WARNING LETTER

Signa SA de CV

MARCS-CMS 605219 — JULY 14, 2020

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Jeff Watson

President & Chief Executive Officer

Signa SA de CV

150 Signet Drive
Toronto ON M9L 1T9
Canada

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-20-40

July 14, 2020

Dear Mr. Watson:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Signa S.A. de C.V., FEI 3002808161, at Avenida Industria Automotriz No. 301, Fracc. Delegación Santa Ana Tlapaltitlan, Toluca, Toluca De Lerdo, Mexico, from December 16 to 20, 2019.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your January 13, 2020, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

Failure to adequately investigate out-of-specification results and implement appropriate corrective actions.

Your investigations into out-of-specification (OOS) test results were inadequate. You failed to appropriately justify potential root causes, expand investigations to all potentially affected batches, and implement adequate corrective actions and preventive actions (CAPA).

a. You obtained OOS results for related substances **(b)(4)** during the release testing of **(b)(4)** USP, batch **(b)(4)**, performed in January 2018 as part of a process validation study. Your Phase I laboratory investigation confirmed the OOS results. You opened a manufacturing investigation that listed multiple hypotheses as root causes for an inadequate **(b)(4)** reaction. Your investigation ultimately concluded, without adequate supporting evidence, that the potential root cause for the impurity OOS was inadequate **(b)(4)**.

You later found this root cause was unsupported because you were using the maximum **(b)(4)**. Your investigation was inadequate and did not include appropriate corrective action.

In response to the FDA-483, you reopened the manufacturing investigation. Your firm emphasized temperature profile and material charging in the updated investigation. Specifically, while the batch was within operational temperatures ranges, your firm found that it exhibited an "anomalous pattern." Your firm had previously identified temperature range as a critical control parameter with the potential for quality impact. Your investigation also noted that the yield was slightly lower for this batch, which may have been related to material **(b)(4)** errors. Your CAPA after the renewed investigation included tightening the temperature range from **(b)(4)**, but it remained uncertain whether the root cause was adequately resolved.

The failing impurity data obtained for this batch was intended to support **(b)(4)** process validation studies. Notably, your firm has experienced several additional failures during the production history of this API.

At least one of the finished API batches from these validation studies was released for the U.S. market.

In your response, you stated that your firm will conduct additional experimental design studies to ensure evaluation of multivariate combinations that replicate the failure mode. However, your response lacked sufficient information about the scope, timeline, and plans to ensure CAPA effectiveness.

b. You obtained an OOS assay result during the release testing of **(b)(4)** USP, batch **(b)(4)**, performed in October 2018. You then obtained passing retest results and invalidated the original OOS result. Your firm indicated that a likely root cause was instability of the analytical balance due to the

presence of too many analysts in the weighing room. There was no evidence that the presence of multiple analysts in the room affected the sensitivity of the analytical balance and therefore contributed to the OOS results.

Your laboratory investigation also indicated that your Plant Manager reported no deviations that could be related to the OOS results. No further documentation of the manufacturing evaluation was available or provided to the investigator during the inspection.

Your firm lacked a meaningful or formal Phase 2 manufacturing investigation, and batch **(b)(4)** was subsequently released.

Whenever an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes must be performed.

We acknowledge that you have initiated efforts to remediate and improve your investigation programs. However, your response lacked adequate details of the remediation approach. In addition, the scope of your assessment is insufficient.

In response to this letter, provide the following.

• A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

• An independent assessment and remediation plan for your CAPA program, including whether your firm assures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality assurance unit decision rights, and is fully supported by executive management.

• A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for U.S. products, irrespective of whether the batch was ultimately distributed in the U.S. and a report summarizing the findings of the analysis, including a detailed chart with the following for each OOS:
  o Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
  o For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
  o For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/ facilities, variability of raw materials, process capability, deviation history, complaint history, and batch failure history). Summarize potential manufacturing root causes for each investigation, and any

manufacturing operation improvements.
  o This review should cover the past three years (i.e., since January 2017) and evaluate any other common issues found beyond that period.

• Provide the full batch history of **(b)(4)** and of its **(b)(4)**, batch disposition decisions, and details regarding any failing results that occurred at any stage or processing.

• A comprehensive review and remediation plan for your OOS result investigation systems. The CAPA should include but not be limited to addressing the following:
  o Quality unit oversight of laboratory investigations.
  o Identification of adverse laboratory control trends.
  o Resolution of causes of laboratory variation.
  o Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified.
  o Adequately scoping each investigation and its CAPA.
  o Revised OOS investigation procedures with these and other remediations.

Repeat Violations and Deviations at Multiple Sites

FDA cited similar CGMP deviations at other facilities in your company's network. These repeated failures at multiple sites demonstrate that management oversight and control over the manufacture of drugs is inadequate.

Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Conclusion

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of these deviations and for preventing their recurrence or the occurrence of other deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in the FDA refusing admission of articles manufactured at Signa S.A. de C.V. at Avenida Industria Automotriz No. 301, Fracc. Delegación Santa Ana Tlapaltitlan, Toluca, Toluca De Lerdo, Mexico, into the United States under section 801(a)(3) of

the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov.

Please identify your response with FEI 3002808161and ATTN: Rafael Arroyo and Rebecca Parrilla.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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