Interpharm Praha A.S. 10/18/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Warning Letter 320-17-02

Via UPS
Return Receipt Requested

October 18, 2016

Mr. Yuke Maki
CEO
Interpharm Praha A.S.
Komoranska 955
Praha 4
Modrany, Czech Republic

Dear Mr. Maki:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Interpharm Praha A.S., at Komoranska 955, Praha, Modrany, from October 12 to 16, 2015.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API) and significant violations of CGMP regulations for finished pharmaceuticals, 21 CFR parts 210 and 211.

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

We reviewed your November 6, 2015, response in detail.

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

API Deviations

1. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.

Your quality control unit did not have basic controls to prevent changes to your electronically-stored laboratory data. Your analysts had user privileges to the Empower-2 system used to generate and analyze chromatographic data that allowed them to eliminate failing, atypical and satisfactory results with no notification; alter peak areas; and add or eliminate samples from sequences without authorization.

During the inspection, we reviewed an audit trail from your Empower-2 system that stored 8,906 entries. Of these, well over half indicated some form of data deletion or manipulation, including at least 1,441 instances of deleted results, at least 3,643 instances of manual integration, and at least 194 instances of altered running sample sets. Your personnel confirmed that these actions are common during chromatographic data processing. We found that you did not have a procedure in place to indicate the requirements and level of restrictions for users of the automated system.

Your quality unit must review all pertinent analytical data when making batch release decisions. However, your automated system permitted analysts to delete and alter test results without authorization. As a result, your quality unit was presented with incomplete and inaccurate information about the quality of your drugs.

According to your response, you restricted access and permissions in the Empower 2 automated data system. However, your response does not demonstrate how the specific controls you have implemented prevent deletion or alteration of data, nor have you shown how you will ensure that these permissions are documented, implemented, and followed. Finally, you have not shown how these controls ensure that records relied upon for batch release and other quality review decisions are complete and accurate.

2. Failure to ensure that test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity.

Your laboratory procedures allowed analysts to modify chromatographic sequences and delete results with no justification.

During our review of chromatograms generated during impurities testing for **(b)(4)**, we observed that your analysts conducted many manual integrations. We also found discrepancies in peak integrations, including inconsistent integrations, and peaks that were not integrated at all. Such peaks could represent impurities: they were not included in data packages presented to your quality unit for batch release decisions. Therefore, your quality review and product release decisions were based on incomplete data regarding the quality of your drugs.

According to your response, you scheduled training on manual integration for all analysts who use Empower-2 software. You have not shown how you will ensure that your test methods are appropriate to determine whether your API conform to established standards and specifications.

In response to this letter, provide your action plan for developing, validating, and implementing chromatographic test methods to analyze the quality attributes of your drugs. Specify the procedures you will implement to process your chromatographic data related to all test results and audit trail functionality. Detail how you will review chromatographic results as part of the batch release procedure and documentation. Specify the controls you will implement to ensure that any manual integration steps are performed only under defined, limited circumstances according to a protocol approved and supervised by your quality unit.

Finished Product Violations

1. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records or other records (21 CFR 211.68(b)).

For example, our investigator reviewed an audit trail for impurities testing conducted on **(b)(4)** validation lot **(b)(4)**, number **(b)(4)** vial # **(b)(4)**, Injections 1 and 2. The audit trail revealed many deleted results and manual integrations.

As discussed above, deleted and altered analytical test results mean that your quality unit is presented with incomplete and inaccurate information about the quality of your drugs.

2. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Your laboratory procedures allowed analysts to modify and delete chromatographic results without adequate justification, and to use manual integration in uncontrolled circumstances.

For example, our investigator found results deleted after repeated manual integrations for **(b)(4)** stability lots **(b)(4)**. Unjustified, repeated manual integrations and deletions indicate that your laboratory controls are not scientifically sound and appropriate to test your products.

In your response to this letter, describe all steps you will take to ensure that appropriate laboratory controls have been implemented to support product quality review and batch release decisions. Include the controls you will implement for the modification, deletion, and manual integration of chromatographic test results. -

Data Integrity Remediation

Your quality system does not adequately ensure the adequacy and integrity of data to support the safety, effectiveness, and quality of drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data, records, and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of your data integrity deficiencies.
- We recommend that a qualified third party with specific expertise in the area where potential lapses were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effect of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse in data integrity, and risks posed by ongoing operations.

C. A management strategy that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- The detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to the FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your data.
- A status report for any of the above activities already underway or completed.

Conclusion

Violations and deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations and deviations, for determining the causes, for preventing their recurrence, and for preventing other violations and deviations in all your facilities.

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

Failure to correct these violations and deviations may also result in FDA refusing admission of articles manufactured at Interpharm Praha A.S., Komoranska 955, Praha 4, Modrany, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles 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 violations and 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Carlos Gonzalez, Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3002807299.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)