DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	04/08/2019-04/16/2019 * FEI NUMBER 3005029956

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Ashish Hajarnis, Vice President (Works)

FIRM NAME	STREET ADDRESS
Torrent Pharmaceuticals Limited	Ahmedabad Mehsana Highway, Taluka-Kadi
CITY, STATE, ZIP CODE, COUNTRY Indrad, Gujarat 382721, India	TYPE ESTABLISHMENT INSPECTED Finished Product Manufacturer & Active Pharmaceutical Ingredient Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Finished Drug Products

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.

Specifically,

The summary of OOS investigations conducted by the firm during the period beginning from January 2017 to March 2019 is as follows:

	2017 to 2019	Valid	Invalid	% Invalid
Finished Product	340*	93	247	73%
Stability	203*	80	123	61%

*excludes on-going investigations at the time of inspection

Review of the firm's OOS investigation revealed that the firm's investigation practices and procedure(s) are deficient. Several examples were found where the original failing results were invalidated without a scientifically sound and justifiable root cause, and results of passing re-test results were reported as the result of record. Examples include, but are not limited to, the following OOS investigations:

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	Lata Mathew, Investigator Jogy George, Investigator Zhao Wang, FDA Center Employee	04/16/2019

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(A)
OOS Investigation Number OOS/IN/F/FP/17/233 for (b) (4) and (b) (4) Tablets (b) (4) mg/(b) (4) mg pertaining to batch number (b) (4) was initiated on 07/01/17 to probe the following OOS results generated during (b) (4) testing for Assay:

	(b) (4)	Mean	RSD%
(b) (4)		102.8	5.57
(b) (4)		97.3	1.74
Specification*	Mean: (b) (4) to (b) (4) % of label amount Individual: (b) (4) to (b) (4) %		

*as in the OOS report

The OOS results were confirmed during preliminary investigation and hypothesis testing (Phase I) with no identified root cause. No manufacturing error was identified during Phase II investigation. The initial OOS results were invalidated based on reserve sample testing of set (b) (4) sample sets. The higher Assay results were invalidated without identifying a definitive root cause. The manufacturing process of this product consists of a (b) (4) process. The investigation could not conclusively identify if there is any laboratory error or manufacturing error and no CAPA was initiated. The (b) (4) was released using re-tested reserve sample set results. (b) (4) was released to U.S. market with an expiry date of (b) (4) In addition, the documents provided to the investigators in support of OOS Investigation Number OOS/IN/F/FP/17/233 included an unsigned OOS Amendment Report. This document had a print date of 8/27/2018.

(B)
OOS Investigation Number OOS/IN/F/FP/17/238 for (b) (4) and (b) (4) Tablets (b) (4) mg/(b) (4) mg pertaining to batch number (b) (4) was initiated on 7/4/17 to probe the following OOS results generated during (b) (4) testing for Assay:

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	Lata Mathew, Investigator LM Jogy George, Investigator JG Zhao Wang, FDA Center Employee ZW	04/16/2019

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	(b) (4)	Mean	RSD%
(b) (4)		100.7	2.13
(b) (4)		103.7	9.24
Specification*	Mean: (b) (4) to (b) (4) % of Label Claim Individual: (b) (4) to (b) (4) %		

*as in the OOS report

The OOS results were confirmed during preliminary investigation and hypothesis testing (Phase I) with no identified root cause. No manufacturing error was identified during Phase II investigation. The initial OOS results were invalidated based on reserve sample testing of set (b) (4) sample sets. The higher Assay results were invalidated without identifying a definitive root cause. The manufacturing process of this product consists of a (b) (4) process. The investigation could not conclusively identify if there is any laboratory error or manufacturing error and no CAPA was initiated. The (b) (4) was released using re-tested reserve sample set results. (b) (4) was released to the U.S. market with an expiry date of (b) (4).

(C)

The same deficient investigative process as in **(A)** and **(B)** above was followed to probe (b) (4) Assay failure in OOS/IN/F/FP/18/070 for (b) (4) and (b) (4) Tablets (b) (4) mg/(b) (4) mg tablets pertaining to batch number (b) (4) Expires (b) (4)). No definitive root cause was identified.

(D)

OOS Investigation Number OOS/IN/F/FP/17/340 for (b) (4) Capsules USP (b) (4) mg for PV batch number (b) (4) was initiated on 11/06/17 to probe the failing (b) (4) result as follows:

	(b) (4)	Mean	RSD%
(b) (4) (%)		97.4	1.07
Sample Wt. (mg).			
Specification	NLT (b) (4) % and NMT (b) (4) % of Label Claim, RSD NMT (b) (4) %		

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The OOS results were confirmed during preliminary investigation and hypothesis testing (Phase I) with no identified root cause. No manufacturing error was identified during Phase II investigation. The initial OOS results were invalidated based on reserve sample testing of set (b) (4) sample sets. Process Validation Report PVR/CD.74.01-2E/17/01-01 approved on 12/27/17 states the following:

> *No specific root cause identified at manufacturing stage for out of specification result observed in* (b) (4) *test. As per mentioned in Laboratory investigation report, the OOS result obtained in the subjected batch for the* (b) (4) (b) (4) *test might be due to sample preparation error i.e. analytical variation which was not established during the investigation.*

The impact (if any) of higher sample weights yielding low assay results was not evaluated in the investigation report. Additionally, the validation batch (b) (4) was manufactured to support the qualification of an alternate API supplier (# (b) (4)) for (b) (4) This alternate API was subsequently deemed qualified and approximately (b) (4) ots of finished drug products shipped to the U.S market have used this API.

(E)
The same deficient investigative process as in **(D)** above was utilized to probe (b) (4) failure in OOS/IN/F/FP/18/103 for (b) (4) Capsules USP (b) (4) mg for batch number (b) (4) (Expires (b) (4) . No definitive root cause was identified.

(F)
OOS Investigation Number OOS/IN/F/ST/18/354 for (b) (4) and (b) (4) Tablets (b) (4) ng / (b) (4) ng for batch number (b) (4) , was initiated on 10/11/18 to probe the failing 3M (25^0 C/ 60 %RH) Assay result of (b) (4) % ((b) (4)) and (b) (4) % ((b) (4) against a specification limit of (b) (4) % to (b) (4) % of the label claim. The OOS results were confirmed during preliminary investigation and hypothesis testing (Phase I) with no identified root cause. No manufacturing error was identified during Phase II investigation. The initial OOS results were invalidated based on passing results

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from triplicate analysis. The investigation report states that the initial failures '…occurred due to sample preparation error i.e. some powder loss while transferring to the volumetric flask'. This presumptive root cause is not scientifically proven nor substantiated in the investigation report. This batch was released to U.S. distribution with an expiry date of (b) (4). Batch (b) (4) is an annual stability batch that represents approximately (b) (4) additional batches released to the U.S. market.

(G)

OOS Investigation IN/F/FP/17/309 for (b) (4) Tablets, USP (b) (4) mg, for batch (b) (4) was initiated on 09/29/17 to probe the Dissolution failures. No root cause was identified in Phase I or Phase II investigations. Data obtained are summarized below:

Tablet No.		S_1 Results	S_2 Results	Additional Test Set -I	Additional Test Set-II	Additional Test Set-III
1		(b) (4)				
2						
3						
4						
5						
6						
Remarks		Avg: 88 Min: (b) (4) Max:	Avg: 77 Min: (b) (4) Max:	(S_3) Avg: 86 Min: (b) (4) Max:		(Set I + II + III) Avg: 92 Min: (b) (4) Max:
USP <711>	S_1 (6 units)	Each unit NLT Q+5%				
	S_2 (12 units)	Average of 12 Units is ≥ Q, and no unit is less than Q – 15%				
	S_3 (24 units)	Average of 24 Units is ≥ Q, and NMT 2 unit < Q – 15%, and no unit is < Q – 25%				

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Product Spec:	**NLT (b)(4) % (Q) in 45 minutes. It must conform to USP general chapter <711> criteria**

The firm failed to follow the USP dissolution criteria for reporting of results. Instead of reporting the average of first 24 units, the firm deficiently reported the average results of additional 18 units (from Set I, II, and III) and ignored the initial S_1 and S_2 results from reporting. In summary,

- Reported results: Avg: 92%, Min: (b)(4) %, Max: (b)(4) % (i.e. from re-tested 18 units)
- Ignored results: Avg: 86%, Min: (b)(4) %, Max: (b)(4) %

This deficient practice resulted in the minimum dissolution value (i.e., (b)(4) %) from not being reported in the Certificate of Analysis. Batch (b) (4) s in U.S. distribution with an expiry date of (b) (4) In addition, the firm's written procedure GTP/USP/022 titled, "Dissolution" was not followed during the reporting of results.

(H)
OOS Investigation Number OOS/IN/F/ST/17/364 for (b) (4) tablets (b)(4) mg, batch number (b) (4) (blister packaging 40°C/75%RH, 2-month sample), was initiated on 09/20/17 to probe the failing Dissolution result of tablet-3 at the 10-hour time point of (b)(4) % drug lease against a specification limit of (b)(4) % to (b)(4) % release. No laboratory error was identified during the investigation. However, the initial results were invalidated without a valid assignable root cause and results from re-analysis (n=18 units) was reported as the result of record. Batch # (b) (4) was manufactured as an Exhibit batch and Bio-batch in support of (b) (4) filing # (b) (4)

(I)
OOS Investigation Number OOS/IN/F/FP/17/295 for (b) (4) tablets (b)(4) mg, batch number (b) (4) was initiated on 09/15/17 to probe the failing Dissolution result of tablet-1 at the 6-hour time point of (b)(4) % drug release against a specification limit of (b)(4) % to (b)(4) %, at the 12-hour time point of (b)(4) %

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Lata Mathew, Investigator LM Jogy George, Investigator JG Zhao Wang, FDA Center Employee ZW	04/16/2019

drug release against a specification limit of (b)% to (b)%, and at the 24-hour time point of (b)% drug release against a specification limit of NLT (b)%. Root cause was assigned to lower length of sinker used for dissolution test. However, the actual length of sinker used was not recorded in the investigation report. The initial results were invalidated and the results from re-analysis was reported as the result of record. Batch # (b) (4) was manufactured as an Exhibit batch in support of (b) (4) filing # (b) (4)

(J)

OOS Investigation IN/F/ST/18/135 for (b) (4) Tablets, USP (b) (4) mg, for batch (b) (4) 25ºC/60%RH, 6-month sample, was initiated on 05/02/2018 to probe the Dissolution failures. Batch # (b) (4) was manufactured as an Exhibit batch support of (b) (4) filing #s (b) (4) No laboratory error was identified from extensive hypothesis testing. However, the firm still assigned the root cause as "suspected laboratory error" and invalidated the original OOS results. Data obtained are summarized below:

Original OOS results (not reported)

Tablet No.	3 hrs (%)	6 hrs (%)	12 hrs (%)	24 hrs (%)
1	(b) (4)			
2				
3				
4				
5				
6				
Ave (Min-Max)	Avg: 26 Min: (b) (4) Max:	Avg: 51 Min: (b) (4) Max:	Avg: 70 Min: (b) (4) Max:	Avg: 81 Min: (b) (4) Max:
Limit	3 hrs (b) (4) %; 6 hrs (b) (4) %; 12 hrs (b) (4) %; 24 hrs NLT (b) (4) %			

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L2 stage sample testing (reported)

Tablet No.	3 hrs (%)	6 hrs (%)	12 hrs (%)	24 hrs (%)
7	(b) (4)			
8				
9				
10				
11				
12				
Ave (Min-Max)	23% (b) (4)	54% (b) (4)	75% (b) (4)	83% (b) (4)
Limit	3 hrs (b) (4) %; 6 hrs (b) (4) %; 12 hrs (b) (4) %; 24 hrs NLT (b) %			

The firm invalidated L1 stage results and stated that L2 stage results shall be considered for reference purpose only.

Then the firm reanalyzed two new sets of dissolution samples (total of 12 tablets), SET-1 and SET-2. However, SET-1 sample failed again in 24 hrs time points and deficiently considered it as L1 of SET-1. So, the firm performed another 6 samples' dissolution and considered it as L2 of SET-1. Finally, the firm reported the average of 18 tablets (i.e., original L2 + SET-1 L2 + SET -2). Data obtained for reanalysis are summarized below:

SET-1 L1 stage (not reported)

Tablet No.	3 hrs (%)	6 hrs (%)	12 hrs (%)	24 hrs (%)
1	(b) (4)			
2				
3				

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4	(b) (4)			
5				
6				
Ave (Min-Max)	23% (b) (4)	51% (b) (4)	72% (b) (4)	78% (b) (4)
Limit	3 hrs (b) (4) %; 6 hrs (b) (4) %; 12 hrs (b) (4) %; 24 hrs NLT (b) %			

SET-1 L2 stage (reported)

Tablet No.	3 hrs (%)	6 hrs (%)	12 hrs (%)	24 hrs (%)
7	(b) (4)			
8				
9				
10				
11				
12				
Ave (Min-Max)	19% (b) (4)	55% (b) (4)	76% (b) (4)	84% (b) (4)
Limit	3 hrs (b) (4) %; 6 hrs (b) (4) %; 12 hrs (b) (4) %; 24 hrs NLT (b) %			

SET-2 results (reported)

Tablet No.	3 hrs	6 hrs	12 hrs	24 hrs
1	(b) (4)			
2				
3				
4				
5				

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6	(b) (4)			
Ave (Min-Max)	26% (b) (4)	54% (b) (4)	75% (b) (4)	82% (b) (4)
Mean of reanalysis 18 tablets	22%	54%	74%	81%
Limit	3 hrs (b) (4) %; 6 hrs (b) (4) %; 12 hrs (b) (4) %; 24 hrs NLT (b) %			

The firm failed to follow the USP dissolution criteria for reporting of results. The firm invalidated the original results without a scientifically sound root cause. The dissolution results would have failed specification limits if the first set of 6 units were considered for reporting. In addition, the firm's written procedure GTP/USP/022 titled, "Dissolution" was not followed during the reporting of results.

(K)

OOS Investigation Number OOS/IN/F/FP/17/304 for (b) (4) Tablets, USP (mg for batch number (b) (4), was initiated on 09/25/17 to probe the failing (b) (4) result as follows:

	(b) (4)	Mean	RSD%
(b) (4) (%)		106.0	1.23
Sample Wt. (mg).			
Specification	Mean: NLT (b) % and NMT (b) % of Label Claim, Individuals: NLT (b) % and NMT (b) %, RSD NMT (b) %		

The OOS results were confirmed during preliminary investigation. Rationale for the selection of (b) (4) (b) (4) for Hypothesis testing (during Phase I) is not detailed in the investigation report. No lab error was found, and no manufacturing error was identified during Phase II investigation. The initial OOS results were invalidated based on reserve sample testing of (b) (4) sample sets. The batch was released to U.S. market with an expiry date of (b) (4).

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
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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.

Specifically,

Review of Process Validation (PV) documents revealed that PV batches that failed process validation protocol requirements and quality attributes were deemed acceptable and counted towards successful manufacturing process validation. For example, Process Validation for (b) (4) Tablets USP (b) mg, and (b) (4) Tablets USP (b) mg for qualifying an alternate API code (# (b) (4)) is deficient. All process validation batches were rejected as summarized below:

Strength	Total PV batches	Total OOS investigations	Batch Disposition
(b) mg	4	6	All rejected
(b) mg	3	3	All rejected

(A)
Process Validation for (b) (4) Tablets USP (b) mg

The following OOS investigations were initiated during testing of process validation batches:

OOS No.	Date of Initiation	Batch #	PV Number	Test Results	Specification
OOS/IN/F/FP/16/257	9/29/16	(b) (4)	1	F_2 = (b	F_2 NLT (b)
OOS/IN/F/FP/16/137	7/23/16		1	Assay = (b) %	(b) (4) (b) (4) %
			1	(b) * (min) = (b) %	%

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
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OOS/IN/F/FP/16/263	10/4/16	(b) (4)	1	(b) (4) = (b) (4) %	NMT (b) (4) %

Due to the failures, an additional PV batch (#4) was added to the validation campaign. However, the 4th batch failed for F_2 dissolution similarity factor as follows:

OOS No.	Date of Initiation	Batch #	PV Number	Test Results	F_2 Specification
OOS/IN/F/FP/17/139	4/10/17	(b) (4)	4	F_2 = (b) (4)	F_2 NLT (b) (4)
OOS/IN/F/FP/17/143	4/10/17		4	F_2 = (b) (4)	F_2 NLT (b) (4)

PV batches (b) (4) (PV# 1) and (b) (4) (PV# 4) were rejected and destroyed leading to only 2 successful process validation batches. The firm's quality unit also rejected the remaining 2 batches. Despite the PV batch failures and rejections, the process validation for the alternate API vendor was deemed successful per interim validation report # PVR/BTL.508.01-33E/18, approved on 01/17/18.

(B)
Process Validation for (b) (4) **Tablets USP** (b) (4) **mg**

The process validation initiated to qualify an alternate API supplier (# (b) (4)) for (b) (4) Tablets USP (b) (4) mg is deficient. Three process validation batches were rejected and destroyed based on OOS investigations for (b) (4) failures. However, despite the critical attribute (i.e. (b) (4) failures, the manufacturing process utilizing the alternate API supplier was still considered valid and acceptable by the Quality Unit. The process validation report # PVR/BTL.510.01-40E/18, approved on 01/05/18 stated that during further review, the route of synthesis for the old API code ((b) (4)) and the new API code ((b) (4)) are only marginally different and would not impact the quality of the finished product.

In both cases **(A)** and **(B)** above, the respective process validation report states the following:

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	Lata Mathew, Investigator LM Jogy George, Investigator JG Zhao Wang, FDA Center Employee ZW	04/16/2019

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	04/08/2019-04/16/2019 * FEI NUMBER 3005029956

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Ashish Hajarnis, Vice President (Works)

FIRM NAME	STREET ADDRESS
Torrent Pharmaceuticals Limited	Ahmedabad Mehsana Highway, Taluka-Kadi
CITY, STATE, ZIP CODE, COUNTRY Indrad, Gujarat 382721, India	TYPE ESTABLISHMENT INSPECTED Finished Product Manufacturer & Active Pharmaceutical Ingredient Manufacturer

Due to change in API there is no impact on manufacturing process & no impact of API quality on finished goods So API code (b) (4) shall be used for commercial and it is recommended to abort validation for further commercial batches in SFG code: (b) (4) and regular commercial batches shall be manufactured with same parameter which are available of SFG code (b) (4) as there is no change in process parameter.

The batch disposition status for the (b) (4) mg and (b) (4) mg batches manufactured and released to U.S. market with alternate API code (b) (4) is as follows.

Product	Batch status	Count
(b) (4) Tab, USP (b) mg	Hold	3
	Rejected	5
	Released	(b) (4)
(b) (4) Tab, USP (b mg	Hold	4
	Rejected	3
	Released	(b) (4)
Grand Total		

(C)
Process Validation for **Lamotrigine ER Tablets 200 mg**

The process validation for Lamotrigine ER Tablets 200 mg is deficient. The pre-validation risk assessment to determine the number of batches required to successfully demonstrate process validation is not scientifically sound. For example, the risk assessment detailed in the process validation protocol (PV/BTL.524.01-5E/17/01-01, approved on 11/04/17) considered the functional coating (b) (4) to be a "minor" risk factor although the (b) (4) is documented as a critical process parameter that could impact the dissolution of the product. This approach led to the determination that only 2 batches are required to demonstrate successful process validation. During review of the batch record for PV batch # BFR5D002, it was noted that a deviation (D/I/F/2017/0477) was initiated for the film coating (b) process.

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This deviation addressed the differences in (b) (4) between the two validation batches. The impact of notable differences in the (b) (4) was not thoroughly understood at the time of batch execution. The impacted batch (BFR5D002) failed for Dissolution on stability at the 3M and 6M time points and consequently the batch was recalled from the market. A thorough retrospective evaluation of the manufacturing process was not conducted after the stability failures, and no consideration was given to establish process robustness with additional PV batches.

It was also discovered that the firm has no procedural requirement during the tablet coating process to calibrate the (b) (4) before the start of a new batch. Without a (b) (4) calibration step, there is no assurance that the volumetric (b) (4) is uniformly maintained (across all (b) (4) during the entire coating process. Lamotrigine ER Tablets 200 mg is an example of a functionally coated tablet product that does not include a (b) (4) calibration step during the tablet coating process.

(D)
The bulk hold time study design is deficient. For example, the following finished products belong to a category of (b) (4) compression and relatively low active content products, where the sample quantities used to establish (b) (4) hold times do not represent the actual batch sizes of the product:

Product	Strength (mg)	Wt. of (b) (4) Tablets (mg)	% Active	Sample Quantity	Batch Size
(b) (4) Tablets	(b) (4)			(b) (4) grams	(b) (4)
(b) (4) and (b) (4) Tablets, USP				grams	
(b) (4) and (b) (4) Tablets, USP				grams	
(b) (4) Tablets				grams	
(b) (4) Tablets				grams	
(b) (4) Tablets				grams	

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OBSERVATION 3

Routine calibration of automatic and electronic equipment is not performed according to a written program designed to assure proper performance.

Specifically,

The qualification of Tablet (b) (4) machine (equipment ID# (b) -03) is deficient. This equipment is proposed for the commercial manufacturing of (b) (4) tablets (b) (4) and (b) mg) for (b) (4) # (b) (4) and (b) (4) Tablets (b) (4) and (b) (4) mg) for (b) (4) # (b) (4) The following issues were observed during the inspection:

Per equipment (b) -03 maintenance manual, the required calibration includes the (b) (4) and the (b) (4) USB interface. These parameters are critical for the quality of the tablet (b) (4) process. The general manager of Engineering department provided the current equipment calibration certificate for equipment (b) -03 with Certificate number TPL/T/0196/01/19. This certificate did not include the two required calibration items. The last calibration provided by the equipment manufacturer expired in January 2019. Additionally, the production operators purportedly trained on the operational aspects of (b) -03 confirmed that they do not know how to set up the vision profile settings for the vision inspection system on the machine. The vision system ensures that the (b) (4) tablets conform to in-process specification limits. A service engineer representative also confirmed that he is unaware of how to correctly setup the vision inspection system. Consequently, during the (b) (4) process demonstration on 04/12/19, several false rejects were found in the reject chute associated with the vision check cameras on the equipment thus providing no assurance of the optimum functionality of the vision system.

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Active Pharmaceutical Ingredients (API)

OBSERVATION 4

Out of Specification Investigation for API products is deficient.

Specifically,

OOS Investigation Number OOS/IN/A/ST/17/013 for (b) (4) pertaining to batch number (b) (4), was initiated on 03/06/17 to probe the following OOS results generated during Assay testing at the 12M time point (25 °C/ 60 %RH and 30 °C/ 75 %RH):

- 25 °C/ 60 %RH: (b) (4) %
- 30 °C/ 75 %RH: %

Note: Specification is NLT (b) (4) % and NMT (b) (4) % (on Anhydrous basis)

As part of hypothesis (Phase I), a re-dilution study was not considered using the diluent allowed by the method to rule out any dilution error. Additionally, a service engineer for the instrument confirmed that there was no instrument failure during initial or hypothesis testing. However, instrument error was still suspected and substantiated by intentionally pumping air bubble into the system and the standard injections yielded results higher than the specification limits. Furthermore, since the method validation for solution stability was deficiently established only for (b) (4), a second set of samples was analyzed in duplicate to invalidate the original failing results.

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Passing results from initial sequence for other batches were also discarded, and re-tested results were reported without a valid justification. No consideration was given to report the average of all passing results when a definitive root cause is not identified.

***DATES OF INSPECTION**

4/8/2019(Mon), 4/9/2019(Tue), 4/10/2019(Wed), 4/11/2019(Thu), 4/12/2019(Fri), 4/13/2019(Sat), 4/15/2018(Mon), and 4/16/2019(Tue).

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