Inspections, Compliance, Enforcement, and Criminal Investigations

Medart A/S 11/19/12

Department of Health and Human Services

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

WARNING LETTER

November 19, 2012

VIA UNITED PARCEL SERVICE

Mark Clements
Chief Operating Officer
MedArt A/S
Enterprise Park
Clos Llyn Cwm.,
Valley Way,
Swansea, SA6 8QY United Kingdom

Dear Mr. Clements:

During an inspection of your firm located in Hvidovre, Denmark, on May 29, 2012, through June 1, 2012, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures medical laser devices. 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 to affect the structure or function of the body.

Our inspection revealed that your firm's 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 - Medical Device Reporting.

We received responses from Olav Balle-Petersen, VP of Research and Development, Innovation and Quality Assurance, dated June 14, 2012, and June 20, 2012, concerning our investigator's observations noted on the Form FDA 483 (FDA 483), List of Inspectional Observations, which was issued to your firm. We address these responses below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

Failure to adequately develop, maintain and implement written medical device reporting (MDR) procedures, as required by 21 CFR 803.17. For example, after reviewing your firm's March 2011 MDR procedure titled, *Quality Manual, 106442 v1, Section 2.3 – 4.1.2, Procedures for Reporting to FDA*, the following issues were noted:

a) Procedure 106442 v2 does not establish internal systems that provide for a standardized review process to determine when an event meets the criteria for reporting under this part. For example:

- There are no instructions for conducting a complete investigation of each event and evaluating the cause of the event.
- There are no instructions for how your firm will evaluate information about an event to make MDR reportability determinations in a timely manner.

b) Procedure 106442 v2 does not establish internal systems that provide for timely transmission of complete medical device reports. Specifically, although your firm includes a web address, http://www.fda.gov/medwatch/report/instruc.htm[1], for access to the MedWatch 3500A Mandatory Reporting Form and instructions for how to complete the form, the address provided is incorrect.

c) Procedure 106442 v2 does not describe how your firm will address documentation and record-keeping requirements, including:

- Documentation of adverse-event-related information maintained as MDR event files;
- Information that was evaluated to determine if an event was reportable;
- Documentation of the deliberations and decision-making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable;
- Systems that ensure access to information that facilitates timely follow-up and inspection by FDA.

We reviewed your firm's response dated June 14, 2012, and conclude that it is not adequate. Although your firm revised its MDR procedure to include an attachment titled, Instruction – MedArt MDR filing evaluation, "Dok. Nr. 106705 Ver: 2," dated June 14, 2012, it still fails to establish internal systems that provide for timely transmission of complete medical device reports. Specifically, although your firm includes a web address, http://www.fda.gov/medwatch/report/instruc.htm[2], for access to the MedWatch 3500A Mandatory Reporting Form and instructions for how to complete the form, the address included in your firm's MDR procedure is incorrect.

We reviewed your firm's response dated June 20, 2012, and conclude that we cannot determine its adequacy. Your firm included completed copies of its MDR evaluation process forms (doc 106705) corresponding to complaints #**(b)(4)**, **(b)(4)**, and **(b)(4)**. However, these forms do not include the information needed to determine if the adverse event meets the criteria for reporting to the FDA. In addition, there is no evidence that your firm's MDR procedure was revised to include a correct reference that will allow your firm to gain access to the MedWatch 3500A, Mandatory Reporting Form, and instructions for how to complete the form.

If your firm wishes to submit MDR reports via electronic submission it can follow the directions stated at the following URL:

http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm107903.htm[3]

If your firm wishes to discuss MDR reportability criteria or to schedule further communications, it may contact the MDR Policy Branch at 301-796-6670 or by email at MDRPolicy@fda.hhs.gov.

Federal agencies may be advised of the issuance of Warning Letters about devices so that they may take this information into account when considering the awarding of contracts.

Please notify this office in writing within fifteen business days from the date you receive this letter of the specific steps your firm has taken to correct the noted violations, as well as an explanation of how your firm plans to prevent these violations, or similar violations, from occurring again. Include documentation of the corrections and/or corrective actions (including any systemic

corrective actions) that your firm has taken. If your firm's planned corrections and/or corrective actions will occur over time, please include a timetable for implementation of those activities. If corrections and/or corrective actions cannot be completed within fifteen business days, state the reason for the delay and the time within which these activities will be completed. Your firm's response should be comprehensive and address all violations included in this Warning Letter. Please provide an English translation of documentation to facilitate our review.

In addition, FDA has noted nonconformances with regard to section 501(h) of the Act, 21 U.S.C. § 351(h), which are deficiencies within your firm's quality system pertaining to current good manufacturing practice requirements specified in the Quality System 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 for implementing corrective and preventive action to include requirements for (1) analyzing quality data to identify existing and potential causes of nonconforming product or other quality problems, using appropriate statistical methodology, where necessary; (2) investigating the cause of nonconformities; (3) identifying actions needed to correct and prevent recurrence of nonconforming product and other quality problems; (4) verifying and validating corrective and preventive actions to ensure that the actions do not adversely affect the products; (5) implementing and recording changes necessary to correct and prevent identified quality problems; and (6) disseminating information related to quality problems and nonconforming product, as required by 21 CFR 820.100(a).

For example, review of three out of **(b)(4)** Corrective and Preventive Action (CAPA) records revealed:

a) Q-case #**(b)(4)** concerned **(b)(4)**. Your firm's investigation identified and processed the corrective actions as a production nonconformance, but statistical methods were not used to quantify the problem. The corrective action of **(b)(4)** was implemented, but validation was not conducted or documented to ensure that the corrective actions was effective and did not adversely affect the product.

b) Q-case #**(b)(4)** documents the corrective action that your firm took to change the version of the **(b)(4)**. Your firm's report did not document that: statistical methods were used to quantify the problem; the root cause was identified; the batch number of the affected **(b)(4)** was identified; validation tests and results were conducted prior to release of the new design into production; the batch number of the new version of the **(b)(4)** was recorded; the effectiveness of the corrective action was evaluated; or that the corrective action was effective and did not adversely affect the new product.

c) Q-case #**(b)(4)** concerns an **(b)(4)**. MedArt A/S issued a corrective action request to **(b)(4)**, its contract manufacturer, but the corrective actions taken by the contract manufacturer were not documented in the CAPA. In addition, this CAPA file did not contain documentation of the effectiveness of the corrective action taken.

We reviewed your firm's response and conclude that it is not adequate. Your firm provided its revised procedure, "Corrective and Preventive Action," in *Section 7.1-4, Quality Manual document #106442 v2,* dated June 26, 2012, and the revised CAPA records. However, your firm did not provide evidence that the remaining **(b)(4)** CAPA reports disclosed during the inspection have been revised and corrected as necessary in accordance with your firm's revised procedure and that the revised procedure has been implemented.

2. 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. For example:

a) Your firm's procedure, *Kvalitetsmanual Dok. Nr: 106442 Section 2.3 Complaints,* requires determination of a complaint as critical or non-critical for adverse event reporting to both

FDA under 21 CFR 803 and to EU authorities. Your procedure is not adequate because it does not specify how to determine criticality, how to document the rationale for not investigating a complaint, or how to document the results of a complaint investigation. Specifically, *Section 2.3-4.1, "Special Procedures in case of serious risk or serious harm,"* includes only two of the three required criteria per your firm's procedure to determine if an incident is "critical" or "not critical" for reporting to the FDA under Part 803. In addition, your firm's Quality Manual does not define what is "critical," "non-critical," and an "MDR reportable event"

b) Review of complaint records disclosed that of the four complaints reviewed – Q-Cases **(b)(4)**, **(b)(4)**, **(b)(4)**, and **(b)(4)** – your firm did not perform an MDR reporting determination.

c) Your firm's *Q-case software Work Instruction Dok. Nr. 104378 Ver. 2,* dated December 5, 2008, requires the responsible individual to document the rationale not to investigate an event with the name of the responsible individual identified. None of the four complaints reviewed above included the rationale.

d) Your firm's procedure for complaint investigations requires that complaints record include all eight required data elements. These include: (1) the name of the device; (2) the date the complaint was received; (3) any device identifications and control numbers; (4) the name, address, and phone number of the complainant; (5) the nature and details of the complaint; (6) the dates and results of the investigation; (7) any corrective action taken; and, (8) any reply to the complainant. None of the four complaint records reviewed included all of the required information.

The adequacy of your firm's responses dated July 14, 2012, and August 27, 2012, cannot be determined at this time. Your firm provided its revised procedure, *Kvalitetsmanual Dok. Nr: 106442 Section Complaint, Q-Case software Work Instruction form 106699 Version 1,* dated June 12, 2012, and new complaint instruction *"MedArt MDR Filing Evaluation" Doc. Nr. 106705 Ver. 2,* dated June 14, 2012. However, your firm did not provide evidence to demonstrate that the revised procedures have been implemented.

3. Failure to establish and maintain adequate procedures to control the design of the device in order to ensure that specified design requirements are met, as required by 21 CFR 820.30(a).

For example, your firm's procedure *Kvalitetsmanual Dok. Nr: 106442* is deficient in that:

a) Section 4.2-5, titled, *Development Monitoring,* requires a development plan, but your firm did not have a design plan for the Model 720 diode laser instrument (510(k) #K110243) in its design history file. Section 4.2-6, titled, "*Prospecting*" requires a development plan to be "produced to describe the main tasks involved in the project." It requires this phase "to be approved by the Development Head and summarized in a Project evaluation Form." This section also requires a description of the rationale if the development process for design projects has been shortened. The design project for Model 720 was shortened, but there was no documentation to describe the rationale as required.

b) Section 4.2-7, titled, *Development of Key Functionality,* requires your firm's Project Engineer to create a Requirement Specification that includes the specifications for the product design inputs and output requirements, and the document to be approved by the Development Manager. The inspection found that the design input or output requirements that would address the intended use of the device, or include the needs of the user and /or the patient were not documented for Model 720.

c) Section 4.2-7, titled*, Development of Key Functionality*, requires design reviews to be planned, conducted, and documented at appropriate stages of the development cycle. Your

firm did not have any documentation for any design review meetings held. In addition, the project manager did not recall any design review meetings held specifically for the model 720 design.

d) *Section 4.2-7,* titled*, Development of Key Functionality,* requires a signed and approved test specification, test protocol, and test verification results, but there was no design verification document available during the inspection.

e) Section 4.2-7, titled *Development of Key Functionality,* includes requirements for design validation methods, the documentation of the results of validation activities, the product name, the date, and the name of the person performing these activities. Your firm did not have any documentation for Model 720 that included identification of the design methods, the results of validation, the date, or the names of individuals performing validation.

f) Section 4.2-7, titled, *Development of Key Functionality,* requires the firm to assess risk and re-assess risk as needed. Although Model 720 was released on November 25, 2010, Software Risk Management Summary Doc. No.: 105927 was assessed in Version 7 on July 14, 2011. The Design History File did not include clinical risk analysis specific to the intended use of Model 720 design.

We reviewed your firm's responses dated July 14, 2012, and August 12, 2012, and conclude that they are not adequate. Your firm provided copies of new and revised documents regarding some Model 720 design deficiencies. Specifically,

(i) To address design plan deficiencies, your firm discusses performance of a software risk assessment on July 14, 2012, but there is no reference to software design, verification, or validation in the above document. Although the revised document was written, approved, and signed by Mr. Balle-Petersen as the project engineer, the Development Manager, and the Quality Manager, there is no other signature to indicate that this plan was reviewed by someone other than Mr. Balle-Petersen, and approved.

(iii) To address design verification deficiencies, your firm provided pages 1 and 2 of a 3-page retrospective *Design Verification Report Doc. No. #106714 Version 1,* dated July 10, 2012. It includes a summary of the verification and reference to Model 700 test specification and test protocol, but there are no actual verification results or a conclusion of the verification activities.

(iv) To address design validation deficiencies, your firm provided *Design Verification report Doc. No. 106714, Ver.1,* dated July 10, 2012. 21 CFR 820.30(g) requires device validation to be performed on "initial production units, lots, or batches, or their equivalents" and since these prototypes are built at different times and under different procedures, the validation result may not be comparable. Also, there is no acceptance/rejection criteria in the verification protocol.

(v) To address risk analysis deficiencies, your firm did not provide any documentation to support its conclusions.

(vi) Your firm's responses to the FDA 483 do not address design input, and design output deficiencies (Items 3b and 3c above) because these items were not listed as an Observation on the FDA 483 form.

4. Failure to establish and maintain adequate calibration procedures that include specific directions and limits for accuracy and precision, and provisions for remedial action to reestablish the limits and to evaluate any adverse effect on device quality when accuracy and precision limits are not met, as required by 21 CFR 820.72(b). For example, your firm's calibration procedure in *Section 6.2,* titled *Calibration* in the *Kvalitetsmanual Doc. Nr. 106442,* requires initiating a Q-case

to investigate when an instrument is out of calibration. During the review of the calibration record for an instrument, it was noted to be out of specification during calibrations conducted in 2010 and 2011, and no Q-case had been initiated.

The adequacy of your firm's response cannot be determined at this time. Your firm states that the calibration data was misinterpreted by your inspector. Your firm contacted the external contractor, clarified the misunderstanding, and to avoid future problems, the contractor has agreed to notify your firm when equipment is found to be outside the specified range. No documentation was provided in your firm's response, but your firm stated that it plans to revise the quality manual in the future.

5. Failure to establish and maintain adequate procedures for identifying valid statistical techniques for establishing, controlling, and verifying the acceptability of process capability and product characteristics, as required by 21 CFR 820.250(a). For example, during the inspection, your firm informed the FDA investigator that **(b)(4)** was used for design validation of Model 720, and that your firm does not have a procedure for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of product characteristics such as new product designs.

We reviewed your firm's responses and conclude that it is not adequate. Your firm states that it has plans to add the statistical technique procedure to its quality manual, but these revisions have not been made as of October 26, 2012.

6. Failure of management with executive responsibility to review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of 21 CFR 820 and the manufacturer's established quality policy and objectives, and to document the dates and results of quality system reviews, as required by 21 CFR 820.20(c). For example, *Section 1.5-8* of your firm's management review procedures,titled*, Management's Assessment* of the Quality System in the *Kvalitetsmanual Dok. Nr. 106442* requires a meeting for **(b)(4)** review of the quality system. Your firm's procedure indicates that the Managing Director, the Quality Manager, and other responsible individuals are required to participate in the **(b)(4)** quality system review meeting. However, your procedure does not require that the date of quality system reviews shall be documented. During the **(b)(4)** Management Review meeting, the Managing Director did not participate in the meeting as indicated by the quality system review meeting attendance record. The **(b)(4)** quality system review meeting attendance records reviewed by the investigator did not include the dates of the meetings.

We reviewed your firm's response and conclude that it is not adequate. Your firm stated that the **(b)(4)** meeting was repeated with all four senior managers present and provided a record of the meeting dated **(b)(4)**. However, your firm did not state that it planned to revise its procedure to include a requirement to document the dates and results of quality system reviews.

7. Failure to establish adequate procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities, as required in 21 CFR 820.25(b). For example, *Section 9.1-4.1,* titled, *Education and training* in your firm's *Kvalitetsmanual Dok. Nr. 106442* requires new, continuing, and future employees to be trained on the current version of the applicable procedures and the version number of the procedure to be recorded in the employee's personnel file. However, review of the training records disclosed that the version number of the documents or the dates of training were not recorded on the training record.

We reviewed your firm's response and conclude that it is not adequate. Your firm states that all training records have been updated to include the date and type of training performed, and provided a copy of a sample training record with the name of an employee but without any training information. Your firm states that it has not completed the remaining training forms and did not

provide an expected completion date.

Your firm's response to this Warning Letter should be sent to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Field Operations Branch, White Oak Building 66, Room 2609, 10903 New Hampshire Ave., Silver Spring, MD 20993. Refer to CMS Case #347460 when replying. If you have any questions about the contents of this letter, please contact: LaShanda Long, Chief, General Surgery Devices Branch, Division of Enforcement A, Office of Compliance, CDRH at 301-796-5770 or 301-847-8137.

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

Sincerely yours,
/S/
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