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30 November 2018

Food and Drug Administration
Office of Pharmaceutical Quality Operations (OPQO)
Divison II

RE: Pace Analytical, Inc. FDA Compliance Inspection.
Firm ID: 2623531 / DUNS # 362250102

Dear Sirs:

During 31 Oct 2018, 01 Nov 2018 and 06-09 Nov 2018, an FDA compliance inspection was performed at Pace Analytical, Inc. by Consumer Safety Officer/Drug Specialist Noreen Muñiz. The attach document is the response which addresses the two (2) observations listed in the FDA Form 483 issued on 09 Nov 2018.

Should you have any questions or need additional information regarding Pace Analytical, Inc. response please contact us at 787-892-2680, 787-659-1137 or 787-659-1138.

Cordially,

Zulma Nazario
Quality Manager
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Enclosure

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 Feb 2017, 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).

   Response: The purpose of SOP 38 *Document and Record Retention and Disaster Recovery* Version 5, Effective Date 21 Feb 2017 is to describe the process for document and record retention. It also describes how PDF versions of documents and records that are stored on the Pace Analytical Life Sciences (PLS) network and on the Pace Port web portal may be used in the event of disaster recovery. These PDFs are intended to be the most recent representation of documents and records; they are not intended to represent true copies. Therefore, SOP 38 is not intended to describe how true copies are generated from original documents records.

   Corrective action: Establish a process for true copies (CAT 1376 PLS PR).

   Responsible person: Cynthia Hansen

   Target date: 31 Dec 2020

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 v 12.

   Response: Corrective actions can be the output of multiple Pace quality management system processes which include:

   - SOP 16 Internal Audits
   - SOP 17 Deviations and Modifications
   - SOP 18 Risk Assessment

- SOP 30 Complaint Handling
- SOP L5 Microbiological Monitoring and Unexpected Results Investigations
- SOP L8 Laboratory Investigations
- SOP L10 Out of Tolerance
- SOP L16 Equipment and Laboratory Area Excursions

It is PLS standard practice that when evidence of a completed corrective action is easily identifiable and readily retrievable, the evidence is not attached to the exception (e.g. investigation) report. However, SOP 42 *Corrective Action Tracking* does not provide instructions to address handling of evidence that is not easily identifiable and readily retrievable. Furthermore, SOP 42 also does not provide adequate guidance on how to establish an appropriate corrective action that prevents recurrence or address corrective actions that do not require tracking (i.e. are completed before an investigation is finalized).

Corrective action 1: Update SOP 42 to provide instructions for establishing an appropriate corrective action that ensures the change is permanent, provide guidelines for extending the target implementation date, to provide instructions for traceability to evidence that a corrective action was implemented, and to address corrective actions completed before complaints and laboratory investigations are finalized (CAT 1377 PLS PR).

Responsible person 1: Christi Richmond

Target date 1: 30 Apr 2019

Corrective Action 2: Update the following SOPs to refer to SOP 42 for creating and handling corrective actions. (SOPs that are listed above, but not included here, already refer to SOP 42 appropriately.)

- SOP 16 Internal Audits (CAT 1383 PLS PR
- SOP 17 Deviations and Modifications (CAT 1384 PLS PR)
- SOP 30 Complaint Handling (CAT 1385 PLS PR)
- SOP L10 Out of Tolerance (CAT 1386 PLS PR)
- SOP L16 Equipment and Laboratory Area Excursions (CAT 1387 PLS PR)

Responsible person 2: (CATs 1383 to 1387 PLS PR): Christi Richmond

Target date 2: 30 Apr 2019

2a. 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.

Correction: LIR 687 was updated on 20 Nov 2018 to incorporate reference to DCR 11620 to issue a Method Memo for Magnesium Stearate by Atomic Absorption (AA)

Testing. According to SOP 2, *Document Management*, Pace Method Memos are used to clarify procedures and permanently implement these clarifications. The Method Memo title "MM Mg Stearate NF/EP by AA" Version 1 was issued on 28 Nov 2018 and training was provided to analysts performing Magnesium Stearate testing by Atomic Absorption. No further action will be taken at this time.

2b. Laboratory Investigation # LIR 539, 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.

Response: Disinfectant efficacy testing was initially performed in the San German facility under protocol PR-MB-012 *Procedure for the Validation of Disinfectants*. Subsequently, VP 485 V1 *Disinfectant Efficacy Test for Pace Analytical, Inc. PLS San German, PR Microbiology Laboratory* was issued so that testing on additional surface types and using additional disinfectants could be performed.

Review of the documents and data revealed that the testing described in these documents is often duplicate testing that has been performed in PLS's Oakdale facility. As long as the surfaces, disinfectants and use procedures are the same, the location in which testing is performed does not impact the results.

Corrective Action 1: Instead of performing additional testing that may not be required, all disinfectant validation data generated to date at all facilities will be evaluated to determine what testing, if any, is required to support currently used disinfectants and existing laboratory surfaces at PLS San Germán. Data will be summarized in a single report that applies to all PLS locations (CAT 1378 PLS PR). If any additional testing is required, a follow up CAT will be initiated to ensure timely completion. Elimination of a site-specific approach will facilitate timely completion.

Responsible person 1: Angela Strantz

Target date 1: 29 Jan 2019

Corrective Action 2: A process will be established to define the requirements for future testing if evaluation of additional disinfectants or surfaces is needed at any Pace location (CAT 1379 PLS PR).

Responsible person 2: Angela Strantz

Target date 2: 28 Feb 2019

2c. 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.

Correction: Complaint COMP 012 (PLS PR) was updated on 20 Nov 2018 to document the evidence of the fix made to the LIMS. No further action will be taken at this time.

OBSERVATION 2

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

1. Environmental Monitoring of Microbiology Laboratory, LM 193, v4, 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 LM 193A2, 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.

   Corrective action: The environmental monitoring (EM) performed under method LM 193 is for non-classified areas. EM is performed to demonstrate that the systems in place (e.g. housekeeping practices, disinfection practices, gowning practices) used to maintain the environmental controls in the laboratory are operating as expected. Method LM 193 and the worksheets were updated through DCR 11593 to clarify the requirements for environmental monitoring and to facilitate documentation of any activities occurring during monitoring that could impact the results. Training on the revised method was performed on 20 Nov 2018 and the revised method (LM 193 V5) became effective on 30 Nov 2018.

   No further action will be taken at this time.

2. PR-MB-012, Rev 1, 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.

   Response: Disinfectant efficacy testing was initially performed in the San German facility under protocol PR-MB-012 *Procedure for the Validation of Disinfectants*. Subsequently, VP 485 V1 *Disinfectant Efficacy Test for Pace Analytical, Inc. PLS San German, PR Microbiology Laboratory* was issued so that testing on additional surface types and using additional disinfectants could be performed.

   Review of the documents and data revealed that the testing described in these documents is often duplicates testing that has been performed in PLS's Oakdale facility. As long as the surfaces, disinfectants and use procedures are the same, the location in which testing is performed does not impact the results.

Corrective action: Instead of performing additional testing that may not be required, all data generated to date at all facilities will be evaluated to determine what testing, if any, is required to support currently used disinfectants and existing laboratory surfaces. Data will be summarized in a single report that applies to all Pace Life Sciences locations (CAT 1378 PLS PR). If any additional testing is required, a follow up CAT will be initiated to ensure timely completion. Elimination of a site-specific approach will facilitate timely completion.

Responsible person: Angela Strantz

Target date: 29 Jan 2019

Corrective Action 2: A process will be established to define the requirements for future testing if evaluation of additional disinfectants or surfaces is needed at any Pace location (CAT 1379 PLS PR).

Responsible person: Angela Strantz

Target date: 28 Feb 2019

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

Response: Incubation temperatures specified for microbiology testing are not set values, instead a temperature range is described. For example, USP <61> provides instructions to incubate the plates for the Total Aerobic Microbial count at 30° to 35ºC and to incubate plates for the Total Combined Yeasts and Molds Count are 20° to 25ºC. The operating ranges for microbiology incubators reflect those ranges. When incubators are qualified, the incubators are set at a temperature within the range, typically the mid-point. The objective of the qualification is to demonstrate that the temperature throughout the incubator is within the required operating range. If an observed temperature range is narrower than the desired operating range, it can be concluded that the incubator is performing as intended.

The set point of an incubator qualified to operate at a defined range is not adjusted to operate at specific temperatures within the range. For example, an incubator with an

operating range of 30° to 35ºC would not be reset at 35ºC for an incubation temperature of 33° to 37ºC. If the set point is changed, a new qualification would be required.

During qualification and re-qualification, multiple LogTags were used simultaneously to verify the temperature throughout the incubator was within the desired operating range. Each LogTag was calibrated at three temperatures that bracketed the operating range. The re-qualification results cited indicate the incubator was capable of operating well within the allowable range.

The long-term approach to ensuring incubator temperature is within the defined operating limits is implementation of the Pace Continuous Monitoring System (CMS). With this system, multiple thermocouples are used to continuously map multiple locations throughout each incubator. The thermocouples are calibrated at temperatures that bracket the operating range. Excursions outside of the calibrated range result in an alarm condition that requires the appropriate actions to be taken to correct the excursion and evaluate potential impact. The CMS is implemented in Building 2. Renovation of Building 1 is underway. All temperature and/or humidity controlled equipment will be continuously mapped by the CMS by 30 Jun 2019. It is expected that the first incubators utilizing the CMS will be operational by 31 Dec 2018. The target date for the CAT represents the completion of the activity.

Corrective Action: The CMS will be implemented for temperature and/or humidity controlled equipment in Building 1 (CAT 1279 PLS PR).

Responsible person: Nilsa Martinez

Target date: 30 Jun 2019

4. Procedure S26, *Use, Monitoring and Testing Deionized and Purified Water Systems*, v 11, 19 Apr 18, 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.

   Correction: Monitoring of the deionized water systems is assigned to the Building Superintendent. A deviation to the procedure (DEV # 1242 PLS PR) was issued to

document the fact that on 06 Nov 2018, the daily DI water quality checks were not performed by the Building Superintendent. Note that the checks were performed on 07 Nov 2018 after the tour was completed.

Corrective action 1: SOP S26 will be updated to include requirements to inspect for leaks and notify management if leaks are observed. In addition, a schematic diagram of the systems will be included in the SOP to facilitate inspection of all components. Personnel will be trained and back-up personnel assigned to ensure DI water quality is monitored as required per SOP S26 (CAT 1380 PLS PR).

Responsible person 1: Zulma Nazario

Target date 1: 30 Jan 2019

Corrective action 2: DI Water system pipes will be identified and labeled appropriately (CAT 1381 PLS PR).

Responsible person 2: Manuel Baez

Target date 2: 30 Jan 2019

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 I 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.

   Response: While the performance qualification protocol does not specify testing must occur on three consecutive days, Pace acknowledges that testing should have been performed on three days after maintenance was completed rather than a combination of days pre- and post-maintenance.

   Corrective action: A retrospective risk assessment will be written to address the decision to not perform the performance qualification in its entirety after the maintenance activities were

performed for GENPro Purified water systems PLS ID: PADC-PUWATER-002 and PADC-PUWATER-003, and to document why testing for three days is appropriate for a laboratory water system (CAT 1382 PLS PR. Elements that will be acknowledged in the risk assessment include:

- PLS has multiple water purification systems from the same manufacturer in operation at the Oakdale, MN and Somerset, NJ facilitates.
- Purified water systems are not used to manufacture any pharmaceutical products or medical devices, rather, the water is used to prepare laboratory supplies such as sample solutions, standard solutions, mobile phase, and dissolution media.
- Water is monitored at time of use for resistivity and must meet requirements before use.
- System suitability and control article requirements serve as verification that water quality is appropriate.

Upon completion of the risk assessment, the qualification reports for GENPro Purified Water systems will be updated to reference the risk assessment (CAT # 1382 PLS PR).

Responsible person: Angela Strantz

Target date: 31 Dec 2018