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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Mid-Atlantic Region

Telephone (201) 331-2901

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

May 29, 1997

WARNING LETTER

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

RELEASE

Mr. Leland F. Wilson
President and CEO
Vivus, Inc.
545 Middlefield Road, Suite 200
Menlo Park, CA 94025

REVIEWED BY UPR 6/11/97
C.O. DATE

FILE: 97-NWJ-39

Dear Mr. Wilson:

During an inspection of Vivus at Paco Pharmaceutical Services, Inc., Lakewood, New Jersey, between February 10 through March 13, 1997, our investigator documented deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 & 211) in conjunction with your firm's manufacturing of MUSE (alprostadil) urethral suppositories.

These deviations cause your drug product(s) to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act as follows:

1. Your firm failed to determine the cause of in-process and finished product out-of-specification results and document your investigation regarding the following:
 - A. Out-of-specification content uniformity results were obtained for lot numbers 60001E and 60002C, (label strength [redacted] and [redacted] respectively). The cause of these results were unknown and corrective actions and process improvements were not made prior to the manufacture of subsequent lot numbers, 60003B to 600010E.
 - B. There was no investigation by your quality unit into a label strength finished product assay result of [redacted] for lot #60007D. This out-of-specification result was not mentioned, discussed, nor reported in the final validation report.

- C. There was no explanation for a [REDACTED] in-process content uniformity test result for lot 60003E, sample plate number 8. Other plates rejected include plate #1 and #2 from lot #60033C; lot #60034C; plate #1 from lot #60018C; plate #5 from lot #60114C; plate #1 and #8 from lot 70072B and plate #1 from lot #70093D. To date, the cause of the content uniformity failures is unknown and corrective actions have not been implemented.
 - D. Your firm failed to have data to support your invalidation of the original test results for the finished product assay testing of lot 60006C, in which both individual and composite samples did not meet labeled strength specification. Furthermore, the initial out-of-specification result was not mentioned, discussed, nor reported in the final validation report.
 - E. For lot #60009B, there was no investigation into the initial ten sample results which did not meet the %RSD requirements for finished product content uniformity.
 - F. There was no explanation for the low plate yield of plate #2, lot #60004E, nor any indication that corrective action was implemented.
2. Investigations were either not conducted by your quality unit regarding out-of-specification results, or if conducted, were found to be incomplete. For example:
- A. Finished product content uniformity specifications were not met for lot 60014E. Four of thirty results, for label strength, were below 85%. There has been no documented investigation by the Quality Unit into these out-of-specification results.
 - B. The initial finished product (%L.S.) assay results for lot numbers 60015B, 60017D and 60018C, were out of specification, (90-110%). The retests, also produced results which did not meet specification for lot #60017D. The laboratory investigation did not provide any conclusive documentation as to why the initial out of specification values were obtained.

- C. There was no documented investigation by your quality unit into the out-of-specification finished product label strength assay results for lot numbers 60095C and 60112C.
 - D. There was no laboratory investigation into why one sample, from lot #70103B, did not meet content uniformity specification upon initial injection and subsequent re-injection, nor why the initial injection and re-injection differed by more than [REDACTED]
 - E. Multiple pellet weights from lot #60054E were found to be below the lower limit target range, during QA weight checks. There was no investigation into why these pellets were not removed during the 100% AGR inspection.
3. There is no assurance that all 500mcg and 1000mcg lots are able to meet dissolution requirements. For example:
- A. Lot numbers 60017D, 60024D, 60025E, 60028E, 60031E, 60037E, 60048E, 60065E, 60169E, 60192D, 60194E, 60195E, 60219E, 70012D, 70016E, 70033D, 70046D, 70050E, and 70059E, failed to meet dissolution on initial release testing. Lot 60013E did not meet dissolution requirements on stability.

No documented investigation could be provided by your quality unit into the above dissolution failures and there were no corrective actions taken.
 - B. During dissolution testing for lot #60212E, an unknown peak was found on the HPLC analysis. This peak was not investigated by the your quality unit and the origins of this peak were not identified.
 - C. Your current dissolution method, #17800D, was not validated by your contract testing laboratory.
4. Your firm lacked cleaning validation for the plates, mixing assembly and manifold, used during the manufacturing process. For example, it was noted that during QC testing of placebo batches, low levels of alprostadil were detected.

5. There was no data to demonstrate that your firm's current impurity method for Alprostadil drug substance, VS-004-2, could detect all potential impurities. Seven potential impurities were identified by the drug substance manufacturer, which were not evaluated during your method validation.
6. Out-of-specification, in-process content uniformity results, obtained for lot numbers 60015B, 60012D, and 60016C by your contract testing laboratory, were excluded for low weight. This exclusion of data was not specified in the analytical method.
7. Your stability program lacked the following:
 - A. A written stability protocol for products manufactured and marketed in September 1996.
 - B. The three month test points were not conducted for lot numbers 60003B, 60004E, 60005D, 60006C, 60007D, 60008D, 60009B, 60010E, 60030B, 60052C, and 60056C.
 - C. The protocol provided, 2/17/97, did not specify which lots would be placed on stability in 1997 nor in subsequent years.
8. Your Master Production Record failed to have established mixing times for your compounding steps. For example:
 - A. There was no maximum processing time in the Pretreatment Section, step #3, Melting the [REDACTED]. Also, it was determined that there was no percent water content specifications for the [REDACTED]. The water content of the [REDACTED] was not checked prior to the addition of the active.
 - B. Your Master Production Record, Drug Compounding Section, for all dosage forms, did not specify mixing times for processing step numbers 4.8-4.11.
9. Your validation protocol for the MUSE product lacked the following:
 - A. The protocol did not specify which commercial sized lots were considered validation lots.

- B. Neither your validation protocol nor your in-process specification stated that all results obtained from suppositories, that were less than [REDACTED] of target weight, would be excluded. However, in-process content uniformity results, which were less than [REDACTED] of target weight, for lot numbers 60003B, 60006C, 60004E, 60007D, 60008D, and 60009B, were excluded from the validation report.
10. There was no qualification data to demonstrate the effectiveness of the [REDACTED] Vision System used for the 100% inspection. Low weight suppositories, which should have been removed during the [REDACTED] 100% inspection, were found during the QA weight checks of validation batches. These QA weight checks were conducted to verify the effectiveness of the 100% inspection system.
11. Your firm failed to have formal training documentation for all operators of the [REDACTED] Vision System. For those individuals which underwent formal training, the SOP failed to describe how training was conducted, what the training consisted of, and there was no challenge at the conclusion of training which would verify the operator's proficiency.
12. Your complaint handling procedures were inadequate. For example:
- A. Several complaints, numbers #15, 17, 22, 26, 36, 46, 48, reported missing suppositories and eight complaints, 4, 8, 16, 21, 23, 38, 40, 41, reported depressed buttons. There was no documented production investigation into the possible causes of such occurrences.
13. Your environmental monitoring program for the Class 100,000 compounding and filling areas did not demonstrate operation in accordance with procedures. For example:
- A. Environmental monitoring samples were not taken until 12/03/96.
- B. There are no approved procedures to describe how or when environmental monitoring is to be conducted.
- C. Organisms found during monitoring were not identified.

14. Regarding your Purified Water System:

- A. The sanitization frequency of the hot and cold loop of the Purified Water System has not been determined.
- B. The [REDACTED] micron filters were not integrity tested prior to use.
- C. There are no written sampling procedures to describe how Purified Water samples for microtesting were to be selected.

15. During a walk-through inspection of the firm's refrigerator, multiple lots of product were observed with no labeling as to the current disposition of product, i.e. in-process, rejected, or released.

On April 30, 1997, New Jersey District provided comments regarding your response, dated March 21, 1997, to the list of Inspectional Observations (FDA-483) issued to Vivus at Paco Pharmaceutical Services on March 13, 1997. Your further written responses, dated April 28, 1997 and May 23, 1997, (provided during our meeting on May 23, 1997, in the NWJ-DO), were also evaluated and appear satisfactory. However, we will confirm your actual corrective actions and compliance with cGMP's, during the next inspection of your facility.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the good manufacturing practice regulations. Until these violations are corrected, Federal agencies will be informed that FDA recommends against the award of contracts for affected products.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunction.

Should your firm have additional comments concerning the FDA-483 or the above points, it should notify this office in writing, within 15 working days of receipt of this letter.

Vivus, Inc.
Warning Letter (97-NWJ-39)

May 29, 1997
Page 7

Your reply should be sent to the Food and Drug Administration,
Newark District Office, 10 Waterview Blvd., 3rd Floor,
Parsippany, New Jersey 07054, Attention: Vincent P. Radice,
Compliance Officer.

Very truly yours,

Edward H. Wilkens

EDWARD H. WILKENS
Acting District Director

VPR:slw

cc: Neil Gesundheit, M. D.
Vice-President
Clinical and Regulatory Affairs
Vivus, Inc.
545 Middlefield Road, Suite 200
Menlo Park, CA 94025

Bruce Decker
Vice President Operations
Paco Pharmaceutical Services Inc.
1200 Paco Way
Lakewood, NJ 08701

Vivus, Inc.
Warning Letter (97-NWJ-39)

May 29, 1997
Page 8

cc: HFA-224
HFC-210 (Div. Compliance Policy)
HFI-35 (Purged)
HFD-300 (CDER)
HFR-MA300 (DD)
HFR-MA350 (DIB/Gp. VI)
PSAU
EF (Vivus Inc., at Paco Pharmaceuticals, Lakewood, NJ)

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