

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 555 Winderly Place, Suite 200 Maitland, FL 32751 (407) 475-4700 Fax: (407) 475-4768	DATE(S) OF INSPECTION 1/9/2017-1/20/2017*
	FEI NUMBER 2000027140

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Dr. Frederick D. Sancilio , President and CEO

FIRM NAME Sancilio & Company, Inc.	STREET ADDRESS 3874 Fiscal Ct Ste 200
CITY, STATE, ZIP CODE, COUNTRY Riviera Beach, FL 33404-1785	TYPE ESTABLISHMENT INSPECTED Prescription 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:

The following deficiencies pertain to the following (b) (4):

(b) (4) (b) (4) Inserts
(b) (4) (b) (4) capsules USP (b) (4)
(b) (4) (b) (4) capsules

LABORATORY CONTROL SYSTEM


OBSERVATION 1

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

Specifically, there was a lack of sufficient analytical method information to ensure proper identity, quality, purity, strength, and/or potency of the finished drug product, (b) (4) Inserts, before distribution for clinical studies.

- A. Test method LTP0129 (b) (4) Inserts, rev 000 (effective date 04/08/2013) and rev 001 (effective date 11/26/2013)" was only qualified without full execution of method validation. In addition, there were method changes of gradient profile and run time for LTP0129 rev 002 (effective dated 08/26/2014). However, no method validation or comparability study was executed for LTP0129 rev 002.

AMENDMENT 1


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- B. The capability to detect and quantitate "Any other individual impurity" at specification level for test method LTP0192 "Analysis of (b) (4) Capsules (b) (4) was not demonstrated in the validation report # RTP1275 rev 000 dated (b) (4) and # OTH-LTP0192-R-0192 rev 001 dated (b) (4) .
- C. Dissolution method validation (RPT1279 rev 000 dated (b) (4)) failed validation for method precision (b) (4)) and intermediate precision (b) (4) and (b) (4)). Dissolution profiles including (b) (4) and (b) (4) time points were reported for release and stability test of clinical and registration batches for (b) (4) Inserts.
- D. Your firm failed to evaluate the presence of unknown peaks for TR 14-0112 (Batch (b) (4) at (b) (4)) present in the placebo (b) (4) at (b) (4) (area counts (b) (4)) that elutes at similar retention time of (b) (4) peak (b) (4) in WSB-14-0112-14001411 (b) (4)) during the execution of Related Compounds test method LTP0116 version 005 "Method for Assay, Related Compounds and Content Uniformity for (b) (4) capsules." For example, on (b) (4) under TR14-0112 for SPL-14-0247-14001449 (b) (4) (Batch (b) (4) for (b) (4)) the presence of unknown peaks was observed at (b) (4) (area count (b) (4)), (b) (4) (area (b) (4) (area count (b) (4) (area count = (b) (4) similar to (b) (4) peak that elutes at (b) (4) (Placebo), (b) (4) (Placebo). Same behavior was observed in TR-16-0298 for Batch (b) (4) in that peaks identified by the analyst as placebo correspond to the same peaks of unknown impurities at (b) (4)) for test conducted on (b) (4) for placebo sample PL-16-0298-01 in which most of the peaks identified as placebo show similar retention times as the peaks of interest.
- E. Your Quality unit failed to detect deficiencies in test method LTP0121, revision 002 (b) (4) Capsules" such as the lack of amount of sample to be pulled at specific time points ((b) (4) and (b) (4)). Even more, the formula calculations do not include corrections for the cumulative amount of drug substance

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dissolved at specified time points that requires a correction by volume in order to consider the amount of sample extracted at each pull time. For example, if (b) (4) are taken at each pull time, then the final volume prior to last pulling time (b) (4) will be (b) (4) instead of (b) (4) as indicated in the formula (i.e. (b) (4) for all pull time intervals. The same formula has been applied at all pull times using (b) (4) value without considering the cumulative amount of drug substance dissolved at each pull time. This method has been used for the evaluation of the drug release (Dissolution test) in the submission batches (b) (4) and (b) (4) of (b) (4) USP Capsules. (b) (4)

- F. Your Quality Unit failed to assess the variability observed for the different stability intervals on the (b) (4) in (b) (4) Capsules USP, (b) (4) submission batches (b) (4) and (b) (4), corresponding to the Dissolution profiles at the (b) (4) and (b) (4). For example,


For Batch (b) (4) Stability studies at (b) (4) for the dissolution profiles, erratic behavior was observed at the dissolution pull times as follows:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

For Batch (b) (4) Stability studies at (b) (4) for the dissolution profiles, erratic behavior was observed at the dissolution pull times as follows:

- (b) (4)

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• (b) (4)
• (b) (4)
• (b) (4)
• (b) (4)

- G. Test Method LTP0114 "Cleaning Verification of (b) (4) was not validated prior to production of (b) (4) clinical batches of (b) (4) capsules (lot #s: (b) (4) thru (b) (4)) manufactured in shared manufacturing equipment between (b) (4) and (b) (4). In addition, this analytical test method validated on (b) (4) (RPT1167) was not challenged for possible interference and/or degradation of API residues in the swab samples that may be impacted by the cleaning detergent residue for the specified API peaks when the cleaning detergent was changed from (b) (4) on 1/22/15.
- H. Your test procedure LTP0122 "Cleaning Verification of (b) (4) does not indicate the stability of swab samples collected from the manufacturing equipment after execution of the cleaning process. Specifically, during review of TR14-0424 (b) (4) Batch (b) (4) , it was observed that swab samples were collected on (b) (4) from at least (b) (4) sampling points but they were not tested until next day ((b) (4)). The validity of results is uncertain due to lack of evidence to support the swab samples stability over the day of collection.
- I. The acceptance criterion of absence of active peak for identification test by (b) (4) for placebo batches using the assay test methods (b) (4) and (b) (4) is subjective without specifying the detection level as one of the acceptance criteria in the specification in order to ensure the absence of residual APIs in placebo batches of (b) (4) Inserts and (b) (4) capsules used in clinical trials.

OBSERVATION 2

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The written stability program for drug products does not include reliable, meaningful and specific test methods.

Specifically, there were constant changes of the analytical test methods used in the stability program for manufactured products during the execution of stability studies without having a scientific rationale and/or appropriate justifications. For example,

- A. An (b) (4) investigational method for Assay of (b) (4) Inserts without having a method validation was used in the analysis of stability samples for (b) (4) Inserts, (b) (4) Batch # (b) (4) at (b) (4) time point under stability storage condition of (b) (4) (TR # 14-1747) and (b) (4) (TR # 14-1748). The revised assay method with sample preparation method (b) (4) resulted in a significantly higher assay value by (b) (4) compared to data obtained from the original sample preparation which was in favor of obtaining **passing higher** test results as evidenced by RTP1233 rev 000 dated (b) (4) . Only the ~~more favorable~~ higher assay values were reported in the Stability Summary Report.
- B. Test method for related compounds was changed from (b) (4) effective (b) (4) to (b) (4) method effective (b) (4) for the (b) (4) stability test for (b) (4) (b) (4) Inserts, (b) (4), Batch # (b) (4) (TR # 15-0224) which was in favor of obtaining passing test results compared to higher results at (b) (4) stability point (TR # 14-0255). This result is contrary to the justification for changing the method documented in LDEV # 15-019 where it states (b) (4)
- C. (b) (4) ~~that showed an increase in the analytical results to provide favorable results.~~
- D. (b) (4) Method for Assay of (b) (4) Capsules” revision 001 effective (b) (4) thru revision 004 effective (b) (4) were not adequately validated prior to

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release and stability testing of clinical batches. Some of the significant changes in the revisions included different (b) (4) conditions, and different sample and mobile phase preparation.


OBSERVATION 3

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

Specifically,

- A. The official assay release test data for (b) (4) Inserts (b) (4), Batch # (b) (4) (TR # 14-1252) and (b) (4) Inserts (b) (4), Batch # (b) (4) (TR # 14-1296) were reported to be within the specification of (b) (4) Label claim (Data file # (b) (4) (b) (4)). However, the (b) (4) data showed that the initial injection data (Data file # (b) (4) (b) (4)) as evidenced by TR # 14-1273 for these (b) (4) batches failed the assay specification with results of (b) (4). Furthermore, the (b) (4) data showed a (b) (4) injection data (Data file (b) (4) 1) with spike test of assay for (b) (4) Inserts (b) (4) Batch # (b) (4) release, TR # 14-1252), (b) (4) Inserts (b) (4), Batch # (b) (4) release, TR# 14-1296), (b) (4) Inserts (b) (4) Batch # (b) (4) and (b) (4) Inserts (b) (4), Batch # (b) (4) TR # 14-0288). The failed assay test results at release (TR # 14-1252 and TR # 14-1296) and on stability (TR # 14-0914) were not recorded in the Certificate of Analysis and/or stability report summary for clinical batches.
- B. There was a lack of placebo injections in the (b) (4) sequences for testing of related compounds using test method LTP0129 (b) (4)(b) (4) (b) (4) Capsules Inserts, rev 001 (effective date 11/26/2013)". Unidentified peaks were excluded from the integration process without appropriate justification or documentation as evidenced by

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TR # 14-0288 (b) (4) Inserts, (b) (4), Batch # (b) (4).
(b) (4) integration process was practiced without appropriate justification or documentation as evidenced by TR # 13-0953 (b) (4) Inserts, (b) (4), Batch # (b) (4).

- C. There was an exclusion of possible placebo peaks without appropriate justification or documentation of peak size for testing of related compounds using test method LTP0129 (b) (4) (b) (4) Capsules Inserts, rev 002 (effective date 08/26/2014)" as evidenced by TR# 14-1747 (b) (4) Inserts, (b) (4), Batch # (b) (4).


OBSERVATION 4

Backup data is not assured as exact, complete and secure from alteration, erasure or loss through keeping hard copy or alternate systems.

Specifically,

- A. (b) (4) data # (b) (4) of TR# 14-1273 for (b) (4) Inserts Placebo, Batch # (b) (4) which included the initial injection data for TR # 14-1252 and TR # 14-1296 and (b) (4) data # (b) (4) for the second injection for TR # 14-1252, TR# 14-1296, TR # 14-0914, and TR # 14-0288 were not appropriately stored in the (b) (4) (b) (4) for (b) (4) in Suite (b) (4). Instead, the (b) (4) data # (b) (4) and # (b) (4) were selectively archived in the (b) (4) (b) (4). Furthermore, (b) (4) data # (b) (4) 1 was inappropriately stored inside the (b) (4) (b) (4) for (b) (4) data # (b) (4).
- B. (b) (4) data # (b) (4) of TR# 13-0737 for (b) (4) Inserts Placebo, Batch # (b) (4) was not appropriately stored in the (b) (4) in the (b) (4).

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for (b) (4) in Suite (b) (4)

- C. During the review of electronic raw data on 1/20/17, it was found that a portable drive containing files of raw (b) (4) data was found within the laboratory around May 2016. These files were reportedly fully copied as (b) (4) " and (b) (4) " into the (b) (4) by the Head of Lab Systems once the drive was found. However, your firm failed to investigate the content of these files to determine if they were back-up files or additional test files not stored in the designated (b) (4) as in the case of Observation 4.A above.

QUALITY SYSTEM

OBSERVATION 5

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, your Quality Control Unit (QCU) failed to fully investigate product stability failures for tests such as assay, related compounds, and dissolution for the following finished drug products used in (b) (4) Clinical Trials and registration batches in support of the following New Drug Application (NDAs) and Investigational New Drugs (INDs) and take timely and appropriate corrective and preventive actions. For example,

A (b) (4) (b) (4) Inserts

The QC unit failed to perform appropriate investigations as per SOP#QC0018 "Out of Specification, Out of Trend and a Typical Result Investigation." For example,

- a) There was a clear trend of decrease of assay from (b) (4) under stability storage condition of (b) (4) and from (b) (4) under

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stability storage condition of (b) (4) for (b) (4) Inserts, (b) (4) Batch # (b) (4). However, the assay results at (b) (4) with new sample preparation method (b) (4) were (b) (4) and (b) (4), respectively. No investigations for these OOT data were conducted.


- b) There were atypical or OOT stability results for test of related compounds for (b) (4) (b) (4) Inserts, (b) (4), Batch # (b) (4) at (b) (4) under storage condition of (b) (4) (b) (4) Inserts, (b) (4), Batch # (b) (4) at (b) (4) under storage condition of (b) (4) and at (b) (4) under storage condition of (b) (4) and (b) (4) Inserts, (b) (4), Batch # (b) (4) at (b) (4) under storage condition of (b) (4) (b) (4) (%). No investigations for these atypical or OOT data were conducted.

B. (b) (4): (b) (4) Capsules for (b) (4) Clinical Studies

- D. DEV-PN0082-51 was opened on 3/8/16 to conduct a manufacturing investigation into the failure of (b) (4) batches ((b) (4) Clinical batches (b) (4), and (b) (4) and registration batches (b) (4) and (b) (4) for (b) (4) at (b) (4). and various time points at (b) (4) long-term stability. Probable root causes for the failures were identified on 9/23/16 as cross-contamination with (b) (4) cleaner used on manufacturing equipment since 1/22/15 (CAPA 16-038), and/or heavy metals and palladium content in the (b) (4) API (CAPA 16-040). However, the investigation was not extended to other products manufactured within the same manufacturing equipment cleaned with (b) (4) and the CAPAs have not been closed in order to implement adequate corrective and preventive action.

- E. DEV-PN0082-52 was opened on 4/7/16 for low (b) (4) assay values at (b) (4) for (b) (4) lot #s: (b) (4) and (b) (4), low assay value for (b) (4) at (b) (4) and low dissolution value for lot

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(b) (4) at (b) (4) Manufacturing investigation was opened 7 months after OOS 15-041 was closed on 9/17/15. A later investigation OOS 16-019 was added to the investigation on 4/22/16. As the manufacturing investigation is still open, your firm has failed to identify the root cause of these failures during stability in a timely manner.

- F. DEV-PN0082-54 opened late on 5/18/16 for an OOS that occurred on 3/8/16 and is still open 8 months later for the failure of lot (b) (4) for dissolution. The investigation identified the root cause as crosslinking; however, the investigation is still open and there is no evidence that corrective and preventive action specified in the investigation has been completed.
- G. Investigation 16-024 for the mix-up of expired and stability samples during testing of (b) (4) capsules did not determine if any of the missing expired blisters/capsules were used for stability testing. In addition, we observed 13 blisters of (b) (4) caps, lot (b) (4) in Stability Chamber (b) (4) on (b) (4) of which one blister contained larger capsules of a darker color mixed with faded smaller capsules labeled with the same lot number. There was no investigation into this discrepancy in capsule size and labeling.
- H. Manufacturing investigations DEV-PN0082-55, 58 & 60 opened between 6/20/16 and 9/29/16 for OOS results for (b) (4) capsules (lot # (b) (4) & (b) (4)) during stability have not been conducted to determine the root cause of the failures.

OBSERVATION 6

The written stability testing program is not followed.

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 555 Winderly Place, Suite 200 Maitland, FL 32751 (407) 475-4700 Fax: (407) 475-4768		DATE(S) OF INSPECTION 1/9/2017-1/20/2017*
		FBI NUMBER 2000027140
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Dr. Frederick D. Sancilio , President and CEO		
FIRM NAME Sancilio & Company, Inc.	STREET ADDRESS 3874 Fiscal Ct Ste 200	
CITY, STATE, ZIP CODE, COUNTRY Riviera Beach, FL 33404-1785	TYPE ESTABLISHMENT INSPECTED Prescription Drug Manufacturer	


Specifically, your firm failed to follow SOP QCA0065 "Stability Program" in that:

- A. Your firm failed to follow the established timeframes for testing stability samples for (b) (4) (b) (4) Inserts, (b) (4) capsules, and (b) (4) capsules in that testing and QA approval was significantly delayed, often as late as (b) (4) after pulling them from the stability chambers.
- B. The inventory of samples in Stability Chamber (b) (4) was not accurately maintained and investigations were not conducted when discrepancies in inventory were found. For example,
- (b) (4) Capsules (b) (4) lot (b) (4) 6-count blisters were placed within the chamber on (b) (4), but a recount of product on (b) (4) showed only (b) (4) 6-count blisters without documenting any samples being pulled.
 - (b) (4) Capsules (b) (4) lot (b) (4) 6-count blisters were placed within the chamber on (b) (4), but a recount of product on (b) (4) showed only (b) (4) 6-count blisters without documenting any samples being pulled.
 - (b) (4) Capsules (b) (4), lot (b) (4) 6-count blisters were placed within the chamber on (b) (4) but a recount of product on (b) (4) showed only (b) (4) 6-count blisters without documenting any samples being pulled.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 7

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Dr. Frederick D. Sancilio , President and CEO

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Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design and of adequate size to facilitate operations for its intended use.

Specifically, your firm lacked the following equipment in the (b) (4) to manufacture (b) (4) Capsules USP (b) (4) as specified in the proposed (b) (4) capsules) commercial batch record:

- A. Stainless steel (b) (4) tank with (b) (4) needed for compounding the fill mass.
- B. (b) (4) in the processing areas to prevent degradation of (b) (4) API due to light exposure.


OBSERVATION 8

Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

- A. On 1/18/17, upon inspection of the (b) (4) (b) (4) Tanks in Room (b) (4) it was observed that the (b) (4) Water System's (b) (4) was tagged as out of service since 7/19/16. However, cleaning of this tank as per PRD0108 Rev. 001 "Operation, Cleaning, and Maintenance of the (b) (4) (b) (4) Tank System and (b) (4) Pump" requires a final rinse of the interior tank surfaces with (b) (4) water for (b) (4) . An interview with a production technician revealed (b) (4) water is obtained from another (b) (4) of Room (b) (4) and brought in. Your firm lacked documentation (e.g. deviation, alternate procedures) to demonstrate this task is properly performed.

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B. Residual water was observed at the bottom of the (b) (4) (b) (4) Tank (SCI 12065) upon inspection of this tank on 1/18/17. According to the tank's clean tag and logbook, the tank was major cleaned on 1/11/17; however, cleaning procedures (step 27) in SOP PRD0108 were not followed in that the tank was not verified as dry before tagging it and closing its hatch.

***DATES OF INSPECTION**

1/09/2017(Mon),1/10/2017(Tue),1/11/2017(Wed),1/12/2017(Thu),1/13/2017(Fri),1/17/2017(Tue),1/18/2017(Wed),1/19/2017(Thu),1/20/2017(Fri)

1/20/2017

1/20/2017

☒ Jennifer L Huntington

Jennifer L Huntington
Investigator
Signed by: Jennifer L Huntington -5

☒ Ivis L Negron Torres

Ivis L Negron Torres
Chemist/Biologist
Signed by: Ivis L Negron Torres -5

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 Redacted cert call

☒ Ileana Barreto-Pettit

Ileana Barreto-Pettit
Investigator
Signed by: Ileana Barreto-Pettit -5

DATE ISSUED

1/20/2017