U.S. FOOD & DRUG ADMINISTRATION

PHARMACEUTICAL QUALITY INVESTIGATION BRANCH
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www.fda.gov

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02/20/2019

DATE RECEIVED 22 Feb 2019
BY

Nilsa Martinez
General Manager
Pace Analytical, Inc.
P.O. Box 325
San German, PR, 00683

Dear General Manager, Nilsa Martinez:

The U.S. Food and Drug Administration (FDA) conducted an inspection at Pace Analytical, Inc., FEI:2623531, located at El Retiro Industrial Zone, San German, PR, 00683 US from 10/31/2018 - 11/09/2018. FDA has determined that the inspection classification of this facility is "voluntary action indicated" ("VAI").[1] Based on this inspection, this facility is considered to be in a minimally acceptable state of compliance with regards to current good manufacturing practice (CGMP).

A VAI inspection classification indicates that, although investigators found and documented objectionable conditions during the inspection, FDA will not take or recommend regulatory or enforcement action because the objectionable conditions do not meet the threshold for action at this time. Despite this facility inspection classification, FDA recommends that you address any observations noted on the Form FDA 483 issued at the the conclusion of the inspection or otherwise conveyed to you following the inspection. If not corrected, the same or similar conditions could lead to a future inspection being classified as "official action indicated" ("OAI").

This letter is not intended as an endorsement or certification of the facility. It remains your responsibility to ensure continued compliance with CGMP.

An inspection classification of VAI for CGMP compliance will not directly negatively impact FDA's assessment of any pending marketing application referencing this facility. Please note, however, that application approval will depend on a product-and application-specific facility assessment conducted by the appropriate CDER or CVM review office. This letter does not address or reflect FDA's decision making with respect to any potential non-CGMP compliance issues.

FDA has concluded that this inspection is "closed" under 21 CFR 20.64(d)(3), and we are enclosing a copy of the narrative portion of the Establishment Inspection Report (EIR). It may reflect redactions made by FDA in accordance with the Freedom of Information Act (FOIA) and 21 CFR part 20. This, however, does not preclude you from requesting additional information under FOIA.

If you have any questions regarding this letter, you may contact Frances DeJesus via telephone at 787-729-8543 or email at Frances.DeJesus@FDA.HHS.GOV.

Sincerely,

Frances L. De Jesus -S

Digitally signed by Frances L. De Jesus -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300178006, cn=Frances L. De Jesus -S
Date: 2019.02.20 14:35:24 -04'00'

Frances DeJesus
SUPERVISORY CONSUMER SAFETY OFFICER
PHARMACEUTICAL QUALITY INVESTIGATION BRANCH

[1] See Inspection Classification Definitions, at https://www.fda.gov/ICECI/Inspections/ucm223231.htm.

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SUMMARY

The comprehensive GMP inspection of this contract control-testing laboratory was conducted according to SJN- DO FY'18, [redacted]. This inspection was conducted in accordance with Compliance Program #7356.002, Drug Manufacturing Operations, and included coverage of the Quality, Laboratory and Facilities & Equipment systems. This will be an abbreviated report.

Previous FDA inspection of June 2015 disclosed two (2) written observations as follows: an adequate compendia method verification was not in place for the test for raw material 2-pyrrolidone; there was no secondary review of notebook for notes relating to the limit of benzene compendia verification. Inspection was classified VAI.

Current inspection included review of firm's corrective actions to observations issued during the previous inspection and confirmed implementation as reported to SJN-DO. Inspectional findings disclosed two multiple-item written observations including: inadequate handling of investigation reports after conversion to electronic records; failure to document corrective and preventive actions, and inadequate laboratory controls for microbial tests, validation of disinfectants, maintenance of incubators and water systems used for testing activities. Inadequate procedures for management reviews and disaster recovery activities after Hurricanes Irma and Maria were discussed verbally during the inspection. No actions were initiated to correct deviations identified during the inspection. Firm's managers stated that a written response to address deviations cited would be forwarded via email to OPQO within 15 days. No refusals were encountered, and no samples were collected.

ADMINISTRATIVE DATA

Inspected firm:	Pace Analytical, Inc.
Location:	El Retiro Industrial Zone, B Street San German, PR 00683
Phone:	(787) 892-2680
FAX:	(787) 892-1054
Mailing address:	PO Box 325 San German, PR 00683
Dates of inspection:	10/31, 11/1,6-9/2018
Days in the facility:	6
Participants:	Noreen Muñiz, Consumer Safety Officer

Upon arrival to the firm I presented my credentials, explained the purpose of my visit to Zulma Nazario, Quality Assurance Manager, who identified herself as the most responsible person at the time and explained the General Manager was not available. I issued an FDA-482, Notice of Inspection, to Mrs. Nazario along with a copy of the Program Alignment Information Sheet. Credentials were also presented to Nilsa Martinez, General Manager, who was present on site on the second day of the inspection and thereafter. Mrs. Nazario, Mrs. Martinez and Maricel Acosta, QA Supervisor, assisted with records and information requested during the inspection. A closing meeting was held on 11/09/2018 to discuss inspectional findings and to issue Form FDA-483 to Mrs. Martinez. See **Attachments #1-#2** for copies of official forms issued during this inspection.

See **Exhibit 1** for copies of local and corporate organization depicting changes implemented since the previous inspection. The firm is an independent subsidiary of Pace Analytical Life Sciences, LLC which is located at 1800 Elm Street NE, Minneapolis, Minnesota-55414. Key Corporate officials were identified during the inspection as follows:

Steve Vanderboom, Chief Executive Officer
Gregory Kupp, VP, Chief Operating Officer
Angela Strantz, General Manager
Cynthia Hansen, Sr. QA Director

Local key officers were identified during this inspection as follows:

Nilsa Martinez, General Manager

Zulma Nazario, QA Manager
Marisel Acosta, QA Supervisor
Manuel Baez, Maintenance Supervisor

Post inspectional correspondence to the local site should be addressed to:
Nilsa Martinez, General Manager email: nilsa.martinez@pacelabs.com
Pace Analytical, Inc.
P.O. Box 325
San German, PR 00683.

Changes Reported since previous inspection

The firm continues to be a contract testing laboratory providing services to Pharmaceutical and Medical Device Manufacturers. Profiles updated in eNspect to discontinue CTL as no longer available and include Microbial and Chemical testing. A change in operations reported since the previous inspection includes the refurbishment of an adjacent building, previously leased by another company, to be dedicated exclusively for Analytical Testing. The site is currently expanding and remodeling the Microbiology Laboratory areas.

INTERSTATE COMMERCE/JURISDICTION

The firm provides customers with contract laboratory testing in FDA regulated products and does not manufacture any ingredients or finished goods. Evidence for the firm's current registration with FDA was provided during this inspection and verified in eDRLS during the completion of this report. The raw materials, finished drug products, and medical devices analyzed on-site are purchased and/or distributed through channels of interstate commerce. See **Exhibit # 2** for a listing of the firm's customers and **Exhibit #3** for a listing of analytical services provided by Pace. Evidence of interstate commerce transactions was not evaluated during this inspection but could be obtained as needed contacting the firm's clients.

MANUFACTURING / DESIGN OPERATIONS

No changes in operations were reported during this inspection. The firm is a contract testing laboratory and uses electronic records to capture test data and data transfer to the client. PacePort is a proprietary system used to convey testing results to the client via an online web portal. The client may access the following on PacePort: testing reports, certificates of analysis, full data packages, including notebook pages, invoices, methods, sample processing data and test results. Paper records

issued on site are maintained until review is completed, then the paper record is scanned and the original document is sent to an off-site storage location.

The current inspection included coverage of elements of the Quality System, Laboratory Controls and Equipment &Facilities with the review of a sample of procedures and records issued since the last FDA inspection of June 2015 to present. Records reviewed by system include:

Quality System: Quality Manual; Procedures for handling and investigation of deviations, on-conforming events, out of tolerance events, issued reports, and associated CAPA actions; procedures for handling and investigation of consumer complaints and issued reports; procedures for change control request system and sample of change requests; sample of data package test results and electronic records, and applicable procedures. Review of procedures for Management Reviews disclosed information to be evaluated under "Quality Objectives" on the annual meetings is not clearly described on the procedure and meeting agendas reviewed are not specific to ensure that information discussed during annual meetings include relevant escalation of potential issues. This deficiency was discussed verbally with area leaders during the inspection and at the closing meeting. I did not review specific training records, but interviews held with Laboratory personnel and personnel associated to sample handling and maintenance disclosed individuals were knowledgeable of assigned duties and applicable procedures.

Laboratory Controls System: Records reviewed included: laboratory activities and organization; procedures and sample of records for sample receipt, storage and distribution; procedures and sample of laboratory investigations for out of specification, out of trends, and CAPA activities; environmental monitoring activities in the Microbiology Laboratory; water monitoring trends; qualification of one HPLC instrument relocated to the new building and associated procedures; sample of four data packages completed for analytical testing and associated procedures. Mrs. Nazario confirmed the firm does not conduct sterility testing and that stability chambers on site are used only to store samples, not to run stability protocols.

Facilities & Equipment System: Records reviewed included annual trends for water and environmental monitoring activities, sample of change controls including movement of equipment from Building 1 to the new Building 2, sample of associated equipment qualification activities and maintenance procedures. Review of activities conducted for evaluation of damages after Hurricanes Irma and Maria disclosed that not all activities conducted were fully documented as discussed verbally with area managers, who reported low impact in operations. Inspection coverage included visual inspection of facilities conducted during a walkthrough of the Analytical and Microbiology Testing Areas and interviews with area personnel. I also discussed verbally with area leaders that cabinets identified as "Personal Items" for lab analysts included laboratory equipment and documents, and some incubators were observed overloaded with materials reported as "tested but not discarded", with dates inscribed over 30 days prior to this inspection.

Written observations identified during the inspection are described in the following section.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

OBSERVATION 1

The responsibilities and procedures applicable to the Quality Control Unit are not followed and documented at the time of performance.

1. Procedure # 38, Document and Record Retention and Disaster Recovery, v5 21 Feb2017, does not include instructions on how to ensure that scanned copies maintained from original paper records are controlled and reviewed for accuracy, when saved as electronic copies and the original paper records are stored at an off-site location. The procedure states that all paper records are scanned into PDF format but does not provide specific instructions on how to ensure that the scanned version is identical to the original paper record, include controls to ensure that changes are maintained and tracked, or description of secure file location. Records provided during this inspection on electronic format for complaint reports and qualification protocols disclosed that the electronic version provided was not always a true copy of the original paper version, and that updates to the paper record were not maintained on the electronic version (changes on electronic files are overwritten with same name).

2. Investigation reports completed for the evaluation of complaints and laboratory investigations do not always include evidence of corrective actions identified to ensure timely and effective implementation to prevent recurrence, when investigated as described in applicable procedures (current and previous versions) SOP30v9, Complaint Handling, and SOPL8, Laboratory Investigations v12. For example:

a. Laboratory Investigations #LIR687, 25 Jul 17: Corrective actions identified to prevent the reported potential contamination during analytical testing of Magnesium Stearate. Actions described for special handling of testing materials were not permanently implemented.

b. Laboratory Investigation # LIR539, 23 May 2016: Corrective actions identified to prevent the reported potential microbial contamination during testing included the change of disinfectant agents used in the Microbiology Laboratory and proposed the revalidation of disinfectants used for cleaning. The change was not permanently or consistently implemented, and the proposed re-validation of disinfectants has not yet been completed.

c. Complaint Investigation 012, 13 Jan 2017, described the investigation of data package error. Corrective actions reported included software changes to prevent recurrence of the event that were not fully documented with the complaint or with any other record on site.

Reference: 21 CFR 211.22(d)

Supporting Evidence and Relevance:
My review of procedures and records associated to the function of the Quality Unit disclosed deviations cited in the observation as follows:

Item 1. Mrs. Nazario explained that all records handled on site are scanned on a monthly basis or when completed/reviewed and maintained electronically as the site uses an off-site storage facility (Iron Mountain) to keep records. Consequently, I chose to request a sample of electronic copies of investigation reports to expedite the record review on the first day of this inspection. As I was reviewing complaint file #012 on the computer (electronic copy), Mrs. Nazario confirmed that my copy of the record did not match her copy of the record as my copy had 12 pages but her electronic copy had 16 pages total. See **Exhibit 4 and #10** for printed copies of both records. As I inquired how could this happen, she explained that the electronic copies maintained were not meant to be "true copies" of the original record.

Mrs. Nazario explained that the site's policy was to maintain "true copies" or the integrity of electronic files generated for client data or associated electronic copies of paper records issued. Mrs. Nazario further described that investigations and qualification /validation protocols would constitute "other records" that were routinely scanned but not necessarily maintained as "true electronic copies", because none of the local procedures required this. Consequently, the electronic version maintained for records that do not include client-test data could be copied, updated, revised as needed after the original record was issued, or would not include the same information as the original record (when the paper record was revised after the electronic version was issued).

Procedure # 38 (**Exhibit 5**), Document and Record Retention and Disaster Recovery, v5 21 Feb2017, does not include instructions on what records to be scanned or how to ensure that scanned copies maintained from original paper records are controlled and reviewed for accuracy, when saved as electronic copies and the original paper records are stored at an off-site location. Procedure L21, Technical Records Review, and SOP L12, Work Order Generation, Completion and Reporting of Result include more detailed and specific instructions on how handle and store client-test data. During my review of a sample of qualification protocols for Incubators in the Microbiology Laboratory, I also noted that the scanned version provided on site had missing data and pages, but the original protocols were not available on site as were over 3 years old.

I explained I had only requested electronic copies because Mrs. Nazario stated that all records were kept as scanned copies on site and that the original was not immediately available. I also added that the practice of scanning copies that do not represent true copies of the original record described

significant data integrity issues and represented a poor practice, as the integrity of all records issued by the Quality Unit should be maintained when transferred to an electronic format. I added that that complaint or laboratory investigations issued on site included actions to support the release of client-test results, and that equipment qualification activities included records to support tests conducted for clients that should be controlled and maintained as any other record on site issued by the QC Lab. After discussion of this deviation, I requested to see original paper records for all documents requested that were then reported as available on site-despite Mrs. Nazario's original statement of transfer to the off-site facility. I discussed with Mrs. Martinez this discrepancy stating that the event disclosed general poor record maintenance activities and that could also be interpreted as interference with the inspection.

Item 2. Sample of investigation reports disclosed lack or incomplete documentation activities for corrective actions reported when investigated as described in applicable procedures SOP 30 v9, Complaint Handling (**Exhibit 6**), and SOP L8, Laboratory Investigations v12 (**Exhibit 7**). For example:

a. Laboratory Investigation #LIR687, 25 Jul 17: **Exhibit 8.** Corrective actions identified to prevent the reported potential contamination during analytical testing of Magnesium Stearate described the need to provide special instructions for analysts while handling testing materials. Actions described for special handling of testing materials were not permanently implemented with changes in the procedure or similar actions that would ensure actions were consistently implemented.

b. Laboratory Investigation # LIR539, 23 May 2016: **Exhibit 9**. Corrective actions identified to prevent the reported potential microbial contamination during testing included the change of disinfectant agents used in the Microbiology Laboratory and proposed the revalidation of disinfectants used for cleaning. The change was not permanently or consistently implemented, and the proposed re-validation of disinfectants has not yet been completed to this date. Further review of cleaning procedures on site disclosed deviations on the validation for disinfectants currently in use as described under **Observation 2.2**.

c. Complaint Investigation 012, 13 Jan 2017: **Exhibit 10:** The complaint describes the investigation of data package error. Corrective actions reported included software changes to prevent recurrence of the event that were not fully documented with the complaint or with any other record on site and that were not available on site as requested during this inspection for review. As I requested evidence for changes implemented by the support group (Minnesota), only partial information could be obtained because the individual who implemented the change did not fully document the activity conducted and provided emails sent that appear to confirm that the changes were made-not how were the changes implemented. I also discussed with Mrs. Nazario the fact that extensions for completion on laboratory investigations and complaints were provided without limit, and failed to include justification for delays over 90 days other than delayed client's response, which could impact other activities conducted while a final resolution was not implemented.

Discussion with Management:

No specific actions were described during this inspection to address deviations cited in this observation. At the closing meeting, Mrs. Nazario and Ms. Cynthia Hansen, Sr. QA Director, stated that a written response with additional information would be forwarded to OPQO via email within 15 days.

OBSERVATION 2

Established laboratory control mechanisms are not followed and documented at the time of performance. Specifically,

1. Environmental Monitoring of Microbiology Laboratory, LM193, v 4, is not always effective to describe and execute activities conducted in the microbiology laboratories. As described in the sampling procedure, routine monitoring conducted in the laboratory are not fully documented to ensure that activities are conducted during normal operations. Records reviewed during the inspection disclosed that sampling activities documented with form LM193A2, during the period of June to September 2018 disclosed that sampling activities were reported on the same room during documentation activities. No evidence of activities conducted or number of analysts in the room was included to confirm normal operations during sampling.

2. PR-MB-012, Rev1, 9/20/2006, Procedure for the Validation of Disinfectant Solutions in the Microbiology Laboratory, describes the validation of agents for use routinely but does not include challenges on all surfaces currently available in the Laboratory. For example, not all disinfectants tested at the time or sporicidal agent "Sporgon" were validated for efficacy in areas such as stainless steel or epoxy-based surfaces.

3. Incubators used routinely in the Microbiology Laboratory and qualified on an annual basis as described in document QP60, Incubation /Refrigerators/Freezers Requalification Protocol v2, 19 Feb 2010 and current, do not include documented evidence to support the reported ranges for use. For example, records reviewed on site for the annual mapping conducted on 3 incubators disclosed that temperature ranges obtained with mapping studies did not achieve the ranges reported for use. In addition, the permanent temperature sensor of each chamber is calibrated at a single point that do not show the expected range of use but that is monitored daily to confirm the storage conditions are maintained within the expected range. For example:

1. PADC-INCUB-012: Range of Use=30-35C: Qualified Range in August 2018 = 32.3-33.6
2. PADC-INCUB-011: Range of Use=35-39C: Qualified Range in August 2018 = 36.4 -37.5
3. PADC-INCUB-025: Range of Use= 20-25C: Qualified Range in August 2018 = 22.1-22.6

4. Procedure S26, Use, Monitoring and Testing Deionized and Purified Water Systems, v11 19 Apr18, is not always followed for the daily monitoring of components on the system installed at the new Building 2 for use in the Chemistry Laboratory (Building 2, Systems PADC-DI-Water 002 and # 003).

Records reviewed during this inspection for the week of 11/5/2018 disclosed that the daily inspection on three (3) components was not conducted on 2 days as requested by the procedure. In addition, a water leak was observed on System 003 during a visit to the area conducted on 11/7/2018.

Furthermore, the procedure does not ensure consistent evaluation of the components of the system as none of the pipes associated to both systems 002 and 003 were observed identified, included indication of flow direction per line, or included identification of water line and drain lines to ensure adequate handling when needed. A schematic diagram of the Deionized water system is not available to ensure all components were installed as intended.

5. Performance qualification protocols executed on site for new GEN Pro Water Purification Systems installed at three (3) Analytical Laboratories at Building 2 and executed during the period of October 2017 to March 2018 are not fully documented to support reported successful completion and release for use. Three protocols were executed simultaneously for units PADC-PUWATER-001/003/004 and reported successful tests conducted on three consecutive days, which does not accurate report findings as confirmed during this inspection.

Executed qualification records reviewed during the inspection disclosed unexpected results for day 1 in all three units with failed acceptance criteria for Micro test, and failed TOC test in one unit, when tested for three consecutive dates in October 2017. Each event was investigated and described the execution of additional maintenance activities in all three units approximately 4 months (March 2018) after the initial sampling date and prior to the final approval of the qualification protocol. No evidence was included with each protocol to identify the impact of the maintenance activities conducted on the original sampling plan defined on the protocol (three consecutive sampling dates). The original testing plan of three days was only repeated in one unit after maintenance, and one sampling day on the other two prior to the reported successful completion of the protocol.

Reference: 21 CFR 211.160 (a)

Supporting Evidence and Relevance:

Item 1. My review of samples of environmental monitoring results, conducted as described in procedure Environmental Monitoring of Microbiology Laboratory, LM193 v 4 (**Exhibit 11**), disclosed that sampling activities are not specific to demonstrate the reported low bioburden levels in general laboratory areas (non-classified rooms). Routine monitoring is reported in forms that do not describe where was the actual sample collected as the procedure only describes general areas but also requires monitoring to be conducted during routine operations. Sample of records reviewed

during the period of June to September 2018 disclosed that sampling activities were reported on the same room during documentation activities but does not report any testing (Room 1023, 1031, **Exhibit 12**).

Mrs. Nazario explained that the sampling activities described do not apply to classified areas, which would include only Laminar Flow Hoods that were sampled with each test. Nevertheless, the monitoring activities reported in non-classified areas are not conducted during routine testing as described in the procedure, but test results are used as reference during investigation of Microbiology investigations and routinely trended as observed during this inspection.

Item 2. During my review of laboratory investigations, I also conducted a review of cleaning procedures and the current validation for disinfectant solutions described by Mrs. Nazario as executed in 2006 under document PR-MB-012, Rev1, 9/20/2006, Procedure for the Validation of Disinfectant Solutions in the Microbiology Laboratory (**Exhibit 13**). The document describes the validation of sanitizers used in the laboratory in 2006, some of which are no longer available as the document is 12 years old. Cursory review of the validation disclosed that the current sporicidal agent "Sporgon" was not validated for efficacy in stainless steel or epoxy-based surfaces, which are now part of the areas used for testing and general, non-classified areas. I also noted that the validation report describes the use of cleaning wipes, which according to Mrs. Nazario have not been used for several years because could not be obtained from the supplier.

During the discussion Mrs. Nazario described a proposed re-validation protocol for disinfectants that was issued in 2016 under CAPA 1313 but has not yet been completed.

Item 3. My review of a sample of records for the initial and most recent qualification of incubators used in the Microbiology Laboratory, documented annually by protocol as described in document QP60, Incubation /Refrigerators/Freezers Requalification Protocol v2, 19 Feb 2010 (included with each executed protocol below), disclosed lack of evidence to ensure that incubators are qualified within ranges for use.

As stated in the observation, the annual mapping is conducted in all incubators by the procedure in the same manner since at least the year 2010. However, records reviewed showed that incubators did not achieve the reported ranges for use on the most recent mapping study of 2018. In addition, as each incubator holds a permanent monitoring device that is used to monitor the temperature daily, records included with the most recent annual mapping did not show working ranges on this device either. For example:

1. PADC-INCUB-012: Range of Use=30-35C: Qualified Range in August 2018 = 32.3-33.6 (**Exhibit 14**). The permanent Temperature sensor was verified as set point of 33 Deg C
2. PADC-INCUB-011: Range of Use=35-39C: Qualified Range in August 2018 = 36.4 -37.5 (**Exhibit 15**). The permanent Temperature sensor was verified as set point of 37Deg C

3. PADC-INCUB-025: Range of Use= 20-25C: Qualified Range in August 2018 = 22.1-22.6 (**Exhibit 16**). The permanent Temperature sensor was verified as set point of 22.5 Deg C.

Mrs. Nazario explained that the chambers were qualified to demonstrate performance within the working ranges. In other words, she explained that the chamber reported for use at 30-35C would need to be set at 30C and then at 35C for the mapping study to be completed to show temperatures at limits within the working ranges. She also explained that the incubators have been mapped in the same way for many years following guidelines established at the Pace-Minnesota Laboratory.

Mrs. Nazario stated that the Lab monitored daily the incubators display and the dedicated reference probe to ensure that the incubators were working within the acceptable ranges. However, as confirmed during this inspection, the reference probes are not calibrated within the incubator's working ranges either but with a single calibration point that would not ensure that excursions would be accurately displayed. I expressed my concerns about the lack of evidence to support working ranges on Incubators on studies with Microbes requiring additional storage conditions. Mrs. Nazario added that some of the incubators included an additional monitoring device, a data logger that was monitored also on a daily basis which according to records provided was verified at a broader range than the fixed thermometer. However, as the incubator was not qualified within the reported ranges, the data collected from this device might not have all the information needed to support the storage of materials within a designated range. I also discussed the fact that the firm reported multiple excursions during the re-calibration on temperature monitoring devices in the Micro Lab during the past year and that appeared to be abnormal as reports impacted multiple instruments. Mrs. Nazario stated the firm had already identified this anomaly and stated the firm already planned an upcoming upgrade to automated monitoring systems to be established by the end of this year.

Item 4. During the inspection, I reviewed records associated to the recently installed De-ionized water system for use at the new QC Laboratory at Building 2, monitored in accordance with procedure S26, Use, Monitoring and Testing Deionized and Purified Water Systems, v11 19 Apr18 (**Exhibit 17**). The new system consists of two independent units identified PADC-DI-Water 002 and # PADC-DI-Water 003, purchased and qualified as described under respective qualification protocols available on site during this inspection and executed in February and August 2017.

Procedure S26 states the system is to be monitored daily by visual inspection and documented on the respective equipment logbook available in the area, as described by Manuel Baez, Area Supervisor. However, records for the week of 11/5/2018 disclosed that the daily inspection on three (3) components (on both systems) was not conducted on 2 days as requested by the procedure. Mr. Baez stated that the person who conducted the inspection had been out and confirmed that when the daily inspection could not be conducted by the designated individual he would conduct it (which had not happened on 11/06 or 11/07). As I visited the room late on 11/07 (after 3:00pm), I noted the lack of inspection for the past 2 days, which was recorded in the morning (around 8:30am) for records available in the system logbook for the past 2 months. At the time, I also pointed an evident leak on System 003, directly above the UV light which includes an electric component that according to Mr.

Baez required immediate attention. During the discussion, Mr. Baez also confirmed that a drawing or schematic diagram for the system was not available as I noted that none of the pipe lines were identified to ensure correct flow of water and identification of processed vs non-processed water lines.

After the discussion of these deficiencies, Mr. Baez stated that corrective actions would be evaluated for immediate implementation. At the closing meeting, Mrs. Nazario stated that the inspection on the system was only missed for one day, stating that the second day had not finished when I visited the area. No additional actions for inspection or evaluation of the observed leak and impact on the system was provided during the inspection.

Item 5. My review of records associated to the performance qualification for 3 new GEN Pro Water Purification Systems installed at three different rooms for use during QC tests at Building 2 disclosed failure to include documentation to support the reported successful completion and release for use. As stated in the observation, three (3) protocols were executed simultaneously for new units purchased for used at the new QC Lab and identified as PADC-PUWATER-001, PADC-PUWATER-003 and PADC-PUWATER-004. Note that the units are located at separate laboratories and do not share components other than the DI water source at different rooms. Respective qualification reports describe successful tests conducted on three consecutive days, which does not accurate report findings as confirmed during this inspection due to unexpected test results obtained which did not meet the criteria reported of 3-consecutive successful testing dates.

The executed qualification packages available during the inspection disclosed unexpected results for day 1 in all three units with failed acceptance criteria for Micro test, and failed TOC test in one unit, when tested for three consecutive dates in October 2017 (See **Exhibits 18-20** for excerpts of qualification reports for each unit). All 3-protocols were executed at the same time and sampled initially on same dates (Oct 30, 31, Nov 01/2017), and each protocol includes the reference investigation for out of specification test results as follows:

Unit 001 (**Exhibit 18**): Investigation LIR 755: TOC failed test in 3 consecutive days (Day1, 2,3) and failed Micro Count for Day 1

Unit 003 **(Exhibit 19)**: Investigation LIR 1028: Micro Count results failed in Day 1 of 3

Unit 004 (**Exhibit 20**): Investigation LIR 1028: Micro Count results failed in Day 1 of 3

Each deviation was investigated, and the final report described the execution of additional maintenance activities in all three units approximately 4 months (March 2018) after the initial sampling date and prior to the final approval of the qualification protocol. However, the reported maintenance activity conducted in all three units was not confirmed during this inspection as only records were available for changes in unit 001 dated February 2018- no records were available on site to demonstrate maintenance on units 003 or 004 until October 2018. The original testing plan of three consecutive days was only repeated in unit 001, after the reported maintenance in February 2018. For the other two units, only one additional sampling day was conducted in March 2018.

During my review of records, the discrepancies were discussed with Mrs. Nazario and Mrs. Martinez. Mrs. Nazario stated not being aware of the specific maintenance activities referenced on the protocols, but all protocols were approved without documented evidence included to describe actions conducted.

I stated that the new systems were not qualified adequately as the need for maintenance was identified during the initial qualification, adding the firm should not rely to current performance to justify adequacy. I had also mentioned that the firm only conducted 3 sampling days during the initial qualification that proved to be unsuccessful; therefore, a better practice would have been to qualify the systems with additional sampling days conducted consecutively for all units repeating the protocol. Mrs. Nazario clarified that the protocol was repeated for unit 001 because of the reported TOC failure on all sampling days, not obtained for the other two units. She also stated that the qualification protocol did not state that the sampling days would be consecutive (as described on respective final reports), to justify that 2 sampling days in October 2017 and a third in March 2018 would still meet the acceptance criteria of three days for the other two units that were reported as subjected to maintenance (no records available to justify this statement). Mrs. Nazario stated that no issues had been reported with samples collected after the units were released for use.

Discussion with Management:
No specific actions were described during this inspection to address deviations cited in this observation. At the closing meeting, Mrs. Nazario and Ms. Cynthia Hansen, Sr.QA Director, stated that a written response with additional information would be forwarded to OPQO via email within 15 days.

VOLUNTARY CORRECTIONS

Corrective actions implemented to address deviations issued in writing during the previous FDA inspection of June 2015 were reviewed during this inspection, as provided by Mrs. Nazario, including response letter package submitted to SJN-DO 28 Jul 2015. See below excerpts of each observation and reported corrective actions:

1. Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that components conform to appropriate standards of identity, strength, quality and purity. Specifically, An adequate compendia method verification was not in place for the test for 2-pyrrolidone.

Corrective action: Compendia method verification was conducted for test methods executed at Pace San German and Oakdale-Minnesota with issuance of CAPA records and revision of applicable procedures. Corrective action appeared to be adequate.

2. The establishment of laboratory control mechanisms including any changes thereto, are not reviewed and approved by the quality control unit. Specifically, There was no secondary review of notebook 00074, from August 6, 2014 to August 8, 2014, pages 38 to 42, for notes relating to the limit of benzene compendia verification.

Corrective Actions: Revision of applicable procedure for Good Documentation Practices, SOP11. Corrective action appeared adequate.

No further actions were reported during the inspection to address deviations cited during the current inspection, as reported earlier on this report. At the closing meeting, Mrs. Martinez stated that additional information would be submitted with a written response to OPQO within 15 days after the completion of this inspection.

REFUSALS

No refusals were encountered during this inspection.

SAMPLES COLLECTED

No samples were collected during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

At the conclusion of the inspection, I had an exit meeting with to discuss the inspectional observations listed in the FDA-483 issued at the same time. Present at the meeting were the following individuals:

Nilsa Martinez, General Manager
Zulma Nazario, QA Manager
Marisel Acosta, QA Supervisor,

The following individuals attended the meeting via telephone:
Cynthia Hansen, Sr. QA Director
Angela Strantz, Sr. General Manager
Gregory Kupp, VP Chief Operating Officer

Prior to the closing meeting, I explained the process of issuance the Inspectional Observations adding the form would need to be issued without eNspect due to technical difficulties. I issued Form FDA-483 to Mrs. Martinez who read each item out loud at the meeting.

All individuals at the meeting acknowledged that written observations had been discussed during the inspection. I also summarized deviations discussed verbally for Management Review Procedures, documentation of impact of Hurricanes Irma/Maria, laboratory areas. No additional information was provided during the meeting to address deviations reported during the inspection.

After discussion of the form, I handed to Mrs. Martinez the Letter for Electronic Submission of FDA-483 Response issued by OPQO/DIV 2 and discussed specific email address created to submit correspondence with FDA. Mr. Kupp stated the site's commitments to implement actions to correct deviations discussed. Ms. Hansen and Mrs. Martinez both stated that a written response with additional information would be submitted via email to OPQO within fifteen (15) working days.

I explained to all individuals present at the meeting that deviations issued in writing and or discussed during the inspection may, after further review by FDA, be considered violations of the FD & C Act and that legal sanctions available to FDA to ensure voluntary compliance may include Warning Letters, Untitled Letters, Seizure, Injunction, amongst others, that could impact site operations and Clients. No additional issues were discussed, and the inspection was closed.

ATTACHMENTS

1. Copy of FDA Form 482, Notice of Inspection, dated 10/31/18
2. Copy of FDA Form 483, Inspectional Observations, dated 11/09/18

EXHIBITS COLLECTED

1. Copy of site and corporate Organization Charts
2. List of the firm's customers
3. Summary List of analytical services provided by Pace.
4. Copies of Complaint record 12-4 pages total- as provided during the inspection
5. Copy of SOP 38, Document and Record Retention and Disaster Recovery, v5 21 Feb2017
6. Copy of SOP 30 v9, Complaint Handling
7. Copy of SOP L8, Laboratory Investigations v12

8. Excerpts of Laboratory Investigation #LIR687, 25 Jul 17:
9. Excerpts of Laboratory Investigation # LIR539, 23 May 2016:
10. Excerpts of Complaint Investigation #12-16 pages total, 13 Jan 2017
11. Copy of SOP LM193 v4, Environmental Monitoring of Microbiology Laboratory
12. Copy of Environmental Monitoring reports June-Sept 2018
13. Copy of PR-MB-012, Rev1, 9/20/2006, Procedure for the Validation of Disinfectant Solutions in the Microbiology Laboratory
14. Excerpts qualification for PADC-INCUB-012
15. Excerpts qualification for PADC-INCUB- 011
16. Excerpts qualification for PADC-INCUB- 025
17. Copy of SOP S26, Use, Monitoring and Testing Deionized and Purified Water Systems, v11 19 Apr18
18. Excerpts of qualification report for PADC-PUWATER-001
19. Excerpts of qualification report for PADC-PUWATER-003
20. Excerpts of qualification report for PADC-PUWATER-004

Noreen Muniz -S

Digitally signed by Noreen Muniz -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Noreen Muniz -S, 0.9.2342.19200300.100.1.1=13001 78186
Date: 2018.12.17 13:57:43 -04'00'

Noreen Muñiz, Consumer Safety Officer