBSERVATION 2

Backup data is not assured as exact, complete and secure from alteration, erasure or loss through keeping hard copy or alternate systems.

The firm uses a manual paper-based data recording system. This has resulted in re-transcriptions, has produced data errors, transcription errors, and stability errors.

Specifically,

A. Inadequate procedures are in place to ensure the accuracy of electronic stability tables generated from the raw data. Three batches of (b) (4) tablets showed results in the electronic stability tables that were changed from the raw data generated. The data discrepancy was also found in the Minor Changes and Stability Reports (MCSRs) for ANADA (b) (4) B0015 / B0020 that was submitted to the CVM for review. Batch (b) (4) reported results for (b) (4) content at the 6 month timepoint of (b) (4) mg (B0015) and (b) (4) mg (B0020). Batch (b) (4) reported results for degradation at the 6 month timepoint of not detected (ND) (B0015) and (b) (4) @ (b) (4) RRT / (b) (4) % (B0020). Batch (b) (4) reported no result (B0015) for friability at the 6 month timepoint and (b) (4) % w/w (B0020).

B. Inadequate controls are in place to ensure the accuracy of information logged into the Trackwise system. The following deviations listed the below dates. Upon discussion with the firm, the date

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deviation occurred (*) was determined to be incorrect.

Deviation ID	Date deviation occurred* (dd/mm/yyyy)	Date opened (dd/mm/yyyy)	Date due (dd/mm/yyyy)
PR10364	02/06/2020	19/02/2019	02/04/2019
PR10422	02/09/2020	21/02/2019	04/04/2019

OBSERVATION 3

Written procedures are not drafted, reviewed and approved by the appropriate organizational units.

The firm has multiple legacy production and analytical methods for the same or related products. Product development, analytical method development, and method validations have been inadequate to assure consistent quality results for drug production, stability tests, and QC release testing.

Specifically,

A. Product development, validation, and stability storage conditions has not been fully established and standardized to assure product stability over the reported storage conditions for (b) (4) The firm has the same product for other markets with slightly different production controls and stability storage conditions.

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(b) (4) for the European market, is stored at (b) (4)C and has not had significant stability or consumer complaints. (b) (4) stored at (b) (4)C has had numerous stability failures, complaints, and recalls since August 2018 due formation of crystals.

B. The firm has multiple versions of QC assays for measuring the same chemical entity for related products. These methods lack consistent standardization, some are incomplete, and these method inconsistencies may lead to more OOS. For example, (b) (4), and (b) (4) each have separate assays for measuring (b) (4). The (b) (4) content assay uses a C1 column, but QCAR-088-05 ((b) (4)% US) specifies to equilibrate the column for (b) (4) hours, whereas QCAR-027-07 ((b) (4)% US) does not have that same information.

OBSERVATION 4

Each component is not added to a batch by one person and verified by a second person.

Inadequate controls are in place to ensure the correct components are used for manufacturing.

Specifically,

A. PR10082 was initiated for (b) (4) (batch (b) (4)) after it was discovered that the incorrect (b) (4) was used during filling. Three bags of the incorrect (b) (4) ((b) (4)) were incorrectly labeled as (b) (4) (b) (4) before being (b) (4). The root cause was determined to be operator error as the result of the operator being under pressure to complete their own duties and to cover duties of another operator in a different area due to absence.

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B. Operators failed to adequately follow proper cleaning procedure between manufacturing of commercial batches in Suite (b)(4). During manufacture of (b)(4) batch (b)(4), it was determined that the (b)(4) on the capping machine was not emptied from the previous batch filled (b)(4) batch (b)(4)). PR10364 was initiated for (b)(4) (batch (b)(4)) filled with incorrect caps.

OBSERVATION 5

Deviations from written production and process control procedures are not recorded and justified.

Specifically,

A. A non-routine intervention was performed during filling of (b)(4) US batch (b)(4). On review of the PCR it was confirmed that the filling room operators did not document the non-routine intervention. As per procedure SOP SWPG-379 "Aseptic Technique in the Filling of Sterile Products in Suite (b)(4) [Armagh Road Site]" the non-routine intervention should be recorded on the intervention log sheet with the letter X. the intervention should then be detailed.

B. (b)(4) fill batch (b)(4) (Station Works Suite (b)(4) failed to simulate a (b)(4) break. Deviation PR5694 was initiated, and the deviation was coded as operator error. PR5694 states that a second PCR deviation occurred for an incorrect intervention being simulated (closure machine breakdown simulated instead of filling machine breakdown). The firm failed to initiate a deviation report in Trackwise for the incorrect intervention. In addition, the deviation occurred 30 April 2018, however, PR5694 was not opened until 1 August 2018. Per SWPG-164

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"Deviation Investigation Procedure and Recording Deviations within the Trackwise System", deviations should be initiated within (b) (4) of the occurrence.

C. PR9659 was opened for (b) (4) batch (b) (4), (SW site). The deviation occurred on 18 July 2018, but the deviation was opened 21 January 2019. Per SWPG-164 "Deviation Investigation Procedure and Recording Deviations within the Trackwise System", deviations should be initiated within (b) (4) of the occurrence.

OBSERVATION 6

Buildings used in the manufacturing, processing and holding of a drug product are not maintained in a good state of repair.

It was observed during facility walk-through inspections that some building and equipment areas were not fully cleaned.

Specifically,

A. Modular stability chambers at the Armagh Road (AR) site maintained outside receive ambient outside air intake, and stability samples are stored in cardboard, styrofoam, or on shelves. Cardboard boxes in the outside (b) (4) C unit showed signs of deterioration, discoloration, and dust. Stability chamber (b) (4) contained a dirty container for a pour-on product. There were no cleaning records of stability chambers or the samples stored within.

B. Dust and apparent chemical residues were observed on the floors and shelf units of in the Station Works

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(SW) microbiology laboratory incubators ((b) (4) The microbiology incubators showed chemical residue in the gap of the (b) (4) floors.

C. Dust and chemical debris were observed around the autosampler chambers and column housing of most of the HPLCs at the AR and SW Chemistry QC labs.

D. Chemical residue was observed with use of a UV blacklight, in the Armagh Road suite (b) (4) tank connection ports, on the control panel buttons, and on a stand-alone mixer. This (b) (4) tank is used for (b) (4) products.

***DATES OF INSPECTION**

1/20/2020(Mon), 1/21/2020(Tue), 1/22/2020(Wed), 1/23/2020(Thu), 1/24/2020(Fri), 1/27/2020(Mon), 1/28/2020(Tue), 1/29/2020(Wed), 1/30/2020(Thu), 1/31/2020(Fri), 2/04/2020(Tue), 2/05/2020(Wed), 2/06/2020(Thu), 2/07/2020(Fri)

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

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

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

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, 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."