

# Inspection Monitor

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

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## Just 56% of firms justify the number of PPQ batches before starting validation: PDA survey says; generics firms rank lower

WASHINGTON —A PDA survey of a pioneer and generic drug makers indicates that a high number — 44% —do not justify the number process performance qualification (PPQ) batches before they start validation, a number that surprised many seasoned quality assurance executives.

Addressing the PDA-FDA Joint Conference here last month, Scott Bozzone, Ph.D., a Pfizer qualifications and validation executive, said out of 131 responses, 56% said they do PPQ batches, but 44% said they do not.

“This surprised me,” said Bozzone, who helped oversee the survey. “To me, I will interpret that to think they have no rhyme or reason to pick three so that was disappointing on that one, and was little thought behind it. It keeps it simple in doing that.”

PDA opened the survey Feb. 18 and closed it May 24. It was not scientific (randomly sampled), but was focused on PDA’s Process Validation Interest Group

members. The objective was to obtain feedback on FDA’s 2011 update to “General Principles of Process Validation” guideline “and see how folks are dealing with it,” Bozzone said

He said 66% of the respondents were from pioneer firms and the remainder from generic houses. The types of products respondents oversee were: 70% pharmaceutical, 47% biotech, 21% generics, 11% animal health, 15% devices, 18% vaccines and 7% “other,” such as consumer goods and excipients. Bozzone said 2% of the respondents worked for firms with fewer than 200 employees, 18%, with 200 to 500 employees and 70% are with companies with 500 workers or more.

The following are some of the questions and responses PDA received:

### Have there been significant changes to how you do performance process validation since release of FDA's 2011 guidance?

Yes	55%
No	45%

### How is process validation defined in the quality standards/policies of your company?

One stage (process validation)	28%
Three stages of process validation: Process Design, Process Performance Qualification, Continued Process Verification	65%
Other	7%

### Do you use the term Process Performance Qualification?

Yes	51%
No	49%

### Do you consider the Process Performance Qualification as a stage of Process Validation in the policies of your company?

Yes	91%
No	9%

### Do you allow use of prior knowledge or knowledge and data from similar processes to support process characterizations or process designs?

Yes	90%
No	10%

Do you allow use of prior knowledge or knowledge and data from similar processes to support regulatory filing?

Yes	63%
No	37%

Do you have documented risk assessment(s) as a requirement for process design/characterization?

Yes	88%
No	12%

What is the size (number of batches) of your process validation/PPQ campaign (excluding revalidation)?

Three successful batches (most of the time)	74%
Variable – depends on the process	26%

What method do you use to determine the size of process validation campaign (number of batches)? (Check all that apply)

Quantitative model/method	58%
Qualitative model/method	64%

Is there a requirement in your company to provide justification for the number of process validation/PPQ batches planned prior the start of process validation/PPQ ?

Yes	56%
No	44%

Is your process validation campaign size (number of batches) same for USA- FDA and rest of the world?

Yes	91%
No	9%

When determining number of samples required during process validation/PPQ, do you use statistical methods?

Where it makes sense	68%
No	27%
Yes, always	5%

According to your company procedures, when does Continued Process Verification (Stage III) or process monitoring start?

First batch of process validation/PPQ	36%
First batch post process validation/PPQ	64%

In your regulatory submissions do you include data from the following:

Continued Process Verification	49%
Process Monitoring	64%

Do you trend and monitor the quality of incoming raw materials as part of the CPV program?

Yes	35%
No	37%
Under a different system,	28%

but not as part of the CPV program

Have you had any regulatory inspections where the inspector(s) asked about or mentioned the 2011 FDA PV Guidance?

Yes	26%
No	74%

Have you had any regulatory inspections where the inspector(s) asked about or mentioned a Continued Process Verification Program (CPV)?

Yes	16%
No	84%

Bozzone, who said PDA will be publishing the results soon, said it was also interesting that nearly half the firms were not doing anything different with process validation since adoption of the 2011 guidance. FDA had not updated the guidance since 1987.

## DRUGS

### Hospira faulted for its handling of complaints of glass in sterile drugs

*Hospira  
McPherson, KS  
Kansas City District*

During their inspection of a **Hospira** facility in McPherson, KS, FDA investigators Shirley Berryman and Janet Abt observed GMP nonconformities related to the presence of glass particulates in some of its sterile drug products.

FDA conducted the inspection July 29-Aug. 16, 2013, and identified the following problems, according to the 483 issued by the investigators:

**Observation 1: An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning significant chemical, physical or other change or deterioration in a distributed drug product.**

NDA-Field Alerts were not submitted within three working days of glass particulate complaints for sterile lyophilized drug products filled on line, including one or more lots each of Erythrocin Lactobionate for I.V., 500 mg; Vancomycin Hydrochloride for injection USP 500mg and Vecuranium Bromide for Injection USP, 500mg.

**Observation 2: Failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.**

“Your investigations of confirmed complaints of glass particulate in sterile lyophilized drug products have not been timely,” the FDAers wrote.

The results of investigations “related to glass particulate complaints were not provided to the sponsor” within the timeframes required. For example, a complaint was registered on April 25, 2013, and the sample of product pertaining to this complaint was received on May 20. “Plant completed investigation and proposed verbiage was forwarded to the sponsor on June 24, 2013,” the inspectors noted.

Further, “a Drug Medical Assessment was not initiated until 07/23/2013 and signed 07/31/2013 for Erythromycin, Vancomycin, Vecuronium Bromide” and other drug products.

*Hospira should have classified the glass particulate “as a critical defect, since there is a potential for causing adverse health consequences.”*

“The 100% visual inspection after lyophilization form... fails to define what type of particulate noted during the 100% visual inspection,” the investigators observed. “The Light Test form has the defect as only “Particulate.” The lack of identification of what type of particulate will not allow an adequate investigation of complaints related to glass particulate.”

Hospira received complaints of glass particulate in several products lots and only the number of defects was recorded, the 483 stated.

**Observation 3: There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality and purity they purport or are represented to possess.**

Hospira should have classified the glass particulate “as a critical defect, since there is a potential for causing adverse health consequences,” Abt and Berryman stated. The firm’s procedure “Sampling and Auditing of Light Inspected Product’ classifies glass particle as a Major A defect instead of critical defect which would likely

result in serious adverse health consequences,” they found.

In addition, the inspectors wrote, “Your operators’ visual inspection for lyophilized drug product qualification program does not include examples of glass particulate in vials for training purposes.”

No record of a warning letter to Hospira regarding this 483 was found.

## Multiple deficiencies found during inspection of drug and cosmetic manufacturer Omega

*Omega Packaging Corp.  
Totowa, NJ  
New Jersey District*

FDA investigator Helen Verdel found **Omega Packaging Corp.** in violation of GMPs for manufacturing drug and cosmetic products, including failure to keep its facilities clean and in repair, during her Jan. 8-28, 2013, inspection.

The investigator noted the following faults, according to the 483 issued:

**Observation 1: The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.**

Specifically, Verdel noted, the company had not established written quality control procedures “to assure the qualification of all equipment used in the manufacture and packaging of mouthwash and toothpaste products.”

The FDAer also found that Omega had not implemented change control procedures and did not train its employees in drug GMPs. Further, Verdel observed that the firm did not have adequate cleaning procedures to ensure prevention of product contamination and its complaint handling and investigation were inadequate.

She also found that Omega did not have the required procedures for “quality unit review of master production and control records and executed batch records to ensure the inclusion of complete instructions and all information critical to the batch.”

**Observation 2: There are not written procedures for production and process control designed to assure that the drug products have the identity, strength, quality and purity they purport or are represented to possess.**

Verdel stated that “studies have not been conducted to identify the critical manufacturing parameters

and control strategies to be documented and monitored during the manufacture of mouthwash and toothpaste products.”

**Observation 3: Equipment and utensils are not cleaned, maintained and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.**

*Omega did not have the required procedures for “quality unit review of master production and control records and executed batch records to ensure the inclusion of complete instructions and all information critical to the batch.”*

“Specifically, there is no assurance that the cleaning of multiuse equipment used in the manufacturing of drugs and cosmetics is adequate to prevent contamination by microbials, cleaning agents or residue from drugs or chemicals to drug products packaged or manufactured on the equipment,” Verdel wrote. “Cleaning validation studies have not been conducted for equipment including mixing tanks, holding tanks and filling lines used” in manufacturing mouthwash and toothpaste as well as cosmetic products such as body lotions.

**Observation 4: Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition.**

The investigator found that Omega’s manufacturing areas were in condition “such that the product may become contaminated with filth,” she stated.

Verdel observed that a metal staircase leading to the mixing tank used during manufacture of mouthwash and the platform used to stage raw ingredients before they are added to the tank were “rusted and covered with various spilled substances.” She also observed rust on the outside of the mixing tank itself. Near the mixing tank Verdel noted “grime and debris visible on the floor and in the drain” and in the floor cavity.

“Raw materials are stored in the mixing room on broken, dirty wooden pallets,” she further observed. Fans located above a filling and packaging line for mouthwash “were coated with dust. Windows in the filling room are lacking protective screens, with broken glass covered with cardboard and cloth.” Verdel saw dust and spider webs above the filling and packing line as well as “missing and stained ceiling tiles located approximately four feet above the loading port” for a mixing tank and holding tanks for mouthwash.

**Observation 5: Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.**

The FDAer stated that Omega had not conducted studies of the equipment used to mix and package its drug products to assure that the equipment is qualified for its intended use.

“Qualification studies for mixing tanks used for the manufacture of mouthwash and toothpaste drug products have not been conducted,” she noted. The holding tanks used for these products “have not been qualified for use,” nor had the firm conducted studies to qualify the filling machines used for the mouthwash and toothpaste products.

**Observation 6: Drug product component testing is deficient in that at least one specific test to verify the identity of each component is not performed.**

Verdel observed that Omega accepted all the components for its drug products “per Certificate of Analysis upon the components’ receipt,” and did not perform any identity testing.

**Observation 7: Laboratory records do not include the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards.**

All laboratory tests for mouthwash and toothpaste products “are performed, reviewed and signed by one person,” Verdel stated. “In addition, the same person is releasing the product to the customer.”

No warning letter was found on the FDA web site.

## Greenway Research Lab slapped with 14-item 483 for poor process and production controls, inadequate procedures

*Greenway Research Lab  
Burnsville, MN  
Minneapolis District*

Drug and cosmetic manufacturer **Greenway Research Lab** lacked written procedures for multiple GMPs and failed to maintain adequate batch production and control records, FDA investigator April Young found during her July 30-Aug. 2, 2013, inspection of the firm.

Young specifically noted:

**Observation 1: 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.**

One lot of the firm’s Cosmetic Day Cream “was purchased as a contract-manufactured product and distributed under your brand,” the FDAer stated. According to a Nonconformance Record, “the product had an issue which involved ‘product turning bad,’” Young wrote. “You retrieved bottles from your retail locations to return to the contract manufacturer but did not investigate nor document your actions. You have not determined the root cause for the issue nor determined whether other batches of drug product were affected.”

One lot of the firm’s Acne Cleanser failed stability testing during the accelerated six-month study but was not investigated, Young found. “The product was assigned a 21-month expiration based on the testing data and released for distribution.”

The investigator also noted that water sample results were high for Total Aerobic Plate Counts but were not investigated. Greenway did not develop specifications for water used as a component in drug products that have been released for distribution, one lot of Acne Relief Gel manufactured March 12, 2013 “using water as a component and released for distribution. One lot of Acne Cleanser was manufactured Jan. 25, 2012 using water as a component and released for distribution.” Results from samples of water taken just before, during and after the manufacture of these products showed colony-forming units (CFUs) per milliliter that were not acceptable.

In addition, Young found that one lot each of Acne Relief Gel and Acne Cleanser were out-of-specification for viscosity. “These occurrences were not investigated and the product was released,” she reported.

**Observation 2: Accelerated stability studies,**

**combined with basic stability information, used to support tentative expiration dates are not supported with ongoing full shelf-life studies.**

“Specifically, there have been no full shelf life studies conducted to support expiration dating on your drug products,” Young noted.

Greenway’s acne cleanser failed stability testing at six months, but “received a 21-month expiration based on” data obtained during assay testing at three, five and six months, the FDAer commented. The firm conducted stability testing in accelerated conditions for its Day Cream SPF-30 and Acne Relief Gel at one, two and three months, and gave both products a two-year expiration date. The company’s contract-manufactured Day Cream SPF-30 “receives a three-year expiration date. There has been no testing done to support this expiration date,” Young stated.

**Observation 3: There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.**

“Specifically, you have not established validated processes to ensure your drug products conform to quality standards of identity, strength, quality and purity,” Young observed. “This includes, but is not limited to:

- Manufacturing equipment
- Production processes
- Cleaning activities
- Product specifications
- Sampling justification
- Water system.”

**Observation 4: Procedures for the preparation of master production and control records are not described in a written procedure and followed.**

The investigator stated, “you have not prepared Master Manufacturing Records for each drug product you manufacture nor have you established a procedure for the

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preparation of Master Manufacturing Records.”

**Observation 5: Batch production and control records do not include complete information relating to the production and control of each batch.**

The firm’s batch production records for Acne Relief Gel, Acne Cleanser and Day Cream SPF30 lack required elements, Young stated, including: “accurate production of Master Manufacturing Records, documentation of the significant steps in manufacturing, processing, packing or holding, identity of equipment used, inspection of the packaging and labeling area, yield calculations, labeling control records, a description of containers/closures and sampling performed.

“Additionally, these batch production records were filled in using pencil.”

**Observation 6: The establishment of specifications and sampling plans, including any changes thereto, are not drafted by the appropriate organizational unit.**

Greenway failed to establish product specifications or sampling plans for Acne Relief Gel, Acne Cleanser, or Day Cream SPF30, the inspector found. “Release testing for these products includes assay testing and microbiological contamination testing.”

**Observation 7: The identity of each component of a drug product is not verified by conducting at least one test to verify the identity, using specific identity tests if they exist.**

Young observed that the company did not conduct an identity test for received components used during drug manufacturing including certain lots of the active ingredients salicylic acid, titanium dioxide and zinc oxide, octinoxate and benzoyl peroxide.

**Observation 8: Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals.**

Greenway did not verify that components used in the manufacturing of drug products conformed to all written specifications, including the active ingredients salicylic acid, titanium dioxide and zinc oxide, octinoxate and benzoyl peroxide, the investigator noted.

“Additionally, you have distributed your Day Cream SPF30 that you have contract-manufactured without establishing specifications for this product and verifying the product meets the quality standards of identity, purity, strength and composition,” Young added.

**Observation 9: Procedures describing the handling of written and oral complaints related to drug products are not written or followed.**

The company had not established written procedures for handling complaints, the inspection showed.

**Observation 10: Written procedures are not established 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.**

Young further found that Greenway had not established written procedures for conducting annual product reviews of its drug products.

**Observation 11: The responsibilities and procedures applicable to the quality control unit are not in writing.**

The investigator stated that “you have not established procedures detailing the responsibilities and procedures for the quality control unit.”

**Observation 12: Written procedures are lacking which describe in sufficient detail the receipt, identification, storage, handling, sampling, testing, approval and rejection of components, drug product containers and closures.**

**Observation 13: Procedures designed to assure that correct labels, labeling and packaging materials are used for drug products are not written.**

Greenway did not establish written procedures for packaging and labeling operations for its drug prod-

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ucts including, but not limited to, prevention of product mix-ups, label reconciliation, handling of unlabeled drug products, examination of packaging and labeling materials, and line clearance activities, the inspection revealed.

**Observation 14: Written distribution procedures are not established.**

The firm had not established distribution procedures inclusive of recall operations.

No warning letter was located.

## DEVICES

### Device maker cited for repeat observations of GMP nonconformities

*Continental Medical Labs, Inc.  
Waterford, WI  
Minneapolis District*

During an Aug. 5-14, 2013, FDA inspection, investigator Michelle Glembin found **Continental Medical Labs** lacking in adequate procedures for complaint handling, CAPA and other GMP requirements, and observed two repeat nonconformities from the previous inspection.

Glembin reported the following observations, agency documents noted:

**Observation 1: A process whose results cannot be fully verified by subsequent inspection and test has not been adequately validated according to established procedures.**

“Your firm failed to follow the Sterilization Protocol for Custom Manufactured Kits,” the investigator stated. Glembin explained that one step of the protocol requires a certain number of “half-cycle sterilizer runs of one-half the normal exposure time to verify” the validity of cycle. A different step requires “full-cycle sterilizer runs meeting minimum acceptable cycle specification parameters to be processed.”

However, the FDAer stated, “Your firm only conducted two runs after approval of the protocol.”

Manufacturing records for the validation test samples do not exist, Glembin also found. “There is no objective evidence to support the sterilization process was performed using your most challenging product/package as required by 7.2.1 of ISO standard 11135, which your firm referenced as following,” the investigator wrote.

She also found that the firm “lacks documented evidence of the sterilization process being validated to

your defined process parameters for the half and full cycles...at your contract sterilizer.”

Further, Glembin noted that Continental failed to ensure its contract sterilizer provided the firm with data and documentation for equipment validation and instrument calibration certification per the “Responsibilities” section of the protocol.

Continental released two loads “prior to receipt of documented evidence of the sterility test results. Your protocol... states. “Test samples must meet acceptance criteria before final product release,” the inspector stated.

“The sterilization process parameters for the Half Cycle, Revision D, approved 05/13/2013 list the minimum and maximum limits of injection concentration as TBD (to be determined),” Glembin pointed out. “This is a repeat observation that your firm promised to correct in your response to the Warning Letter.”

The firm lacked validation data to support its established expiration dating period and failed to address the resterilization process, the investigator continued. “During the inspection, you reported you are no longer resterilizing product; however, this is not documented in any procedures,” she wrote, noting that this also was “a repeat observation that your firm promised to correct in your response to the Warning Letter.”

*“There is no documented evidence of cleaning procedures being performed in any of the designated clean rooms at your firm.”*

Continental failed to compare the revalidation results from July 2012 with the original validation to confirm that the original performance has been maintained as required by its re-validation procedure.

“This is a repeat observation that your firm promised to correct in your response to the Warning Letter,” Glembin added.

In another repeat observation from the previous inspection, Glembin found that Continental “failed to complete a validation of the current heat seal parameters as promised in your response to the Warning Letter.”

**Observation 2: Procedures to control environmental conditions have not been adequately established.**

“Your firm failed to document the procedure used, the person performing the sampling, the conditions and the equipment used for environmental sampling of your three clean rooms performed on April 5, 2013,” as required by the company’s environmental monitoring procedure, Glembin stated.

“There is no documented evidence of cleaning procedures being performed in any of the designated

clean rooms at your firm,” the investigator wrote. “A requirement or schedule does not exist for the maintenance or frequency of filter changes within the clean rooms.”

The company also failed to follow its procedure for “Review of Recorder and Daily Reading Logs and Temperature Monitoring” to ensure the temperature range recorded on the temperature charts is within the allowed range in all temperature-controlled rooms. The temperature was out of range on the temperature charts on several days, Glembin observed.

The investigator also found that an “Out-of-Range Notification” form was not completed for these occurrences as required by procedure.

Temperature readings taken from the digital display on the chart recorder in Continental’s temperature-controlled rooms are recorded on an internal form entitled “Daily Temperature Readings,” the inspector stated. Several such readings showed temperatures out of the acceptable range and “Out-of-Range Notification” forms were not completed for these occurrences as required.

Further, Glembin noted, the “Daily Temperature Readings” form lists a different acceptable temperature range from that set forth in the firm’s procedural requirement.

This was a repeat observation from the previous inspection.

**Observation 3: Procedures have not been adequately established to control product that does not conform to specified requirements.**

“Your firm lacks objective evidence to support the final disposition of the dry alcohol swabsticks that were the subject of nonconformance 20 13-02NC evaluated on 04/05/2013,” Glembin wrote. She further found that Continental “lacks a procedure that defines the responsibility for review, the authority for the disposition of nonconforming product and the review and disposition

process.”

The company failed to follow its nonconformance procedure, which requires the following items to be documented in the “Nonconformance Logbook:”

- Detailed description of the nonconformance
- Lot number
- Product name
- Disposition of nonconforming product
- Person who evaluated the nonconformance and date
- Test results

“A review of the ‘Nonconformance Logbook’ revealed the above items were not documented in the log book for the only two nonconformances logged to date,” the investigator observed.

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

The inspection revealed that Continental’s Corrective and Preventive Action procedure is inadequate, Glembin explained, because it does not include the following requirements:

- Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;
- Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;
- Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

“Your firm closed Corrective Action Request (CAR) 0001 regarding without any objective evidence to support the corrective actions taken by the supplier were effective,” she wrote. “In addition, there is no objective evidence to support a review of other potentially affected product to ensure the problem was isolated to the implicated lot only.”

A CAR opened regarding a customer complaint of receipt of dry alcohol swabsticks

“does not address the actions taken with the implicated lot that may have still been in available inventory at your firm,” the inspector added.

**Observation 5: Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been adequately established.**

“Your firm received a complaint via e-mail regarding dry alcohol swabsticks, a component which was included in their convenience kit,” the investigator reported. “There is no documented evidence to support this customer feedback was processed as an entry in your complaint handling system.”

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Continental's procedure on handling complaints and product-related feedback "requires all complaints to be entered into a complaint log book with the date the complaint was received, the device type, and a brief description of the complaint," Glembin detailed. According to this procedure, "if the complaint is device-related, the complaint is to be categorized and placed in the appropriate color-coded folder (red or white) to facilitate identification of potential medical device reportable events." However, she noted, "Your firm lacks a complaint log book and color-coded folders."

**Observation 6: Personnel training is not documented.**

Specifically, Glembin stated, "your firm lacks documented evidence of personnel training on several procedures that were created or revised in response to your firm's Warning Letter issued March 6, 2013." Most of these personnel "include management who are making key decisions related to quality system activities," she added.

This inspection identified that a number of procedures are not followed by the firm and resulted in repeat or new observations, the investigator stated, including procedures on complaint handling, CAPA, management review, nonconformances, general sterilization validation protocol, environmental monitoring of cleanrooms, cleaning of cleanrooms and the review of recorder and daily reading logs and temperature monitoring.

FDA issued a close-out letter in November 2013 in which the agency stated that its evaluation of Continental Medical Lab's corrective actions determined that the firm had adequately addressed the violations detailed in the March 2013 warning letter.

No warning letter was found in reference to the August inspection.

## FDA inspection shows Weber Medical lacking in records, procedures for device manufacturing

*Weber Medical GmbH  
Lauenfoerde, Germany  
CDRH*

German device manufacturer **Weber Medical GmbH** which makes medical laser systems, was cited for six nonconformities with GMPs by FDA investigator Stephen Eich at the conclusion of his Jan. 14-17, 2013, inspection.

According to the 483, Weber had the following objectionable conditions:

**Observation 1: Records of acceptable suppliers have not been adequately established.**

Specifically, the FDAer found, Weber's supplier acceptance procedure "indicates that new suppliers will have QM [quality management] systems." However, the contract manufacturer for the laser-diode modules for the Weberneedle system does not have a QM system, Eich stated.

"There is no assurance that the contractor is following the Quality System Regulation for manufacturing of the Laser module device," he wrote. "Also, the supplier acceptance procedure...involves grading of the suppliers for various elements including quality. There were no criteria in the SOP for when a supplier corrective action would be required."

**Observation 2: A device history record has not been adequately maintained.**

Eich noted that "there is no design history record for the manufacture of the Laser Module."

**Observation 3: Procedures for finished device acceptance have not been adequately established.**

"I observed the testing of the Weberneedle Product/Serial number 81212051," Eich reported. "The testing for the power of the laser did not provide a consistent result. The power level varied between 110mW to 140mW. The expected power is 100mW with acceptance criteria of 100mW +/- 20."

There is no final test for the laser wavelength, he stated.

**Observation 4: Certain measuring and test equipment is not suitable for its intended purposes.**

The testing of a Weberneedle system for laser power and wavelength, as reported above, "was made using test system PM2 but consistent results could not be obtained. Another test system (PM3) was utilized," Eich stated. "Testing device PM3 was due for recalibration in December 2012."

**Observation 5: Risk analysis is incomplete.**

The firm's Device Hazard Analysis summary of software validation "identifies a potential malfunction of failure of timer ...and an identified action that 'the patient has the opportunity to shut down the device by using the patient switch,'" the FDAer stated. However, he observed, "There is no discussion of the use of the patient switch in the user manual and no assurance that the switch is actually included with the product."

**Observation 6: Design verification does not confirm that design output meets design input requirements.**

"The design input for laser quality of the Weberneedle Basic Laser did not fully define the laser quality including the laser power and acceptable tolerance, the wavelength and the acceptable tolerance and the tol-

erance for the laser size,” Eich commented. “The design verification for the laser performance includes information to support safety evaluation but not the characterization of the laser quality for the Weberneedle device.”

FDA issued a warning letter to Weber Medical in May 2013, in which the agency referenced the inspectional observations and the firm’s written responses to the 483. In most cases, FDA found that it could not assess the adequacy of the responses due to lack of documentation supporting the firm’s corrective actions. The agency it would need to conduct a follow-up inspection to confirm that the corrective actions had been taken.

There was no record of a close-out letter or report of a follow-up inspection available from FDA.

## King Systems procedures inadequate, inspection shows

*King Systems Corp.  
Noblesville, IN  
Detroit District*

Medical device manufacturer King Systems Corp. received a five-item 483 from FDA investigator Joseph Strelnik after his July 31-Aug. 14, 2013, inspection revealed nonconformities in the firm’s procedures and processes.

Strelnik reported the following issues:

**Observation 1: A process whose results cannot be fully verified by subsequent inspection and test has not been validated according to established procedures.**

The investigator identified inadequacies in the company’s validation procedures.

“Extruders have not been validated to ensure that the process will continue to meet predetermined specifications,” Strelnik wrote. “These extruders are used to produce tubing to be assembled into the King Flex 2, King F2, King PedF2 and King F breathing circuits which are used to administer medical gases and/or anesthetic gases to a patient during anesthesia for inhalation or respiratory care inhalation.”

King Systems’ validation of the Flex 2 Assembly Automation system “did not adequately determine if the leak test performed on finished product was capable of detecting leaks of varying size in various locations in the tubing of a collapsed circuit,” the FDAer stated. “Your firm has not conducted any studies on leak testing collapsed tubing to ensure that holes of various sizes and locations can be accurately and precisely measured.”

**Observation 2: Procedures for the acceptance of in-process product have not been adequately established.**

Strelnik commented that the firm’s “in-process occlusion testing of coaxial pediatric breathing circuits is not performed in a manner that would detect nonconforming product and prevent it from leaving the facility.”

He noted that on Aug. 2, during the inspection, “I observed an employee holding coaxial pediatric breathing circuits up to the occlusion tester on production line, for amounts of time less than one second; this did not allow the occlusion tester readings to stabilize.”

**Observation 3: Procedures for the control of storage areas and stock rooms have not been adequately established.**

The investigator found King Systems’ inventory management procedures inadequate, he stated, because “raw materials in the warehouse are not stored in a manner that would prevent mix-ups.” He noted that during his inspection of the warehouse storage bin area, some bins were found to contain components that were not the same as the components listed on the Physical Inventory Count Sheet.

Further, Strelnik found the staging areas for the circuit assembly product lines were not organized appropriately to prevent confusion. “For example, I observed lines of boxes from adjacent product lines coming together in a manner so that we could not distinguish what components belonged to respective production lines without finding the job order for each line.”

The investigator also observed that King Systems “inventory management personnel supply boxes of unlabeled raw materials for use in production.” A stack of boxes containing components was staged in front of the breathing mask assembly line, he explained. The top box was unlabeled “and the identity of the components could only be verified by physical comparison to the labeled boxes in the remaining stack.”

**Observation 4: Procedures for receiving, reviewing and evaluating complaints by a formally designated unit have not been adequately established.**

Strelnik found that King Systems complaint records “are not maintained in a manner that preserves the complaint details, investigations performed and corrective actions taken to resolve a complaint.”

Further, when the firm did not investigate a complaint, the files did not include a reason for the decision not to investigate nor the signature of the person who made the decision.

**Observation 5: A violation of the FD&C Act involving a device which might present a risk to health was not reported to FDA.**

Strelnik referenced three incidents in which King Systems received complaints regarding mislabeled products, including products that contained latex that were la-

beled “latex free.” None of these incidents was reported to FDA.

## CONTRACT TESTING LABORATORY

### Inspection finds two nonconformities at SA Analytical laboratory

*SA Analytical  
Mundelein, IL  
Chicago District*

FDA investigator Christopher Leach noted just two observations on the 483 he issued to **SA Analytical**, following a Jan. 9-16, 2013, inspection of the contract testing laboratory that performs component and finished drug testing exclusively for **Nexus Pharmaceuticals**.

Leach explained in the Establishment Inspection Report (EIR) that the inspection was regarding an ANDA under review. “SA Analytical is performing release testing on the active pharmaceutical ingredient (API) and the finished drug product as well as stability sample storage and testing in support of the product expiration date.”

Leach noted the following issue, according to the records:

**Observation 1: Appropriate controls are not exercised over computers or related systems to assure that change in master production and control records or other records are instituted only by authorized personnel.**

The FDAer observed that “the firm has not documented a validation for their intended use of the software to ensure the analytical data obtained is secure from alteration. I observed this software being used to control the generation and storage of raw analytical data for the approval and release of components and finished drug products.”

During the inspection Leach noted:

- The time and date code from the system was not secured from change to prevent the loss of data integrity.
- The firm has not assigned user roles for each employee using individual user names and passwords to restrict the ability to perform operations only authorized by management.

- A written procedure does not exist for Quality Assurance to review analytical data to ensure it is accurately represented by the hard-copy printouts of chromatograms used in the approval and release of drug products.

**Observation 7: Routine checking of mechanical equipment is not performed according to a written program designed to assure proper performance.**

Raw and in-process material storage areas “may not meet the established requirements in that studies to determine the optimal environmental monitoring locations for several storage/warehouse areas...were found to be deficient,” the FDAers stated.

They found “no adequate rationale for the placement of the temperature and relative humidity monitoring device in Raw Materials Warehouse 1” because the permanent monitoring location differs from the worst-case location as determined by a temperature mapping study.

The investigators also determined that there was “inadequate data to support the placement of the temperature and relative humidity monitoring device in Raw Materials Warehouse 2, in that there was missing data for several locations and scientific rationale was not utilized in accepting the study with missing data.” Further, the impact of that missing data was not assessed during the temperature mapping study for this facility.

“There is no adequate justification for the placement of the temperature and relative humidity monitoring device in In-Process Storage 2,” the FDAers stated, because “excursions from the predefined acceptance criteria were experienced and were not handled in accordance with” the protocol that concluded the room was uniform and monitoring could occur at any location.

**Observation 8: Washing and toilet facilities lack hot and cold water.**

The FDA investigators observed that during the inspection “the toilet facility adjoining changing room MWS04 of the Raw Material Storage area did not have running water for hand washing and toilet flushing. The water supply was reportedly turned off during maintenance and inadvertently left off.”

Further, the team noted, “there are no procedures to direct employees to wash hands with soap and water after toilet use and prior to gowning, and no adequate facilities and procedures for employees to wash their feet prior to donning factory-issued work sandals, which expose bare feet and are authorized footwear in the unclassified areas.”

**Observation 9: Adequate exhaust systems or other systems to control contaminants are lacking in areas where air contamination occurs during production.**

The Air Displacement Unit (ADU) used in tablet bottling operations “does not contain adequate filters

(e.g., HEPA) to prevent the release and recirculation of dust created during the bottling operation,” which creates a situation in which cross-contamination may occur, the FDAers reported.

**Observation 10: Established test procedures are not documented at the time of performance.**

The inspection found that “the analytical green sheets used by analysts to record the testing of various materials do not contain sufficient information to verify actual reagents and apparatus used in analyses.” Microbiology green sheets for certain finished products “do not contain complete information on how analyses are performed, and “some green sheets contain preprinted instructions that do not always contain relevant information on concentrations of reagents for certain analyses.”

**Observation 11: Written procedures are lacking which describe in sufficient detail the testing, approval and rejection of components.**

The approval of certain components, the FDA team noted, “does not include a review of the monitoring system inputs to ensure the system is consistently functioning as intended.” For example, they explained, “your firm does not adequately monitor established operating parameters such as flow rate, water pressure and power...to ensure that appropriate operating conditions are met” during the manufacture of certain components and products.

In addition, the FDAers pointed out that the water source is located outdoors and “is not fully protected from entry of potentially contaminated water and filth such as rainwater runoff. Raw water tanks have air vents not fully protected and ill-fitting manhole covers that may allow access of pests and other contaminants.”

No warning letter related to this inspection could be located.

## 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-RETRIEVE 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. (Weeks of AUGUST 11-15 and 18-22, 2014) were 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](mailto:SERVICE@FDAINFO.COM)***

<u>Plant</u>	<u>Location</u>	<u>483/EIR Date</u>	<u>FOIA File</u>	<u>Requested by</u>
AKORN	KILICH, INDIA	NONE GIVEN	2014-6654	STERNE AGEE
MYLAN INSTITUTIONAL	IRELAND	NONE GIVEN	2014-6610	ELIOT WILBUR
GE HEALTHCARE	BARRINGTON, IL	NONE GIVEN	2014-6724	GE HEALTHCARE
AARTI DRUGS	INDIA	NONE GIVEN	2014-6748	ACETO CORPORATION
VIGNESH LIFE SCIENCES	INDIA	NONE GIVEN	2014-6728	BLOOMBERG NEWS
IPCA	INDIA	7/18/14	2014-6740	MYLAN
ATUL LIMITED	NONE GIVEN	1/1/2012	2014-6744	MORGAN LEWIS & BOCKIUS LLP
COVIDIEN	AUGUSTA, GA	NONE GIVEN	2014-6754	WOOD BURDITT GROUP
HOSPIRA	NONE GIVEN	NONE GIVEN	2014-6773	ARISTOTLE CAPITAL MANAGEMENT
BECKMAN COULTER	PALATINE, IL	NONE GIVEN	2014-6795	JAMES ALEXANDER CORPORATION
PANTHEON	MISSISSAUGA, ONT	WREXHAM, UK	2014-6846	SANDRA COLANTUONO
CP PHARMACEUTICALS LTD	WREXHAM, UK	7/16/10	2014-6893	SIDNEY AUSTIN
DR BERNADETTE D'SOUZA	NONE GIVEN	NONE GIVEN	2014-6804	ALKERMES