U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

AGFA healthcare Corp. 4/15/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New England District
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Stoneham, Massachusetts
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WARNING LETTER

NWE-15-11W

CMS case # 16275

April 15, 2011

VIA UPS EXPRESS

Mr. Christian Reinaudo
President
AGFA Healthcare NV – Corporate Headquarters
Septestraat 27, 2640 Mortsel, Belgium

Dear Mr. Reinaudo:

During an inspection of your firm located in Westerly, RI on 11/30/2010 through 1/6/2011, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures AGFA IMPAX Cardiovascular Suites. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 2: 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.

Our inspection revealed that your IMPAX Cardiovascular Suites (CV) is 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 - Medical Device Reporting (MDR) regulation. Significant violations include, but are not limited to, the following:

1. Failure to submit all information that is reasonably known to you in the MedWatch 3500A Form, as required by 21 CFR 803.50(b)(1).

For example, MDR **(b)(4)** does not indicate that the patient was in respiratory failure and subsequently died after delayed heparin treatment.

2. Failure to submit a complete MDR to indicate in Form 3500A, Block B, the outcome attributed to the adverse event, as required by 21 CFR 803.52(b)(2).

For example, Block B2 for the initial and supplemental MDR submitted **(b)(4)** does not indicate that the patient had died.

3. Failure to initially submit a correct MDR **(b)(4)** and supplement MDR to indicate in Form 3500A, Block H1, the type of the reportable event, as required by 21 CFR 803.52(f)(1).

For example, Block H1 from the initial MDR **(b)(4)** indicates the type of the event as "Other: delayed treatment." In your supplemental MDR, you indicated in Block H1 the type of the reportable event as "Malfunction." There is no evidence from the MDRs submitted that indicate that the patient died.

4. Failure to have an adequate written MDR procedure establishing an internal system that provides for timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements, a standardized review process or procedure for determining when an event meets the criteria for reporting, timely transmission of complete medical device reports, and documentation and recordkeeping requirements, as required by 21 CFR Part 803.17.

For example:

a. Your procedure fails to indicate where to submit the MedWatch Form 3500A to FDA.
b. Your procedure does not clarify what is your reportability criterion to determine when an even meets the criteria for reportable as death, malfunctions and serious injuries to FDA.

To improve the quality of your MDR Procedure we have the following recommendation:

We recommend removing from your procedure any references to baseline reporting on FDA Form 3417 as this is no longer a requirement. Please refer to the Federal Register Notice dated September 17, 2008 (Volume 73 Number 181), Page 53686 located on the FDA website at:
http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/ucm124086.htm [1].

We reviewed your responses dated January 27, 2011 and February 25, 2011 and have concluded that they are not adequate because your conclusion that the patient did not die as a result of device failure is based on the limited information from the physician's discharge report. The physician's report does not reference the cause of the patient's death. In addition, you have stated that there was a device product problem. This resulted in delayed treatment of the patient with heparin for fifty-four (54) minutes. Your HEALTH HAZARD EVALUATION FORM, HHE_HQ_0904220006, states that there is a potential risk to the patient resulting from delayed treatment. Without additional information from you demonstrating that the device did not cause or contribute to the patient's death, we conclude that the information included for the event which occurred on **(b)(4)**, (MDR #**(b)(4)**) reasonably suggests that your device may have caused or contributed to the death o the patient.

If you wish to discuss any concerns related to 21 CFR Part 803, you may contact the MDR Policy Branch, at 301-796-6670 or by email at MDRPolicy@fda.hhs.gov.

Our inspection also revealed that your AGFA IMPAX Cardiovascular Suites 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 806 – Reports of Corrections and Removals regulation. Significant violations include, but are not limited to, the following:

1. Required information regarding device correction and removal actions was not sent to FDA within 10 days of initiating the correction or removal as required by 21 CFR 806.10(b).

For example:

a. Your firm failed to file a report with FDA regarding the complaint **(b)(4)** that resulted in the correction of IMPAX CV CRS versions 2.12.05 to 2.14.03. SU1, containing an error with the "Point - Trace method of heart volume measurement which would result in erroneous measurement if the protocol mode is re-enabled after measurement is made." According to the Health Hazard

Evaluation Report, in unusual circumstances (e.g. using only **(b)(4)** tracing points for the area) th **(b)(4)** difference in measurement values could be as large as **(b)(4)**. Your firm classified the problem as a Device Malfunction failing to meet its performance specifications or perform as intended. A service bulletin was sent to **(b)(4)** impacted customers and, as a result, the software was upgraded to version CRS 2.14.03.SU2 and applied to the impacted sites.

b. Your firm failed to file a report with FDA regarding the complaint **(b)(4)** that resulted in the correction of IMPAX CV RMAT versions RM2.03, 2.04, and 2.06, where units modified within **(b)(4)** were causing the mismatch of unit measurements. According to your firm's Cardiovascular R & D Manager, the user could change the units of the measurements but the calculation formulas in the software would not adjust to the change of the measurement units and would calculate incorrectly and produce incorrect measurements. According to your firm's Clinical/Medical Expert, not all resulted measurement are erroneous and clearly detected and they may lead to delayed patient diagnosis and care or misdiagnosis such as aortic valve stenosis. The measurements are used in patient's heart health assessment such as the size of the heart, the heart and heart valve performance assessment. A service bulletin was sent to **(b)(4)** impacted customers and as a resul the upgraded software version IMPAX CV 2.08 was applied to the impacted sites."

Specifically, AGFA, Inc. conducted two field corrections:

1. "...correction of IMPAX CV CRS versions 2.12.05 to 2.14.03. SU1 - in response to complaints # **(b)(4)**."

2. "...correction of IMPAX CV RMAT versions RM2.03, 2.04, 2.06 - in response to complain # **(b)(4).** NOTE – complaint number corrected to **(b)(4)**."

Your action was reviewed by FDA and determined to meet the requirements of a Class II (precedent) recall (Z # 2112 - 2010) which also meets the threshold for a 21 CFR 806 report as specified in 21 CFR 806.2(j) (2) Therefore, your firm's actions should have been reported to FDA within ten days as required by 21 CFR 806.10(b).

The adequacy of the responses dated January 27, 2011 and February 25, 2011 cannot be determined at this time because modifications to your firm's 806 process, training, etc., will require a follow-up inspection to determine if the changes have been implemented and are effective. However, your firm maintains that its fiel corrective actions are Class III and, therefore, not subject to reporting under 21 CFR 806. While it is correct that a Class III recall does not require the submission of a C/R report, it would require documentation under 21 CFR 806.20 and the Agency has determined that the recalls are Class II. This difference in evaluating risk/severity may result in future unreported Correction or Removal reports.

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, 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.

Please notify this office in writing within fifteen (15) business days from the date you receive this letter of the specific steps you have taken to correct the noted violations, as well as an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrections and/or corrective actions you have taken. If your planned corrections and/or corrective actions will occur ove time, please include a timetable for implementation of these activities. If corrections and/or corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which these activities will be completed. Your response should be comprehensive and address all violations included in this Warning Letter.

Your response should be sent to: U.S. Food and Drug Administration, New England District Office, One Montvale Ave, Stoneham, MA 02180**.** If you have any questions about the content of this letter please contact: Compliance Officer Todd Maushart at (781) 587-7486.

In addition, FDA has noted nonconformances with regards to section 501(h) of the Act (21 U.S.C. § 351(h)), which are deficiencies of the following Current Good manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at 21 CFR Part 820. These nonconformities include, but are not limited to, the following:

1. Failure to establish and maintain adequate procedures to ensure that devices conform to defined user needs and intended uses; to ensure proper risk analysis is completed; and to ensure the results of the design validation, including identification of the design, methods, the date, and the individuals performing the validation are documented in the design history file, as required by 21 CFR 820.30(g).

For example:

a. The document titled Product Validation Strategy **(b)(4)** Acceptance Criteria, requires "**(b)(4)** pass for Safety and Effectiveness, where as the Software Verification and Validation procedure **(b)(4)**, states: "If open bugs will not be resolved before release, the final verification report must contain a section addressing and motivating this issue." The **(b)(4)**, reveals the validation summary report was determined successful overall even though **(b)(4)** Image and Report Display Remote Functionality tests failed. The comment section of this Functional test case reveals compression settings were changed to address the failed tests, "however the client has not responded with further testing results." The comment section also states that pending future testing by the client, the recommendations for the launch team is to proceed with product release schedule. There is no documentation available to ensure all functional tests were eventually **(b)(4)** passed.

b. The justification for the acceptance of the failed test results was not documented. Validation Summary Report CV 7.8 Document number 29297042, page 2, states that issues were discovered during validation of CRS Remote 7.8 have been identified and a plan acceptable to the project control team (PCT) is in place for resolution. However, your firm could not provide documentation of the plan.

c. Your firm was unable to further provide documented justification for the **(b)(4)** test stops involved in the verification of the CRS Remote Functionality that were not performed, according to IMPAX CV Imaging CRS 7.8 Test Log: CRS Remote Functionality (verification), dated 12/28/2009.

d. IMPAX CRS Remote Validation Test case, dated 11/3/2009, and IMPAX CV Imaging CRS 7.8 Test Log: CRS Remote Functionality (verification), start dated 12/28/2009, were conducted prior to approval of the Remote CRS Validation strategy, dated 1/6/2010. Finally, your firm lacks established procedures for qualification of the clinical sites used for the validation of the device.

The adequacy of the responses dated January 27, 2011 and February 25, 2011 cannot be determined at this time. Your firm has committed to improving their procedures and has updated training as evidenced by provided training records, as well as procedures and templates were provided. It should also be noted that th object of the validation has since been recalled from the market. However, there is inadequate proof of implementation of software validation processes for your firm.

2. Failure to establish and maintain adequate procedures for the identification, documentation, validation o where appropriate verification, review, and approval of design changes before their implementation, as required by 21 CFR 820.30(i).

For example, your firm was unable to provide a documented design development timeline or work instruction for IMPAX CV 7.8.SU1 of the IMPAX CV 7.8 software design change that resulted in **(b)(4)**, approval for Global Release and Delivery on 7/30/2010.

The adequacy of the responses dated January 27, 2011 and February 25, 2011 cannot be determined at this time. Your firm has committed to improving their procedures and has updated training as evidenced by provided training records, as well as procedures, work instructions and templates were provided. However, your firm has not provided evidence of systemic review to determine if other areas have similarly been reviewed for potential changes required.

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 management 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,
/S/
Mutahar S. Shamsi

District Director
New England District

Cc: Mr. Olivier Kagan
Management Representative, Cardiology R&D Manager
AGFA Healthcare Corp.
1 Crosswind Dr
Westerly, RI 02891-3679

Links on this page:

1. http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/ucm124086.htm