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	7/26/2022-8/5/2022*
	FEI NUMBER 3002984011

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Sudhir Ghule, Sr. Vice President, Head of Technical Operations

FIRM NAME	STREET ADDRESS
ZYDUS LIFESCIENCES LIMITED	Survey No. 417, 419&420, Moraiya, Sarkhej Bavla National Highway No 8A
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Ahmedabad, Gujarat, 382210 India	Finsihed Drug Manufacturer (Non-Sterile)

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

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

REPEAT OBSERVATION

Specifically, your firm failed to establish scientifically supported conclusions and lack prompt corrective and preventive actions (CAPAs) to decrease or minimize the likelihood of reoccurrence for confirmed out-of-specification (OOS) investigations for commercialized drug products intended for the US market. We reviewed numerous OOS investigations for (b) (4) Tablets USP and (b) (4) (b) (4) (b) (4) Capsules USP, where the root cause was not determined and no CAPAs were initiated for two (2) years while manufacturing continued. In total, (b) (4) batches (b) (4) doses) of tablets and capsules were released without an established root cause and appropriate measures taken for correction. For example, including, but not limited to:

A. In confirmed OOS investigation, OOS/0301/2020/0091 dated 11 Aug 2020 for (b) (4) (b) (4) (b) (4) Capsules (b) (4) mg, batch # (b) (4) (rejected), your firm obtained an OOS result for (b) (4) at the (b) (4) time point during finished product analysis for batch release. The limit is not less than (b) (4) % and the obtained result is (b) (4) %. Your firm opened a manufacturing investigation which documented:

- The OOS was due to an "inadequate [processing] method" (batch record manufacturing

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instructions).

- Your firm monitored (b) (4) batches for critical process parameters (CPPs); however, your management reported your firm manufactures approximately (b) (4) batches of (b) (4) (b) (4) (b) (4) Capsules (b) (4) Each batch contains approximately (b) (4) caps deviation investigation DEV/0301/20210149, dated 7 May 2021, from this batch (b) (4) your firm only took a sample size of (b) (4) % ((b) (4) of your (b) (4) production volume of (b) (4) (b) (4) Capsules, and used this information, which is not statically significant, to approve continued manufacture of the drug product and released to the commercial US market, though the root cause was still unknown at this time.

The manufacturing investigation for (b) (4) (b) (4) Capsules USP OOS/19/273 dated for 6 Mar 2019 was the first OOS of 2019 your firm obtained an OOS result for (b) (4) at the (b) (4) time point during finished product analysis for batch release. The limit is (b) (4) %-(b) (4) % and the obtained result was (b) (4) %. Your firm failed to identify a root cause though the issue was documented as being caused by the [processing] method and further documented as and inadequate test method. Your firm failed to attempt to fix the processing method (manufacturing instructions) and build quality into the process to ensure the safety and efficacy of the drug.

From this OOS/19/273 in May 2019, your firm went on to manufacture and commercialize (b) (4) batches (b) (4) doses) without determining a root cause and establishing appropriate corrective and preventive actions until the root cause was established in January 2020. During this period of time, your firm continued to identify the issue as being caused by an inadequate processing method (batch manufacturing instructions) over nine (9) related/similar OOSs for this product, yet your firm never initiated any improvements or changes to the batch manufacturing record and no deviations were recorded.

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B. In confirmed OOS investigation, OOS/19/236 dated 13 May 2019, (b) (4) USP (b) (4) ng batch# (b) (4) (rejected), your firm obtained an OOS result for Assay during finished product analysis for batch release. You opened a manufacturing investigation which documented:

- The OOS was due to an "inadequate [processing] method" (batch record manufacturing instructions).
- The investigation documented the root cause for the assay failure was, in, part due to a (b) (4) kg loss of during the (b) (4) which left the (b) (4) quantity at (b) (4) kg (specification for yield range is (b) (4) kg (b) (4) kg). The yield comparison (b) (4) (b) (4) study concluded in part "…OOS due to yield is ruled out". The n specification.
- The Critical Processing Parameters (CPP) during the (b) (4) stage reads in part (b) (4) (b) (4)

Your firm identified the root cause as follows, in part, (b) (4) (b) (4) (b) (4)

The batch record did not document any deviations and all processing parameters were executed as per the manufacturing instructions. The yield is within the range of the three (3) validation batches performed for (b) (4) USP. The (b) (4) was held (b) (4) for Lot (b) (4) (b) (4) and Lot (b) (4) These hold times are not v ere not considered during the investigation. The inve only considers (b) (4) hold times which are validated.

Your Senior Vice President-Central Quality noted that any yield within the allowable range of (b) (4) kg-(b) (4) kg may or may not result in an OOS when the batch is executed without incidence, and this cause

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was still unknown at the time the OOS was closed.

From this OOS in May 2019, your firm went on to manufacture and commercialize (b) (4) batches ((b) (4) doses) without unequivocally determining a root cause and establishing appropriate corrective and preventive actions until the root cause was established in June 2019. During this period, your firm never initiated any improvements or changes to the batch manufacturing record and no deviations were recorded though the issue was documented as being caused by an inadequate [processing] method.

All of the above-mentioned examples were confirmed repetitive OOSs (Critical). Event investigation procedure, "0301-SOP-QA-00269, Handling of Event Investigation - TrackWise, V. 3.0, Effective Date: 25 Dec 2021". Section 5.26 establishes a critical event as any event related to quality, safety identity, strength, efficacy and/or purity of drug product, which may cause irreversible medical situation, potential risk to the patient, or on-compliance with regulatory authorization or critical failure systems. For a critical event, which is described in the table as a confirmed OOS/Product Failure the action expected is as follows:

(b) (4)

Though this event falls under the critical classification, the above-mentioned steps were not taken, and batch manufacturing continued to be produced before a root cause was determined and appropriate corrective and preventive actions were initiated and completed.

C. Your firm failed to initiate CAPAs after ten (10) related laboratory OOS investigations from 2018-2020. For example, in stability failure OOS investigation (not confirmed), OOS/0301/2020/0209 dated 09 Nov 2020, (b) (4) Tablets USP (b) (4) mg, (b) (4) 6 month(s), 40°C/75%RH (accelerated) your firm obtained an OOS result for related substances.

- In section 3.0 of the investigation, the root cause of the stability failure was documented as, "attributed to [redacted]
- [redacted] of this investigation documented the issue as occurring ten (10) times from 2018-2020 for the same root cause including the current investigation.
- Your firm failed to initiate CAPAs and closed each investigation without a scientifically supported justification.

OBSERVATION 2
There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

REPEAT OBSERVATION

Specifically, your firm failed to establish a validated process for [redacted] Tablets USP that ensures a state of control of the process throughout its lifecycle. Your firm did not provide assurance that each significant stage of the manufacturing process is designed appropriately to assure the quality of raw material inputs, in-process materials, and finished drugs across [redacted] batches [redacted] of [redacted] For example, both [redacted] Tablets USP batch records for OOS/19/236 [redacted] and OOS/19/296 [redacted] were manufactured within the "validated process para [redacted] both process validations listed above for 2017 and 2019, with no deviations from the validated processing method. However, validated process did not consistently yield finished drug products that were within specification for release and did not include the evaluation of the [redacted] Your firm failed to address or revalidate the [redacted] Tablets USP manufacturing process when finished results within specification at in-p [redacted] nd finished product testing were out-of-

specification, when the process was executed as per the batch manufacturing record.

OBSERVATION 3

Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

Specifically, your firm failed to establish scientifically supported hold times for (b) (4) drug products which can be held at the (b) (4) in-process stage while it is in a (b) (4) The hold times range from (b) (4) across all (b) (4) roducts, which includes your firm's highest volume products:

(b) (4)

Your Chief Technical Officer and Senior Vice President-Central Quality reported, "This is not a logical stopping point, so no hold time has been established for this time period." Additionally, your Senior Vice President-Central Quality reported that (b) (4) will result in a (b) (4) Additionally, your firm fai (b) (4) ld time data on t f the drug products manufactured at your firm.

For example, on 2 Jun 2021, your firm initiated a change control, with OMS number CC/0301/2021/1141 which allowed hold times of the (b) (4) of (b) (4) Tablets USP (b) (4) ng to be (b) (4) from (b) (4) to Not More Than (NMT) (b) (4) (b) (4) stage. This decision was based on an I on Report Deviation, DEV 1/0149, dated 7 May 2021 where the deviation concluded after monitoring (b) (4) batches. Further, the report stated that major rejections are generated at the (b) (4) stage due to (b) (4) nature of (b) (4)

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during the (b) (4) stage (b) (4). The firm documented that the (b) (4) of (b) (4) (b) (4) produced (b) (4) at the inspection stage. Your firm failed to provide a statistically significant rationale for only using (b) (4) to make this change when your firm manufactured (b) (4) batches of (b) (4) tablets USP (b) (4) mg from (b) (4)

The following (b) (4) batches were monitored and used to justify the (b) (4) of the hold time:
(b) (4)

Your management reported that there was no risk to the product that was released for distribution in the US Market without a formal (b) (4) hold study because routine quality control analyses are performed by your firm.

OBSERVATION 4

Written procedures are lacking which describe in sufficient detail the identification, handling and sampling of components and drug product containers.

Specifically, on 3 Aug 2022, (b) (4) sampling was observed for (b) (4) tablets USP (b) (4) mg, batch # (b) (4) and at sampling is done on the ex pling employee in accordance with SOP 0301-SOP-QA-00003, with effective date 10 Mar 2022. According to pages (b) (4) and (b) (4) of the SOP (b) (4)
(b) (4)

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While interviewing the Deputy Manager of Manufacturing Employee #(b) (6) who performed sampling, he stated that when sampling is performed, he uses the (b) (4) thieve (b) (4) (b) (4) (b) (4). He added that batch sizes are sometimes different from batch to batch and there is variability in (b) (4) While witnessing the (b) (4) samples, we observed that the thieve used to take samples does not have any markings or identifications showing measurements.

***DATES OF INSPECTION**

7/26/2022(Tue), 7/27/2022(Wed), 7/28/2022(Thu), 7/29/2022(Fri), 8/01/2022(Mon), 8/02/2022(Tue), 8/03/2022(Wed), 8/04/2022(Thu), 8/05/2022(Fri)

X Dipesh K Shah
Office of Global Policy and Strategy Employee
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