Inspections, Compliance, Enforcement, and Criminal Investigations

Artsana S.p.A 6/3/11

Department of Health and Human Services

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

WARNING LETTER

JUN 3 2011

VIA UNITED PARCEL SERVICE

Mario Merlo
Director and Legal Representative
Artsana S.p.A.
Via Saldarini Catelli 1
22070 Gandate (Como),
Italy

Dear Mr. Merlo:

During an inspection of your firm located in Como, Italy, on January 24, 2011, through January 27, 2011, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures sterile insulin syringes and pen needles. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h), these products are 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 function of the body.

This inspection revealed that these devices 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) regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.

We received a response from Alberto Munzone, Plant Manager, dated February 16, 2011, concerning our investigator's observations noted on the Form FDA 483, List of Inspectional Observations, that was issued to you. We address this response below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. Failure to establish and maintain adequate procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198(a). For example:

a. Complaint handling procedures are not established for various Artsana Group departments

such as Export Managers, Hospital Office, and Customer Service which receive, document, review, and forward complaints to the Quality Department at Plant UP **(b)(4)**. The three Artsana departments described do not operate under the UP **(b)(4)** or any Artsana Group quality system.

The adequacy of your firm's response cannot be determined at this time. Your firm updated its flowchart (14.03.01.02 Rev. 03) to add channels for receiving and forwarding complaints. However, no documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

b. Complaint Procedure 14.03.00.00 does not define how complaints will be evaluated by the Quality Department to determine whether the complaint represents an event that is required to be reported to FDA under 21 CFR Part 803, Medical Device Reporting.

The adequacy of your firm's response cannot be determined at this time. Complaint Procedure 14.03.00.00 Rev. 06 was updated to include identification of adverse events and complaint evaluation. However, no documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

c. Seven of seven complaints reviewed did not contain documentation of the original complaint event as reported by the complainant (only a description of the reported defect).

The adequacy of your firm's response cannot be determined at this time. No documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

2. Failure to adequately ensure that, when the results of a process cannot be fully verified by subsequent inspection and test, that the process is validated with a high degree of assurance and approved according to established procedures, as required by 21 CFR 820.75(a). For example:

a. The **(b)(4)** process for sterile barrier packaging of pen needles has not been adequately validated. The only existing verification study was completed as part of the pen needle assembly line validation. The study tested **(b)(4)** pen needle closures using **(b)(4)** testing. There is no documentation of sealing equipment qualification, no documentation of validation of **(b)(4)**, which monitors sealing temperature, no establishment of a maintenance schedule for the sealing equipment, no identification of processing variables and verification controls for proper sealing, and no documented rationale for the selected sampling plan. This is a repeat observation.

The adequacy of your firm's response cannot be determined at this time. Your firm intends to complete process validation by July, 2011, to include qualification of sealing equipment, validation of **(b)(4)** for temperature alarm management, maintenance plans to supplement control of **(b)(4)**, a capability study on medical paper sealing, and an update of control plan according to validation results. However, no documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

b. The **(b)(4)** process used for the **(b)(4)** following sterilization of pen needles has not been adequately validated. No thermal mapping studies were done for the **(b)(4)** in which all sterilized products are **(b)(4)**. There are no designated locations **(b)(4)** for placement of product during **(b)(4)** and pallets are placed by the **(b)(4)** in **(b)(4)** racks throughout the **(b)(4)** as **(b)(4)**. Temperature is monitored at **(b)(4)** locations within the (b)(4), at the (b)(4) of the **(b)(4)**. Routine **(b)(4)** results for release do not include documentation of the pallet locations **(b)(4)** during **(b)(4)**. There are no documented quality system procedures for the control of the **(b)(4)** process or product **(b)(4)** where **(b)(4)** occurs.

The adequacy of your firm's response cannot be determined at this time. A study will be carried out to include evidence of the **(b)(4)** time frame related to the environmental temperature (**(b)(4)** curve) and verification of **(b)(4)** results for documenting the location of the pallets**(b)(4)**. However, no documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

3. Failure to adequately document software validation activities and results for computers or **(b)(4)** systems used as part of production, as required by 21 CFR 820.70(i). For example, there is no documentation of validation having been performed on the software systems that operate the **(b)**

(4), which moves **(b)(4)** pallets from **(b)(4)** to shipping **(b)(4)**. There are no documented quality system procedures for the control of the **(b)(4)** finished product warehouse (UP **(b)(4)**) and your firm's **(b)(4)** department does not operate within your firm's quality system.

The adequacy of your firm's response cannot be determined at this time. Your firm intends to update documentation of validation being performed on the software systems by July, 2011. However, no documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

4. Failure of management with executive responsibility to adequately ensure that the quality policy is understood, implemented, and maintained at all levels of the organization, as required by 21 CFR 820.20(a). For example, the Quality Policy for production plant UP **(b)(4)** has not been established by any member of executive management within Artsana Group. The quality system under which plant UP 30 operates is only established for plant UP **(b)(4)** and the Artsana Group does not have any established quality system.

The adequacy of your firm's response cannot be determined at this time. Your firm updated its quality manual. However, no documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

5. Failure to adequately establish procedures for quality audits, as required by 21 CFR 820.22. For example, the 2010 audit plan was not performed for nine of **(b)(4)** departments to be audited and the plan does not include auditing all areas of the quality system. Complaint handling is not covered by any of the defined areas.

The adequacy of your firm's response cannot be determined at this time. Your firm intends to complete the remaining 2010 internal audits to include complaint handling by May, 2011. However, no documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

6. Failure to adequately review the suitability and effectiveness of the quality system by management with executive responsibility, as required by 21 CFR 820.20(c). For example, management review does not include members of Artsana's executive management nor do management review procedures define the dissemination of information regarding management review to executive management. Management review is performed only at the UP **(b)(4)** production plant level and only UP **(b)(4)** has an established quality system. Neither the Artsana Group nor the Health and Beauty Care Division of Artsana Group (which includes all medical device production) has established quality systems.

The adequacy of your firm's response cannot be determined at this time. Your firm updated its quality manual. However, no documentation or evidence of corrections, corrective actions, or systemic corrective actions was provided.

Our inspection also revealed that your devices are misbranded under section 502(t)(2) of the Act, 21 U.S.C. 352(t)(2), in that your firm failed or refused to furnish material or information respecting the device that is required by or under section 519 of the Act, 21 U.S.C. 360i, and 21 CFR Part 803 – the Medical Device Reporting (MDR) regulation. Significant violations include, but are not limited to, the following:

Failure to develop, maintain, and implement written MDR procedures, as required by 21 CFR 803.17. For example, there are no procedures for reporting MDR events to FDA. Complaint procedures only define reporting requirements for other Competent Authorities. They do not define how or when to report to FDA or what an MDR reportable event is, and do not include a standardized review process for determining when reporting is required.

The adequacy of your firm's response cannot be determined at this time. Your firm updated its procedure (14.03.00.00 Rev. 06: Management and product definition reported or rejected by the customer) to include requirements for reporting MDR events to FDA. However, no documentation or evidence of corrections, corrective actions or systemic corrective actions was provided.

U.S. federal agencies are advised of the issuance of all Warning Letters about 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 devices have been corrected.

Please notify this office in writing within 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 15 working days, state the reason for the delay and the time within which the corrections will be completed. Please provide a translation of documentation not in English to facilitate our review.

Your response should be sent to Allen Wynn, Field Operations Branch, Division of Risk Management Operations, Office of Compliance. Refer to CMS case #178513 when replying. If you have any questions about the content of this letter please contact Valerie A. Flournoy at 301-796-5770 or 301-847-8137 (facsimile).

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Sincerely yours,

/s/

Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

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