#### DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION DISTRICT ADDRESS AND PHONE NUMBER 04/08/2019-04/16/2019 \* ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 3005029956 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Mr. Ashish Hajarnis, Vice President (Works) Torrent Pharmaceuticals Limited Ahmedabad Mehsana Highway, Taluka-Kadi CITY, STATE, ZIP CODE, COUNTRY TYPE ESTABLISHMENT INSPECTED Indrad, Gujarat 382721, India Finished Product Manufacturer & Active Pharmaceutical Ingredient 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:

### **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:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Lata Mathew, Investigator  Jogy George, Investigator  Zhao Wang, FDA Center Employee	DATE ISSUED 04/16/2019
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DISTRICT ADDRESS AND PH		RUG ADMINISTRATIO		
	ONE NUMBER		DATE(S) OF INSPECTION 04/08/2019-04/16/20	110 *
ORA OPQO HQ,	Room #2032		FEI NUMBER	119
	wn Drive, Rockville, MD 20		3005029956	
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Industry Informatio	na variant file any landindricter	-		
NAME AND TITLE OF INDIVID	n: www.fda.gov/oc/industry  UAL TO WHOM REPORT ISSUED			90
Mr. Ashish H	Majarnis, Vice President (W	orks)		
FIRM NAME		STREET ADDRESS		
The The Control of th	maceuticals Limited		d Mehsana Highway, T	aluka-Kadi
Indred Cuis	rat 382721, India	TYPE ESTABLISHM	entinspected  Product Manufacture	r c Natiro
indiad, Guja	rat 302/21, india	No. of the state o	utical Ingredient Ma	
0.				
Tablets (b) mg/	non Number OOS/IN/F/FP/17/2 mg pertaining to batch num results generated during (b) (4)	ber (b) (4) ting for Assay	and (b) (4) was initiated on 07/01/	
		5+6		
	) (4)			Mean RSD%
(b) (4) (b) (4)				102.8 5.57
Specification*	Mean.	(D) (U) (4) % O	f label amount	97.3   1.74
Specification	Mean.	Individual: (b) to		
		(4)		s in the OOS repor
OOS results were Assay results were this product conthere is any labor using re-tested results (4) In a	ratory error or manufacturing errorserve sample set results. (b) (4) (d) (d) (d) (d) (d) (d) (d) (d) (d) (d	ample testing of a definitive rest. The investion and no CAP was released to the investion.	oot cause. The manufactor gation could not conclust. A was initiated. The odd to U.S. market with a gators in support of OO	sets. The higher uring process of ively identify in was released
				S Investigation
		,		S Investigation
(B)		- 150/0	Th VA	S Investigation
OOS Investigati	on Number OOS/IN/F/FP/17/23	38 for (b) (4)	and (b) (4)	S Investigation ment had a print
OOS Investigati	<sup>(4)</sup> mg pertaining to batch num	iber (b) (4)	was initiated on 7/4/1	S Investigation ment had a print
OOS Investigati	on Number OOS/IN/F/FP/17/2: b) (4) mg pertaining to batch number of the control o	iber (b) (4)	was initiated on 7/4/1	S Investigation ment had a print
OOS Investigati	<sup>(4)</sup> mg pertaining to batch num	iber (b) (4)	was initiated on 7/4/1	S Investigation ment had a prin
OOS Investigati	<sup>(4)</sup> mg pertaining to batch num	iber (b) (4)	was initiated on 7/4/1	S Investigation ment had a print
OOS Investigati	<sup>(4)</sup> mg pertaining to batch num	iber (b) (4)	was initiated on 7/4/1	S Investigation ment had a print
OOS Investigati	<sup>(4)</sup> mg pertaining to batch num	iber (b) (4)	was initiated on 7/4/1	S Investigation ment had a prin
OOS Investigati	<sup>(4)</sup> mg pertaining to batch num	ting for Assay:	was initiated on 7/4/1	S Investigation ment had a print
OOS Investigati Tablets(b) mg/0 following OOS r	esults generated during (b) (4) test	iber (b) (4)	was initiated on 7/4/1	PS Investigation ment had a print
OOS Investigati Tablets(b) mg/0 following OOS r	esults generated during (b) (4) test	ting for Assay:	was initiated on 7/4/1	S Investigation ment had a print
OOS Investigati Tablets(b) mg/0 following OOS r	esults generated during (b) (4) test	ting for Assay:	was initiated on 7/4/1	PS Investigation ment had a print
OOS Investigati Tablets(b) mg/0 following OOS r	esults generated during (b) (4) test  employee(s) SIGNATURE  Lata Mathew, Investigator	ting for Assay:	was initiated on 7/4/1	PS Investigation ment had a print
OOS Investigati Tablets(b) mg/0 following OOS r	EMPLOYEE(S) SIGNATURE Lata Mathew, Investigator Jogy George, Investigator	ting for Assay:	was initiated on 7/4/1	PS Investigation ment had a print

	DEPARTMENT OF HEALT FOOD AND DRUG			
ORA OPQO HQ,			DATE(S) OF INSPECTION 04/08/2019-04/16/ FEI NUMBER	2019 *
12420 Parkla	wn Drive, Rockville, MD 20857 rnational483responses@fda.hhs		3005029956	•
Industry Information	n: www.fda.gov/oc/industry			
Mr. Ashish H	ajarnis, Vice President (Work		5	
Torrent Phar	maceuticals Limited	STREET ADDRESS  Ahmedabac  Type establishmen	d Mehsana Highway,	Taluka-Kadi
	rat 382721, India		Product Manufactu utical Ingredient	
(b)	) (4)			Mean RSD%
(b) (4)				100.7 2.13
(b) (4)	, (b)	(b) (4)		103.7 9.24
Specification*	Mean: (4)	to (b) (4) 6 of lividual: (b) to	(b) %	
		(1)		*as in the OOS report
OOS results wer Assay results we this product con there is any labor using re-tested re of (b) (4)	ratory error or manufacturing error a eserve sample set results. (b) (4)	ole testing of definitive ro The investig and no CAP. was release	f set (b) (4) sample oot cause. The manufagation could not conclete A was initiated. The (b) and to the U.S. market was	e sets. The higher acturing process of dusively identify if (b) (4) was released with an expiry date
failure in OOS/II tablets pertaining	ent investigative process as in (A) N/F/FP/18/070 for (b) (4) to batch number (b) (4) Expire	and <sup>(b) (4)</sup> es (b) (4)	Table. No definitive root ca	ets $_{(4)}^{(b)}$ mg/ $_{(4)}^{(b)}$ mg use was identified.
(D) OOS Investigationumber (b) (4)	on Number OOS/IN/F/FP/17/340 for was initiated on 11/06/17 to pro	(b) (4) be the failin	Cansules USP (b) (d) re	ng for PV batch esult as follows:
(b) (4) (%) Sample Wt. (mg).	(b) (4)	(h) (4)		Mean RSD% 97.4 1.07
Specification	NLT(0) % and NMT	of Lat	pel Claim, RSD NMT(b)	0
, ×				
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE  Lata Mathew, Investigator  Jogy George, Investigator  Zhao Wang, FDA Center Employ	JG ee 2W		DATE ISSUED 04/16/2019
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	DEPARTMENT OF HEALT FOOD AND DRUG			
DISTRICT ADDRESS AND PH		ADMINISTRATIO	DATE(S) OF INSPECTION	
			04/08/2019-04/16/201	9 *
ORA OPQO HQ,			FEI NUMBER	
	wn Drive, Rockville, MD 20857		3005029956	
ORAPHARMInte	rnational483responses@fda.hhs	.gov	3003027730	
Industry Informatio	n: www.fda.gov/oc/industry			
FIRM NAME	ajarnis, Vice President (Work	STREET ADDRESS		
			d Mahaana Washii ma	1 77
CITY, STATE, ZIP CODE, COU	maceuticals Limited	TYPE ESTABLISHME	d Mehsana Highway, Ta	Tuka-Kadi
		Table 2511 161 115	Product Manufacturer	c Activo
indiad, Guja	rat 382721, India	Figure Department of a constitution		The street description of the
		Pharmace	utical Ingredient Man	uracturer
OOS results we Validation Repo  No specific test. As per (b) (4)  the investig.  The impact (if investigation requalification of a deemed qualification of a deemed qualificat	any) of higher sample weights yie port. Additionally, the validation be an alternate API supplier (# (b) (4) ots of finished and approximately (b) (a) Capsules (b) (a) Capsules (b) (b) (a) Capsules (b) (b) (a) Capsules (c) (b) (a) Capsules (c) (b) (a) Capsules (c) (b) (a) Capsules (c) (c) (c) (d) Capsules (c) (d) (d) Capsules (d)	ple testing oved on 12/ age for out of ort, the OOS report i.e. analy elding low atch (b) (4) for (b) (4) shed drug p  bove was ut as USP (b) m fied.  or (b) (4) inted on 10/ b) (b) (4) inted on 10/ c) (b) (c) (d) inted on 10/ c) (d) (d)	of set (b) (4) sample 27/17 states the following:  specification result observed in esult obtained in the subjected by tical variation which was not evaluated assay results was not evaluated. This alternate API was roducts shipped to the U.  filized to probe (b) (4) g for batch number (c) (4)  and (b) (4)  711/18 to probe the failing against a lits were confirmed during root cause. No manufactured are the same and the same against a same against a lits were confirmed during root cause. No manufactured are same as the same against a same against a lits were confirmed during root cause. No manufactured are same as the same against a same against	(b) (4)  atch for the (1) (4)  stablished during  aluated in the to support the subsequently S market have  failure (Expires  Tablets  3M (25° C/ 60 a specification of preliminary uring error was
SEE REVERSE OF THIS PAGE	Jogy George, Investigator	JG		DATE ISSUED 04/16/2019
	Zhao Wang, FDA Center Employ	ee w		7
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			sponses@fda.hh		3005	029956	
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Ind	ustry Informatio	n: www.fda.gov/oc/indu	ustry				
		Majarnis, Vice	President (Work				
2000	NAME			STREET ADDRESS	9 1919		can and a said as
	rrent Phan STATE, ZIP CODE, COU	maceuticals Li	mited	Ahmedaba Type establishm		nsana Highway,	Taluka-Kadi
		rat 382721, In	dia	Finished	Pro	duct Manufactur al Ingredient 1	
prepcaus U.S repr (G) OOS initi	paration erro se is not scie distribution esents appro S Investigati ated on 09/2	r i.e. some powder intifically proven read with an expiry date oximately (b) additional oximately (c) additional interpretation IN/F/FP/17/30	r loss while transfer nor substantiated in the of (b) (4) onal batches release 09 for (b) (4) Dissolution failure	Batch (b)  Tablets, Uss. No root of	yolunigation (4) S. ma	metric flask'. This n report. This bat is an annual rket.  mg, for batch	red due to sample spresumptive root ch was released to stability batch that  (b) (4) was Phase I or Phase II
inve	stigations. 1	Data obtained are	summarized below	¥.			* *
	Tablet No.	S <sub>1</sub> Results	S <sub>2</sub> Results	Additional Set -I	Test	Additional Test Set-II	Additional Test Set-III
	1	(b) (4)					
	2						
	3						
_		_					
	4	_					
	5						
	6						
	Remarks	Avg: 88 Min: (b) Max: (4)	Avg: 77 Min: (b) Max: (4)		(S Avg Min Max	: 86 (b)	(Set I + II + III) Avg: 92 Min: (b) Max: (4)
٨	S <sub>1</sub> (6 units)	Each unit NLT Q+5%					
USP <711>	S <sub>2</sub>		nits is ≥ Q, and no				
P	(12 units)		han Q – 15%				
NS)	S <sub>3</sub>		ge of 24 Units is ≥ Q,		nit < Q	- 15%,	
160	(24 units)		and no unit i	s < Q - 25%	_		
	REVERSE THIS PAGE	EMPLOYEE(S) SIGNATURE Lata Mathew, Jogy George, Zhao Wang, FD	Investigator	JG vee ZW			DATE ISSUED 04/16/2019
FORM F	DA 483 (09/08)	PREVIOUS EDITION OBSC	DLETE INSP	ECTIONAL OB	SERVA	TIONS	PAGE 5 OF 17 PAGES

	DEPARTMENT OF HEALTH FOOD AND DRUG A			
DISTRICT ADDRESS AND PHO			DATE(S) OF INSPECTION	
	T-10000		04/08/2019-04/16/201 FEI NUMBER	.9 *
ORA OPQO HQ,			PEI NUMBER	
	wn Drive, Rockville, MD 20857	~~~	3005029956	
ORAPHARMINTE	rnational483responses@fda.hhs	•gov	*	
Industry Informatio	n: www.fda.gov/oc/industry		4	
NAME AND TITLE OF INDIVIDU	n: www.fda.gov/oc/industry JAL TO WHOM REPORT ISSUED			9,
Mr. Ashish H	ajarnis, Vice President (Works	s)		
FIRM NAME		STREET ADDRESS		
Torrent Phar	maceuticals Limited	Ahmedaba	d Mehsana Highway, Ta	luka-Kadi
CITY, STATE, ZIP CODE, COU	250,00	TYPE ESTABLISHME		
Indrad, Guja	rat 382721, India		Product Manufacturer utical Ingredient Man	
Product Spec:	NLT(b) 6 (Q) in 45 minutes. It m	nust conform	to USP general chapter <711	l> criteria
Reported     Ignored r  This deficient pr the Certificate of	n's written procedure GTP/USP/022	(b) % (i.e. f	from re-tested 18 units)  le (i.e., (b) %) from not be tion with an expiry date o	f <sup>(D) (4)</sup> In
(H)	on Number OOS/IN/F/ST/17/364 fo	or (b) (4)	tablets	(b) mg, batch
number (b) (4) the failing Disso limit of (b) % to (initial results we	(blister packaging 40°C/75%RH, lution result of tablet-3 at the 10-hour b) % release. No laboratory error ware invalidated without a valid assigned as the result of record. Batch # (b) (c)	2-month sar time point as identified hable root of	mple), was initiated on 09, tof (b), drug lease against during the investigation.	/20/17 to probe a specification . However, the analysis (n=18
(b) (4) was	on Number OOS/IN/F/FP/17/295 for initiated on 09/15/17 to probe the fai g release against a specification limit	ling Dissol	tablets (b) mg, ution result of tablet-1 at to (b) /6, at the 12-hour time	the 6-hour time
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE  Lata Mathew, Investigator  Jogy George, Investigator  Zhao Wang, FDA Center Employe	JG		DATE ISSUED 04/16/2019
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FORM FDA 483 (09/08)

PREVIOUS EDITION OBSOLETE

		ENT OF HEALTH AND HUN FOOD AND DRUG ADMINISTRA				
DISTRICT ADDRESS AND PHO		FOOD AND DROG ADMINISTRA	DATE(S) OF INSPECTION			
OPA OPOG NO	Doom #2022		04/08/2019-04/ FEI NUMBER	16/2019 *		
ORA OPQO HQ,	wn Drive, Rockville	MD 20857	A. C.			
	rnational483respons		3005029956			
oran manufacture						
Industry Information	n: www.fda.gov/oc/industry			9		
Mr. Ashish H	ajarnis, Vice Presi	dent (Works)				
FIRM NAME		STREET ADDRE	ESS			
Torrent Phar	maceuticals Limited		oad Mehsana Highw	ay, Taluka-Kadi		
Indrad, Guja	rat 382721, India		ed Product Manufa ceutical Ingredie			
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) mg, for batch (b) (4)  was manufactured as an Exhibit batch support of (b) (4) filing #s (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:			*			
	sults (not reported)	agire water		AF DE SE SE		
Tablet No.	3 hrs (%)	6 hrs (%)	12 hrs (%)	24 hrs (%)		
1	(b) (4)					
2						
3						
4						
5						
6				200.0		
Ave	Avg: 26	Avg: 51	Avg: 70	Avg: 81		
(Min-Max)	Min: (b)	Min: (b)	Min: (b)	Min: (b)		
	Max: (4)	Max: (4)	(b) (d)	Max: (4)		
Limit	3 hrs (b)	(4) 6; 6 hrs (b) (4) 6; 12	2 hrs (6) (4) 6; 24 hrs N	LT(4) 6		
SEE REVERSE OF THIS PAGE	EMPLOYEE(s) SIGNATURE  Lata Mathew, Invest  Jogy George, Invest  Zhao Wang, FDA Cent	tigator JG	/	DATE ISSUED 04/16/2019		
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	wn Drive, Rockville					
	rnational483respons		3005029956			
Industry Informatio	n: www.fda.gov/oc/industry					
Mr. Ashish H	ajarnis, Vice Presi	dent (Works)				
FIRM NAME		STREET ADD				
Torrent Phar	maceuticals Limited		abad Mehsana Highv	vay, Taluka-Kadi		
	rat 382721, India		hed Product Manufa	acturer & Active		
		Pharm	aceutical Ingredie	ent Manufacturer		
L2 stage sample	e testing (reported)					
Tablet No.	3 hrs (%)	6 hrs (%)	12 hrs (%)	24 hrs (%)		
7	(b) (4)	0 1113 (70)	12 1113 (70)	24 1113 (70)		
8						
9						
10						
11	_					
12						
Ave (Min-Max)	23% ((b) (4)	54% ((b) (4)	75% ( <sup>(b) (4)</sup>	83% ((b) (4)		
Limit	3 hrs (b	(4) %; 6 hrs (b) (4) %;	12 hrs <sup>(b)</sup> (4) %; 24 hrs 1	NLT(b %		
				)		
The firm invalid	ated L1 stage results an	d stated that L2 sta	ge results shall be co	nsidered for reference		
purpose only.	and an angel and an		8			
purpose only.						
Then the firm re	analyzed two new sets	of dissolution samp	oles (total of 12 tablet	s), SET-1 and SET-2.		
	sample failed again in					
	ormed another 6 samples	-				
The state of the s	age of 18 tablets (i.e., o					
are summarized		3		•		
			4.4			
SET-1 L1 stage	(not reported)					
Tablet No.	3 hrs (%)	6 hrs (%)	12 hrs (%)	24 hrs (%)		
1	(b) (4)					
2						
3						
				2		
				-		
				DATE VICINE		
SEE REVERSE	EMPLOYEE(S) SIGNATURE  Lata Mathew, Invest	igator		04/16/2019		
OF THIS PAGE	Jogy George, Invest					
	me mi			* 1 × 3		
	Zhao Wang, FDA Cent	er Employee	V			
FORM FDA 483 (09/08)	PREVIOUS EDITION OBSOLETE	INSPECTIONAL	OBSERVATIONS	PAGE 8 OF 17 PAGES		

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DISTRICT ADDRESS AND PHON		1000		DATE(S) OF INSPECTION 04/08/2019-04/	16/2010 *
ORA OPQO HQ,	Room #2032			04/08/2019-04/	16/2019 ~
12420 Parklaw	wn Drive, Rockville			3005029956	
ORAPHARMInter	rnational483respons	es@fda.hns	.gov	00000	
Industry Information	n: www.fda.gov/oc/industry				
No. of the Control of	ајаrnis, Vice Presio	dent (Work	·e1		
FIRM NAME	IJainis, vice in	dente (	STREET ADDRE	ESS	
Torrent Pharm	maceuticals Limited	į.		bad Mehsana Highwa	ay, Taluka-Kadi
	rat 382721, India	.e	Finish	ed Product Manufac ceutical Ingredie	
N. J.	(b) (4)				
4	(D) (4)				
5					
6					
Ave (Min-Max)	23% <sup>(b) (4)</sup>	51% (b)	(4)	72% (b) (4)	78% <sup>(b) (4)</sup>
Limit	3 hrs (b	) (4) %; 6 hrs	b) (4) / <sub>0</sub> ;	12 hrs <sup>(b) (4)</sup> %; 24 hrs N	NLT(b %
SET-1 L2 stage (	- T:			H .	
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		) (4) %: 6 hrs(	b) (4) 6; 1	12 hrs <sup>(b) (4)</sup> 6; 24 hrs N	л.т <b>(b</b> %
			147	2 1110	)
SET-2 results (re	eported)		4		
Tablet No.	3 hrs	6 hrs	S	12 hrs	24 hrs
1	(b) (4)				
2					
3					
4					
5					
				*	
	EMPLOYEE(S) SIGNATURE	,	on		DATE ISSUED
SEE REVERSE	Lata Mathew, Invest	tigator			04/16/2019
OF THIS PAGE	Jogy George, Invest	tigator	JG		
	Zhao Wang, FDA Cent	ter Employ	ee Zw	/	4 4 16
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INSPECTIONAL OBSERVATIONS

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	DEPARTMENT OF HEA	ALTH AND HUMA RUG ADMINISTRATION		
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ORA OPQO HQ,	Room #2032		04/08/2019-04/16/20 FEI NUMBER	19 *
	wn Drive, Rockville, MD 208	357	200500005	
ORAPHARMInte	rnational483responses@fda.h	nhs.gov	3005029956	
Industry Information	n: www.fda.gov/oc/industry		*	
	ajarnis, Vice President (Wo	orks)		
FIRM NAME	.,,	STREET ADDRESS		
Torrent Pharm	maceuticals Limited	Ahmedaba	d Mehsana Highway, T	aluka-Kadi
CITY, STATE, ZIP CODE, COUN		TYPE ESTABLISHM		
Indrad, Guja	rat 382721, India		l Product Manufacture eutical Ingredient Ma	
6	(b) (4)			
Ave	26% <sup>(b) (4)</sup> 54% <sup>(c)</sup>	(b) (4)	75% <sup>(b) (4)</sup>	2% <sup>(b)</sup> (4)
(Min-Max)	2076		1370	270
Mean of reanalys	sis 22% 54%		74%	1%
18 tablets		(b) (d)		
Limit	3 hrs (b) (4) %; 6 h	ors (b) (4) 6; 12	hrs <sup>(b) (4)</sup> %; 24 hrs NLT <sup>(b)</sup>	%
for batch number follows:	n Number OOS/IN/F/FP/17/304 (b) (4), was initiated on 09			result as  Mean RSD% 106.0 1.23
Specification	Mean: NLT	b) % and NMT (b	) % of Label Claim,	Maria de la companya del companya de la companya de la companya del companya de la companya de l
			(b) %, RSD NMT(b)%	
(4) for Hypothesi found, and no ma were invalidated	were confirmed during preliminals testing (during Phase I) is not nufacturing error was identified based on reserve sample testing an expiry date of (b) (4)	detailed in th during Phase	e investigation report. No	al OOS results
	V			
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Mr. Ashish H	Hajarnis	s, Vice Pr	resident (W	orks)				
FIRM NAME				STREET ADDR	RESS			
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					cess controls de			
drug products	have the	e identity,	strength, qua	ality, and p	urity they purpo	ort or are r	epresented to	
possess.								
-								
Specifically,								
~p~~~~,								
Review of Proc	ecc Valid	dation (PV)	documents r	evealed tha	t PV batches that	t failed prov	ness validation	
					acceptable and co	ounted towa		
manufacturing p							Tablets USP	
(b) mg, and (b) (4					ifying an alternate	e API code	(# (b) (4) ) is	
deficient. All pro	ocess val	idation bate	hes were reje	ected as sum	marized below:			
		T						
Strength		Total	PV batches	Total O	OS investigations		Batch Disposition	
(b) mg			4		6		rejected	
(b) mg			3		3	All r	rejected	
			1.7					
(A)		) (4)						
Process Validat	ion for (t	0) (4)	Tab	olets USP (b	mg			
The following O	OS inves	stigations w	ere initiated of	during testin	g of process valid	lation batch	es:	
OOS No.		Date of	Batch #	PV	Test Results		Specification	
		Initiation		Number				
OOS/IN/F/FP/16/2		9/29/16	(b) (4)	1	$F_2 = (b)$	F <sub>2</sub> N	VLT(b) 4)_(b) (4) ½	
OOS/IN/F/FP/16/1	137	7/23/16		1	Assay = (b) $\%$			
				1	(b) * (min) = (b) %	,	- %	
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ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov			FEI NUMBER 3005029956				
Industry Informatio	Industry Information: www.fda.gov/oc/industry  NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED						
Mr. Ashish H	Mr. Ashish Hajarnis, Vice President (Works)						
Torrent Pharmaceuticals Limited Ahmedabad Mehsana Highway, Taluka-Kad					y, Taluka-Kadi		
Indrad, Guja		721, Indi	a	Finished Product Manufacturer & Active Pharmaceutical Ingredient Manufacturer			
OOS/IN/F/FP/16/	263	10/4/16	(b) (4)	1	(b) = (b) %	NMT(b) 6	
				-	(4) –(1)	(b) (4)	
Due to the failure batch failed for h					the validation campa	ign. However, the 4 <sup>th</sup>	
OOS No.		Date of Initiation	Batch #	PV Number	Test Results	F <sub>2</sub> Specification	
OOS/IN/F/FP/17/		4/10/17	(b) (4)	4	$F_2 = (b)$	F <sub>2</sub> NLT (b)	
OOS/IN/F/FP/17/	143	4/10/17		4	$F_2 = (4)$	F <sub>2</sub> NLT (4)	
successful proce Despite the PV	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) mg							
The process validation initiated to qualify an alternate API supplier (# (b) (4) ) for (b) (4)  Tablets USP (b) 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) 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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12420 Parklawn Drive, Rockville, MD 2089 ORAPHARMInternational483responses@fda.hh	3005079956	
Industry Information: www.fda.gov/oc/industry NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED		
Mr. Ashish Hajarnis, Vice President (Wor		
FIRM NAME	STREET ADDRESS	
Torrent Pharmaceuticals Limited	Ahmedabad Mehsana Highway, Taluka-Kadi	
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED	
Indrad, Gujarat 382721, India	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) mg and (c) mg batches manufactured and released to U.S. market with alternate API code (b) (4) is as follows.

	Product	Batch status	Count
		Hold	3
(b) (4) Tab, USP (b) m	Tab, USP (b) mg	Rejected	5
	IX	Released	(b) (4)
(b) (4)	1	Hold	4
	Tab, USP (b mg	Rejected	(5) (4)
		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 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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	arat 382721, India		Finished	d Product Manufacturer & Active eutical Ingredient Manufacturer		
impacted batch (BFR5D002) tailed 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	Wt. of (b) (4)	% Active	Sample	Batch Size
		(mg)	Tablets (mg)		Quantity	
	autoto	(b) (4)			(b) grams	(b) (4)
(b) (4)	and (b) (4) Tablets, USP			-	grams	+
(b) (4)	and (b) (4) Tablets, USP				grams	+
(b) (4) Tableto	Tablets				grams	
(b) (4) Tablets (b) (4)	Tablets				grams grams	+-
					<u> </u>	
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Industry Informatio	on: www.fda.gov/oc/industry			
NAME AND TITLE OF INDIVID	on: www.fda.gov/oc/industry ual to whom report issued			
Mr. Ashish H	Hajarnis, Vice President (Work	s)		
FIRM NAME		STREET ADDRESS		
	maceuticals Limited		d Mehsana Highway, Ta	luka-Kadi
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Indrad, Guja	rat 382721, India	The production of the Authority	Product Manufacturer utical Ingredient Man	
	ON 3  ation of automatic and electronic ended to assure proper performance.		s not performed accordi	ng to a written
-1,	*			
is proposed for to (b) (4) # (b) (4) following issues  Per equipment (b) the (b) (4) USB general manager equipment (b) -0 required calibrate 2019. Additional confirmed that the on the machine. Ilmits. A service vision inspection several false rejuited to the machine.	the commercial manufacturing of (b) and (b) (4)  were observed during the inspection (c) 03 maintenance manual, the requirement of Engineering department provided (c) 3 with Certificate number TPL/T/0 ion items. The last calibration provided (c) the production operators purposely do not know how to set up the vision system ensures that the (b) engineer representative also confirm a system. Consequently, during the ects were found in the reject chute	ted calibratical for the ced the current 196/01/19. The ced by the equivalent of the ced that he (b) (4) associated	and (b) mg) for (b) (4)  con includes the (b) (4) quality of the tablet (b) (4) ent equipment calibration This certificate did not in uipment manufacturer exp ed on the operational asp settings for the vision insublets conform to in-process is unaware of how to corr process demonstration with the vision check c	and process. The certificate for include the two prects of (b) -03 pection system as specification ectly setup the in on 04/12/19,
	providing no assurance of the optimu			
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12420 Parklawn Drive, Rockville, MD 2 ORAPHARMInternational483responses@fda	3005029956		
Industry Information: www.fda.gov/oc/industry	* * * *		
Mr. Ashish Hajarnis, Vice President (	Works)		
FIRM NAME STREET ADDRE		ESS	
Torrent Pharmaceuticals Limited Ahmeda		Ahmedabad Mehsana Highway, Taluka-Kadi	
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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: 1/6

Note: Specification is NLT (b) % 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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Industry Information: www.fda.gov/oc/industry NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED				
Mr. Ashish Hajarnis, Vice President (W	orks)			
FIRM NAME	STREET ADDRE	SS		
Torrent Pharmaceuticals Limited	Ahmedak	bad Mehsana Highway, Taluka-Kadi		
CITY, STATE, ZIP CODE, COUNTRY		HMENT INSPECTED		
Indrad, Gujarat 382721, India	Finishe	ed Product Manufacturer & Active		
STATE OF THE PROPERTY OF THE P	Pharmac	aceutical Ingredient Manufacturer		
Passing results from initial sequence for other large reported without a valid justification. No consideresults when a definitive root cause is not identified.	deration was			
*DATES OF INSPECTION 4/8/2019(Mon), 4/9/2019(Tue), 4/10/2019(Wed), 4/11/2019(Tue).	019(Thu), 4/12	/2019(Fri), 4/13/2019(Sat), 4/15/2018(Mon), and		
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