DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration - New Jersey District, 10 Waterview Blvd, 3rd Floor, Parsippany, NJ 07054 973-331-4900 Industry Information: www.fda.gov/oc/industry	07/27/2020-08/21/2020* FEI NUMBER 3002889358

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Nellie D. Clark Eliza, VP Site Head of Manufacturing

FIRM NAME	STREET ADDRESS
ImClone Systems, L.L.C.	33 ImClone Drive
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Branchburg, NJ 08876-3904	Biological Drug Substance 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:

QUALITY SYSTEM

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,

Incidents that occur during GMP activities that may have impact on the quality of products are classified as either "Observation" or "Deviation" in the (b) (4) system (SOP# QAS-NC-0001). While an "Observation" does not require investigation, a "Deviation" requires investigation to find the root cause and potential corrective actions are taken. Below are instances where the firm failed to conduct a detailed investigation when serious GMP violations occurred in the production area. Instead, the firm recorded these occurrences as an "Observation" and closed the incident without documenting all the investigation details, the root causes surrounding the issue and implementing CAPAs. In other instances, we observed that the firm's "Deviation" investigations are deficient in finding root causes that are supported by scientifically sound evidence.

For example,

A. TR# (b) (6), (b) (7)(C): An "Observation" titled, " (b) (4); Batch Discarded" in (b) (4) was opened on 5/27/2020 and closed on 5/28/2020. This Observation documented very limited information and did not provide any investigative details. However, upon further inquiry during this inspection, the firm's Vice President, Manufacturing stated that the firm conducted an investigation and identified potential data (b) (6), (b) (7)(C). However, no such details were provided in the closed (b) (4) document. He also stated that the

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	Tamil Arasu, Investigator Ko Min, Investigator	08/21/2020

personnel involved in these GMP violations are no longer employed with the firm due to the firm's investigative findings and the severity of the issue. This (b) (4) record was not elevated as a "Deviation" despite the firm's Deviation Management procedure, QAS-NC-0001, requiring classification as "Deviation" when there is a departure from quality standards like "controls in place to protect or assure product quality" and "GMP compliance requirements". The firm's rationale for not opening a Deviation investigation is documented in this (b) (4) Observation report as "This was an isolated occurrence". However, we found similar incidents, where incorrect materials or material lots were used by operators, second person verified and signed, and have been reported as an "Observation" and closed without further investigation:

1. TR# (b) (6), (b) (7)(C): This Observation record was opened approximately four months earlier on 1/20/2020 and closed on 1/21/2020 (Observation Title: "(b) (4) ; batch discarded").

2. TR# (b) (6), (b) (7)(C): This Observation record was opened approximately four months earlier on 1/24/2020 and closed on the same day (Observation Title: "(b) (4) ").

3. TR# (b) (6), (b) (7)(C): This Observation record was opened on 5/8/2020 and closed on 6/17/2020 (Observation Title: "(b) (4))").

It cannot be determined from the (b) (4) Observation write-up for the four TR#s mentioned above who the Operators are and if any corrective and preventive actions were put in place. (b) (4) are used during critical purification steps of drug substances for (b) (4) and (b) (4) of the columns and for formulation of drug substances.

B. TR# (b) (6), (b) (7)(C): A Deviation titled, "Atypical result (unexpected peaks) in (b) (4) profile for Galcanezumab Drug Substance" in (b) (4) was opened on 2/19/2019 and closed on 10/21/2019. On 2/13/2019, Galcanezumab drug substance, (LOT# D039975, Run# R2Y18R05S1) showed an unexpected increased peak area in the electropherogram when tested for (b) (4) by (b) (4)) Non-reduced method QCA-GN-0049 ((b) (4)). The analyst, without conducting an investigation, retested (b) (4)

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using a different sample on 2/28/2019 ((b) (4)) and invalidated the original result and the new data was released in LIMS. The product was released on 3/18/2019. However, on 3/25/2019, after identifying the missing root cause investigation, the firm added a hypothesis study with a rationale, "(b) (4) . This study was based upon the hypothesis that the root cause was a laboratory error if a retest of different sample gave a passing result. However, the investigation did not extend to find what caused a potential sample contamination and the source of the extra peak and prevent future recurrence. According to the firm's written procedure, QCA-GN-0001, "Investigations of Out of Specification and Atypical Test Results", a minimum of (b) (4) retest is required if a root cause cannot be identified.

C. TR# (b) (6), (b) (7)(C): This Deviation investigation was initiated after Out of Specification (OOS) results were obtained for (b) (4) from the swab samples taken during the (b) (4) Cleaning Monitoring of (b) (4) and (b) (4) on 11/01/2018. The root cause, identified in this Deviation Record for the OOS results for (b) (4), that cleaning of the (b) (4) with IPA prior to use, had no scientific justification. The tanks were cleaned using the validated cleaning cycle however, samples gave the following OOS results (specification: (b) (4) ppb):

(b) (4) Tank	Sample	(b) (4) Observed (ppb)
(b) (4)	B00099998002	(b) (4)
	B00099998004	
	B00099998007	
	B00100001002	
	B00100001007	

Due to an ongoing trend of (b) (4) OOS samples, the firm previously conducted a study on 10/26/2018 to identify the sampling process that may have caused the (b) (4) failures and reported that the IPA

cleaned sample (b) (4), which is used to carry the stoppered vials containing the swab back to the lab, contains (b) (4) results between (b) (4) ppb (b) (4) The firm proposed in TR# (b) (6), (b) (7)(C) that the IPA cleaned (b) (4) was the most probable root cause for this recent set of OOS results.

(b) (4) Study

(b) (4)

However, the OOS samples were observed between (b) (4) ppb above the specification of (b) (4) ppb. In addition, the Deviation Record and the (b) (4) study lack details and do not explain how the samples are prepared, what samples are filled in the (b) (4) vials for Test (b) (4) and the descriptions of the different modes of transport for Test (b) (4) Furthermore, when the Cleaning Monitoring was repeated on 11/16/2018, only the (b) (4) OOS areas were re-sampled (out of (b) (4) areas) yet the tanks were released and used in the subsequent processing and re-cleaned. These (b) (4) are used in support of US commercial product Galcanezumab, and Dulaglutide which is pending approval.

LABORATORY CONTROL SYSTEM

OBSERVATION 2

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug substances conform to appropriate standards of identity, strength, quality and purity.

Specifically,

The (b) (4) obtained for purity method by (b) (4)) are not consistently (b) (4) cannot be reproduced, and remain uncontrolled. The Quality Control Laboratory analysts routinely perform (b) (4) (b) (4) to process their (b) (4) methods for three commercial products, Galcanezumab, Necitumumab, and Ramucirumab. The (b) (4) techniques are used to (b) (4) , and/or (b) (4) at the analyst's discretion. However, there is no describes the requirements

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and conditions under which (b) (4) can be performed using (b) (4) to ensure consistency. Furthermore, the firm does not require analysts to justify for the need to perform (b) (4) The current practice is to apply the (b) (4)) and use (b) (4) to (b) (4).

For example, the purity method by(b) (4) for Galcanezumab, "Determination of Purity of (b) (4)), showed that the analyst reported (b) (4)peaks and utilized (b) (4) for the Sample, and reported (b) (4)peaks and utilized (b) (4) for the Reference Standard (b) (4) total Reference Standard injections). Every injection with the exception of the blank in the sequence run contained (b) (4) to (b)(4 (b) (4) peaks. However, review of (b) (4) indicated no justification for the (b) (4) of (b) (4) to (b)(4) out of a total of(b) (4) peaks. In addition, different (b) (4) are performed for each injection, yet the sequence run shows one processing method.

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*DATES OF INSPECTION

07/27/2020(Mon), 07/28/2020(Tue), 07/29/2020(Wed), 07/30/2020 (Thu), 08/03/2020(Mon), 08/07/2020(Fri), 08/10/2020(Mon), 08/11/2020(Tue), 08/13/2020(Thu), 08/19/2020(Wed) and 08/21/2020(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."