U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

IBA Molecular, Inc 24-Oct-08

Department of Health and Human Services

Public Health Service
Food and Drug Administration

Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215-3215
Telephone: (410) 779-5454

WARNING LETTER
CMS# 11506

October 24, 2008

Via FedEx

Mr. Olivier LeGrain, President
IBA Molecular, Inc.
Chemin du Cyclotron, 3
1348 Louvain-la-Neuve
Belgium

Dear Mr. LeGrain:

Over four days during the period May 12 to May 27, 2009, the U.S. Food and Drug Administration (FDA) conducted an inspection of your manufacturing facility located at 100 Executive Drive, Sterling, Virginia, USA. The inspection revealed significant deviations from the United States Pharmacopoeia (USP) compounding standards and official monograph for Positron Emission Tomography (PET) drugs in the manufacturing of **[(b)(4)]** for injection. These deviations were listed on an FDA-483 Inspectional Observations form issued to Nasrin Pourkiani (Pharmacy Manager - Sterling, Virginia) at the close of the inspection. These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(C) [21 U.S.C. § 351(a)(2)(C)] of the Federal Food, Drug, and Cosmetic Act (the Act).

In addition, the inspection revealed your firm failed to register as a drug establishment, as required under Section 510 of the Act [21 U.S.C. § 360].

We also have completed review of your June 4,2008 response to the FDA-483 observations. The deficiencies identified during the inspection need more comprehensive corrections than the actions you have proposed or taken.

We note that you distribute one single PET drug product and that this is your firm's initial inspection. Nonetheless, the inspection documented serious deviations, included below, that require corrective actions. The inspection revealed that systems employed during the manufacture and processing of your firm's drug products are not in compliance with USP compounding standards and official monograph for PET drugs. The systems that are not in compliance are as follows: 1) Quality Control 2) Production 3) Laboratory 4) Facilities and 5) Equipment.

The deviations observed during the inspection include, but are not limited to the following:

1. Your firm failed to establish appropriate analytical procedures and to conduct testing appropriately.

a. Your firm conducts a 30 minute **[(b)(4)]** assay test which has not been run to completion. A standard 60 minute endotoxin test must be performed on each batch as indicated by the manufacturer and compendial expectation. There is no assurance that your endotoxin test results are accurate and reliable.

We acknowledge your June 4, 2008 response and commitment to perform the test as specified by the manufacturer with completion due date of August 31, 2008. However, you need to evaluate the impact of the reduced test time in the quality of your released batches as it relates to patient safety and provide us with such evaluation.

b. Your firm was found to conduct at least one sterility retest of an out-of-specification (OOS) result (batch # **[(b)(4)]**). You disregarded the first failing test result without demonstrating whether the test was invalid for causes unrelated to the product. Your practice does not assure the sterility of your product.

We acknowledge your June 4, 2008 response and commitment to revise your procedure **[(b)(4)]** Please note that your procedure number does not appear correct. Your response states in part "The revision will clarify our concurrent investigation with the beginning of the second test." We are not sure what you intended to communicate with the foregoing statement and request clarification and supporting information. In addition, whether it is a test or retest, you need to evaluate (e.g. determine test validity, most probable cause, and the impact of the failure on released batches) every instance where evidence of microbial growth was found and provide your findings.

2. Your firm failed to establish, document, and perform sterilization activities to assure that the finished drug product is sterile. Aseptic techniques used to make sterile products and operator qualification have not been evaluated through a process simulation (i.e., media fill), and verification of the media's growth promotion capability in the PET drug container is not performed.

We acknowledge your June 4, 2008 response and commitment to implement a procedure for media fill for production staff by July 31, 2008, in order to perform an evaluation of aseptic techniques and to qualify operators. We acknowledge your response concerning the acceptance of components (i.e., the media) by obtaining vendor's Certificate of Authenticity to address growth promotion. However, your response is not adequate in that it fails to include verification of the media's growth promotion capability for its intended purpose.

3. Your firm failed to a) investigate any unplanned deviations in, or unexpected results of, verified compounding procedures or processes, b) investigate quality control out-of-specification (OOS) test results, and c) document the outcome of such investigations. Specifically, your firm failed to investigate:

a. Out-of-specification (OOS) test results for the lack of **[(b)(4)]** activity in eleven batches of the drug,
b. OOS release test results for **[(b)(4)]** and lack of **[(b)(4)]** activity in two batches respectively, and
c. Unplanned deviation regarding a computer failure which stopped the manufacturing process.

We acknowledge your June 4, 2008 response and commitment to conduct training of pertinent staff. However, your corrective action is not adequate. Although the batches were rejected, you still need to investigate and document the OOS failures to determine the root cause and implement corrections to prevent recurrence.

4. All aseptic manipulations are not performed using appropriate aseptic technique in an appropriately controlled environment.

a. Microbiological testing of the laminar flow hood is only performed before the start of manufacturing each day (and not during or after the run).

We acknowledge your June 4, 2008 response and understand the challenges you have expressed between the ALARA commitment to protect your operators from excessive radiation exposure and using appropriate aseptic technique. However, your response is not adequate because you fail to

provide a timeframe for the completion of your evaluation to enhance sterility control. Please provide your projected timeframe and the rationale for this timeframe.

b. Aseptic operations are not performed by operators wearing appropriate laboratory clothing. On two occasions, a quality control specialist failed to put on a bouffant cap and disposable shoe covers before entering the aseptic filling room as directed by your firm's procedure to gown appropriately.

We acknowledge your June 4, 2008 response and commitment to conduct training of pertinent staff. Please ensure that your training includes the personnel responsible for supervising the activities as part of the corrections.

5. Equipment used for compounding of PET drugs is not inspected for suitability immediately before use to ensure proper maintenance has been completed according to appropriate, written procedures **[(b)(4)]** titled "Synthesizer Unit Maintenance"). Your firm did not provide any supporting information to demonstrate that the daily, weekly, and monthly maintenance steps have been performed on the Synthesizer Units 3 and 4 as per written procedure.

We acknowledge your June 4, 2008 response and commitment to conduct training of pertinent staff on **[(b)(4)]** However, we find your response is not adequate in that your correction does not state when maintenance of the unit will be performed.

We note that the designated, qualified, and trained personnel [typically known as your Quality Control Unit (QCU)] responsible for ensuring that activities at your facility are carried out do not always perform their functions adequately. For example, our investigator found that review of batch record **[(b)(4)]** revealed data inconsistencies in reporting results of a second sterility test which should have been identified, addressed, and corrected by the QCU. The QCU also failed to ensure that investigations into OOS results are investigated to determine the root cause of the failures and implement adequate corrections. Further, the QCU failed to properly review and approve procedures to ensure they are adequate and in compliance with compendial standards and failed to ensure procedures are followed (e.g. **[(b)(4)]** LAL Testing for Bacterial Endotoxins; **[(b)(4)]** Synthesizer Unit Maintenance; Process Deviation Investigation partially identified with Control Number EI-104-B). Please advise the agency of the actions your firm will take to mitigate the failure of the QCU to perform their functions adequately.

We also note that you intend to implement procedure **[(b)(4)]**, Effective Date: TBA (Final Product Sterility Test/Investigation of Positive First Stage Sterility Test Results). Note that this procedure is unacceptable. Specifically, your firm's SOP allows for an automatic second sterility retest of the drug product without adequate evaluation of the first sterility positive. The procedure does not address the criteria to use to invalidate a positive sterility test. As per compendial standards, if evidence of microbial growth is found, the product does not comply with the test for sterility, unless it can be clearly demonstrated that the test was invalid for causes unrelated to the product. Also, your firm's procedure allows the sterility test of the drug product to start 48 hours after production of the batch. There is no information to support the adequacy of the time extension from 24 hours (as per compendial expectations) to 48 hours for the detection of contaminants in the drug product.

Section 510 of the Act requires manufacturers, repackers, and relabelers that engage in the manufacture, preparation, propagation, compounding, or processing of human or veterinary drugs and human biological products to register their establishment(s) and submit a listing of every product in commercial distribution with the FDA. For more information and guidance regarding registration, please visit the *Drug Registration and Listing* website: http://www.fda.gov/cder/drls/registration_listing.htm[1].

The issues and violations discussed in this letter and on the Form FDA 483 are not intended to be an all-inclusive statement of the violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of the Act.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A re-inspection may be necessary.

Please respond to this office in writing within fifteen working days of receiving this letter. Your response should describe any specific actions, other than those already submitted, you will take, or have taken, to correct the violations described above including the dates the corrective actions were completed, and proposed timeframes for completion of each remaining corrective action. Include an explanation of how each action being taken will prevent recurrence of similar violations, as well as copies of related documentation. Please state the reason for any delays in implementing the corrective actions along with the time frames within which corrective actions will be completed. We will review and evaluate the implementation and adequacy of your corrective actions during our follow-up inspection of your firm.

Please direct any correspondence to: Randy F. Pack, Compliance Officer, U.S. Food and Drug Administration, 6000 Metro Drive, Suite 101 Baltimore, MD 21217. If you have any questions, please contact Mr. Pack at (410) 779-5417.

Sincerely yours,

/S/

Kirk Sooter,
Acting District Director

Links on this page:

1. http://www.fda.gov/cder/drls/registration_listing.htm