

DEPARTMENT OF HEALTH AND HUMAN SERVICES

CONFIDENTIAL

FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER

4040 North Central Expressway, Suite 300
Dallas, TX 75204

DATE(S) OF INSPECTION

01/18-30/2017*

(214) 253-5200 Fax:(214) 253-5314

Industry Information: www.fda.gov/oc/industry

FEI NUMBER

3010199915

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. John S. Strokis, Head of Quality

FIRM NAME

ZS Pharma, Inc.

STREET ADDRESS

508 Wrangler Dr Ste 100

CITY, STATE, ZIP CODE, COUNTRY

Coppell, TX 75019

TYPE ESTABLISHMENT INSPECTED

API 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

Process validation procedures do not ensure the integrity of process validation, and the quality unit does not retain the authority to accept or reject batches conducted in accordance with process validation.

Specifically, your firm's manufacturing process validation of (b) (4) does not predefine batches of drug product subject to the validation.

Protocol (b) (4) and (b) (4) specify "At least (b) (4), acceptable challenges shall be achieved." Per your firm's Validation Director, this requirement means that your firm must successfully manufacture (b) (4) batches of API. Both these validation protocols state "Each protocol deviation requires a written investigation with the impact to the validation documented."

There is no documentation specifying that batches of (b) (4) were chosen prospectively. The validation protocols and batch records are silent with regards to which batches are intended to support process validation.

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H.L. Jamillah Selby, Investigator

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Furthermore, there is no consideration of process validation in light of (b) (4) batch campaigns. Specifically per document TD16-042-RPT major cleans occur between (b) (4) batches and it is not addressed how your process validation accounts for this event. Additionally, validation for Reactors (b) (4) and (b) (4) began immediately after an end of campaign (b) (4) cleaning, thus there is no assessment of how a (b) (4) batch validation is representative of a (b) (4) batch campaign.

Additionally, the following anomalies / deviations from the validation protocol were noted:

a) During validation of Reactor (b) (4) an initial validation batch was manufactured ((b) (4)). Subsequently, a non-validation, development batch was manufactured (b) (4) on this reactor. Per your firm's Validation Director, this batch is solely for development and not intended to be considered a process validation batch (this batch is intended to address difficulties meeting specification for (b) (4)). There is no formal documentation that the Quality Unit authorized this nonconformity with the validation protocol, and no protocol deviation was initiated. The manufacturing parameters for batch (b) (4) varied from the validation parameters of batch (b) (4).

b) During validation of Reactor (b) (4) batch (b) (4) the (b) (4) validation batch of this reactor was aborted by manufacturing due to an equipment malfunction with no concurrence by the Quality Unit. Manufacturing (b) (4) this material on November 04, 2016, and a nonconformance was not opened until November 07, 2016. There is no formal documentation that the Quality Unit authorized this manufacturing event to be aborted, and no protocol deviation was initiated.

c) During validation of Reactor (b) (4) batch (b) (4) the (b) (4) validation batch of this reactor was aborted. Your firm then manufactured an additional validation batch ((b) (4)) and subsequently began the manufacture of (b) (4). The requirement of "At least (b) (4) acceptable challenges shall be achieved" per validation protocol was not met. There is no documentation supporting completion of process validation given this lack of adherence to the respective validation protocol (b) (4). The Quality Unit has not approved this decision.

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d) (b) (4) validation batches were manufactured on Reactor (b) (4) as a part of process validation. Subsequently, (b) (4) batches deemed "(b) (4) Batch" were manufactured. However, your firm's Quality Unit has failed to complete review of any of the validation batches per document FORM-QA-018.

For all aforementioned events, there is no documentation of authorization by the Quality Unit to deviate from the respective validation protocols.

OBSERVATION 2

Buildings, facilities and equipment are not maintained to ensure the API's identity, strength, quality and purity.

Reactor (b) (4)

On 01/19/2016 we observed the interior face of the (b) (4) gasket was worn-out with lose threads visible. Black particulates were visible on the interior face of the gasket. Additionally, black, white and red colored residues were visible in the interior of the reactor.

See below for nonconformance reports related to particulates / residues.

Reactor (b) (4)

We observed tearing of the head gasket in the interior of the reactor (product contact surface), such that extended portions of the gasket were missing in several locations. Throughout the inspection we were unable to ascertain the (b) (4) of the gasket and potential product impact. The interior face of the (b) (4) gasket exhibited warping and wear (lose threads separating from this gasket towards the interior of the reactor was observed).

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This same reactor was the subject of nonconformance NCC16-022 (opened 10/31/2016), which was opened for a "tear in the head gasket". This nonconformance then goes onto identify that "gasket material was missing that could have potentially transferred into the (b) (4) while processing lot (b) (4)." Subsequently this gasket was replaced. Nonetheless, a similar condition was observed in January of 2017, after installation of a new gasket.

(b) (4)

On 01/19/2016 we observed the mesh to contain gray and black residue / material. It was noted that the drug product subject to (b) (4) is white.

Your firm has initiated investigations related to gray and back residues / materials as follows:

a) Nonconformance NCC16-017 (10/05/2016) (supported with Research Report TD16-150 (January of 2017)) was opened in response to "discolored material (residue) was discovered during the (b) (4) of the (b) (4)." The probable cause was determined to be a (b) (4) like material with a "slightly" different elemental composition.

b) Nonconformance NCC16-033 (12/07/2016) was initiated due to address particulates in (b) (4) (b) (4) samples of various lots of (b) (4). This report goes on to explain "There is no good guidance from the FDA on what can be considered an acceptable level of insoluble particulate matter within product" under the product impact assessment. This nonconformance is an interim report.

c) Nonconformance NCC15-035 (12/21/2015) was opened due to "grey particles" in a sample for lot (b) (4) (supported with Research Report TD16-008). This report concludes that the particulates are

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"composed of the (b) (4) and their (b) (4) composition very likely caused their gray appearance to the naked eye."

We identified additional reports from your auxiliary laboratory related to unknown or foreign material relating to the manufacturing process.

OBSERVATION 3

The specification of (b) (4) (b) (4) - (b) (4) designated (b) (4) is not justified with regard to the manufacturing process of (b) (4).

The manufacturing process for (b) (4) has progressed from (b) (4), and finally (b) (4). The (b) (4) for the various manufacturing scales is presented in the table below:

Actual (b) (4) Values Observed	(b) (4)
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Given the table above, your firm had failed to conduct an investigation to isolate the factor contributing to the elevated (b) (4) values upon scale-up of the manufacturing process. Moreover, your firm opened nonconformance NCC17-002 in January of 2017 to identify the root cause of the (b) (4) trending towards

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failing specification. Since October of 2016, 5 out-of-specification reports have been generated for (b) (4)

On 01/25/2017, to address the (b) (4) values near specification, your firm's Head of Quality specified that upon (b) (4) your firm intends to (b) (4) to adjust the specification. Furthermore, firm management expressed that failures in (b) (4) were expected to result in failing batches based on the current specification and could be dealt with through rejecting batches. Therefore, it is unclear how the firm is addressing the manufacturing process with regards to specifications of (b) (4).

OBSERVATION 4

Proper controls are not exercised over computerized systems used for analytical testing to ensure drug products meet their specified quality attributes.

I. Proper controls have not been implemented to ensure the integrity of electronic data in various analytical laboratory instrumentation:

(b) (4)

a) In testing of an analytical standard termed "(b) (4)", your firm conducted duplicate testing due to anomalous results obtained during initial testing. The initial run was conducted (b) (4) and termed "(b) (4)" and the duplicate testing was conducted (b) (4) and termed "(b) (4)". No investigation was opened in response to the initial test results.

b) On 07/20/2016, file "(b) (4)" was deleted. No investigation into the file deletion had been conducted. Your firm's Quality Assurance Engineer could not explain this event.

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(b) (4)

a) Your firm's (b) (4) Instrument operating with software (b) (4) lacks audit trails. Your firm failed to conduct any sort of analysis into the implications of this instrument lacking appropriate controls. This equipment is used to assess the compliance of all batches to specification.

b) Samples (b) (4) and (b) (4) were re-run due to "instrument issues". No investigation was conducted.

(b) (4)

(b) (4) System:

a) Power outages and instrument errors hindered testing of (b) (4)

(b) (4) Moreover, such a situation rendered data for (b) (4) – (b) (4) deleted and not retrievable. There are no investigations into these events.

b) (b) (4) and (b) (4) were re-tested due to a "failed (b) (4) verification." The (b) (4) verification failed; subsequently the samples were tested and then re-tested. This practice is inconsistent with SOP SOP-QC-060, which specifies "Prior to analyzing samples analyze the (b) (4)". No investigation was conducted.

c) During the analysis of (b) (4) on July of 2016, a communication failure resulting from a breaker being inadvertently switched off hindered analysis. No investigation was conducted.

(b) (4) System:

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d) The (b) (4) operates with software that has no user restrictions and enables deletion of data.

(b) (4)

(b) (4) :

a) (b) (4) and (b) (4) experienced an "(b) (4) error."
(b) (4). No investigation was conducted.

(b) (4) :

b) The (b) (4) Instrument operating with (b) (4) Version (b) (4) that has no user restrictions and enables deletion of data.

II. Moreover, analytical samples and testing lack traceability:

Individuals designated as R&D personnel utilize the aforementioned equipment and conducts analytical testing. As such, the purpose and content of analytical testing conducted in the QC department is not readily identifiable.

Additionally, there is a lack of complete traceability or accountability for manufacturing samples submitted for analysis by your auxiliary laboratory. There is not sample reconciliation for samples indicated in "Sample log-in" and the respective "Request For Analysis" forms.

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OBSERVATION 5

Cleaning validation of the equipment used to manufacture APT is not established to ensure that contamination that would alter the safety, identity, strength, quality or purity of the drug product is prevented.

Specifically,

Between March 2016 and January 2016 your firm has manufactured (b) (4) batches of (b) (4) (b) (4)

The studies performed to support the validation of the cleaning of processing equipment used in the manufacturing process of (b) (4) :

- a) There is no prospective justification for equipment cleaning, the maximum campaign length (b) (4) batches), and equipment hold times.
- Document CV-15-001-RPT "Verification of Cleaning Processes for Manufacture of (b) (4) (b) (4)" was limited to a retrospective review of batch release testing data for (b) (4) batches manufactured between November 2015 and April 2016. This study was presented as evidence to support equipment cleaning, the "maximum number of batches in a campaign" and hold times. Your firm's Head of Quality acknowledged that these studies relied on API passing specification to determine cleaning effectiveness.
 - Document TD16-042-RPT "Evaluation of (b) (4) API for Bracketing of Cleaning Campaigns", Revision 00 is an update to Document CV-15-001-RPT. This study further assesses (b) (4) process development batches via (b) (4) testing

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with additional sampling and microbiological testing utilized to support an extended campaign length. No assessment of manufacturing equipment was conducted.

- b) The processes and acceptance criteria used to justify the adequacy of the removal of the white residues observed on the inner surfaces of your reactors used in the manufacturing process was not defined prior to execution (TD-16-034). This study consisted solely of an undefined collection of samples and then analyzing this material with (b) (4) and (b) (4). (b) (4) The sampling strategy and rationale for samples analyzed were not discernable from this report.

OBSERVATION 6

The reliability of test method TM-026 to quantitate elemental composition of (b) (4) (b) (4) has not been demonstrated.

Your firm's specifications for (b) (4) (SPEC-DS-001) define a limit of (b) (4) content to (b) (4)%. Upon review of (b) (4) testing for multiple batches of (b) (4) (b) (4) we noted sample preparations had been re-tested. The re-testing of samples exhibited the variation summarized by the following chart:

(b) (4) Batch	Initial Test Results	Second Test Results
(b) (4)	(b) (4)	(b) (4)

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(b) (4)

(b) (4)

(b) (4)

I asked your firm's Manager, Analytical services if this variation in testing of the same sample preparations have been addressed or investigated. They stated "no". They specified that per the protocol for method validation (TD15-009), the allowable difference in intermediate precision is (b) (4)%.

It is unclear how your firm ensures the compliance of drug product (b) (4) content, as the table above indicates a variation of approximately (b) (4)% in (b) (4) content for the same preparations of analytical samples (the acceptance value has a range of (b) (4)%).

***DATES OF INSPECTION**

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