

Inspection Monitor

Analysis of FDA 483s & EIRs for Drugs, Devices & Biologics

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Advent of Q10 ‘shifts’ GMP audit focus; trouble with any formulations could delay approval

ARLINGTON, VA – FDA might view a company’s quality system as faulty if it is producing one dosage form fine, but is having problems with another dosage form, a senior Center for Drugs compliance official said Oct. 4.

Richard Friedman, acting associate director of CDER’s Office of Manufacturing and Product Quality, told a **Parenteral Drug Assn.** meeting here that FDA will examine all of a company’s systems, including materials systems, equipment and facilities, production, laboratory, packaging and labeling, the quality system, etc.

“If any one of these is out of control, that means all the profiles at the site are considered out of control,” he said. “Before ICH Q10, we may have considered, if you’re having trouble with capsules, but

you’re not having trouble with tablets, fine. We’ll improve your production of tablets. But we have shifted our view and the overall systems management approach.”

He reminded industry that FDA looks at whether a company has implemented a good quality system through its quality system inspections program and ensures the quality system has a foundation for assuring an ongoing state of control.

At the same meeting, jointly sponsored by FDA and the European Medicines Agency, Steve Lynn, M.S., acting director of CDER’s Office of Manufacturing Product Quality, told PDA, “FDA expects companies to be accountable for the quality of their products, with senior management that recognizes and leads with the philosophy that a proactive, preventative paradigm must be ingrained in the organization’s daily operations.”

He added, “Robust supplier relationships and neural networks are essential to limit variability in materials and processes.”

Lynn said quality should be “customer focused,” with the intended use and target audience considered.

“Quality is achieved and consumer risk is minimized by a robust quality system,” Lynn continued. “You need to know your processes inside and out. You need to know where you outsource. You need to know what you’re buying.”

A robust quality system, he said, is science- and risk-based, vigilant and proactive, culture-focused and able to identify issues while they are still small. It also is responsible for assuring any contracted site is qualified to do the function, and performs it satisfactorily.



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Friedman added that a pharmaceutical quality system should establish and maintain a state of control, facilitate continual improvement and facilitate effective knowledge transfer and management.

A pharmaceutical quality system should not be reactive and solely a procedural approach, Lynn said.

He added that the support and ownership of quality goes beyond the quality and compliance units.

“A culture of quality yields many benefits,” Lynn said. “Enhanced process stability drives productivity and performance.”

Senior management, he said, must be supportive of product quality. They should establish mechanisms to ensure science- and risk-based decision-making throughout the lifecycle, and remain vigilant about new variables or events that may affect product quality.

Senior management also should assure clear and open communications, within the company and without. FDA should be notified when a problem arises that has the potential to adversely impact public health.

Lynn added that prevention also reduces compliance risks and costs, and protects the brand. *Story by Melissa Winn*

Quicker approval of manufacturing changes promised to stave drug shortages

A part of President Obama’s executive order to FDA to take steps to reduce drug shortages is a mandate to the agency to accelerate review of applications to change manufacturing production processes.

The order, signed in the Oval Office Oct. 31, also instructed FDA to take action in broadening its reporting of potential drug shortages and giving the Justice Department more information about possible instances of collusion or price gouging.

Patient deaths have been blamed on the shortages, which tend to affect cancer drugs, anesthetics, drugs used in emergency medicine, and electrolytes needed for intravenous feeding. Hospitals have been forced to buy from secondary suppliers at huge markups. Surgeries and cancer treatments have been delayed.

“Even though the FDA has successfully prevented an actual crisis, this is one of those slow-rolling problems that could end up resulting in disaster for patients and health care facilities all over the country,” Obama said.

The president ordered the new steps without congressional approval, saying his administration refused to wait for lawmakers to act on similar legislation pending on Capitol Hill. The measure is part of a White House effort to use executive action to get around congressional Republicans.

Obama said the White House would continue to push lawmakers to pass bipartisan legislation to prevent drug shortages, but said “we can’t wait for action on the Hill, we’ve got to go ahead and move forward.”

The President was joined in the Oval Office by Health and Human Services Secretary Kathleen Sebelius, FDA Commissioner Margaret Hamburg, M.D., pharmacy manager Bonnie Frawley, and Jay Cuetara, a 49-year-old San Francisco cancer patient who told an FDA workshop last month how he grappled with a shortage in his chemotherapy drug.

There are more than 200 scarce medicines this year alone, up from 56 in 2006, according to FDA. Most of them are cheaper generic drugs that have been around for years, but yield low profit margins for their manufacturers. Others are said to be quality or manufacturing problems, or delays in receiving components from suppliers. FDA does not have authority to force drug makers to continue production of a drug.

Administration officials characterized it as one step in a long and complicated effort. Indeed, Obama eschewed more ambitious proposals — like government drug stockpiling or manufacturing — that would have injected the government more directly into the nation’s drug market and cost more, but that might have been more effective.

But Hamburg said, “We can make a very real and meaningful difference by expanding our network of early warnings.”

Indeed, officials said FDA has managed to prevent 137 drug shortages over the past 21 months when companies told regulators they were having trouble. Options include getting other manufacturers to ramp up their own production, helping to find alternative suppliers of key ingredients, even sometimes allowing temporary importation of competitors usually only sold abroad.

Along with Obama’s order, the administration re-

leased two government reports that mostly blame a dysfunctional marketplace for drug shortages, directly contradicting assertions by some commentators that government rules are to blame. The analyses found that 74% of the medicines in short supply in 2010 were sterile injectables.

The economic and technical hurdles to participating in this market have made it exceedingly inflexible, the analyses found. Just five large hospital buying groups purchase nearly 90% of the needed medicines, and only seven companies manufacture the vast majority of supply. In most cases, one company produces at least 90% of a drug’s supply, and crucial ingredients — many of them made in mammoth plants in India and China — are often difficult to find, verify and approve, so years are needed to create new capacity. While demand has grown steadily in recent years, supply capacity has remained largely unchanged.

In a statement, the **Pharmaceutical Research and Manufacturers of America** said: “While the majority of drug shortages involve generic drugs, with FDA specifically referring to an increase in shortages among ‘older sterile injectable drugs,’ this problem concerns us all and requires our combined attention.”

The administration will also send letters to manufacturers reminding them of their legal responsibility to report pending supply disruptions of certain drugs and to encourage them to notify FDA of events that could possibly lead to disruptions even when not required to do so.

The rules needed to expand required notifica-

tions will take time to finalize, but the president’s order will speed that process, administration officials said. The president will also announce his support of legislation proposed in both the House and Senate to expand even further reporting requirements from manufacturers. *By Inspection Monitor Staff*

HUMAN DRUGS

Inspection finds multiple repeat observations at Aire-Master

*Aire-Master of America, Nixa, MO
Kansas City District*

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 Mas-

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ter 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.

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

*Cascadia Manufacturing, Bellevue, WA
Seattle District*

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 specification 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.”

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.”

“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.”

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 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."

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.”

“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.”

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 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.

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 ob-

served: “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 area 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 towels 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

*Xoran Technologies, Ann Arbor, MI
Detroit District*

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 “me-

chanical 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.

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 meets 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 sup-

plier 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 that Xoran did not investigate or determine the cause for.

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.

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.

BIOLOGICS

Aseptic processing failures and quality issues yield extensive 28-item 483 for Regenerative Sciences

*Regenerative Sciences, Broomfield, CO
Denver District*

Biologic drug manufacturer **Regenerative Sciences LLC** (RSL) received an extensive 28-item 483 from FDA investigators Matthew Dionne, Kevin Kallander, Kelly Moore and Gang Wang after a June 2-16, 2010, inspection revealed serious violations of GMPs.

The FDA team found that the firm had no quality control unit. They noted that “Finished Expanded Mesenchymal Stem Cell product (EMSC) is released for distribution...without a second verification of work conducted or a review of finished product labeling prior to patient injection.” The company “could not provide documentation for the approval or rejection of any component, container, closure or packaging material used in the production of EMSC” nor were the responsibilities of a quality control unit in writing.

RSL lacked laboratory controls, as well. The FDAers observed that “the firm has not established specifications for components, raw materials, in-process product or finished product as related to the manufacture or distribution of the EMSC biological drug product for injection.”

The company “does not conduct any testing of raw materials or finished product pertaining to identity, quality, potency, sterility, endotoxin and microbial limits and continues to not have any established finished product specifications for release,” the 483 stated.

Further, the team determined that Regenerative Sciences “has not validated its aseptic processing of mesenchymal stem cells and platelet rich plasma

derived products, nor has RSL carefully controlled each step of the aseptic process to maintain sterility of these products.”

No media challenge study simulating aseptic processing procedures and sterility testing of the final released products was performed to ensure sterility and no smoke studies were performed to evaluate air flow patterns during aseptic processing, the inspectors noted. They also observed that “aseptic processing technicians would leave the aseptic processing rooms while gowned” and return after lunch or restroom breaks without re-gowning. “We observed aseptic processing technicians on numerous occasions moving out and into the BSC [biological safety cabinet] sterile processing environment and begin aseptic processing without disinfecting their hands.”

The investigators noted that it was “common practice for aseptic processing technicians to take off their sterile sleeves when leaving the BSC processing area and place them on a non-sterile chair or table and then don the same sleeves” when returning. Technicians were also seen to leave the aseptic area, “walk through two warehouse/storage areas to receive samples or supplies and then would return to aseptic processing without re-gowning.”

The aseptic processing areas were found deficient in regard to air supply filtered through HEPA filters under positive pressure. “No specifications for differential pressures are established nor monitored during production,” the FDAers wrote. “Air change rate is not sufficient to generate sufficient differential pressures to maintain adequate positivity in the aseptic processing labs relative to the adjacent non-production areas.”

HEPA filters were not installed in the production areas, the team reported. “Only regular air filters are installed at the supply and return ducts. Frequency of the pre-filter replacement for intake air is not established. No qualification testing on the air quality is performed after each filter change.”

Air supplying the entire facility, including both aseptic areas and restrooms, “is provided by one single air handling unit with about 20% fresh and 80% recirculated air. Air is recirculated within the facility. No controls are in place to assure redistribution of dust or other contaminants to prevent cross-contamination of aseptic areas.”

RSL had no environmental monitoring program, no procedures or specifications to evaluate the aseptic processing environment during processing, the team found. “For example, no settle plates or ac-

tive air samplers are used,” they wrote. “No personnel monitoring is performed after the aseptic processing of each batch to evaluate the... technician’s ability to maintain contamination-free gowns and to assure technicians are not a source of contamination.”

The water bath in aseptic processing is used to pre-warm buffers and tissue culture media and to thaw certain components. “All the materials placed into the water bath are then brought into the BSC aseptic processing environment. The water in this water bath has not been tested to assure that it is not adding bacterial contamination.”

The company did not perform microbiological testing on each batch of final release products. Instead, the testing was performed by a contractor on “randomly selected EMSC samples.”

RSL could not provide documentation demonstrating the testing method used or the validations of testing performed, the FDAers stated. The company also had no written testing program designed to assess the stability characteristics of drug products. The team determined that “the stability of the final released products has not been adequately validated. There is no data to support the viability, stability and quality of the products for the two-hour shelf life under actual conditions of container and transportation.”

The firm had not validated its cleaning products and methods on BSC aseptic processing surfaces or other surfaces in the aseptic processing laboratories, FDA judged. “All disinfectants have not been qualified for use. The effectiveness of these disinfectants has not been assessed for their ability to ensure that potential contaminants are adequately removed from surfaces.”

The team observed cleaning of the aseptic processing labs, during which the cleaner “used a wooden-handled push broom that contained visible clumps of hair and dust particles on its floor-contact surface.” The cleaning technician would “push the broom a few feet and then shake the broom, creating a visible cloud of dust. This broom is stored in the bathroom in contact with the bathroom floor approximately four feet from the toilet.”

When disinfecting the aseptic area, the technician used “a wooden handled mop with a non-sterile mop head. The mop was rinsed in water after use and placed into a plastic bucket. The bucket con-

taining the wet mop is then stored in the bathroom approximately four feet from the toilet.”

The integrity of containers and closures for 1cc-syringes “for injection of cellular products and the sterile cryogenic vials for storage of cellular products are not validated to be sterile pyrogen-free. There is no established expiration date of sterility for the 1cc syringes and cryovials used.”

The aseptic processing area’s floors, walls and ceilings are not smooth, hard surfaces that are easily cleaned and disinfected, the inspection revealed. “RSL does not perform any cleaning or sanitizing of walls, ceilings or blinds in their aseptic processing areas.”

Reprocessing procedures lacked the steps to be taken to ensure that reprocessed batches conform to standards, specifications and characteristics, the investigators commented. “There is no required assessment for cell viability, time limitations for acceptance or any other established specifications by which the returned sample is accepted and approved for use in reprocessing,” they stated. “The procedure does not include coverage for the removal of EMSCs from finished product syringes. MSCs removed from finished product syringes are then refrozen in cryo-freeze for later use.”

The FDAers commented that EMSCs were “loaded to syringes and then transported to the clinic for injection. However no process validation or any study has been performed by RSL to evaluate the effects of conditioned media on EMSCs and vice versa.”

BSCs and laminar flow hoods had not been completely qualified for use, the team determined, noting that “particle counts were not performed to verify class 100 air quality” in these cabinets and hoods, which are used in aseptic processing. “No temperature mapping has been performed on all of the firm’s incubators, refrigerators or freezers.”

The company rejected some individualized batches of EMSCs without thoroughly reviewing the manufacturing process, including root cause analysis and correction action, the investigators found.

“RSL does not practice quarantining or testing of any raw materials prior to use in production and has never verified sterility certificates of analysis for components or containers used in production of finished product,” the 483 reported.

FDA found that the facilities used in processing sterile biological drug products were inadequate because the Class 100 BSCs or laminar flow hoods used for processing were “located in a non-classified environment that lacks environmental monitoring and cleaning.” The company had made changes to non-validated manufacturing processes for EMSCs and finished product labeling, but “could not provide documentation supporting any assessment of these changes on manufacturing operations or to the quality of finished product produced by their laboratory.”

Written procedures for production, process control and receipt and handling of components were not followed, the inspection revealed. No time limits were established for critical production steps.

Master production records and laboratory notes, which serve as individual batch records, did not include complete instructions, such as detailed instructions for procedures performed; documentation of aseptic processing controls; specifications for in-process materials and final released products; timeframe for completing each critical process; cleaning and sanitizing; changeover and line clearance.

The investigators observed that “there is no established program to regularly assess or audit conformance of personnel to relevant aseptic manufacturing requirements. RSL has no aseptic gowning

qualification program to assess the ability of aseptic processing technicians to maintain the quality of the gown.”

The company’s procedures for complaint handling were also deficient. The FDA team noted that the written procedures did not include “provisions for distinguishing between a complaint and an adverse event, assessing the severity of the event and its status as expected or unexpected [and] identifying when an investigation is warranted.” The procedures also did not define requirements for reporting to FDA.

“Patient complaint tracking records are now solely recorded into and maintained in a computerized database. The firm was not able to provide evidence that the computerized system was evaluated to ensure the reliability and integrity of the data,” the investigators reported.

RSL had “no documentation to support that the firm’s personnel have been trained” in GMPs, the team found. “Additionally, each of the employees interviewed during this inspection, including all cell biologists who perform manufacturing processes and one employee who perform cleaning operations for the RSL facility, stated that they had not received training in GMPs while employed by RSL.”

INSPECTION LOG

The following is a partial list of inspection documents that have been requested under the Freedom of Information Act by various parties, according to FDA’s Freedom of Information (FOI) Log, which Inspection Monitor subscribers can obtain electronically. Copies of these 483s and EIRs, which have to be obtained from FDA in most cases and in some cases may NOT be available, can be ordered through RECORD-RETRIEVE by referencing the FOIA file # (e.g., 03008075), or readers can submit requests on their own using the file number. The FOI Log on Diskette can be purchased for \$20 per disk, which contains all FOIAs filed in that given week. (Weeks Of Sept. 12-16 and 19-23, 2011, were used to compile this list.) To order the Log on Diskette, call RECORD-RETRIEVE at (703) 779-8777, or e-mail us at SERVICE@FDAINFO.COM

*Indicates EIR is being requested by a company regarding its own facility.

<u>Plant</u>	<u>Location</u>	<u>483/EIR Date</u>	<u>FOIA File</u>
COMMONWEALTH SERUM LABS	MELBOURNE, AUSTRALIA	LAST 18 MONTHS	2011-6662
AMERICAN RED CROSS*	GREENVILLE, NC	4/26-19/10	2011-6709
NATIONAL GENETICS INSTITUTE*	LOS ANGELES, CA	2/9-20/09,1/11-21/11	2011-6710
PREPAK SYSTEMS INC	COOKEVILLE, TN	8/16-20/10	2011-6714
BIONICHE PHARMA	CO GALWAY, IRELAND	MOST RECENT	2011-6815
BRAINTREE LABORATORIES INC*	HOLBROOK, MA	1/09 TO PRESENT	2011-6817
ASTHMATX INC	SUNNYVALE, CA	3/2-22/11	2011-6818
BIORELIANCE CORP	ROCKVILLE, MD	8/10-2/11	2011-6866
SAGEMAX BIOCERAMICS	AUBURN, WA	6/29/10 TO 7/2/10	2011-6876