

# ✓ VALIDATION TIMES

Insight on GMP validation: News, 483/warning letter analysis, compliance tips

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### Microorganisms/Impurities

## FDA investigators say having a list of objectionable organisms to test for can actually be a detriment

By **Melissa A. Winn**  
Managing Editor

BETHESDA – Drug companies that have a formal list of objectionable organisms that they test for and monitor during pharmaceutical manufacturing can actually be working to their detriment, despite the fact many firms have such lists and believe FDA inspectors expect them, agency officials

told PDA's 6<sup>th</sup> Annual Global Conference on Pharmaceutical Microbiology.

The officials told the Oct. 19 meeting that such a list can actually deter ensuring the production of a quality product unless there is a scientific basis for having one.

Bryan Riley, Ph.D, a microbiology reviewer in the Center for Drugs Office of Pharmaceutical Science, told attendees, "A list excludes thought. What you need is trained microbiologists who can evaluate and test. A list can be a detriment."

Microorganisms/Impurities cont'd page 3

### Stability

## FDA recommends stability testing on mostly pilot scale batches to simulate commercial manufacturing and product

By **Melissa A. Winn**  
Managing Editor

WASHINGTON – FDA recommends stability testing of three selected batches for drug substance and drug product for NDAs, and drug substance batches should be pilot scale in size while at least two of the drug product batches should be pilot scale in size, but one batch can be smaller in size with justification.

That's the advice from Ramesh Sood, Ph.D, a branch chief in FDA's Office of New Drug Quality Assessment, who also told an AAPS workshop on stability Oct. 22 that manufacturing of the selected drug substance batches should be representative of the proposed commercial material and should be stored in a container closure that is the same as or simulates the one proposed for commercial storage.

Stability cont'd page 4



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## Quality Systems

## CDRH's 'QSIT' approach suggested to drug manufacturers, especially for sterilization, production control and even 'design'

By Melissa A. Winn  
Managing Editor

BETHESDA – FDA's medical device Quality System Inspectional Technique (QSIT) was outlined at a recent PDA microbiology conference as having some benefit to drug manufacturers, especially when evaluating sterilization processes and production controls.

Patrick Weixel, a consumer safety officer in FDA's Center for Devices, told PDA's 6<sup>th</sup> Annual Global Conference on Pharmaceutical Microbiology that medical device inspectors use a "top-down" approach, looking at the firm's systems for addressing quality problems before actually looking at specific quality problems.

FDA is looking for a good quality system, he said, "making sure procedures are in place, such as design controls, production controls, etc. We then look down from that to determine if the firm has met the basic requirements of regulation, and ensure the basic requirements have been implemented."

The quality systems technique, Weixel said, includes seven subsystems the agency is looking for. FDA looks at a firm's management controls, design controls, production and process controls and corrective and preventive action (CAPA) system first and foremost.

"Then we will also look at others," Weixel said, "including

material controls, equipment and facility controls and records and documentation controls."

Design controls required by federal regulations include a design plan, outputs, inputs, design review, design verification and validation and design transfer.

Investigators will inspect to ensure the plan identifies the overall design project and also includes other interfaces of groups involved in the design, contract manufacturers, sterilizers, etc.

Firms also should identify throughout the design process where reviews will be made "to make sure specific requirements are being met and that they involve management," Weixel said.

Maintaining a design history file also is required.

Examples of sterilization design controls, Weixel told attendees, may include material compatibility to radiation, sterility assurance, ensuring functionality is identified and has not been affected, identifying bioburden limits and developing the sterilization dose.

Sterilization needs to be looked at early on in the development process," He said. "It needs to be worked into the design project early on."

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### ***Investigators will review cleaning procedures for equipment and manufacturing areas, with special scrutiny paid to how it affects sterilization.***

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Production control requirements may include production and process changes, including having procedures to make sure changes don't change the product, Weixel said. They also should include environmental controls, contamination controls, equipment controls and ensuring that personnel are trained, performing well, use appropriate hygiene, gowned, etc.

Weixel said process controls that could impact sterilization include a change in manufacturing site, storage of components, microbial monitoring of manufacturing areas, whether facilities

have proper storage and gowning of employees.

Investigators will review cleaning procedures for equipment and manufacturing areas, with special scrutiny paid to how it affects sterilization.

Other process controls investigators will review include ensuring the building prevents mix-up of sterile and non-sterile products, ensuring equipment meets specified requirements and is routinely maintained and periodically inspected, ensuring manufacturing material is removed and automated processes are validated.

Weixel advised to attendees, "When it comes to radiation and sterilization, you're going to have equipment used for measurements. Make sure it is calibrated to a national standard."

Investigators will review firms for process validation, as well.

"When results cannot be fully verified by subsequent inspection and test, the process needs to be validated," Weixel said.

Examples of processes that require validation include sterilization and packaging processes and test methods.

"Packaging is a main area for review," Weixel said. "Don't forget to look at the packaging. Make sure the packaging is evaluated and see how that may be impacted by the sterilization process."

He also advised attendees that purchasing controls are being examined more closely. Firms should establish procedures to ensure that purchased or otherwise received product or services conform to specified requirements. They also should evaluate suppliers, contractors or consultants; and establish requirements to be met by suppliers, contractors or consultants. ■

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## Microorganisms/Impurities Continued from page 1

Dennis Guilfoyle, Ph.D., pharmaceutical microbiologist international expert in FDA's Office of Regulatory Affairs, agreed, saying during the same Oct. 19 "Ask the Regulators" panel, "I'm not a list guy. I don't believe a list approach is flexible enough to accommodate changes in personnel, materials, environment, etc."

He continued: "If you're going to have a list, it should have some scientific basis, including isolates commonly found in your environment or materials. Those microbes might have a greater chance of ending up in your product. If you're going to have a list, you need to have a basis for how that list was derived."

Thomas Arista, an investigator and national expert on the Pharmaceutical/Biotechnology team in FDA ORA's Division of Field Investigations, added, "For myself, I don't care to look at a list of organisms. I usually ask, 'What do you have in your facility?' If you do have a list, I ask, 'Why do you have this list and why these organisms?'"

If a company does have a generated list, Arista said, he wants to know, "What is the purpose of the list. What is the quality department using the list for? I'm interested in what did this list provide you?"

The regulators agreed that a list of objectionable organisms can give a firm a false sense of security, and exclude the monitoring or testing for organisms not included on the list.

Typically firms refer to objectionable organisms listed out by the U.S. Pharmacopeia or the FDA "Big Bug Book." But Guilfoyle cautioned that even these references can be inflexible and outdated.

"Sometimes the lists even handcuff FDA," he told attendees. "We have that big bug book, and even that is not completely up to date. It gives you a comfort zone when you look at that book or list and don't find the organism you've found on it. But it shouldn't, because even that list is not up to date."

Tony Cundell, Ph.D., director of Analytical Sciences-Microbiology at **Merck Research Labs**, disagreed,

## Pharmaceutical ingredients pose greatest risk for microorganism growth, product recalls

BETHESDA – Impurities in pharmaceutical ingredients, followed by ingredient water, process equipment, the manufacturing environment and manufacturing personnel, are the top reasons for microorganisms being isolated from non-sterile drug products, according to a **Merck Research Labs**' analysis of recent pharmaceutical product recalls.

But Tony Cundell, Ph.D., director of Analytical Sciences-Microbiology at the firm, told a recent **PDA** conference that the exclusion of objectionable organisms from non-sterile drug products can be achieved by selecting pharmaceutical ingredients with good microbiological quality attributes, developing formulations that do not support microbial growth, robust manufacturing processes, appropriately designed and operated utilities, equipment and facilities, general GMP compliance and, when necessary, product release testing.

"You should know which of these materials develop microbial growth and your monitoring program should be directed at those," Cundell said.

The exclusion of objectionable organisms from non-sterile drug products is achieved by the selection of pharmaceutical ingredients with good microbiological quality attributes, he said. Firms also should develop formulations that do not support microbial growth, use robust manufacturing processes and use appropriately designed and operated utilities, equipment and facilities.

When necessary, Cundell said, product release testing should be performed.

"I advocate always a risk-based testing program," he said.

Firms should evaluate the relative risk associated with different starting materials and excipients' manufacturing processes.

Cundell said a risk assessment should be performed on pharmaceutical ingredients, including classification. Ingredients can be classified as synthetic, semi-synthetic and derived from plant, animal or mineral materials, he said. In the latter classification the material may be from slightly to highly processed.

The risk of microbial infection due to the administration of a drug product to a patient will depend on the invasiveness of the route of administration of the product, the numbers and types of microorganisms (i.e., bioburden) in the drug product, the physical and chemical attributes of the drug product, the dosing regime and the medical status of the patient.

Clearly, Cundell said, injectable products, because of their invasiveness, must be sterile while tablets and capsules, in the absence of foodborne pathogens, may contain a moderate bioburden without impacting the recipient of the drug product.

Concomitantly, he added, pharmaceutical ingredients contaminated with high numbers of microorganisms will impact nasal sprays, vaginal products, topical products and oral liquids more than tablets and capsules. ■ *Story by Melissa Winn*

saying, "A list can give some consistency across many manufacturing sites."

His company, Cundell said, has 65 manufacturing sites and using a list of objectionable organisms provides some assurance of consistency across the board. He added, however, "The list should not exclude other organisms."

He said there should be some cross-utilization of a list and the expertise of microbiologists.

Arista recognized the challenge to multi-site companies and agreed the list could be a tool for consistency, but cautioned that the expertise of microbiologists should be utilized to address organisms not on the list and evaluate continued changes in risk to the product from the environment, materials, personnel, etc.

"There is some utility to that," he said, about the use of a list to maintain consistency throughout company sites. "But that list is going to be outdated. If

the document is well-written, it can be used but should not be all-inclusive.”

Arista added, “I do understand that challenge across multi-site companies and their use of the list.” But, he added, “The list could still be a detriment.” The expertise of microbiologists should also be utilized.

As well, he said, microbiologists should be at the table in discussions about risk evaluation and assessments, utilizing scientific expertise to develop the company’s approach. ■

**Stability  
Continued from page 1**

Sood added that manufacturing of the selected drug product batches should be performed using different drug substance batches. The formulation, container closure, and manufacturing process should be representative of the commercial product. Firms also should represent each strength and container closure, unless matrixing or bracketing is being applied.

Stability studies at the NDA stage are used to establish the appropriate retest or expiration dating period applicable to all future drug substance and drug product batches manufactured, packaged and stored under similar circumstances, Sood told attendees. Additionally, they establish long-term storage conditions and provide evidence of the effect of various environmental conditions on the quality of the drug substance and drug product.

FDA regulations, Sood said, require companies to assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, and require the product to bear an expiration date determined by appropriate stability testing described in 21 CFR 211.166.

He said 211.166(a) mandates a written testing program designed to assess the stability characteristics of the drug products. Further regulations also require a full description of the drug substance

including its physical and chemical characteristics and stability.

Long-term testing should be conducted every three months during the first year of manufacturing, every six months the second year and annually thereafter, Sood said. Accelerated testing should be performed at a minimum of three time points, including initial and final (i.e. zero, three and six months). In-use studies for reconstituted/diluted solutions should be done at initial and final time point for primary batches.

“What you’re trying to do is establish the stability profile,” Sood said.

Stability data also is required in all phases of an IND to demonstrate that the drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, Sood advised.

“The amount of data will depend upon the duration of the proposed clinical study,” he added.

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***FDA regulations, Sood said, require companies to assure that a drug product meets applicable standards of identity, strength, quality and purity at the time of use, and require the product to bear an expiration date determined by appropriate stability testing described in 21 CFR 211.166.***

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FDA guidance on Phase I studies recommends a brief description of the stability study and test methods used to monitor the stability of the product packaged in the proposed container/closure system and storage conditions, as well as preliminary tabular data based on representative material.

FDA recommendations for Phase II studies include a list of tests,

analytical procedures, acceptance criteria, time points for each test, storage conditions and duration of study that covers the trial duration. Firms also should include available stability data from Phase I studies that were not reported previously. Any data from Phase II clinical material should be provided as it becomes available, for instance in an annual report, Sood said. FDA also encourages early performance of drug substance stress studies.

For Phase III studies, FDA recommends companies provide any changes in the stability program from Phase II studies, any available stability data from Phase II not reported previously and data from Phase III clinical material as it becomes available. Stress studies to assess potential changes in physical and chemical characteristics also should be provided, if not performed earlier.

At this stage, Sood said, companies also should develop protocols for formal stability studies to support the filing of its NDA. ■

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## Quality By Design

# QbD approach ensures a robust technology transfer as defined in ICH Q10

By **Melissa A. Winn**  
Managing Editor

ARLINGTON, VA —Using a Quality-by-Design approach ensures a robust technology transfer, which is a valuable step in the developmental life cycle leading to successful commercial manufacturing, George Millili, Ph.D., senior director of Pharmaceutical Commercialization Development at **Merck** told a **PDA/FDA Pharmaceutical Quality System (ICH Q10) Conference**.

The goal of technology transfer activities, as defined in ICH Q10, is to transfer product and process knowledge between development and manufacturing and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.

“It is essential we utilize a sound development approach, including quality by design,” Millili said about technology transfer activities.

Using a QbD approach, he told the October meeting, technology transfer in the development stage would start with the formation of a diverse, skilled and collaborative team. The team would review a process flow diagram for key input and outputs that could impact quality and would lead to uni/multi-variant experiments to study relationships and gain information on potential sources of variability.

“You need to know where quality could be impacted,” he said, adding that there should be a thorough knowledge and understanding of measuring capacity, as well.

Following the experiments, Critical Process Parameters, Critical Quality Attributes and other important data are identified. And, once identified, the design space should be defined and understood consisting of input ranges that provide a high probability of meeting specification.

The control strategy then needs to be put in place to assure focus on critical points, as identified.

“There’s a lot of rigor that goes into a development process,” Millili said.

Moving through the lifecycle, he told attendees, technology transfer should take all the gathered knowledge and use it as the basis for the manufacturing control strategy, the approach to process qualification and on-going continuous improvement.

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***Personnel is a key element, prescribing an integrated interdisciplinary team of cross-functional experts. Roles and responsibilities of the development group and the site staff should be clearly defined as early as possible.***

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The transfer should transition the product/process/analytical method knowledge between development and all manufacturing sites. It also should ensure variability of process and parameters are controlled and sufficient in the face of the rigors of a commercial production environment.

It also needs to verify parameters established during the development are still within the determined design space and/or adjusted at scale-up.

Key elements of technology transfer, Millili told attendees, include documentation and information, including consistent and controlled procedures for technology transfer and running your process. There also

should be clear documentation of all process/product knowledge.

“It’s also important to have an understanding of prior knowledge from similar products,” he said. “A lot can be learned from successes.”

Personnel is a key element, Millili said, prescribing an integrated interdisciplinary team of cross-functional experts. Roles and responsibilities of the development group and the site staff should be clearly defined as early as possible.

From an execution perspective, technology transfer should include the successful manufacture of demonstration batches.

“This aids in site training and demonstrates that the receiving site has the ability to perform the process adequately and is the basis for process validation,” Millili said. ■

## **New Service analyzes FDA GCP and GLP inspections...**

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## Analysis of 483s/EIRs for GMP validation issues

By Rebecca Mashaw

### Human Drugs

## Inspection finds multiple repeat observations at Aire-Master

All but one observation made by FDA investigator Audra Ashmore during her Nov. 3-9, 2010, inspection of **Aire-Master of America** were repeat observations from a January 2007 inspection, she noted in the 483 issued at the close of the investigation.

Ashmore found that the company, which manufactures OTC products such as antibacterial soaps and hand sanitizers, was not using a master production record for its products and had “no procedures in place to describe the preparation of Master Production records.”

The company’s batch production records did not describe in-process or finished product testing, the investigator further found.

Aire-Master had not established and documented the accuracy, sensitivity, specificity and reproducibility of its test methods, Ashmore observed. Specifically, she reported that as of Nov. 5, 2010, the gas chromatography method “used for the active ingredients triclosan and ethanol in hand sanitizer and antibacterial soaps has not been validated. Batches of antiseptic soap and hand sanitizer have been released based on these testing methods since 2006.”

Results from an examination of packaged and labeled products were not documented in the batch production records, the FDAer stated.

### Checklist: Aire-Master

- ✓ **Lack of written policies and procedures**
- ✓ **Inadequate documentation**
- ✓ **Failure to validate**

Ashmore also found that Aire-Master exerted “no control over label issuance and use. The labels for OTC drug products are stored alongside labels for cosmetics and cleaning products manufactured at your firm in an unsecure area of the warehouse and there is no limitation on access or control of issuance for OTC drug product labels.”

The investigator added that the company had “no procedures in writing that describe the issuance of labels for OTC drug products produced at your firm.” Further, Ashmore noted that the firm had “no documentation of the examination and review of labels upon receipt for conformity with established specifications.”

In the only new observation out of the 11 items detailed on the 483, the inspector reported, “The policy and procedure

for the sanitation of equipment used to manufacture OTC drug products fails to define the cleaning schedule or interval.”

Ashmore found that Aire-Master had no written policies or procedures for the quality control unit. She also observed that the company lacked written procedures describing “the receiving, handling and examination of labels, packaging materials or containers” for the firm’s OTC drug products.

Aire-Master also failed to document any annual visual checks of OTC drug products’ retain samples to determine if the products showed evidence of deterioration, the investigator wrote.

The company did not ensure that backup data was exact, complete and secure from alteration or loss by keeping hard copies or providing alternate systems, Ashmore observed. She noted that as of the date of inspection, “there are no audit trail capabilities in the internal software used to create and store electronic batch production records. Changes can be made to the production record with no way of determining when the change was made and what information existed prior to the change being made.” ■

## Cascadia gets 23-item 483 for GMP violations in sampling, procedures and processing

FDA investigators Lori Brown and Lawrence Lee found multiple GMP violations, including a number of repeat observations, during their Oct. 19-Nov. 16, 2010, inspection of **Cascadia Manufacturing**, resulting in a 23-item 483 for the OTC drug maker.

Lee and Brown noted that although the company had been manufacturing its OTC product CankerMelts since July 2009, “None of the lots have laboratory testing to determine their conformance with final specifications, identity and strength. In practice, your firm relies on an oral examination of the finished product to determine ‘the quality and ratio of ingredients’ and the products’ conformance to identity and strength specifications.”

The investigators also found that acceptance criteria for sampling and testing conducted by Cascadia’s quality control unit was not adequate to assure that batches of the firm’s drug products met all specification and quality control criteria as a condition of approval for release. Although the company “is now performing microbial testing on each lot” of its CankerMelts product, “your firm has not established criteria or scientifically sound specifications for the release tests that you perform.”

Brown and Lee noted that Cascadia’s SOP for production and packaging of CankerMelts states: “There is no scientifically valid way to establish a limit for numbers of microbes other than by graphing sample data to establish a normal level and then setting significantly higher numbers as an upper limit.”

The FDAers stated: “You did set limits for salmonella, enterobacteracea and mold. You did not have documents showing an analysis of data or the scientific rationale to establish those limits. Acceptable microbial limits for aerobic plate count, yeast count or total yeast and mold in your finished drug product CankerMelts have not been set.”

#### Checklist: **Cascadia**

- ✓ **Failure to perform testing**
- ✓ **Lack of written procedures**
- ✓ **Inadequate CAPA**

The investigators further noted: “A test for visual inspection for mold growth on your finished drug product CankerMelts is reportedly performed for each lot of drug product. There is no written procedure for this test or specification of acceptance (or rejection) criteria for visual mold inspection.”

In addition, Brown and Lee wrote, the firm had no written procedure for its “oral sampling for quality and ratio of ingredients” test reportedly performed for each lot of CankerMelts.

Cascadia did not extend its investigation of unexplained discrepancy or the failure of a batch or any of its components to meet specifications to other batches of the same product or other products that might be associated with the failure, the FDAers stated. They observed that when one lot of CankerMelts did not meet specifications when sent out for microbiological testing, the batch was retested and a CAPA was opened. The CAPA form noted that “further investigation needs to be done,” but no additional investigation was described on the record.

This CAPA form also noted under the “Root Cause” section only “Hand washing or temperature control.” The FDA team observed: “There was no explanation of how this was determined. There was no record of an investigation into previous or subsequent manufactured lots of CankerMelts GX, including those which were manufactured from the same lots of components/ingredients. There was no record of an investigation of the components/ingredients used to manufacture the contaminated lot or previous and subsequent lots.”

The investigators cited the firm for its failure to conduct microbiological testing on the components, including gelatin, used to manufacture the lot of CankerMelts that was rejected due to contamination.

Cascadia had not established written procedures describing in-process controls, tests and examinations to be conducted on appropriate samples of in-process materials of each batch of its OTC drug products, FDA found.

The inspectors judged that the firm’s procedures were “not sufficient to monitor the output, evaluate your in-process procedures and to validate the performance of those procedures based on suitable scientifically supported data that allows for the determination of the identity, strength, quality and purity of your finished drug product between batches of the same lot and/or between lots.”

FDA also observed that the company accepted, in lieu of testing each component, reports of analysis from its component suppliers without performing at least one specific identity test on each component and without establishing the reliability of its suppliers’ analyses through validation of test results at appropriate intervals. Brown and Lee specifically noted that Cascadia had not “independently verified the certificate of analysis provided by your suppliers for components used to manufacture Canker Melts.”

In addition, the FDAers wrote: “You could neither supply a certificate of analysis for your current active ingredient, gelatin, received on March 3, 2005, nor have you retested or re-examined this component after long periods of storage to verify the suitability of its continued use.” The company had also failed to conduct a specific identity test on the gelatin or other components.

Cascadia’s complaint handling was faulted by the investigators. They observed that six complaints about CankerMelts had been recorded between Dec. 7, 2009, and Oct. 10, 2010, but the firm’s complaint handling procedure had not been followed in any of these cases. No record was found to indicate that the firm had evaluated any of these complaints to determine if they met the definition of an adverse drug experience. None of the records of these complaints showed the name of the employee who received the complaint or the lot number of the product.

Cascadia’s procedures require that all complaints be recorded on a customer complaint form and that QA assign a unique number to each complaint; these complaints are also required to be entered into a customer complaint log and tracked. These steps were not completed for any of the six complaints cited. Further, no formal response letter was issued for any of the complaints, no reason was given justifying the lack of response, and no record or documentation was found to show that the procedures required for closing complaints were followed, the inspection revealed.

Brown and Lee also found several problems with the conditions of Cascadia’s facilities and equipment. They reported that a substance identified by the firm as rust was observed in the hopper and on the nozzle plate screen of the MI dispensing machine—both direct contact surfaces. “There were accumulations of dust-like substance and white powder on the table on which components are stored in the mixing/weighing area. This area is directly adjacent to the area where ingredients are weighed and drug is mixed.”

In a separate observation, the inspectors also noted that the rust was a “reactive material” in direct contact with in-process materials, and could affect the product’s strength, quality, purity, safety or identity.

Cascadia’s written procedures for cleaning and maintenance failed to include schedules for both tasks; descriptions in sufficient detail of the methods, equipment and materials used; and instructions for protecting clean equipment from contamination prior to use. The company had also failed to demonstrate that its cleaning procedures were capable of removing certain residual material from equipment, the FDA team found.

The company’s facilities were not appropriate in design to facilitate cleaning and maintenance, as well, the investigators observed. In Cascadia’s “clean room” the team observed that

the walls of the mixing and weighing area were “constructed of hanging plastic tarps supported by 2 x 4 rough wood supports. The entrance to this area is a plastic tarp which is lifted and moved aside to gain entry to the area.”

A collapsible wooden table in the mixing/weighing area made of compressed wood material had a broken corner, the inspectors noted, “and has an area of exposed particle board with obvious particles and pieces of the materials on the table and on the immediately adjacent table where the scales are used to weigh components for drug product.”

The FDAers also observed a “wall behind the mixer in the mixing/weighing area has a sheet of plastic, supported by duct tape, covering a hole in the wall where an electric appliance was previously mounted. The plastic and tape appear to be coated with old residual drug component material.” This same residual material was found on the knob of a door in the area that was “constructed of notched/gouged rough wood.”

Brown and Lee detailed several examples of Cascadia’s failure to follow written production and process control procedures. The company did not, as required by procedure, include the product name and strength of batches and lots in the Master Production Record; SOPs were not signed and dated; SOPs were not maintained in a notebook in a central location; SOP version numbers were inconsistent.

In addition, the Quality Assurance staff was required to create files for all subcontractors and suppliers “for applicable Purchasing Specifications as well as evaluation documentation used in the approval process.” However, the 483 noted, “you could not demonstrate that this Quality Unit had a file containing these specified documents.” Cascadia also was unable to demonstrate that its QA unit had, as required, compared COAs to purchase specifications for its components and supplies and was “unable to produce written specifications for ingredients/components used in the manufacture of CankerMelts.”

Drug production and control records were not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures

before a batch was released or distributed. The inspectors reviewed the batch production records and found that some forms were not dated and some were not completely filled out. As a result, Brown and Lee reported, they could not determine “that batch record review was performed by QA/QC prior to release.”

In reviewing laboratory controls, the inspectors found: “There is no scientifically sound laboratory method to assure that each disc delivers the active ingredients in a controlled release.” They noted that the labeling for CankerMelts stated that the product “uses a patented dissolving time-release disc” and that the box label states the product provides “2-6 hours pain relief per disc.”

Cascadia also had “no scientifically sound sampling plan to select CankerMelts from a given lot for microbiological testing.” The company’s scales verification checklist states an acceptable weight deviation for CankerMelts “based on the base weight check, not on the manufacturer’s recommendations. You were unable to demonstrate that your established acceptable deviation range is supported by scientifically sound data.”

Equipment “used to perform a function of drug manufacturing process to satisfy critical process parameters” lacked documentation to show that the equipment had been calibrated or inspected against a written program to ensure their proper performance. Brown and Lee noted that the electronic scales had not been calibrated consistent with the manufacturer’s recommendation; controls over the heating element temperature and rate of agitation for the mixer were not written or validated; the thermometer on a hopper was labeled to show that it “reads high,” and there was no justification for the system used to determine when the water distilled is “descaled,” among other deviations noted.

Cascadia had not conducted stability testing for CankerMelts, the FDAers reported. They explained that the expiration date on the finished product label for one lot of the product manufactured on March 2, 2010, was given as December 2014. The SOP for the product’s production and

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packaging justifies the expiry by stating that “dry, partially hydrolyzed collagen (gelatin) is stable over thousands of years and the product is dry.” However, the FDA investigators commented: “You did not provide stability data for CankerMelts to support an expiry date” or the actual expiration date used on the product.

The company did not have written procedures for how sampling should be conducted for CankerMelts... ‘for mouth and other testing,’ orally sampled for quality and ratio of ingredients, visual inspection for mold growth and sample sent out for any chemical or microbial testing,” the inspection report continued. The SOP states: “When discs are dry and before heat sealing, fill a polybag with loose samples, mark lot number and give to Quality Unit for mouth testing and microbial testing.”

However, the investigators observed: “In practice, samples for testing are collected from product ‘rejected’ during the manufacturing procedure. There was no written scientific or statistical justification for this sampling procedure or clear instructions on how to take a representative sample from the batches that make up the lot.”

Cascadia had no procedures for determining theoretical yield at any stage of manufacturing, processing, packaging and holding of its drug product. “There is no documentation of determination of yield at any stage of production,” Brown and Lee reported.

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***During the inspection, Cascadia received a box of returned product. However, the team observed: “There are no written procedures for how to hold, test or reprocess returned drug product.”***

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Although both the production manager and president of Cascadia informed the inspectors that some percentage of CankerMelts were rejected and not packaged during a visual “grading” process, the FDAers determined that there was “no SOP which describes the grading process. There is no record or report that enumerates the rejection of CankerMelts cards or the reasons for their rejection. The master production record does not specify a threshold for rejected finished product at which an investigation must be performed to account for a low (or high) theoretical yield.”

The company did not examine packaging and labeling materials for suitability and correctness before performing packaging operations, the team found. They noted that two lots of brown CankerMelts Natural “were packaged into boxes labeled for the new formulation of white/clear CankerMelts All-Natural.”

The company also received labeled boxes or package insert labeling without examining a representative sample for conformance to standards when received.

“There is no record of sampling or examination of new labeled boxes or package insert labeling,” Brown and Lee wrote.

During the inspection, Cascadia received a box of returned product. However, the team observed: “There are no written procedures for how to hold, test or reprocess returned drug product.”

Cascadia’s facilities for handwashing lacked air driers or single-service towels to ensure cleanliness. The investigators reported that “the sink in the production area for hand washing did not appear clean. The sink had areas with unidentified materials flaking in the sink and splotchy areas... which appeared to be dirt or grime and areas of greenish algae-like material. There were no paper towels or other single-service towels in the production area near the handwash station. There was a green towel and rags near the sink” that employees used to dry their hands during the inspection. “These appeared well used, worn and not clean.” ■

## Medical Devices

### Xoran cited for violations of MDR, radiological health regulations

Medical device maker **Xoran Technologies** was not only out of conformity with GMPs but also violated FDA regulations regarding corrections and removals, MDR and radiological health, investigator Gary Urbiel Goldner reported after his Aug. 4-Oct. 14, 2010, inspection.

The FDAer observed that Xoran did not notify the agency “of defective MiniCAT and xCAT ENT computer tomography (CT) devices that your firm produced, assembled and installed at customer sites.” The company received 367 complaints about 169 CT devices between March 5, 2009, and Aug. 10, 2010, “that failed to function as intended” in the field, Goldner found.

Of those complaints, 108 were identified by the company “as failures of Printed Circuit Boards (PCBs), failures of x-ray detector panels, failures of x-ray source tubes/power supplies, and/or overhead gantry rotation failures in 83 MiniCAT and xCAT ENT devices.” The complaints lodged ranged from “patient chair vertical translation issues” and “mechanical failures including system lockups during calibration” to image quality errors including “ring artifacts, image streaks and blurred images.”

In one complaint the customer told Xoran that “the image quality of the CT scans have become unusable” and commented that the images looked “pixilated.” This customer said physicians at the office were no longer willing to perform CTs with the Xoran scanner. The company replaced x-ray controller to resolve the problem. Another customer required the replacement of a shutter board, which was malfunctioning.

Urbiel Goldner reported that 18 complaints alleged out-of-specification dose readings. “Your firm subsequently reported that this nonconformity has been confirmed at 13 customer sites and could affect all sites with x-ray sources manufactured by your firm’s suppliers. Your firm did not notify FDA...of these defective CT devices.”

Another 241 complaints charged that the software on Xoran devices was “locking up” while in use on 122 MiniCAT CT devices in the field. The company’s own risk analysis “documents that your firm has determined that the effect of software freezes includes unnecessary exposure of the patient.” Again, the firm failed to notify FDA of this issue.

The investigator found that the company’s management with executive responsibility had not ensured that certain components of the quality system had been fully implemented and maintained throughout the organization. Those components were: quality audits; medical device reporting; purchasing controls; corrective and preventive actions; complaint handling; and reports of corrections and removals.

Urbiel Goldner commented: “This is a repeat observation from previous FDA inspections” conducted in 2007 and 2009, and was identified as an observation in an FDA warning letter in 2008.

#### Checklist: Xoran

- ✓ **Inadequate quality system implementation**
- ✓ **Failure to notify FDA of complaints**
- ✓ **Failure to follow procedures**

Xoran had not adequately established procedures for quality audits, the inspector found. He noted that although the firm’s procedure on internal audits calls for such audits to be conducted at specific intervals, “your firm has conducted quality audits at defined intervals and with sufficient frequency during 2010 only for manufacturing processes, complaint handling and design controls.”

Audits for document control of SOPs, product life cycle, CAPAs, servicing, installation training, procurement, management responsibility, order to remittance and nonconforming product management, which were scheduled for the first and second quarters of 2010, had not been conducted. This, too, was a repeat observation from the 2007 inspection and referenced in a warning letter to the firm in 2008.

Urbiel Goldner noted that procedures for complaint handling and regulatory reporting had not been followed. In a CAPA the firm documented that “current procedure has not been followed/limited objective evidence to support that complaint reviews are scheduled or held as defined in SOP.” The company’s director of operations/quality engineer and customer service manager “both stated that your firm has no documentation to support that complaints are reviewed for Medical Device Reporting (MDR) submission to FDA.”

One complaint referred to difficulty in getting the proper image until after three scans and stated: “I have fears of patients figuring out that they are being scanned multiple times, and we could get investigated by the state for overscanning.”

The company had also received 18 complaints about out-of-specification dose readings and the 483 referenced a complaint concerning a MiniCAT that “would emit radiation but not rotate.” None of these reports was evaluated for MDR reportability.

The inspection revealed that Xoran had not established requirements to be met by suppliers. The FDA investigator reported that the company documented in a product change request, “Like most of our suppliers, we do not have contractual agreements for the specific workmanship of conformance testing necessary to ensure a supplier is providing parts which meet our requirements.”

Xoran receives all its PCB and programmable logic controller (PLC) components for its MiniCAT and xCAT ENT systems from a single supplier, Urbiel Goldner reported. However, documentation from the firm showed that Xoran “does not have adequate specifications for part conformance tests, test methodology and PC programs pertaining to the PCBs and PLCs that this supplier manufactures,” and further, “any documentation that does exist either at Xoran or at the supplier has not been reviewed and approved.”

The company also receives all x-ray source tubes and x-ray source power supplies; x-ray detector (receptor) panels; and CT frames and gantries from single suppliers, but has not ensured that these suppliers can provide these components “according to specifications and overall workmanship quality.”

The 2007 inspection cited this as an observation, which was also referenced in the 2008 warning letter.

Xoran had not fully implemented its CAPA procedure, the investigator found, noting that the company “has conducted incomplete investigations” and “has not determined the cause of 104 out of 108 complaints,” or 96% of complaints received March 2009-August 2010 identified as failures in the field of PCBs, x-ray detector panels, x-ray source tubes/power supplies or overhead gantries. The FDA investigator noted several examples of failures for which Xoran did not investigate or determine the cause.

The company also failed to ensure that its CAPAs were effective and did not adversely affect the finished device, the inspection revealed. In one example, a MiniCAT device was considered repaired after Xoran replaced the x-ray source tube and power supply. A later complaint resulted in the replacement of the x-ray controller. However, the company documentation showed that “the customer complained of reappearance of the issue after repair.” The company again replaced the components.

Not all complaints were reviewed and evaluated to determine if an investigation was necessary, the inspection further found. One customer complaint involving a MiniCAT that would emit radiation but not rotate reported that “this is the second time in the past two business days that the customer has seen this issue.” The firm documented that the complaint was not reviewed. A complaint involving a MiniCAT leaking oil was also not reviewed, although the device, which was under warranty, was repaired.

Urbiel Goldner observed that “corrections of MiniCAT and xCAT ENT CT devices conducted by your firm to reduce risks to health posed by these CT devices were not reported in writing to FDA.”

Corrections in the field that were conducted by the firm of 83 CT devices should have been reported as corrections to the agency. ■

**Warning Letter Analysis**  
**Details of key FDA warning letters released in**  
**September and October 2011 that contain**  
**citations for validation issues**  
*By Rebecca Mashaw*

**Human Drugs**

## Dental Technologies failed to follow procedures, perform tests, FDA warns

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 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 contributed 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

### Warning Letter Code Legend

- **BPD**—Biologic product deviation
- **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
- **L-B**— Labeling issues
- **Lab** — Laboratory control issues
- **MDR** — Medical Device Reporting violations
- **NDA** — Lack of new drug application
- **OOS** — Out-of-specification results
- **Pak** — Packaging
- **PMA** — Lack of premarket approval
- **QC/QS** — Quality Control/Systems deviations
- **Stab** — Stability
- **Ster** — Sterility
- **Val** —Validation

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**

## FDA warns SmithKline Beecham about significant GMP violations

Oct. 7 - CDER

FDA informed drug manufacturer **SmithKline 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  $\geq 4$ , Fungi  $\geq 3$ ) 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. SmithKline’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 finished 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 warned about procedures, adverse event reporting

### 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 postmarketing 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 center and pharmacy.”

The company was cited for failure to submit reports of adverse drug experiences (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 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.”

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.” **AE**

## Medical Devices

# FDA warns Measurement Specialties about problems with establishing and following procedures

## 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 re-evaluation 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.”

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 out of conformance with GMPs, FDA warns

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.

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.”

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

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.

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

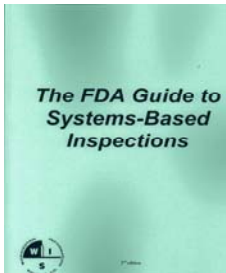
Rocket Medical’s Control of Nonconforming Product procedure, FDA found, “requires a scrap record sheet to be completed. The testing of Embryo Bulb Tip ET Embryo Transfer Catheters/R57635-00-18 Lot 436023 revealed that it was found that 51 of the pieces were found to have defects. The 51 pieces were reportedly 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**

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