DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
555 Winderly Place, Suite 200 Maitland, FL 32751 (407)475-4700 Fax:(407)475-4768	3/14/2016-3/25/2016* FEI NUMBER 1811396

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Dina Kostakis , General Manager

FIRM NAME	STREET ADDRESS
Catalent Pharma Solutions, LLC	2725 Scherer Dr N
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Saint Petersburg, FL 33716-1016	Drug 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

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,

A. Investigation PR 440585 opened on 2/11/14 to investigate the presence of foreign dark matter in a gel receiver was not adequate for the following reasons:

a) The foreign dark matter was not identified but was described as dark particles coming down from the (b)(4) shaft. The work order showed the replacement of the shaft seal of the (b)(4) ; however, the investigation did not extend to other batches (b)(4) with the same (b)(4) prior to detecting the leak on 1/30/14.

b) The investigation did not extend to the previous seal change for this (b)(4) which had occurred two (2) days earlier on 1/28/14. An interview with the mechanic during the FDA inspection revealed that the (b)(4) had leaked all of its lubricant ((b)(4)) due to a broken seal; the seal was replaced on 1/28/14 but a manufacturing investigation was not opened to assess the impact of this lubricant on the quality of the gel batches previously (b)(4) with this (b)(4) .

c) A total of (b)(4) sub-batches of gel mass were (b)(4) with this (b)(4) between 1/28/14 and 1/30/14 when it was observed leaking again. The impact to the quality of these batches was not accessed.

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d) SOP OTS-QA-0038 "Investigations" was not followed in that the investigation was opened eleven (11) days later and not within (b)(4) of the incident.

B. The investigations for Valproic Acid Capsules, USP 250 mg (detailed in PR #s 408449, 414181, 478203, 488400, 500065, 513500) are deficient in that a detailed root cause analysis has not been conducted to determine the potential root cause of the multiple complaints received for blue spots on the finished capsules. Since 2013, a total of six (6) complaints were received by your firm for released commercial bulk lots 1291888, 1391388, 1391390, and 1460931. Our review of the associated investigations revealed that you have not documented detailed assessment of potential root causes that include, but not limited to; (a) potential impact of chipped and worn-out areas with blue paint on the encapsulation machines that are in close proximity to the product-contact surface areas, b) potential impact of the use of blue (b)(4) gloves and other gloves that are routinely used by the operators during routine manufacturing, etc. In addition, finished product retains representing the (b)(4) of the packaging run were evaluated as part of the investigation for lot # 1291888. Evaluation of the retain samples representing the (b)(4) of the packaging runs (for the same lot) were not conducted before they were discarded (approximately 1 year after the finished product expiry date). In the absence of a documented and detailed root cause analysis, your common conclusion on all the investigations that the issue is not related to manufacturing operations at your firm is unsubstantiated and potentially incomplete.

C. Investigation PR# 441713 was generated on 2/9/2014, when temperature of (b)(4) refrigerator, (b)(4) was found to be out of acceptable operating range. Your firm issued a work order# 1457847 to investigate and repair the refrigerator. Review of temperature data recorder indicated that refrigerator (b)(4) was repaired and started working on 3/25/2014. As part of this investigation, your firm failed to:

a. Identify what material or products were stored in the refrigerator when incident happened.
b. Identify the equipment (refrigerator) where impacted materials/product were moved from affected refrigerator.
c. Assess any damage to the materials/products stores in affected refrigerator.

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OBSERVATION 2

An NDA-Field Alert Report was not submitted within (b)(4) of receipt of information concerning significant chemical, physical, or other change or deterioration in a distributed drug product.

Specifically, since 2013 your firm has received six (6) product complaints associated with foreign material for marketed batches of Valproic Acid Capsules, USP 250 mg (product number 10258780).

a) An NDA-Field Alert was submitted for ONLY two (2) out of the six (6) complaints received as detailed below:

Date Received	Lot Number	Complaint	Field Alert Status
6/20/2013	1291888	Blue Spots on Capsules	Initial Field Alert submitted on 08/05/2013
7/31/2013	1291888	Blue Spots on Capsules (2nd compliant for the same lot)	
10/31/2014	1391388	Blue Spots on Capsules	Field Alert not submitted
01/16/2015	1391390	Blue Spots on Capsules	Field Alert not submitted
04/06/2015	Unknown	Capsules with Speckling Blue dye	Field Alert not submitted
08/21/2015	1460931	Blue Spots on Capsules	Field Alert not submitted

b) The initial Field Alert for the complaint associated with lot number 1291888 was not submitted within (b)(4) of receipt of information. Specifically, the 1st complaint was received on 06/20/2013, and the initial Field Alert was not submitted until after the 2nd complaint was received for the same lot on 7/31/2013.

c) You have not established written procedures to identify and describe the roles and responsibilities

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for submitting Field Alerts to the FDA.

OBSERVATION 3

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically, your firm failed to adequately validate the (b)(4) In addition, there is no traceability of these incidents as the audit trail of the (b)(4) does not record in-process check results which were automatically captured but not acknowledged by the operator.

For example, during the end of the encapsulation run of Targretin softgel capsules, lot 1583104, the fill and seal thickness in-process checks taken on 3/21/16 at 2014 hrs. were inadvertently lost due to errors by the operator and his supervisor. A review of the audit trail showed no evidence of in-process checks performed at that time.

OBSERVATION 4

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.

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Specifically, your Site Validation Master Plan (Document No. V-133A.15, Effective: 07/02/15) states that (b)(4) and evaluation therein serves as a method for Continuous Process Verification. The content of your current (b)(4)s was found to be deficient in that it only trends and compares critical quality attributes (mainly Assay data) during two consecutive review periods. The (b)(4) does not take into account any potential process drifts that may have occurred since the original validated status of the product. For example, during the inspection we discovered a potential trend in the Assay results for Lubiprostone, 24 mcg Capsules (product number: 10258848) in approximately 99 commercially released batches since 2008. Additionally, a potentially more significant trend in the Assay results was discovered during review of the Assay Data for Lubiprostone, 8mcg Capsules (product number: 10258838) in approximately 45 commercially released batches since 2007. The trends that we discovered during the inspection were previously unknown to the firm. Trending Assay values as part of Continuous Process Verification may potentially serve as critical tool for gleaning additional process understanding for products such as Lubiprostone. This product exhibits therapeutic effect at microgram levels of the Active Pharmaceutical Ingredient (API) in the dosage form.

OBSERVATION 5

Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

A. Your current Cleaning Validation program is deficient in that the current Clean Equipment Hold Time (detailed in Document ID: V-175A.01, Approved 07/24/2013) is not substantiated by holding the equipment in a "clean" status for the established period of study ((b)(4)). For example, your encapsulation stations were not held in a "clean" status to establish the clean hold time of (b)(4). Instead, the clean hold time studies are based on review of historical environmental monitoring data. This approach does not take into account the continued cleanliness of individual equipment and equipment surfaces that are at higher risk for potential

microbial proliferation during the holding period. During the environmental monitoring period between January 2010 and March 2013, there were four (4) recorded events during which the microbial levels exceeded the action levels and a definitive root cause for the excursions was not identified. Additional commercial production equipment that utilized environmental monitoring to establish the Clean Equipment Hold Time study include, but not limited to: (b)(4) .

B. During the inspection on 3/24/16 of the (b)(4) equipment ID (b)(4), which was tagged as "Clean" and intended for the preparation of the (b)(4) softgel capsules it was observed that white powder residue remained around the edge of the (b)(4) hole after it was (b)(4) cleaned. According to SOP OTS-GEL-0047 "Operation/Cleaning (b)(4) version 1.0, a visual inspection is required through the sight glass to confirm the equipment is clean; however, this residue could only be observed if the (b)(4) cover is opened.

OBSERVATION 6

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically,

a) Your quality unit failed to follow SOP OTS-GM-0029 "Production Master Records- Production Events Log" in that production events/deviations reported by email or phone to QA by the (b)(4) production shifts were not adequately tracked, documented, and investigated to determine the root cause and take appropriate corrective and preventive action.

b) Your firm lacks written procedures for the segregation of in-process material when a deviation occurs or the material requires further evaluation.

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c) Section 6.3.3 of SOP OTS-QC-0034 for lab investigation requires opening investigation within (b)(4) when lab becomes aware of the OOS results. Investigation PR# 434491 was initiated on 12/30/2013 in response to Palonosetron HCl out of specification assay results. The Quality Control Unit became aware of OOS results on 12/19/2013 but the investigation was not initiated until 12/30/13 (11 days later).

d) Extension requests for investigations that are not completed within due dates are not justified in the (b)(4) system. More specifically investigation PR# 469043 was created on 8/29/2014 and was closed after 322 days on 7/17/2015. Another investigation, PR# 455373, was created on 5/22/2014 and closed after 321 days on 4/8/2015. Current version 5.0 of SOP OTS-QA-0005, (b)(4) Task System, Effective: 10/14/2015 does not require any justification for granting extension for investigations.

OBSERVATION 7

Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance.

Specifically, during the walk-thru inspection of the East Wing Encapsulation Area on 3/21/16 around 4:00 p.m., it was observed that the softgel encapsulation machine in Station (b)(4) was partially disassembled and was tagged with "Repair in progress" and Work Order # 3012261 dated 3/21/16 which stated "pump failure, gears do not engage." An interview with production personnel revealed that (b)(4), was being encapsulated when the operator heard a loud noise coming from the equipment. The encapsulator was stopped at 9:54 a.m. and the few capsules remaining on the conveyor belt were rejected. The filled capsules continued with processing even though in-process checks for fill weights had not been performed for an hour since 8:42 a.m. The encapsulation machine was partially disassembled, the gel mass and fill materials were disconnected and held, but the incident was not documented in the Production Event Log within the electronic batch record when it occurred and QA was not notified as required by SOP OTS-GM-0029 "Production Master Records-Production Events Log" when equipment malfunction or breakdown occurs. Production supervisors had stated during the walk-thru that QA notification was not required; therefore, it is unknown how many

incidents of equipment malfunction/breakdown have occurred during production that have not been notified to QA for further evaluation of product impact.

OBSERVATION 8

Component weighing operations are not adequately supervised.

Specifically, adequate controls for weight verification of components were not in place between 8/15/14 and 10/20/14 when a glitch was found in the (b)(4) system that interfaces with the scales and the (b)(4) display unit which resulted in weight discrepancies upon taring. According to investigation PR 465555 opened on 8/1/14 to investigate OOS results for (b)(4) for (b)(4) lots, the root cause was identified as weight discrepancies caused by connectivity issues between the systems. As an interim corrective action, your quality unit implemented a "Production Event Advisory" on 8/15/14 to add additional steps for weight verification by a supervisor who had to initial and date every weight performed on Scale (b)(4) /Room (b)(4). However, as the verification was reportedly documented on the label of each raw material which was discarded upon dispensing, your firm lacked documentation to demonstrate that every component weighed on the affected scale was verified for accuracy. The (b)(4) system was not modified and qualified until 10/20/14 to incorporate acknowledgment codes to verify scale connectivity and accuracy of weights.

OBSERVATION 9

The control systems necessary to prevent contamination or mix-ups are deficient.

Specifically, on 3/24/16 a stack of unidentified trays containing yellow softgel capsules were observed inside drying tunnel (b)(4) in suite (b)(4). This material was not logged in the (b)(4) Clearance and Usage Log for Tunnel ID (b)(4)

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Employees are not given training in the particular operations they perform as part of their function.

Specifically, upon interview of operators in the warehouse and production areas it was found that they lacked training on how to access the electronic SOPs in Documentum and therefore we not routinely referring to them for the performance of their duties. Deviations from written procedures were observed during the inspection.

OBSERVATION 11

Laboratory controls do not include the establishment of scientifically sound and appropriate standards and test procedures designed to assure that components , in-process materials and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically, the identification test by (b)(4), performed as part of the release testing of (b)(4) active pharmaceutical ingredients (API) (i.e. (b)(4) is not appropriately performed. As part of the test, the (b)(4) The reference standard (b)(4) are not generated concomitantly and under the same conditions as the tested samples. In addition, there are no procedures for limiting the number of samples tested concurrently resulting in several (b)(4) printed on the same graph making it difficult to determine differences in the (b)(4) profile.

OBSERVATION 12

Procedures describing the calibration of instruments, apparatus, gauges and recording devices are deficiently written or followed.

Specifically,

A. Your firm did not perform all the required tests to qualify high performance liquid chromatography (HPLC) system ID: (b)(4) in Sep 2015 as per the vendor requirements and

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specifications. More specifically, the following studies were not performed as part of qualification of (b)(4):

No	Test Name	Set Points and Parameters	Limits
1	(b)(4)	Injection Vol. Column: (b)(4)	Height RSD: (b)(4) Area RSD: (b)(4)
2		Injection Vol. on Column= (b)(4) (b)(4)	Height Carry (b)(4) % Area Carry (b)(4)
3		(b)(4)	Accuracy: (b)(4)

On 3/23/2016, your Analytical R&D Group Leader stated that these studies were covered under other studies but there were no such comments, justification or explanation documented in equipment qualification report for this particular equipment.

B. More specifically your QC and micro labs use (b)(4) micro pipettes to prepare various solutions of samples, standards, and reagents. These solutions are used to access the quality of drug product as if it meets the specifications for commercial release. During inspection we reviewed calibration reports of following pipettes:

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No	Pipette Name	Serial No	Range	Cal Due
(b)(4)				

During our review, we discovered that micropipettes are shipped for calibration to a vendor in (b)(4). Vendor performs calibration and ships back these pipettes with "As Returned" data without performing any "As Received" studies. Lab management stated that micropipettes are calibrated on (b)(4) basis and lab does not perform any verification checks between the uses during (b)(4) of use. There is no documented evidence that these pipettes were working as intended when they were originally received by vendor for calibration.

OBSERVATION 13

Established test procedures and laboratory control mechanisms are not followed and documented at the time of performance.

Specifically,

A. Your SOP QTS-QC-0049, Version: 12.0, Effective Date: 1/28/15, section 6.1.1 states "Each refrigerator/freezer's reading will be recorded (b)(4) and

AMENDMENT 1

documented in the front temperature log section of the OTS-QC-0049-F01". However, the following tasks performed in QC Lab do not comply with this SOP:

1) Review of temperature data within the last four (4) months showed measurements were not taken on the following 13 days: 3/4/16, 3/10/16, 2/5/16, 1/3/16, 1/4/16, 1/12/16, 12/16/15, 12/17/15, 12/18/15, 12/20/15, 12/23/15, 12/24/15, 12/28/15.

2) Heavy frost was observed in the freezer that is used to store reference standards. As per procedure OTS-QC-0049 (b)(4) .

B. Many entries were not made on "Performed By" column on logbook of stability chamber, ID: SM1001 that is used to store products at room temperature. More specifically, on 11/24/15, and 3/2/16 stability samples for lot# (b)(4) , and (b)(4) were pulled and no record was entered as to who pulled the samples.

C. A review of the raw data for Palonosetron HCl in-process assay (for fill material lot# (b)(4) and FP lot# 125353) in notebook# 8624, page# 19, project# 1459 revealed that the preparation of the (b)(4) that was used to run the analysis was not documented on the notebook. Analyst performed this test on 10/29/2015 and data was reviewed on 11/02/2015. In this particular case, the analyst failed to document (b)(4) information and the reviewer failed to detect the missing information.

OBSERVATION 14

Written procedures have not been developed for the receipt and evaluation of post marketing adverse drug experiences.

Specifically, during the inspection, your firm provided a Quality Call Handling worksheet that outlines the handling of telephone calls involving potential Adverse Events for the products owned by Catalent.

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This document is deficient in that it is: (a) not a controlled document, (b) there is no review or approval information on this document to indicate that it is formally reviewed and approved by your quality unit and other groups that are responsible for collection and evaluation of potential Adverse Events, and (c) there is no documentation to indicate that the personnel involved in the receipt and evaluation of the adverse events are trained on this procedure.

***DATES OF INSPECTION**

3/14/2016(Mon),3/15/2016(Tue),3/16/2016(Wed),3/17/2016(Thu),3/18/2016(Fri),3/21/2016(Mon),3/22/2016(Tue),3/23/2016(Wed),3/24/2016(Thu),3/25/2016(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."