U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

AMRI Burlington, Inc. (formerly Hyaluron, Inc.) 8/17/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New England District
One Montvale Avenue
Stoneham, Massachusetts 02180
(781) 596-7700
FAX: (781) 596-7896

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: NWE-10-18W
CMS Case: 107145

August 17, 2010

Thomas E. D'Ambra
Chief Executive Officer
Albany Molecular Research, Inc.
21 Corporate Circle
Albany, NY 12203

Dear Mr. D'Ambra:

During our March 2, 2010 to April 1, 2010 inspection of your pharmaceutical manufacturing facility, AMRI Burlington, Inc. (formerly Hyaluron, Inc.), located at 99 South Bedford Street, Burlington, Massachusetts, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations 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 (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response of April 21, 2010, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed, nor has your firm extended investigations to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy [21 C.F.R. § 211.192]. For example:

a. Your firm did not thoroughly investigate particulate contamination found in lot **(b)(4)** of **(b)(4)** injection. This particulate contamination ranged in size from less than 0.5 to 5 mm for vials and less than 0.2 to 8 mm for syringes. During a second inspection, particulate contamination was discovered in a syringe sample. Despite this finding, your firm did not re-inspect the remainder of the syringe sub-lot or the vial sub-lot. In addition, your firm did not conduct a formal risk assessment of the particulate contamination found in the drug product and its possible impact on product quality.

b. Your firm did not thoroughly investigate particulate contamination found in lot **(b)(4)** of **(b)(4)**.

c. Your firm did not thoroughly investigate particulate contamination found in lot **(b)(4)** of **(b)(4)**. The particulate contamination was described as short, dark, and fiber-like in appearance.

Your firm's response is inadequate because you failed to thoroughly investigate and identify the root cause for the particulate contamination described above. You have not evaluated other product lots or other products manufactured at your facility for the possibility of a similar contamination. We acknowledge your statement regarding your client's request to destroy lot **(b)(4)** of **(b)(4)** injection and your client's support to release lot **(b)(4)** of **(b)(4)**. However, your firm is required to thoroughly investigate any unexplained discrepancy or the failure of a batch whether or not the batch has already been distributed. Our inspection revealed significant amounts of products across several different products rejected due to visible particulate matter.

In addition, we are concerned with your firm's response regarding the failure to investigate particulate contamination of injection described above. Your response states that the products were manufactured in compliance with CGMP because all release specifications were met and all non-conforming units were rejected. Please review all product batch records for lots within expiry for all rejects to determine trends and severity of the visual inspection rejects, and inform both the appropriate client and FDA of your findings and all follow-up corrective and preventative actions you intend to take.

2. Your firm has not established and followed written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)]. For example:

a. Investigators observed poor aseptic technique for manufacturing and quality control microbiology personnel working inside the aseptic fill

suite and core.
Documented examples include:

- Stabbing at stoppers with the blade end of a scalpel to move them around the stopper feed line;
- Sweeping the blade end of a scalpel down the stopper feed line to remove stoppers;
- Two technicians wiped their sterile gowning pant legs on the floor; and
- Technicians removed non-sterile gloves in the sterile suite gowning rooms, thereby exposing their bare hands. The aseptic suite operator then donned a pair of sterile gloves in the aseptic gowning suite.

b. Regarding environmental and personnel monitoring:

- There is no assurance that manufacturing employees' sterile garments and gloves remain sterile after lying on the bench in the gowning rooms.
- The procedure "Environmental Monitoring Program for the GMP Manufacturing Facility," QC-008-001-06, §8.5.2, does not specify how to perform fingertip monitoring. Investigators observed fingertips being monitored on contact plates as they were tapped instead of rolled to maximize surface evaluation area.

c. Regarding materials brought into the aseptic core:

- There is no documentation or procedure to demonstrate that tools used in the aseptic filling suites and cores are autoclaved prior to use. These tools used in the aseptic core are not monitored for microorganisms. There is no procedure that states the tools used in the aseptic filling suites are dedicated to these areas.
- There is no procedure for bringing in a handheld communication radio into the aseptic manufacturing suites that is used by quality control microbiology personnel.
- Your firm purchases autoclavable paper for the batch history records, but does not autoclave the paper prior to use in the aseptic filling suite.

Your firm's response identifies plans to address the issues mentioned above by discontinuing poor practices, revising procedures, and providing additional employee training. In addition to those corrections, your firm should review all SOPs and clean room practices for the manufacturing of aseptic drug products to identify and address practices that would jeopardize drug product quality. In your response, please provide a time frame for completing this review.

3. Your firm has not established valid in-process specifications derived from previous acceptable process averages and process variability estimates where possible, and determined by suitable statistical procedures where appropriate [21 C.F.R. § 211.110(b)].

For example, the established in-process specifications in your procedure, IP-001-001-13, are not supported by data to demonstrate that they are scientifically sound. Your procedure assigns a tighter action limit to a non-critical rejection criterion (**(b)(4)**") than to a critical rejection criteria (**(b)(4)**"). Further, although both are defined as critical in your procedure, the rejection criterion " **(b)(4)** and "**(b)(4)**" have different action limits, and respectively. No study was conducted and no scientific data was developed to support these established action limits. The establishment of action limits for manufacturing process control should be based on adequate data such as process averages, process variability estimates, nature of the defect and characteristics of the process design.

We acknowledge that your firm has been working with consultants since January 2010. However, it is important that you also have a statistical expert, with experience in aseptic in-process controls, review your implemented procedures and practices for adequacy.

The violations cited in this letter are not intended to be an all-inclusive statement of 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 and the occurrence of other violations. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

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, seizure, and 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 drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture the drug product(s) manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address:

U.S. Food and Drug Administration
c/o Amber G. Wardwell, Compliance Officer
One Montvale Avenue
Stoneham, Massachusetts 02180

Sincerely,

/S/

Mutahar S. Shamsi
Acting District Director
New England District

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