Food & Drug

Inspection Monitor

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

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Inspections Featured This Month

67% of CDER warning letters since 2012 cite data integrity issues; Indian, Chinese firms top the list

WASHINGTON – Since 2012, some 67% of Center for Drugs (CDER) warning letters—98 total —contained citations for the inspected facility for data integrity, with drug firms in India, China and Mexico topping the list, the **Parenteral Drug Assn.'s** (PDA) Sept. 14 data integrity workshop here was told.

According to data presented by Ronald Tetzlaff, Ph.D., senior corporate vice president, **PAREXEL International**, Duluth, GA, the agency issued 66 warning letters involving data integrity during this four-year period (ended August 20160, and 30 letters were from India, 12, China, five, Mexico, three, Canada, two each from Italy and Germany, and other nations one each.

Paula Katz, director, manufacturing quality guidance and policy staff in CDER's Office of Compliance, acknowledged Tetzlaff's data, but said the scope of FDA's concerns – evident by the recent guidance issued on data integrity – is worldwide, including in the U.S.

She said there is "intentional" and "unintentional" data integrity issues, and the agency has to figure out which is which from an enforcement standpoint.

In the case of non-U.S. products, if the firm has a data integrity issues, more often than not, they will not be allowed to export the product to the U.S., meaning it is put on the Import Alert.

Tetzlaff said all of the warning letters issued to Indian drug firms this year and 65% of Chinese letters involved data integrity issues. But 18 countries overall had firms with data issues – some 59% of letters, followed by 27% for quality system (overall QA oversight), 12% for productions systems and 2% for packaging and labeling.

Falsification was evident in 27 cases, he said.

Asked if FDA's decision to have "enforcement discretion" of its 1992 electronic signature/records regulation (21 CFR Part 11) may be a factor in the rise of integrity-related warning letters, Katz said the integrity of all electronic or paper records is embedded in other regulations, notably GMPs.

"I think Part 11 enforcement has been something that has been questioned over time, but what we can do is enforce what we know we can enforce," Katz said. "Data integrity underlies what's in [ICH] Q7, and in Part 211 [GMPs]. We feel we don't have to go to part 11 to get to security and reliability of the data for drug GMP purposes."

The conference was attended by about 170, according to PDA's attendance list, and none appeared to be with India-based drug firms.

At a news conference Sept. 12 to launch the 25th PDA-FDA Joint Conference, Richard Johnson, chairman of PDA, said acknowledged the attendance from the areas of the world with the most data integrity issues.

In 2016 (YTD Thru August)

60% of CDER Warning Letters (WL) Included Data Integrity Issues (10/17)

30% of WL citing Data Integrity issues were for Companies in India (5/17)

100% of WL in India involve Data Integrity issues (5/5)

65% of WL in China Involve Data Integrity Issues (4/6) Germany had one W/L Involving

Source: Ron Tetzlaff, Parexel Intl. to PDA

However, Johnson said PDA has conducted data integrity seminars in India, South Korea and Brazil, but has been blocked for China because "the Chinese government passed a rule concerning foreign nonprofits operating in China."

At the joint conference, however, Stephen Solomon, Ph.D., deputy associate commissioner, FDA Office of Regulatory Affairs, said FDA has held three meetings in China to address data integrity issues, which he said was attended by China's state FDA officials "who we have been training in this issue." He was unsure, however, whether many in Chinese drug industry attended.

Solomon also reported FDA has had "no problems" gaining access to inspect China-based drug companies, which has been an issue in recent years.

Johnson felt: "We'd be making a big mistake to feel it's just isolated to a couple of countries in the world. It's a much broader issue." *Story by Ken Reid, editor*

DRUGS

Procedures, testing faulted at OTC drug firm

Genlabs Corporation
Chino, CA
Los Angeles District

FDA investigators Djamila Harouaka and Marcus Yambot issued a 10-item 483 to the over-the-counter drug manufacturer **Genlabs Corporation** following a Dec. 7-11, 2015, inspection that revealed multiple nonconformities with GMPs.

The investigators noted the following, according to the 483:

Observation 1: Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

During the inspection the FDAers observed the following deficiencies regarding the sanitary conditions around mixing tank B- 36, which is dedicated for manufacturing antibacterial hand soaps:

- "I observed pitting and rusting on the segment of the…mixer attached to the shaft positioned directly above a large opening (approximately 1 foot in diameter) in the top of mixing tank B-36.
- The metal frame to which the mixer was attached was also rusted and pitted and was located directly above the large opening. Mixing tank B-36 was holding in-process material.
- The metal lattice platform above tank B-36 was rusted and material had fallen from the platform onto the tank. I observed corroded material deposited on the top of the tank on the lip of a small opening (less than 1 foot in diameter) and on the lip of the larger opening. I also observed a thick layer of dust accumulated on the metal lattice platform. An unused hose was placed around the smaller opening on top of the metal platform.
- I observed a thick layer of dust and rust on the piping and tubing running just below the ceiling but located directly above the metal lattice platform located above the large and small openings on the top of the B-36 mixing tank. The insulation was starting to come off of portions of the ceiling. A thick layer of dust was also visible on the tops of the mixing tanks adjacent to tank B-36.
- Tubing attached to a pump located on the top of the metal platform appeared to be repaired with a towel that was tied around the tubing. Plastic wrap was also loosely wrapped around the pump. The pump is used to charge in liquid raw materials…into tank B-36 for the compounding of antimicrobial hand soap products.
- A leak was observed at a valve on the piping emerging from the tilter used to generate materials used in the manufacturing of antimicrobial hand soaps as an ingredient and used for cleaning. This material is metered into tank B-36 for the manufacturing of antibacterial hand soaps."

Observation 2: Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

The cleaning validation for mixing tanks and filling valves used for the manufacture of antimicrobial hand soaps was deficient, the FDA team found.

The report on the cleaning validation of the mixing and filling valve used in the manufacture of antibacterial hand soap "did not identify which product(s) the cleaning procedure was validated for," the investigators noted. The product formulations differ for various products, they stated. In addition, the product specification for one product was changed on Nov. 11, 2013, but cleaning validation was not repeated for the updated formulation.

"The summary report does not state how many batches were used during the validation," the FDAers also reported. Microbial test result data reflected the completion of testing for two samples, but the validation report summary stated that a different number of samples were to be collected for testing.

"Cleaning procedures do not follow procedures used in the cleaning validation. The cleaning logs indicate that mixing tanks used to manufacture" a particular product were cleaned and disinfected with certain compounds, but the cleaning validation report did not describe the use of these compounds or describe how residues are removed from the tank prior to compounding the next batch of product.

"The firm primarily manufactures industrial grade chemicals including laundry detergents, carpet cleaners, degreasers and surface cleaners," Harouaka and Yambot stated. However, they noted, Genlabs "did not have cleaning validation records or other documentation to show that cleaning of nondedicated mixing tanks used to manufacture chemical cleaners was performed to ensure that no chemical contaminants would he carried over into batches of antibacterial hand soap."

The investigators observed products mixed in two different tanks that are not dedicated to manufacture industrial cleaners.

The company's Mixing Tank and Filling Equipment Cleaning Procedure "does not contain detailed instructions for how the tank or the spout is to be cleaned. No number/code is used to identify the spout, pumps or hoses to track which items have been cleaned," the inspectors found.

Observation 3: Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, Harouaka and Yambot stated, "the firm's water system has not been validated to produce [redacted]. The firm uses [redacted] as an ingredient and for cleaning product contact surfaces during manufacturing of antibacterial hand soap. Genlabs "does not have a diagram documenting the piping system used to deliver [redacted] or to indicate the location of sampling points for routine testing. In addition, the firm does not have an established schedule for routine water testing and does not perform TOC [total organic carbon] testing."

Observation 4: Drug product component testing is deficient in that at least one specific test to verify the identity of each component is not performed.

"Specifically, the firm has not performed any identity testing on any of the components used in the manufacture of antimicrobial hand soap products," the investigators observed. "Between Jan. 15, 2014, and Dec. 7, 2015" several lots of the active ingredient were received. Identity and assay testing were not performed for any of these lots; assay and identity were accepted based on the manufacturer's Certificate of Analysis.

Observation 5: Changes to written procedures arc not reviewed and approved by the quality control unit.

Genlabs does not have "a controlled system to allow the quality unit to review changes, evaluate the impact of the changes, approve the implementation of changes and assess the effectiveness of changes made postapproval to SOPs, equipment, materials, methods or processes used in the manufacture of antimicrobial hand soaps," Harouaka and Yambot stated. Further, they noted, "The firm does not have a written procedure for change control and has no system in place to record changes to SOPs, equipment, materials, methods or processes."

The formulation for a product was changed on Nov. 11, 2013, according to the firm's procedure for Product Specifications. The previous revision was not available for review. "No tests were conducted or documented to ensure that the altered formulation did not impact different steps in production such as mixing and filling operations," the investigators observed, "and cleaning validation was not performed for the new formulation to ensure the established cleaning procedure removed all traces of contaminants."

Observation 6: There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Genlabs does not conduct investigations into deviations or out of specification (OOS) test results to determine the root cause or appropriate corrective or preventive action needed. The FDA team found that deviations are recorded "but are not thoroughly investigated to determine whether the investigation should be extended to other batches. In addition, the OOS results are not recorded
in the batch records. Only repeat test results that are within specification are recorded in the batch record."

Observation 7: The written stability testing program is not followed.

"Specifically, no testing has been performed to determine the stability of the current formulations of the antimicrobial hand soap products," the inspection found. "There is no data to support the one-year expiration date listed on these products."

Observation 8: Written procedures are not followed for evaluations done at least annually and including provisions for a review of complaints, recalls, returned or salvaged drug products and investigations conducted for each drug product.

No Annual Product Review was performed for several products during 2012, 2013 or 2014. This is a repeat observation.

Observation 9: Distribution records do not contain the lot or control number of drug product.

Batch distribution records for antimicrobial hand soap products do not contain the lot or batch number of the shipped products. The firm does not have a system to trace the distribution of manufactured antimicrobial hand soap products by batch number, the FDAers noted.

Observation 10: Procedures describing the calibration of instruments, apparatus, gauges and recording devices are deficiently written or followed.

Specifically, the pH meter is not calibrated to cover the pH ranges listed in the specifications for certain raw materials and finished products for the antimicrobial hand soaps, the investigators observed.

American Antibiotics failed to follow procedures, justify deviations

American Antibiotics
Baltimore, MD
Baltimore District

Drug maker **American Antibiotics** received a seven-item 483 following a Dec. 14-18, 2015 inspection conducted by FDA investigators Cheryl Clausen and Dell Moller.

The FDA team found the following nonconformities:

Observation 1: The accuracy of test methods have not been documented. Electronic records are used, but they do not meet system access limitation and audit trail requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records.

Specifically, the FDAers observed, "laboratory analysts are allowed to write and edit test methods." Further, they noted, "laboratory personnel…are assigned user roles as instrument administrators and the QC Manager is both a system and instrument administrator."

In addition, the firm's quality control manager stated that audit trails are not reviewed.

Observation 2: The quality control unit lacks responsibility to approve and reject all procedures or specifications impacting on the quality of drug products.

Clausen and Moller observed that "the procedure and accompanying documentation for the calibration of the UV-VIS Spectrophotometer do not have the same specification for the resolution testing."

Observation 3: The responsibilities and procedures applicable to the quality control unit are not in writing.

The FDA team found "no evidence to show the responsibilities and authorities for the Quality Control Manager and Quality Assurance Manager as defined in their respective job descriptions are reviewed or approved by the appropriate reporting authority."

Observation 4: Written procedures are not followed for the storage of components.

On Dec. 15, the inspectors wrote, "we observed drug product components…stored on the same pallet as other components in warehouse 125 Aisle-1." The firm's procedure on storage "states materials and drug products should be stored separately in designated areas."

Observation 5: Deviations from written specifications are not justified.

An OOS [out of specification] "determination of residual content in a cleaning swab sample with a result of 63.3 microgram/swab…was invalidated. You were not able to show evidence the result obtained was not valid," the investigators stated.

The FDAers also reported that "your QC Manager and QA Manager stated the corrective action you conducted was to reclean the equipment to remove the residual drug product and to retrain the cleaning personnel. The recleaning CAP A was not recorded in the investigation."

The investigation result form was not approved by the firm's quality assurance unit, they also noted.

Observation 6: Established test procedures are not followed.

Supervisory Investigator Moller observed the procedure for dissolution testing of samples on Dec. 15, the team reported. The procedure for maintenance of operation, calibration and preventive maintenance for dissolution apparatus that was effective during the inspection was not followed, Moller reported. "The order of events specified in the procedure was not the order of events conducted by the analyst performing the testing."

Observation 7: Obsolete or outdated labels, labeling and packaging materials are not destroyed.

Moller and Clausen observed labeling for Amoxicillin 250mg per 5 mL, for oral suspension on the labeling machine. "The Production Manager stated a new employee had retrieved these labels and placed them on the

labeling machine for R&D and training purposes," the investigators stated. "These labels were later identified as being from the previous owner's stock of labeling and obsolete."

Pharma firm cited for multiple problems with sterility assurance, stability

Auro Pharmacies
La Habra, CA
Los Angeles District

FDA investigator Uttaniti Limchumroon issued a nine-item 483 to Auro Pharmacies after a Sept. 22-Nov. 11, 2015, inspection that found GMP nonconformities, including failure to ensure drug products' sterility.

According to the 483, the inspection reported:

Observation 1: Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.

"Your firm did not perform endotoxin testing before the product was released," the inspector stated. For example, two lots of Ascorbic Acid 500 mg/ml with preservatives, one lot of the same product without preservatives and one lot of Glutathione 200 mg/ml with preservatives were tested not tested before release. Some lots of these products were tested but not until well past the dates on which they were released for distribution, the inspection found.

"Your firm does not performed endotoxin testing on every sublot manufactured of the finished sterile drug product," the inspector stated. Further, the FDAer observed that the firm's
"endotoxin method has not been validated to ensure the reliability of the results generated by the test method."

The inspection also revealed that Auro's sterility test method is inadequate "in that suitability was not determined for Ascorbic Acid 500mg/ml without preservative." The suitability test conducted by an outside laboratory was a different method than that which the firm uses.

The number of containers taken for sterility testing is inadequate, Limchumroon also found.

Observation 2: Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

The investigator observed that the firm does not perform certain tests after processing and filling bulk sterile drug solutions into the finished vials, as required by procedure. In addition, Limchumroon noted, "Process simulations conducted by your firm is inadequate in that growth promotion was not conducted on the media used to perform the process simulation to ensure that it can support microbiological growth."

Auro had not conducted process simulation of the lyophilization process nor for the vial and rubber stoppers for use in aseptic processing, the inspector noted.

The firm had not validated the lyophilization [redacted] for use in manufacturing of the sterile drug products HCG Injection and Glutathione Lyophilize 600 mg/vial Injection.

Limchumroon observed, during the inspection, "an operator…placing hands on the surface of the laminar flow hood and continue to perform aseptic processing without sanitizing the gloves. The operator was processing Ascorbic Acid 500mg/ml with preservative." He also observed an operator "sitting down on a chair with elbow on the surface of the laminar flow hood and leaning forward inside the laminar flow hood during the aseptic processing operation. The operator was processing Germanium Sesquioxide Injection 100 mg/ml.

Observation 3: Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Limchumroon stated, "Your environmental monitoring program of the aseptic processing is inadequate" for a variety of reasons. He noted that "viable air environmental monitoring stopped on 08/12/15" for reasons that were redacted from the 483. "No viable air monitoring has been performed until 10/5/15."

In addition, "Personnel is not monitored after each operational shift. The personnel is monitored" only a specific unstated number of times, "regardless of how many times operators performed aseptic processing."

During the course of inspection, "an operator was observed spraying and sanitizing gloves immediately before taking the fingertips monitoring. The operator was processing Magnesium Chloride Injection 200 mg/ml."

No action and alert limits were established for the personnel monitoring of sleeves, chest, and forehead.

The firm's environmental monitoring procedure "was drafted after the initiation of the current inspection."

Observation 4: Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Auro did not perform growth promotion of the media used in sterility testing and environmental monitoring to ensure that the media used will support microbiological growth, the investigator stated.

Observation 5: Approved components, drug product containers, and closures are not retested or reexamined as appropriate for identity, strength, quality and purity after exposure to conditions that might have an adverse effect with subsequent approval or rejection by the quality control unit.

"Your firm does not have a study or data to support that processed depyrogenated vials and stoppers…can be stored for indeterminate amount of time in the ISO 8 and ISO 7 area before being used in processing of sterile drug products in ISO 5 area."

Observation 6: Failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

"There were no documented investigations conducted for out of specification endotoxin test results," Limchumroon reported. The inspector observed that six lots of preservative-free ascorbic acid that showed OOS results "were retested and results met the specification. Lots were subsequently released. No explanations why the original failed to meet the specification." The investigation was not conducted as required by the firm's procedure Central Drugs Quality Nonconformance Policy Sterile Compounding Pharmacy. The procedure stated that nonconformance would be documented when nonconforming events occurred.

Investigations into other quality-related events also were not documented, the inspection showed, including two from quality-related event meetings stating "Clinic suspected medications have high endotoxin level" and "Medical office report patient reaction to injection site using Vit D3 Oil injection." In addition, an incident report dated Sept. 9, 2015 stated, "Patient complained about respiratory distress, swelling, aches, and pain." None of these events was investigated.

Investigations were not conducted for personnel monitoring recoveries including six recoveries from forehead and one from chest, ranging from six colony-forming units Too Numerous To Count. "Your firm did not have alert and action limits for sleeves, chest and forehead monitoring recoveries," the investigator noted.

Observation 7: There is no written testing program designed to assess the stability characteristics of drug products.

"Your firm has not conducted stability testing program for Ascorbic Acid 500mg/ml Injection with preservative to ensure that the product can support the assigned shelf life of six-month expiration date," Limchumroon stated, and in addition, the firm did not "have the ongoing stability programs to ensure that sterile drug products maintain the potency and sterility throughout the assigned six-month shelf life."

The inspection also found that Auro "has not conducted preservative effectiveness determinations for all sterile drug products that contain a preservative to ensure that the preservative system is effective to inhibit microbial growth through the product shelf life. The preservative is not assayed to determine the concentration in the sterile drug solutions."

Observation 8: Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Auro does not use sporicidal agents for disinfecting the laminar flow hoods used for aseptic processing of sterile drug products.

Observation 9: Clothing of personnel engaged in the manufacturing, processing, packing and holding of drug products is not appropriate for the duties they perform.

The firm's gowning certification program does not include personnel monitoring as part of the evaluation. Its procedure for gowning and gowning certification was not established until Sept. 22, 2015. This procedure includes provision for personnel monitoring during the certification.

DEVICES

Bard procedures for incoming product and control of nonconforming product inadequately followed

C.R. Bard Inc.
Queensbury, NY
NY District

Following a Dec. 7, 2015-Jan. 8, 2016, FDA inspection, investigator Jacqueline Warner cited drug-coated balloon catheter manufacturer C.R. Bard for two nonconformities with GMPs for medical devices.

Warner noted these observations in the 483:

1: Procedures for acceptance of incoming product have not been adequately established.

"Specifically, as it relates to written procedures for handling incoming raw material, Paclitaxel Semi-Synthetic Powder used in the manufacture of Paclitaxel Solution, which is a component intended to coat Lutonix 035 Drug Coated Balloon Catheters, the acceptance activities as described per Inspection Plan…did not fully define packaging specifications for the above ingredient," Warner stated.

She explained that the document failed to provide sufficient details for ingredient packaging in terms of the container's size, material type and configuration. "In addition, packaging specifications were not established for similar product held inside miniature containers, as substance could potentially be used to support QC release of similar substance held in larger containers or to evaluate product quality issues during investigations," the FDAer wrote.

During her review of Bard's ingredient storage area in an ISO 7 clean room Warner "found two different packaging types for the same ingredient. Specifically, the mini container held one plastic bottle in a thin plastic film-like pouch with no airlock lid, whereas the larger container had multiple plastic bottles inside a heavy duty PE bag with a plastic airlock closure. In light of noted sporadic cases where this ingredient was found to have insolubility issues, more detailed packaging specifications are required to control the stability of the above mentioned ingredient."

2: Procedures have not been adequately established to control product that does not conform to specified requirements.

In regard to the Paclitaxel Coating Solution used to coat Bard's balloon catheters, Warner found that prior to Dec. 7, 2015, the firm "had no requirement to handle drug insolubility issues as a nonconformity or require completion of a Material Review Report (MRR), in order to comply with your existing procedure titled 'Material And Systems Deviations.'" Numerous batches of the solution were discarded without filing a MRR, she found.

Complaint handling, CAPA and other procedures trip up Medical Specialties

FDA investigators Gamal Norton and Christopher May noted five observations of nonconformities with GMPs for medical devices during their Nov. 3-9, 2015, inspection of **Medical Specialties**.

The maker of various joint supports and braces was found to be deficient in the following instances, according to the 483:

Observation 1: Procedures for receiving, reviewing and evaluating complaints by a formally designated unit have not been adequately established.

Norton and May found that the company's "management has not established procedures that describe and define the complainant's information that must be recorded by all personnel that receive a complaint involving the firm's medical devices."

They further observed that Medical Specialties "has not established procedures that define the time frame permitted to investigate complaints to ensure timely complete investigations."

The firm had not followed their written procedure for receiving, documenting, evaluating and investigating device complaints, the FDAers also noted.

Observation 2: Procedures for corrective and preventive action have not been adequately established.

"The firm has not established adequate procedures for identifying nonconforming device trends in the quality system," the FDA team wrote, and also "has not established adequate Quality System procedures to investigate and evaluate corrective and preventive actions to ensure that the proposed corrective actions were effective to correct the identified nonconformance and the results of the preventive action are not reviewed and documented."

Observation 3: Procedures for acceptance activities are not adequately established.

May and Norton observed that the company has not established adequate inspection procedures "to ensure that manufactured and distributed devices are properly labeled with the proper device labels that correctly identify the device type."

Observation 4: Procedures for training and identifying training needs have not been adequately established.

During the review of the training procedure, the FDAers "asked to see the quality training records for a department supervisor. Firm management stated that the department supervisor doesn't have any documentation of having received quality training."

The firm's management told the investigators that "quality training is provided to their employees in individual, team or group settings, but no documentation could be provided. There is no documentation for complaint training being provided to sales personnel or the customer service department that receives customer complaints."

Medical Specialties also was un able to provide records that document quality training that was provided to the quality manager.

Observation 5: Personnel training is not documented.

During the review of a CAR form regarding the poor stitching on compressors, Norton and May observed that "the firm did not make personnel aware of device defects that occurred from the improper performance of their jobs, nor did the firm document it."

Implant and prosthetics maker gets 7-item 483 for validation, MDR issues

Arthrosurface
Franklin, MA
New England District

A Sept.15-Oct. 5, 2015, inspection of device manufacturer **Arthrosurface** revealed gaps in the firm's validation processes, complaint handling procedures and other nonconformities with GMP, according to the 483 issued by FDA investigator Elizabeth Griffin.

The 483 cited the following observations:

1: The design was not validated using initial production units, lots or batches or their equivalents.

Griffin found that lot numbers were not documented for HemiCAP: shoulder implants (Arthrosurface Contoured Articular Prosthetic (CAP) Devices; Articular Prosthetic Devices; Humeral Head Resurfacing Device; Taper-Posts; Tapered Screws; Implants and Tapered Threaded Screws; and Removal Tools; nor for Hip/Shoulder Contoured Articular Prosthetic Devices and Large Tapered Fixation Screws that were used in the following design validation tests:

- Comparative Biomechanical Testing of Arthrosurface's HemiCAP Humeral Head Resurfacing Device dated 1/27/2015
- Testing of Arthrosurface Hemi-Cap HHXL Shoulder Articular Prosthetic Device dated 11/7/2014
- Testing of Arthrosurface Hemi-Cap Articular Prosthetic Device dated 9/24/2014
- Mechanical Testing of the Arthrosurface Distal Femoral Contoured Articular Prosthetic Device dated 11/9/2012
- Testing of Arthrosurface Hemi-Cap Articular Prosthetic Device dated 5/20/2011
- Mechanical Testing of the Arthrosurface Hemi-Cap Implant Removal Tool dated 10/19/2010
- Mechanical Testing of Arthrosurface 40mm Articular Prostheses dated 3/17/2006. The report states that other tests were also performed, but the wrong screw size was tested with the articular devices.
- Mechanical Testing of Arthrosurface 0.156 Taper Contoured Articular Prosthetic Device dated 4/14/2005
- Mechanical Testing of the Arthrosurface Hip/Shoulder Contoured Articular Prosthetic Device dated 8/4/2003.

"There is no way to verify…if the posts tested in each study were from one lot or multiple lots, whether they were manufactured by engineering personnel or production personnel, or whether the tested posts were reworked following manufacture to obtain a specific thread height," Griffin reported.

2: Corrective and preventive action activities and/or results have not been adequately documented.

Corrective and preventive action (CAPA) 13-013 opened on Oct. 30, 2013, "to address five complaints involving the use and/or implant of expired products, was closed on July 25, 2014, although there was no documentation addressing two of the five corrective actions listed: the contact and reminder for regional managers involved to review labels for expiration dates; and review of procedures for necessary improvements or clarification regarding the inventory control process," the FDAer observed.

3: Procedures for receiving, reviewing and evaluating complaints by a formally designated unit have not been adequately established.

Griffin's review of at least 57 complaints revealed that complainant addresses and phone numbers are not documented and that device names and complete details of the complaints are not always documented. For

example, she reported, a "complaint received on June 10, 2013, involving two broken and one damaged peg drill during a surgical case where the drill bits had to be recovered, and which resulted in an update to the IFU:

- Was listed as a noncritical complaint rather than a critical complaint, as required by SOP 'Customer Complaints and Feedback.'
- Did not include details of the surgical procedure (i.e.: type of procedure, lot numbers of devices involved)."

Another complaint received on May 7, 2013, involving a failed weld between the reamer blade and shaft on a reamer "was closed on June 4, 2013, without documenting the reason for not opening a CAPA as required" by the company's own procedures. Further, the FDAer noted that the file "did not include an MDR determination or a rationale for not submitting" an MDR.

Griffin also reviewed a complaint received on April 9, 2013, involving a Uni (knee) implant reportedly becoming loose after only six months with revision to a total knee, that was listed as a noncritical complaint rather than a critical complaint.

The investigator also reviewed a complaint Arthrosurface received on Nov. 14, 2012, describing a MedWatch form received from a hospital regarding persistent pain in the left shoulder of a patient with a HemiCAP Humeral Head Resurfacing implant which was revised to a total shoulder arthroplasty. She noted that this, too, was listed as a noncritical complaint rather than a critical complaint and did not include details regarding the implant (i.e.: lot numbers and part numbers).

4: An MDR report was not submitted within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device may have caused or contributed to a death or serious injury.

Griffin found that MDRs were not submitted for the following complaints:

- Complaint opened on Nov. 17, 2011, involving a bone (humeral shaft) fracture during range of motion manipulation immediately following implantation of a HemiCAP shoulder implant.
- Complaint opened on April 29, 2008, involving two patient infections following HemiCAP shoulder implant surgery.
- Complaint opened on Aug. 21, 2006, involving a patient with a 15mm toe implant who had an infection and 10-15 degrees of motion, in need of a pelvic graft due to bone loss.

5: An MDR report was not submitted within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Griffin observed that Medical Device Reports were not submitted for the following complaints:

- Complaint opened on June 10, 2013, involving a surgical case with three broken peg drills with subsequent recovery of the tips of two drill bits which had snapped off.
- Complaint opened on April 9, 2013, regarding a Uni (knee) implant reportedly becoming loose after only six months, with revision to a total knee.
- Complaint opened on Nov. 14, 2012, involving persistent pain in the shoulder of a patient with a HemiCAP Humeral Head Resurfacing implant which was revised to a total shoulder arthroplasty, as reported by the hospital on a MedWatch form to Arthrosurface.
- Complaint opened on Sept. 21, 2010, involving failure (fracture) of a 20mm knee implant resulting in a subsequent revision surgery. The complaint states that the implant was under an IDE so the complaint would be submitted with the next annual report. The annual reports for IDE G030174 dated Sept. 18, 2010, and Sept. 18, 2011, did not include this complaint.
- Complaint opened on Jan. 26, 2006, involving a patient with a hip implant complaining of pain, with follow-up noting the stem under the im-

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plant had fractured.

- Complaint opened on Jan. 26, 2006, involving a patient with a hip implant complaining of pain; the investigation states that the x-rays are not conclusive if the stem dislodged, broke or was misaligned during the procedure.

6: A supplemental report was not submitted to FDA within one month following receipt of information that was not provided when the initial report was submitted.

Specifically, a supplemental report was not submitted after learning on Oct. 25, 2012, that a revision surgery was performed for the patient listed in a complaint involving the fracture of a femoral implant.

7: A justification for not reporting the correction or removal action to FDA that included conclusions and follow-ups and reviews by a designated person was not included in the record.

There were no documented justifications for not reporting to FDA the following corrections and removals:

- A mismarked instrument, reported through complaint on July 16, 2015. "Your firm determined there were units in the field that were potentially affected; corrective and preventive action (CAPA) 15-002 was opened which included notifying Regional Sales Managers so that they could contact each distributor location and replace units as needed."
- The Patello-Femoral extra-large (PFXL) Hex Driver which did not mate with the PFXL Taper Post, reported through complaint on Aug. 14, 2013. The company determined there were units in the field that were affected. CAPA 13-008 states that all customers in the field were sent replacements.

Repeat observations mark inspection report for Del Medical

Del Medical
Bloomingdale, IL
Chicago District

Several repeat observations from previous FDA inspections were featured in the five-item 483 issued to device maker **Del Medical** following investigator Patricia McIlroy's inspection conducted July 8-Sept. 23, 2015.

McIlroy cited the following in the 483:

Observation 1: A correction or removal, conducted to reduce a risk to health posed by a device, was not reported in writing to FDA.

After receiving six complaints due to falling counterweights on wallstands, Del Medical issued Service Bulletin #1065, dated Dec. 1, 2014, for the VS200 & VS300 Wallstand was sent electronically. This document contains instructions to "improve mechanical operations of the Wallstands." The firm required product preventive maintenance to be performed on VS 200 and VS 300 wall stands made from January through May 2014.

"This field correction has not been reported to FDA," the investigator stated. "This is a repeat observation that was cited on the form FDA 483 issued at the conclusion of the inspection dated Sept. 15, 2006."

Observation 2: An MDR report was not submitted within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Specifically, the FDAer noted, "during the past two years Del Medical has received six complaints of their VS200 wallstands malfunctioning, causing the receptor to fall to the floor and one complaint of a DCTM overhead Tube Crane malfunction allowing the x-ray tube and collimator assembly to fall onto the tabletop. These incidents have not been reported to FDA."

This too was a repeat observation, McIlroy stated.

Observation 3: Corrective and preventive action activities and/or results have not been documented.

"Six complaints regarding the VS200 Wallstand cassette holder suddenly dropping due to a fractured bolt holding the counterweight were received between August 2013 and October 2014," McIlroy explained.

One CAPA was opened, dated April 14, 2014, after the second wallstand was received. The root cause analysis states, "The bolt broke due to nonflat surface of the counterweight casting."

No other CAPAs were opened as the firm continued to receive complaints relating to the same issue for devices manufactured after the CAPA was closed on June 6, 2014.

Observation 4: Procedures for corrective and preventive action have not been adequately established.

The FDA investigator found that Engineering Change Notices (ECN) were initiated between August 2013 and July 2015 for changes to the VS200 and VS300 wallstands to address the counterweight issue and for various other issues. "However," she remarked, "the ECNs were not linked to Corrective or Preventive Actions. Further, the ECNs were created to correct complaints of device malfunction as outlined in 'Memo to File' dated Nov. 19, 2014."

McIlroy further noted that the firm's CAPA procedure "is inadequate because CAPA 2014.001 was fully verified and validated as being effective." This CAPA was initiated by a complaint dated April 10, 2014. The "Corrective Action Report" refers to ECN #081316 dated Aug. 23, 2013. "The CAPA is incomplete because it fails to consider the effect of the failure mode of the devices in the field," the investigator stated.

The inspection also revealed that "lnstallation & Preventive Maintenance instructions were initiated in the form of Service Bulletin #1065, dated Dec. 10, 2014, to improve the mechanical function on the VS200 & VS300 wal!stands without being linked to a CAPA."

This observation was also a repeat from previous FDA inspections conducted in 2006 and 2012.

Observation 5: Risk analysis is inadequate.

During March 2014 Del Medical conducted a risk analysis for their RT100, EV 650 and EV800 tables. "There is no evidence or data to support the probability of a hazard occurring for either premitigation or post-mitigation," McIlroy commented.

BIMO

Oklahoma IRB nets one observation for failure to report noncompliance

University of Oklahoma Health Science Center IRB
Oklahoma City, OK
Dallas District

FDA investigator Lloyd Payne noted only one observation following his May 27-June 4, 2015, inspection of the **University of Oklahoma Health Science Center's** institutional review board (IRB).

The following is the lone observation on the 483: *The IRB did not follow written procedures for ensuring prompt reporting to appropriate institutional officials and the FDA of any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB.*

Specifically, Payne found, "the Institutional Review Board failed to follow revision 8/31/14 of SOP 308: Reporting to Regulatory Agencies and Institutional Officials, which states … 'This SOP addresses the reporting requirements of the IRB to regulatory agencies when serious or continuing noncompliance, unanticipated problems involving risks to participants or others, or suspension/ termination of IRB approval occurs. Noncompliance, unanticipated problems and suspension /termination are described in detail in SOP 903: Noncompliance/Scholarly Misconduct; SOP 407: Protocol Deviations and Unanticipated Problems; and SOP 411: Suspension or Termination of IRB Approval."

The reporting procedure further states in paragraph 1.1 Notification. 1.1.1, "The HRPP Director shall be notified when non-compliance, unanticipated problems involving risks to participants or others, or suspension/termination of IRB approval occurs. The HRPP Director shall notify the Director of Compliance, the University Senior Vice President and Provost or designee, the HSC VPR, OHRP, FDA, the University Controller, ORA/ORS, Legal Counsel, and/or sponsors/agencies as applicable," Payne detailed. "The HRPP Director is responsible for distributing the written communication to the Senior Vice President and Provost or designee, prior to distribution to any outside agency."

On Nov. 4, 2013, the Institutional Review Board Executive Committee was informed someone had contacted the Office of Compliance with concerns regarding several research studies including one particular approved study.

"The allegations involved data manipulation, deviating from the protocol, not following inclusion/exclusion criteria and poor record keeping," the FDAer noted. "The allegations focused on one research coordinator. The IRB Chairpersons were consulted and a for-cause audit was initiated. Between Oct. 30 and Nov. 15, 2013, an audit by the Quality Improvement Specialist found that there were multiple protocol deviations and IRB requirement violations. The findings were presented to each Board in an Outcome Letter regarding the For-Cause Quality Improvement visits. However, these were evaluated by the Boards involved to have been administrative in nature and did not involve serious or continuing noncompliance or unanticipated problems involving risks to participants or others."

On June 12, 2014, the Institutional Review Board Director was notified of alleged wrongdoings related to the conduct of the approved study. "The Study Coordinator was observed completing the physicians' assessments page without the Principal Investigator or Sub-investigators being present," Payne stated. "The ensuing audit by the Quality Improvement Specialist found that there was continuing noncompliance by study personnel at the clinical site. The findings were presented to the Principal Investigator in a Letter of for Cause Evaluation dated Aug. 5, 2014. The letter was copied to the Director of the IRB and the Chairman of Board."

The Board notified on Sept. 5, 2014, the Principal Investigator that the Institutional Review Board reviewed the Letter of For Cause Evaluation dated Aug. 5,

2014 and the Principal Investigator's rebuttal letter dated Aug. 19. The Chairperson for the Board reported the Institutional Review Board determined that the results of the investigation constituted a serious and continuing Noncompliance," and according to the University and federal regulations, such findings required reporting to the institutional officials and regulatory authorities.

A letter dated Sept. 14 was drafted to notify the institutional officials and regulatory authorities of the serious and continuing noncompliance. "However, the letter was never finalized nor distributed to the appropriate institutional officials and regulatory authorities," Payne stated.

Pharma Medica Research
St. Charles, MO
Kansas City District

The bioequivalence firm Pharma Medica was found to have violated informed consent regulations during the conduct of a clinical study, according to the three-item 483 issued by FDA investigators Dustin Hampton and Kathleen Swat at the conclusion of their Sept. 21-29, 2015, inspection.

The FDAers found:

Observation 1: Legal informed consent was not obtained from a subject or the subject's legally authorized representative, and did not meet the criteria in 21 CFR 50.23-50.24 for exception.

The informed consent document for a study subject did not contain the signature of the subject.

Observation 2. The general requirements for informed consent were not met in that you did circumstances that minimized the possibility of coercion or undue influence.

Informed consent for two studies was obtained from the study subjects after check-in, Swat and Hampton found. "Urine sample, blood draw and/or vitals obtained from subjects were advanced to the study clinic" before informed consent was obtained.

Observation 3. Study protocol used drugs known to increase the risk of suicidal thoughts and behaviors.

There is no guidance in the study protocol on the administration and evaluation/ utilization Severity Rating Scale (C-SSRS) prior to dosing. There is no guidance in the study protocol on the administration and evaluation/utilization of the Columbia-Suicide Severity Rating Scale (C-SSRS) prior to dosing. There is no documentation in the subject case report forms relating to evaluation of the Columbia-Suicide Severity Rating Scale (C-SSRS) prior to giving psychiatric drugs to subjects.

A study employee administered the Columbia-Suicide Severity Rating to subjects on May 31, 2014, and did not complete the training to administer the C-SSRS until Nov. 7, 2014.

An employee administered the C-SSRS but was not delegated by the Principle Investigator to perform this task.

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. 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-RETREIVE by referencing the FOIA file # (e.g., 2012-4082), or readers can submit requests on their own using the file number. The FOIA Log in PDF can be purchased for $10 per entry, which contains all FOIAs filed in that given week. (Week of AUG. 29-SEPT. 2, 2016, was used to compile this list) To order the Log in PDF, call RECORD-RETRIEVE at (703-779-8777,) or email us at SERVICE@FDAINFO.COM

Plant	Location	483/EIR Date	FOIA File	Requested by
PRAXAIR INC	TORRANCE, CA; WILMINGTON, CA	11/20/2013 - 09/23/2015	2016-7089	KITE PHARMA
HOSPIRA INC	MCPHERSON, KS	01/01/2016 - 08/26/2016	2016-7092	Cempra Pharmaceuticals, Inc.
BECTON DICKINSON	CANAAN, CT	01/01/2013 - 08/26/2016	2016-7100	OASIS MEDICAL INC
CMC BIOLOGICS	BERKELEY, CA; BOTHEL, WA	8/16	2016-7185	Catalent Pharma Solutions
IMMUCOR	NORCROSS, GA	11/20/15	2016-7233	THOMSON REUTERS
AAI PHARMA	WILMINGTON, NC	LAST FIVE YRS	2016-7273	BIOSCREEN TESTING SERVICES INC