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DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration  
New England District

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Stoneham, Massachusetts 02180  
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**WARNING LETTER**

NWE-16-08W

VIA FEDERAL EXPRESS

July 2, 2008

Charles H. Sherwood, Ph.D.  
President and CEO  
Anika Therapeutics, Inc.  
32 Wiggins Avenue  
Bedford, Massachusetts 01730

Dear Dr. Sherwood:

During an inspection of your firm located at 236 W. Cummings Park in Woburn, Massachusetts on March 10 through March 21, 2008, investigators from the United States Food and Drug Administration (FDA) determined that your firm manufactures various medical devices for human use and one animal drug product. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), your products Amvisc, Amvisc Plus, Staarvisc II, Shellgel, and Orthovisc are considered devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease or are intended to affect the structure or any function of the body. Hyvisc, the animal product manufactured by your firm, is a drug within the meaning of section 201(g)(1)(B) of the Act, 21 U.S.C. § 321(g)(1)(B), because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

The inspection revealed that these devices (Amvisc, Amvisc Plus, Staarvisc II, Shellgel and Orthovisc) are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351 (h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current Good Manufacturing Practice (cGMP) requirements of the Quality System (QS) regulations found at Title 21, Code of Federal Regulations, (C.F.R.), Part 820. These violations include, but are not limited to, the following:

1. Failure by management with executive responsibility to ensure that an adequate and effective quality system is implemented and maintained at all levels of the organization, as required by 21 C.F.R. § 820.20.

For example, we observed that your quality department does not observe critical steps in the manufacturing process of your products or take environmental monitoring samples to monitor your aseptic manufacturing operations. We also observed that there was not a basic hand washing sink outside your sterile gowning room, even though your own standard operating procedure (SOP) requires hand washing to be completed. Based on an interview with a Quality Control (QC) Microbiologist during the inspection, it was determined that this issue was discussed previously but your Quality Assurance (QA) management determined that the lack of a hand sink was acceptable. Because of your QA management's decision that the lack of a hand washing sink in such basic aseptic manufacturing operations is acceptable, we are concerned that an effective quality system has not been implemented and maintained.

*We have received your responses to the FDA-483 dated March 28, April 30, and May 30, 2008, and reviewed them as they relate to the specific observations noted on the FDA 483. In your response to this Warning Letter, we ask that you describe the changes being made to your quality system that will prevent such QS regulation violations from recurring.*

2. Failure to ensure that when the results of a process cannot be fully verified by subsequent inspection and test, that the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results shall be documented, as required by 21 C.F.R. § 820.75(a).

For example, we observed that your media fills executed per Aseptic Media Fill OPM-062, for validation of the aseptic manufacturing process, do not completely simulate routine manufacturing of sterile bulk concentrate used to manufacture Amvisc, Staarvisc II, Shellgel, Amvisc Plus, and Orthovisc. For example, process simulations do not incorporate the numerous manual aseptic steps performed, nor do they incorporate the same equipment and times that are routinely used during the actual manufacturing process.

Additionally, qualification of critical areas did not include evaluation of unidirectional air flow patterns under dynamic conditions with equipment in place to demonstrate and evaluate unidirectional airflow over and away from exposed product. Manual aseptic manipulations, transfer, formulation, filling, and sterility testing of Amvisc, Staarvisc II, Shellgel, Amvisc Plus, and Orthovisc occur in these critical areas.

Also, your environmental monitoring program does not provide meaningful information on the quality of the aseptic processing environment and ancillary areas used in the manufacture of Amvisc, Staarvisc II, Shellgel, Amvisc Plus, and Orthovisc. For example, your sampling and testing procedure does not incorporate the use of positive or negative controls; the frequency of routine environmental monitoring was changed from [REDACTED] per DCR 05-678 in February of 2006 without adequate justification or rationale for the change; and an evaluation of environmental monitoring sampling locations had not been conducted to assure the locations provide a true and accurate assessment of microbial flora and in the production areas they represent locations of microbiological risk to the product. Furthermore, no evaluation had been performed to assure cleaning solution residues do not negatively impact environmental monitoring sampling or testing.

*Your response letters describe a number of corrective actions that your firm has been implementing in response to the validation issues that are discussed above. For example, you will now be initiating appropriate studies to assure that your processes have been validated. We believe that once these studies are completed they will address our concerns. Please provide documentation of your completed corrective actions in your response to the Warning Letter. We also request that you address how you plan on preventing these validation lapses from recurring.*

3. Failure to establish and maintain procedures for implementing corrective and preventive actions, including investigating the cause of nonconformities relating to product, processes, and the quality system, as required by 21 C.F.R. § 820.100(a)(2).

For example, an investigation was initiated at your facility in October 2007 after a [REDACTED] was recovered in excess of the action limit [REDACTED] CFU) in gowning room 111 during monthly environmental monitoring. The investigation, INV-07-086, was opened on October 30, 2007 and closed on March 3, 2008. The investigation report revealed that the investigation was performed for the wrong room. The investigation was performed for Room 110 (an uncontrolled environment). A root cause was never determined for this excursion. Furthermore, two of the three lots that were manufactured during this excursion were released in November 2007. This was three months prior to your QA disposition, which was made on March 14, 2008, and stated, "Release – all product met specification."

*Your response to the above items is inadequate. We acknowledge that you have initiated further investigation into these areas. However, an effective Quality program includes thorough investigation and documentation of these types of nonconformances. In your response to the Warning Letter, please provide us with how you plan on preventing these items from recurring.*

Also, an investigation was initiated at your facility in June 2007 to address the contamination of sterile bulk concentrate. Your investigation determined that contamination may be attributed to [REDACTED] on the inner lid of the batch vessel. [REDACTED] is believed to have occurred because of a high fill volume allowing product to contact the [REDACTED]. FDA investigators observed that a CAPA 07-092 was approved by QA to examine the possibility of a maximum fill volume on August 28, 2007. However, during the inspection this CAPA had not yet been closed nor were the FDA investigators able to review any documentation that a preventative action had been implemented to mitigate the known risk of product contamination.

*Your response indicates that a preventive action was implemented. Please provide documentation of this completed CAPA in your response to the Warning Letter.*

4. Failure to establish and maintain process control procedures that describe any process control procedures necessary to ensure conformance to specifications where deviations from device specifications could occur as a result of the manufacturing process, as required by 21 C.F.R. Part § 820.70(a).

For example, [REDACTED] sampling of purified water is not conducted in a manner which is representative of purified water collection for use in manufacturing of bulk concentrate prior to sterilization. Specifically, samples are not collected from the collection hose, which is not flushed, cleaned, or sanitized prior to collection during routine use.

Additionally, the pre-sterile filtration bioburden sample is collected prior to filling concentrate into [REDACTED] pressurization tanks on the [REDACTED] day of filtration. Filtration can span [REDACTED] during which the approximately [REDACTED] transfer hose is stored coiled on top of the bulk tank in the ISO 8 tank room. This hose is not cleaned or sanitized prior to reuse on subsequent days of filtration, and samples are not collected on subsequent days of sterile filtration to evaluate bioburden levels.

Also, sterility of microbiological media plates used for environmental monitoring is not confirmed by incubating for not less than [REDACTED] days. You use [REDACTED] incubation period. Your procedures reference the current USP which requires sterility of media be confirmed by incubation for not less than [REDACTED] days.

*We understand from your response letters that these items have been corrected. In your response to this Warning Letter, please provide your plan for how you will prevent these violations from recurring.*

5. Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 C.F.R. § 820.198.

For example, your complaint handling procedure does not assure that complete information is obtained in order to evaluate the event thoroughly. Your SOP 14-001, step 5.4.2.1, indicates that when additional information is needed to proceed with the investigation, [REDACTED] attempts should be made to acquire additional information from the complainant. We observed that when you receive a complaint, you are not contacting the original complainant to obtain the information required to make a thorough investigation. Instead you are only dealing with the distributor, even though you are provided with the complainant's name. Also, information regarding the number of events, the final diagnosis, and specific treatment were not always obtained for complaints reviewed. Without this information, it is difficult to make a conclusion that further investigation is not warranted or an event is not reportable under 21 C.F.R. Part 803.

Additionally, we observed complaints of cases of inflammation, endophthalmitis, and Toxic Anterior Segment Syndrome (TASS) involving your ophthalmic products. We are concerned that thorough investigations are not being conducted on these complaints to determine that a root cause is not due to the above validation deficiencies. For example, you received a complaint from a distributor, CF-2006-21, regarding 10-15 cases of inflammation which may have occurred after use of lots B060404 and B060215A of Amvisc. The complaint was received on July 7, 2006, and was closed on August 1, 2007. There was no documentation in your file to demonstrate that your firm attempted to obtain further information from the individual complainants regarding these specific events.

Your firm also received a complaint from a distributor, regarding acute inflammatory reaction in a patient after use of Orthovisc lot N060106 and opened complaint CF-2006-36 on August 25, 2006. Contact information was received, however, no attempt was made to collect information regarding a specific diagnosis from the complainant and the complaint was closed on March 5, 2007.

Also, your firm received a complaint from a distributor regarding a case of TASS associated with lot B070023A of Shellgel and opened complaint CF-2007-84 on January 7, 2008. Your firm closed the complaint file on January 29, 2008 without contacting the doctor to obtain any additional information. We are concerned that your firm is not conducting root cause investigations for these complaints of potential sterility or pyrogen issues.

*We acknowledge that your responses did not address the issue described above.*

6. Failure to establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality, as required by 21 C.F.R. § 820.70(e).

For example, your firm's gowning procedure requires personnel to "Wash hands vigorously using the hand disinfectant in the scrub area." However, expired hand sanitizer was observed as available prior to entering gowning room 111 (gowning room 111 is used for entry to the aseptic processing area where sterile filtration, precipitation, manual removal, compression, and collection of product occur).

Additionally, we observed that the dissolution of bulk concentrate in [REDACTED] tank is conducted in cooler #7 (room 110) directly below one of the condensing units for the cooler. The tank can be stored in this area for several days pending in-process test results. The sterilized bulk concentrate is used in the manufacture of Amvisc, Staarvisc II, Shellgel, Amvisc Plus, and Orthovisc.

We also observed purified water collection hoses (approximately [REDACTED] that were not cleaned, sanitized, or stored in a manner which prevents microbial or bacterial endotoxin contamination of the bulk concentrate prior to sterilization. Specifically, the collection hose used to collect water from the purified water drop in cooler # 7 (room 110) was observed to be stored with water remaining in the hose between usage. Operators demonstrated the manner in which the hose is routinely drained prior to being used for water collection. However the hose is not cleaned or sanitized prior to use in collection of purified water.

*We have reviewed your responses and believe your proposed corrections, once fully implemented, will correct these above violations. In your response to this Warning Letter, we request that you provide your plan on how you propose to prevent these types of violations from recurring.*

7. Failure to have buildings that are of suitable design and contain sufficient space to perform necessary operations, prevent mix-ups, and assure orderly handling, as required by 21 C.F.R. § 820.70(f). For example, we observed that:
  - No hand washing sink is provided adjacent to gowning room 111 (ISO 7) even though the gowning procedure requires personnel to "Wash hands vigorously using the hand disinfectant in the scrub area."
  - In room 113, the ISO 7 area adjacent to the ISO 5 shroud is used as a gowning area for operators to change into appropriate gowning (a.k.a. "bunny suits"), however, the area's intended function is for sterile filtration of product, not gowning.
  - The microbiology lab was crowded by lab material storage.

- The ISO 5 hood (used for product sterility testing) was located in the ISO 7 packaging area, located under a HEPA filter air supply duct and an exposed wet line sprinkler head.
- Filled and stoppered syringes were on carts with cart covers and stored in cooler #7 (room 110) directly below condensing units for the cooler; your firm does not have a program for cleaning or sanitization of the cart covers.

*We have reviewed your responses and believe your proposed corrections, once fully implemented, will correct the aforementioned violations. In your response to this Warning Letter, we request that you provide your plan on how you propose to prevent these types of violations from recurring.*

8. Failure to establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities, as required by 21 C.F.R. § 820.25(b).

For example, an operator exiting cooler #7 with both hands filled with clean equipment parts was observed removing disposable shoe covers, opening a trash receptacle, and disposing of the shoe covers into the trash receptacle while holding clean equipment parts in both hands. Also, expired [REDACTED] hand sanitizer was being used prior to entering gowning room 111 in lieu of scrubbing hands with disinfectant and water.

We are concerned that your training program is ineffective when such practices are observed during an FDA inspection. We look forward to reviewing your plans for an effective training program that will include training of individuals that are associated with aseptic processing and thorough evaluation of the quality system that will serve to prevent these actions from recurring.

*We acknowledge that your responses did not address the issue described above.*

Our inspection also found deviations from FDA's cGMP regulations for the manufacture of finished pharmaceuticals, 21 C.F.R. Part 211, in regards to your animal prescription drug product, Hyvisc Sterile Injection (hyaluronate sodium) (NADA 122-578). Failure to conform to the drug cGMP regulations causes drug products manufactured by your facility to be adulterated within the meaning of section 501(a)(2)(B) of the Act, 21 U.S.C. § 351(a)(2)(B), in that the test methods used in, and procedures and controls used for, the manufacture, processing packing, and holding of drugs do not conform with cGMP regulations to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess. FDA investigators found the following deviations from the cGMPs for finished pharmaceuticals:

1. Failure to thoroughly investigate any unexplained discrepancy, whether or not the batch has already been distributed, as required by 21 C.F.R. Part 211.192. *See corresponding Warning Letter item # 3 under the QS regulation violations.*
2. Failure to have buildings, used in the manufacture, processing, packing or holding of a drug product, that are a suitable size, construction and location to facilitate cleaning, maintenance and proper operations, as required by 21 C.F.R. Part 211.42. *See corresponding Warning Letter item # 7 under the QS regulation violations.*
3. Failure to have personnel engaged in the manufacture, processing, packing, or holding of a drug product wear protective apparel, to protect drug products from contamination, as required by 21 C.F.R. 211.28(a). Specifically, the investigators observed an operator exiting cooler #7 with both hands filled with clean equipment parts (connectors, etc.) removing disposable shoe covers, opening a trash receptacle, and disposing of the shoe covers into the trash receptacle while holding clean connections in both hands.

The issues and 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 or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

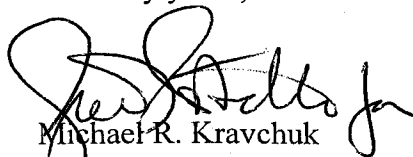
You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, and/or injunction and, with respect to the device violations described in this letter, could include civil money penalties. Also, federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject products have been corrected. In addition, FDA may withhold approval of pending new animal drug applications and abbreviated new animal drug applications listing your facility as a manufacturer until the above violations are corrected. A reinspection may be necessary.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. If corrective action cannot be completed within

fifteen (15) working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to Ms. Karen Archdeacon, Compliance Officer, Food and Drug Administration, One Montvale Avenue, Fourth Floor, Stoneham, Massachusetts 02180. If you have any questions about the content of this letter please contact Ms. Archdeacon at (781) 596-7707.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Michael R. Kravchuk". The signature is stylized and cursive, with a large initial "M" and "K".

Michael R. Kravchuk  
Acting District Director  
New England District