

Warning Letter *Bulletin*

The Inside Alert to FDA Enforcement Activities, Inspections & Compliance Programs

Vol. XIX, No. 11

November 2011

Inside This Issue...

FDA released the following Warning Letters during September and October 2011

HUMAN DRUGS

Dental Technologies	1
SmithKline Beecham.....	3
Jazz Pharmaceuticals	4

MEDICAL DEVICES

Measurement Specialties.....	6
Rocket Medical.....	8

CLINICAL INVESTIGATORS

Leslie E. Diaz, M.D.....	9
--------------------------	---

HUMAN DRUGS

Dental Technologies Inc. Lincolnwood, IL, Sept. 15 Chicago District

FDA notified contract drug manufacturer **Dental Technologies** in a warning letter that its March 16-April 12 inspection not only identified significant violations of GMP regulations for finished pharmaceuticals but also revealed that the firm makes “a number of prescription drugs without approved applications.”

The firm had not conducted at least one specific identity test and had not established the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals, the agency explained.

“For example, your firm has failed to perform the required identification tests for Glycerin

USP (i.e., limit of Diethylene Glycol and Ethylene Glycol) as required by the USP monograph,” the letter stated. “Furthermore, our investigators confirmed that your employees failed to perform these critical identification tests for Glycerin USP as required by your specification. Diethylene Glycol and Ethylene Glycol are both dangerous contaminants that have been found in Glycerin raw materials.”

The firm replied that it was performing the test and submitted a copy of the specifications. “Your response is inadequate because your firm has yet to provide actual identification test results for the presence of Diethylene Glycol and Ethylene Glycol in Glycerin USP, an ingredient in each of your drug product lots,” FDA stated in the warning letter.

The inspection also revealed that Dental Technologies had not thoroughly investigated the failure of a batch or any of its components to meet its specifications. FDA observed that the firm’s “investigation into microbial testing for the presence of *Pseudomonas aeruginosa* identified in water samples collected on Dec. 20, 2010, and Dec. 27, 2010, was inadequate. Your investigation concluded that the microbial contamination occurred at the water delivery spigots. Your investigation, however, failed to include information regarding the swab test results of the spigots and the test results of the spigots following sanitization. Further, your firm continued to manufacture drug products with purified water that may have failed to meet your specifications.”

Dental Technologies responded that it tested all drug product lots manufactured during this period and the test results were negative for *Pseudomonas aeruginosa*. FDA found the response inadequate “because you did not include any information regarding



Copyright 2011, Washington Information Source Co. Photocopying prohibited, including faxes, electronic transfer “F.Y.I. memos,” without WIS’ permission. Authorization to copy is granted provided that \$5-per-Page fees are paid directly to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA, 01923. Copy code 1550-5332/11/11+5.00. All non-copyrighted documents in this newsletter are available from RECORD-RETRIEVE (703)779-8777 FAX (703)779-2508 E-mail. SERVICE@FDAINFO.COM. Check out www.FDADocuments.org

CODES

- **AE** — Adverse event reporting violations
- **510(k)** — Failure to file 510(k)
- **BiMo** — IRB, sponsor/monitor, CRO, clinical investigator issues
- **BLA** — Biologics License Application
- **CAPA** — Corrective/preventive action
- **C-H** — Complaint handling
- **Cal** — Calibration
- **Compound** — FDCA drug-compounding violations
- **Comp/Soft** — Computer software validation
- **Design** — Design controls
- **E-M** — Environmental monitoring
- **E-Sig** — 21CFR Part II, Electronic Signatures /Records Rule
- **F-B** — Lack of fair balance in promotions
- **Lab** — Laboratory
- **L-B**—Labeling issues
- **Mark** — Marketing and misbranding
- **MDR** — Medical Device Reporting violations
- **NDA** — Lack of new drug application
- **O-L Use** — Off-label use
- **OOS** — Out-of-specification results
- **Pak** — Packaging
- **PMA** — Lack of premarket approval
- **QC/QS** — Quality Control/Systems deviations
- **Stab** — Stability
- **Ster** — Sterility
- **Val** — Validation
- **Web** — Internet promotion irregularities

how many samples of each lot were tested. Further, your response fails to include corrective actions regarding changes to the operation of your purified water system to assure that it will produce water that meets your company's quality standards (e.g., frequency and method of water system sanitization, assessment of the microbial quality of the feed water and SOP revisions.)"

FDA found that the company failed to follow written procedures describing the handling of all written and oral complaints regarding drug products, noting that the "Quality Control Unit (QCU) failed to ensure consumer complaints were adequately investigated as required by your complaint handling procedure." The company evaluated patient complaints for nausea and vomiting and concluded that the patients were hypersensitive to fluoride, the letter detailed. Subsequently, Dental Technologies' corrective action included discontinuance of the Cherry flavor 2% NaF Rinse product and the destruction of the remaining lots.

"Your firm's investigations, however, failed to evaluate the manufacturing process, raw materials or packaging components that could have contrib-

uted to the patient reactions," the agency explained. "Moreover, your investigations did not extend to similar patient illness complaints your firm has received regarding other sodium fluoride oral rinse products manufactured by your firm."

FDA found the firm's response inadequate because it failed to address how the company will investigate the patient illness complaints for its remaining sodium fluoride oral rinse products.

Dental Technologies had not established scientifically sound and appropriate specifications designed to assure that components and drug products conform to appropriate standards of identity, strength, quality and purity, the agency stated.

The company uses "a rapid diagnostic test method" to test water samples from its purified water system and drug products, FDA observed. "This culture media system has not been shown to be equivalent to current compendial microbiological test methods. Your firm lacked any studies to show fitness for use of these methods for your firm's drug products. Furthermore, your firm does not perform growth promotion testing on the media systems utilized for purified water and finished drug product testing."

Dental Technologies "proposes to develop new protocols at your contract laboratory with appropriate method validation. Your response, however, fails to provide the completion and/or implementation dates of the proposed protocols and method validation. In addition, your firm has yet to provide an update on the use and qualification of the current rapid diagnostic media test kit," the agency wrote.

In addition to violating GMPs, Dental Technologies also manufactures and markets unapproved prescription drugs, the warning letter advised.

FDA referred the firm to its guidance entitled "Marketed Unapproved Drugs—Compliance Policy Guide (CPG)," which explains FDA's policies aimed at ensuring that all drugs marketed in the U.S., prescription and over-the-counter, have been shown to be safe and effective.

"The guidance clearly articulates FDA's expectation that illegally marketed products, those products marketed without required FDA approval, be removed from the market," the warning letter noted. "As described in the CPG, all drugs marketed without required applications are subject to enforcement action at any time, without additional notice."

During the inspection, FDA found that the

firm is manufacturing the prescription drugs Acidulated Phosphate Fluoride Foam, 2.59% (1.23% Fluoride Ion) 250 mL and Oral Solution, 2% (0.9% Fluoride Ion) 1853 mL. “Based on information your firm submitted to FDA’s Drug Registration and Listing System and the information collected during the inspection, there are no FDA-approved applications on file for these drug products,” the agency commented.

FDA added: “Finally, we have concerns about your firm’s fundamental understanding of the regulatory expectations and requirements when conducting testing of Glycerin for Diethylene Glycol. Please review the FDA Guidance entitled, “Guidance for Industry Testing of Glycerin for Diethylene Glycol” which explains FDA’s policy on analytical testing procedures for all containers of all lots of glycerin under 21 CFR § 211.84(d)(1).” **C-H; NDA; QC/QS**

SmithKline Beecham Worthing, UK, Oct. 7 CDER

FDA informed drug manufacturer **Smith-Kline Beecham** in Worthing, UK, that its March 2011 inspection identified significant violations of GMPs for finished pharmaceuticals.

“Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile,” the agency wrote. The inspection found that the qualification of a disinfectant failed to demonstrate that it is suitable and effective to remove microorganisms from different surfaces. Specifically, this disinfectant failed to meet qualification criteria when challenged with multiple organisms, the letter noted.

“Your disinfectant qualification for bi-spore disinfectants documented that the log reduction criteria (Bacteria ≥ 4 , Fungi ≥ 3) were not met when challenged with multiple organisms in a variety of surfaces,” FDA detailed. “After disinfection, you recovered *Micrococcus luteus* on vinyl, stainless steel, glass and wall laminate and *Enterobacter cloacae*, *Rhodococcus sp*, *Burkholderia cepacia*, *Pseudomonas aeruginosa*, *Methylobacterium mesophilicum* and *Acinetobacter lwoffii* on glass. However, your procedures for routine cleaning of the aseptic manufacturing area continue to require the use of unqualified disinfectants during

certain intervals of your disinfectant program.”

The firm’s response indicated that the failure to meet the log reduction criteria was due to the test conditions and not the efficacy of the disinfectant. “However,” the agency commented, “You did not include documentation to support this conclusion. Moreover, your firm submitted an updated Technical Report signed by your Quality Assurance (QA) on July 27, indicating that one disinfectant has been unable to comply with the three-log reduction for *Micrococcus luteus* microorganism on some surfaces.”

The company’s procedure “Aseptic & Support Area Sanitization Following Maintenance Shutdown” was found to be inadequate. FDA added:

“A media fill conducted during January 2011 resulted in two contaminated units,” the letter stated. “Your firm attributed the failures to stopper bags left inside the class 100 area for a long period of time (throughout a shutdown that took place prior to the media fill.)” FDA found that there was inadequate information available to support this conclusion, including information regarding the microorganisms recovered from the stopper bags and the sterility test conducted, along with an evaluation of the sampling procedure and environmental monitoring program.

“Significantly, your firm had intended to use the media fill data to extend the sterility holding times for product contact components, without the approval of your Quality Unit,” the letter continued. “We also are concerned that your SOP did not require manufacturing materials to be removed to an appropriate area for storage during shut-down of operations and prior to bringing the area back into classified status.”

Personnel gown monitoring conducted during routine aseptic filling was inadequate, the agency determined.

The inspection documented that SmithKline Beecham conducts personnel monitoring for the classified manufacturing rooms by only sampling the hood, goggles and sleeves. “We are concerned about your current gowning monitoring approach as operators may perform substantial interventions into the Restricted Access Barriers (RABs), where sterile product is exposed, several times per week,” FDA commented. “In addition, the investigators noticed during the inspection one of the operators sanitizing his hands immediately prior to conducting his own personnel monitoring sampling. Your personnel monitoring program should include appropriate sampling and practices to reflect whether personnel

maintain asepsis during sterile drug manufacture.”

The agency requested that the firm respond to the letter with “a detailed description of the controls implemented to ensure operators that enter the class 100 (ISO 5) area are sampled adequately in the QA Grade B Room (ISO 6). Also provide this same information for operators who enter the aseptic processing room for non-aseptic filling activities. Please include your rationale for these monitoring schedules.”

The “Dynamic Airflow Visualization” video provided in the firm’s response shows an operator spraying his hands directly over the air viable microbial plate, FDA noted. “This practice is unacceptable because the environmental monitoring results from plates sprayed with the compound may be inaccurate and may not reflect the actual microbiological environment of the Class 100 (ISO 5) room.”

The inspection revealed that several laboratory investigations were conducted without having Form B completed and approved by the company’s Quality Unit, as required by its procedure. Smith-Kline’s procedure “Investigation [of] Out of Specification (OOS) Test and Atypical Results Procedure” establishes that the Form B is intended to document any retest or root cause investigation and whether any remedial corrective and preventative actions are required.

“Your firm’s response indicates that although the Form B was not used, the quality of the investigations is equivalent to those investigations in which the Form B was completed,” the warning letter noted. “However, you provided no support for this conclusion. In addition, your response failed to justify the retest that was conducted without authorization by your Quality Unit.”

FDA requested that the company provided a response to the warning letter that included a review of all the OOS investigations for product within expiration date to determine if the investigation procedures were properly followed. The agency also asked the firm to include any retest analyses conducted without the approval of the Quality Unit, a list of the investigations evaluated and a summary of each investigation’s outcome.

The quality control unit does not adequately exercise its responsibilities to approve procedures or specifications that may impact the identity, strength, quality and purity of the drug product, FDA found.

The inspection documented that the visual inspection certification program (VIC) for some fin-

ished product does not adequately challenge the technician(s) performing the inspection. The VIC program only requires that some of the five critical defects be included in the challenge set.

Although identified critical defects include a vial with a cracked neck, a missing cap, a missing stopper, high/low weight and a foreign body, only a missing cap defect is included in the visual inspection program. This test will only show that the technician(s) is capable of detecting a missing cap, but it does not show that the technician is capable of detecting other critical defects, the agency observed. Additionally, the SOP does not require that the critical defect challenge vial selected be rotated to ensure that each inspector is challenged to detect each critical defect.

“In the response to this letter, please indicate what specific steps you have taken to ensure that all distributed lots are properly evaluated for all critical defects,” FDA requested. **E-M; OOS; QC/QS; Ster**

Jazz Pharmaceuticals Palo Alto, CA, Oct. 11 San Francisco District

An April 27-May 6 FDA inspection of **Jazz Pharmaceuticals** identified significant violations of regulations that require an applicant to establish and maintain records, and to report data relating to clinical experience, along with other data or information, for drugs in which an approved application is in effect.

FDA found that Jazz Pharmaceuticals failed to develop adequate written procedures for the surveillance, receipt, evaluation and reporting of post-marketing adverse drug experiences (ADE) to FDA.

“Your firm does not have adequate written procedures to ensure that adverse drug experiences are detected, correctly identified, assessed and reported to FDA in accordance with postmarketing regulations,” the agency wrote in a warning letter. The lack of adequate procedures “appears to have contributed to your failure to timely report to FDA adverse event information in the possession of the specialty pharmacy under contract with you as the sole distributor and dispenser of Xyrem, as required by the Risk MAP under which Xyrem was approved.”

While the firm’s contract with the pharmacy

refers to SOPs for adverse event reporting and specifies that no SOPs may be created or modified without Jazz's approval, no such adverse event reporting SOPs were provided during the inspection, the letter commented. "You further indicated that prior to the discovery of the unreported deaths in April, you had no procedures for monitoring the pharmacy's compliance with the terms of your contract as relevant to adverse event reporting."

Up to the time of the most recent inspection, the firm also failed to establish SOPs to ensure that all ADE information obtained from all sources was promptly conveyed to appropriate Jazz personnel and reviewed, in particular information obtained by the contracted central pharmacy and call center; that all ADEs were evaluated against the U.S. package insert for seriousness and expectedness; that all adverse experiences were reported accurately from source documentation to FDA Form 3500A; and that all ADEs that were the subject of 15-day alert reports were promptly investigated and that all attempts to obtain additional information about the adverse experiences were recorded.

"Your response describes the implementation of certain corrective actions, including establishing SOPs and retraining your staff on established ADE related procedures," FDA wrote. "Your response, however, is inadequate because your firm did not provide an evaluation of the impact of your new SOPs or provide the details for retraining your staff (i.e., an assessment of training effectiveness) and whether there is a need to retrain staff at the call cen-

ter and pharmacy."

The company was cited for failure to submit reports of adverse drug experience (ADE) that are both serious and unexpected to FDA within 15 calendar days of initial receipt of the information by the applicant.

"Your firm failed to submit 74 serious unexpected ADE reports within 15 calendar days of initial receipt between January 2003 and December 2010, including 10 reports of deaths," the letter detailed.

FDA acknowledged Jazz Pharmaceutical's subsequent submission of the 74 completed 3500As on May 5 and its May 20 response.

During the course of the inspection, the firm's senior vice president and chief regulatory officer acknowledged the dates referenced by the warning letter as being the dates on which the company received the reports of ADEs. In its response to the 483, however, "your firm states that you did not receive or have knowledge of the ADEs until April 21, 2011, because prior to that date, these reports were received by and in the possession of the specialty pharmacy that is the exclusive distributor of Xyrem. You therefore now appear to dispute that you were responsible for reporting these events until 15 business days after April 21," the warning letter commented.

"We disagree with this position, given the exclusive and contractually specified role of the pharmacy in performing tasks required for meeting your legal obligations under the Xyrem REMS," FDA stated. Under the contract for the "Xyrem Success

Warning Letter Bulletin

Kenneth Reid, Editor & Publisher
Rebecca Mashaw, Managing Editor
Melissa Winn, Associate Editor
Kathy Thorne, Subscriptions Dept.

Washington Information Source Co.

19-B Wirt Street S.W.
Leesburg, VA 20175
Editorial Offices
(703) 779-8777
(703) 779-2508 Fax
Web site: www.FDAINFO.com

Sign up for a 12-month subscription to Warning Letter Bulletin — \$1,580 per year.
Distributed via e-mail monthly in PDF format.

Name/Title: _____

Company: _____

Address: _____

City/State/Zip: _____

Phone: _____ Fax: _____

Email: _____

(Required for delivery)

Payment Options: (check one) Check Enclosed P.O. Enclosed Bill Firm

Charge: (check one) Visa MC AmEx Diners

Card No: _____ Exp. Date: _____ Sec. Code _____

Signature: _____

Mail to: WIS, 20940-C Frederick Road #500, Germantown, MD 20876-4017. Tel: (240) 477-5577, Fax: (240) 599-7679, E-mail: Support@FDAinfo.com Subscriptions can be placed through subscription agencies worldwide...money-back guarantee.

Program,” the pharmacy is responsible for “Adverse Event Reporting: Collecting and reporting of all adverse events per standard operating procedures,” the agency explained. That contract further specifies that the pharmacy must provide reporting as required by federal and state laws, including the Xyrem REMS, and must provide reporting of adverse events “to Jazz Pharmaceutical’s Medical Information; reports also submitted to Jazz Pharmaceuticals’ Quality Assurance if associated Product Adverse Events Quality Complaint (PQC).”

Under these circumstances, FDA stated, “your firm is responsible for the adverse drug experience information received by the contract specialty pharmacy, and the ADEs above were not reported within the 15 calendar day requirement.”

“Your firm failed to submit 74 serious unexpected ADE reports within 15 calendar days of initial receipt between January 2003 and December 2010, including 10 reports of deaths,” the letter detailed.

In addition, Jazz’s response describes the implementation of certain corrective actions, including auditing the pharmacy and the call center, and reconciling its safety databases with both regarding all ADEs. FDA determined that the response “fails to specify details on the search criteria and method for reconciling the safety databases. Your response also did not state a specific timeframe for completion of corrective actions. The proposed corrective actions did not consider the root cause of the deviation.”

The warning letter noted that Jazz Pharmaceuticals had received a 483 on Sept. 27, 2007, “for similar postmarketing adverse drug experience violations. However, your corrective actions for that observation, including optimizing the receipt, work flow, communication and submission processes for ADE reporting, were not sufficient to prevent subsequent reporting violations, nor to make you aware of the newly-discovered adverse events reports received by the contract pharmacy prior to our 2007 inspection. As discussed above, sponsors of new drug applications must establish procedures that will assure that adverse drug experiences are looked for, received and promptly recorded and evaluated to determine whether or not 15-day alert reports should

be submitted to FDA.” **AE**

MEDICAL DEVICES

Measurement Specialties Inc. Hampton, VA, Oct. 12 Cincinnati District

During an inspection May 17-July 25 of **Measurement Specialties**, FDA investigators found several problems with the establishment and following of procedures that constituted violations of GMPs for medical devices and resulted in the issuance of a warning letter from the agency.

Measurement Specialties, which makes temperature probes for pediatric and adult use, failed to implement and maintain adequate procedures for implementing corrective and preventive action, the inspection revealed. The warning letter noted: “Your Corrective Action Procedure does not adequately address the statistical methods that will be utilized to analyze quality data to identify existing and potential causes of nonconforming product or other quality problems.”

FDA noted that the firm was “not analyzing nonconformances found during finished device assembly based on a statistical methodology that will detect recurring quality problems. A total of nine of the 11 device history records reviewed had the reasons for the nonconformances during finished device assembly that were dispositioned as scrap recorded, but this data is not being analyzed based on a statistical methodology to detect recurring problems.”

The company’s analysis of scrap was only performed on “total dollar value of scrap for all products” which includes medical, aerospace and industrial, the letter added.

The company responded to the original inspection report that by Sept. 1 it would establish procedures for analyzing and documenting scrap, and for determining when a corrective action should be taken in regards to scrap. FDA requested a copy of the new procedures and any other supporting records in order to assess these corrective actions.

The firm also failed to establish and maintain procedures to control product that does not conform to specified requirements.

Specifically, the warning letter explained,

Measurement Specialties' Control of Nonconforming Product procedure was found inadequate because it states: "The separated nonconforming product is identified with a red tag, placed in a red container or marked such that its status is clearly identified for later disposition of disposal as solid waste." On June 2, FDA investigators observed an assembler of a general purpose probe set a probe aside and go on break.

The agency added that another assembler working in that area picked up the probe, packaged and sealed it. The inspectors discussed the incident with the original assembler who set the probe aside and were told that the probe was nonconforming because it contained "little ink." The assembler did not follow the firm's procedure of identifying the nonconformance with a red tag. "As a result, the probe was packaged and sent for sterilization," the agency noted.

According to the warning letter, the procedure states that, "For medical products, the number of in-process adjustments is limited and is defined within the work instructions." A total of four of the 11 work instructions reviewed allow for in-process adjustments, but the number of in-process adjustments is not defined in the work instructions, the investigators observed.

FDA stated that it could not assess the firm's response to this observation because it "lists several timeframes and dates for revising procedures, training employees, updating the device history record work instruction page and reviewing all procedures to ensure that adequate instructions exist to carry out the requirements stated in each procedure. Please provide the revised procedures and documentation that all of these corrective actions have been completed. If they are still in-progress, please provide an update on the status of these corrective actions."

Inspectors found the firm had failed to establish and maintain procedures for rework, to include retest and reevaluation of nonconforming product after rework, to ensure that the product meets its current approved specifications. The letter commented that Measurement Specialties' "rework and in-process adjustments requirements listed in the individual work instructions for medical temperature probes are not being followed. For example, on May 25, the FDA investigators observed a manufacturing employee rework four temperature probes for failing their resistance tests." The employee did not follow the directions listed in the work instruction for in-

process adjustments, "in that the directions on how to perform the adjustments were not followed and the rework was not documented in the device history record."

Again, FDA could not assess the firm's response. The company provided a timeline to have revised its device history record (DHR) procedures and the DHR page of all medical product work instructions to include the same rework requirements contained on its revised procedures. The agency requested revised procedures and documentation that they had been completed and an update on the status of corrective actions still in progress.

The site manager, the investigators reported, "has been acting Quality/Regulatory Manager since April and has not received training to perform his assigned responsibilities."

Measurement Specialties further failed to establish and maintain procedures for identifying valid and statistical techniques required for establishing, controlling and verifying the acceptability of process capability and product characteristics.

The inspection revealed that "there is no statistical methodology used for establishing the acceptable alert levels listed in the work instructions for the temperature probes. For example, the work instruction states: 'If more than 10% of the probes are out of specification, contact Manufacturing Engineer for troubleshooting and corrective action.' There is no statistical basis for setting the alert level at 10% for failures that occur during this operation."

The firm did not address this observation.

FDA also found that "changes to the manufacturing process of several temperature probes, which includes changes to the tip cleaning process, were not verified or validated."

The company's response "lists several timeframes and dates for revising design change procedure, your document change form, training employees and reviewing all waivers," the warning letter stated. "Please provide the revised procedures and documentation that all of these corrective actions have been completed. If they are still in progress, please provide an update on the status of these corrective actions."

Measurement Specialties' Receiving Inspection procedure "does not contain clear definitions

and instructions to ensure the employee chooses the correct inspection level for determining the number of samples to pull for acceptance activities for incoming components,” the letter observed.

“For example, an employee performed a General Inspection Level II AQL 1.0 sampling for inspection of incoming thermistors, which are components of airway temperature probes,” FDA detailed. “According to your procedures a Level II inspection, which is defined as 100% inspection, should have been performed.”

FDA again asked for copies of the revised procedures and documentation that this corrective action had been completed.

The inspection revealed that the firm had not established procedures for identifying training needs and ensuring all personnel were trained to adequately perform their assigned responsibilities. The site manager, the investigators reported, “has been acting Quality/Regulatory Manager since April and has not received training to perform his assigned responsibilities.”

The company responded with “several timeframes and dates for revising procedures; identifying and defining skill levels for ‘critical positions;’ requiring the qualification for temporary replacement personnel; conducting ongoing training; and implementing a new training and evaluation program.” The agency again requested copies of procedures, documentation of their implementation and in-progress reports for CAPAs.

The company’s Quality/Regulatory Manager audited areas for which he is directly responsible, the warning letter added. **CAPA; QC/QS; Val**

Rocket Medical Tyne & Wear, UK, Oct. 13 CDRH

An FDA inspection July 11-14 revealed that **Rocket Medical**, a maker of catheters, fetal bladder stents, uterine sound devices and other IVF devices, was not in conformity with GMPs, according to an agency warning letter.

Rocket Medical failed to establish and maintain adequate procedures to control the design of the device in order to ensure that specified requirements are met, the letter stated.

For example, the firm’s design procedure did not include requirements or the location of records

for design planning, design inputs, design outputs, design verification, design validation, design transfer and risk assessment.

The company’s response stated only that it would review and update the SOP. “Information on the systemic corrective action was not provided,” FDA wrote in declaring the response inadequate. “Additionally, this observation was observed during the previous inspection conducted in 2006, and an adequate corrective action has still not been implemented.”

The letter also stated that Rocket Medical had failed to establish and maintain adequate procedures for implementing corrective and preventive actions.

For example, FDA wrote, the firm’s SOP “Corrective & Preventative Action Report” did not include the following requirements:

- Analysis of potential causes of nonconforming products or quality problems does not take into consideration a review of work processes, service records, and returned products
- Investigating the cause of nonconformities
- Verification or validation of the corrective or preventive actions
- Ensuring that information related to quality problems on nonconforming product is disseminated to those directly responsible for assuring quality of products or prevention of problems.

The company opened a CAPA in September 2010 for assay testing failures for IVF product, FDA commented. “The CAPA does not include a documented investigation but identifies some process steps as potential corrective actions, which were not implemented,” the agency wrote. “The CAPA had a target completion date of December 2010. At the time of FDA inspection, the investigation by the testing laboratory was not complete.”

Another CAPA was opened due to a complaint relating to a Bulb Tip Catheter. FDA noted that there was no documented investigation of the problem and no documentation that the corrective action was verified.

“Your firm’s response received July 29, 2011, is not adequate,” FDA judged. “Your firm has indicated that it will review and update the SOP. The systemic corrective action was not provided nor was any corrective action mentioned for the missing information in the CAPAs.”

The company further neglected to adequately establish and maintain adequate procedures to control environmental conditions that could reasonably be expected to have an adverse effect on product quality.

FDA stated that Rocket Medical's "SOP does not describe the acceptance criteria, the alert and action levels, or where this information can be obtained. Also, the SOP does not describe the acceptance criteria or the alert and action levels used to determine when a corrective or preventive action needs to be opened."

Rocket Medical did not establish and maintain adequate procedures to ensure that device history records (DHRs) for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the device master record (DMR) and the DHR requirements.

For example, the agency detailed, "The Device History Record does not provide documentation to demonstrate that products were manufactured in accordance with the Standard Procedure. In particular, the device history record for one lot of Embryon Bulb Tip ET Catheter/R57635-00-18 does not include documentation that it was 100% inspected as required per the procedure.

The company "indicated that its operator will confirm the completion of each manufacturing stage of the device history record; however, the systemic corrective action was not provided or discussed," the warning letter stated in finding the response inadequate.

FDA further observed that the company failed to establish and maintain adequate procedures to control products that do not conform to specified requirements.

Rocket Medical's Control of Nonconforming Product procedure, FDA found, "requires a scrap record sheet to be completed. The testing of Embryon Bulb Tip ET Embryo Transfer Catheters/R57635-00-18 Lot 436023 revealed that it was found that 51 of the pieces were found to have defects. The 51 pieces were reportedly scrapped, but there is no documentation of the disposition of these pieces."

Although the firm told FDA that it is conducting investigations on how to utilize the QA Infinity software to control and record products that do not conform to specification, the agency found the response inadequate because it did not address the systemic corrective action.

FDA informed Rocket Medical that a follow-

up inspection will be required to assure that corrections and/or corrective actions are adequate. **CAPA; E-M; Comp-Soft; QC/QS**

CLINICAL INVESTIGATORS

Leslie E. Diaz, M.D.
North Palm Beach, FL, Nov. 4
CDER

Between Jan. 12 and March 8 FDA conducted an inspection and met with **Leslie Diaz, M.D.**, to review the conduct of two clinical investigations of an investigational drug, concluding that Diaz did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations.

Diaz failed to personally conduct or adequately supervise the clinical investigations, the agency stated in a warning letter.

"Our investigation indicates that your supervision over the studies was not adequate to ensure that clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations," FDA wrote. "This lack of adequate involvement in and oversight of the studies raises concerns regarding the protection of the rights, safety and welfare of subjects enrolled into the studies and the integrity of the data from your site."

In a written affidavit Diaz signed March 8, the physician stated that "even though your practice went through multiple ownership changes, you always remained as the principal investigator for the above trials, you were fully aware that you always had the ultimate responsibility for these clinical trials, and you continued to take full responsibility for their conduct and oversight," the letter detailed. In that document Diaz "acknowledged a number of significant instances of inadequate oversight and supervision."

For example, Diaz conceded in the affidavit: "In searching for study documentation, I also found letters that were sent to me that I had never opened and/or had seen before. These letters were from monitors, sponsors and IRBs, including some which involved the termination of my clinical studies."

The letters informed Diaz that approval of the audited protocols had been suspended or terminated “due to your failure to submit continuing review reports; inability to contact you after multiple attempts; or your failure to respond to multiple communications,” FDA wrote.

Diaz also acknowledged that adverse experiences were not evaluated/graded as required by study protocols, and further admitted to “having ignored the clinical trials.” The clinical investigator also said: “All study documentation ended in early December 2007 after my study coordinator left.”

The warning letter stated: “The statements in your affidavit, when taken in conjunction with the violations described below, indicate systemic failures in your conduct of investigational research. As a result, we have significant concerns about the safety and welfare of subjects enrolled into these studies and the integrity of the data from your site.”

The protocol for one of the investigational drugs “specified that subjects with severe renal insufficiency were to be excluded from the study,” the letter noted. “Source records available at your clinical site during the FDA inspection showed that Subject 02145 was screened for enrollment into the study on May 8, 2007. However, the medical history showed that this subject had continuing chronic renal failure prior to enrollment. Thus, the enrollment of this subject into the study violated the investigational plan.”

The protocol provided instructions for evaluating adverse events (AEs) and stated that an investigator who was a qualified physician was to evaluate all AEs with regard to maximum intensity, seriousness, duration, action taken and relationship to test drug. In the written affidavit, Diaz acknowledged that AEs that included the clinical symptoms recorded in the subjects’ charts were not evaluated or graded.

Further, the protocol specified that any serious adverse experience (SAE), including death due to any cause, that occurred to any subject in the study within 14 days following cessation of treatment or within the follow-up period, whether or not related

to the investigational product, must be reported to the sponsor within 24 hours.

One subject enrolled into the study on March 2, 2007, while still in the study, underwent cardiac catheterization that revealed an SAE of triple-vessel coronary artery occlusive disease and required surgery. FDA noted that Diaz characterized this SAE as “immediate[ly] life-threatening” on the sponsor’s SAE reporting form. However, Diaz did not report this SAE to the sponsor until July 30, 2007. In addition, Diaz did not provide all of the information requested on the sponsor’s SAE form, including whether the SAE was related to the study drug.

The study protocol specified that the subject was to receive the investigational medication once eligibility was confirmed after completion of the screening form and evaluation by the sponsor or its designee. Source records indicate that a subject was dispensed study drug on June 27, 2007, nearly two weeks before Diaz received confirmation of the subject’s eligibility for enrollment. “You therefore failed to follow the protocol requirements by dispensing investigational medication to a subject prior to confirming the subject’s enrollment into the study,” FDA found.

“During our inspection, unreturned investigational drugs for both studies were found at your site,” the letter stated.

The identification of these unreturned investigational drugs “raises significant concerns regarding the adequacy of your oversight and control of investigational drugs,” FDA wrote, adding:

In your signed affidavit, you admit to a lack of involvement and oversight in the conduct of these clinical trials. This general lack of oversight, when taken in conjunction with your failure to maintain control of investigational drugs, serves to undermine the confidence we have in your drug dispensation to subjects. As a result, we have significant concerns about the safety and welfare of subjects enrolled into these studies and the integrity of the data from your site,” FDA wrote. **BIMO**

Get Regulatory Documents from our Web site: www.FDAINFO.com, or call **RECORD-RETRIEVE** to place an order. *WLB* is available on line via Dialog, Lexis/Nexis, Dow Jones and other services. Violators of *WLB*’s copyright are subject to up to \$100,000 in damages per infringement. Call the publisher to report any illegal copying, faxing or electronic transfer at (703) 779-8777. Up to \$20,000 reward offered for information leading to judgment or settlement of claims. Confidentiality assured.