protected by emergent biosolutions

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May 08, 2020

Attn: Office of Pharmaceutical Quality Operations (OPQO), Division I

Re: **GMP Inspection April 9-20, 2020**
Response to 483 Issued April 20, 2020
FEI Number 3015448605
In Support of (b) (4)

Dear Sir or Madam,

From April 9th to 20th, FDA Investigator Marcellinus Dordunoo conducted a Testing Laboratory PAI / General GMP Inspection of our Baltimore, Maryland (Bayview) facility in support of the Prior Approval Supplement (PAS) transfer of (b) (4) drug product manufacturing and transfer of drug product analytical methods submitted (b) (4) b) (4) Attached is our response to the Form-483 observation issued at the conclusion of this inspection.

At Emergent BioSolutions, we view quality improvement as a continuous process, and we value feedback received from regulatory authorities as we continue to improve our quality systems.

We acknowledge the observations from this recent inspection and, as part of our ongoing efforts to maintain the highest standards of quality, have taken immediate, holistic and comprehensive measures to address the deficiencies noted.

Sincerely,

Joseph A. Rogalewicz
Sr. Director, Quality
Emergent Manufacturing Operations Baltimore

CC: Marcellinus Dordunoo (via email: Marcellinus.Dordunoo@fda.hhs.gov
John Ducote, SVP, Global Quality (via email: (b) (6)
Robert Hull, VP & General Manager, Maryland (via email: (b) (6)

Observation 1.

1 APPROPRIATE CONTROLS ARE NOT EXERCISED OVER COMPUTERS OR RELATED SYSTEMS TO ASSURE THAT CHANGES IN MASTER PRODUCTION AND CONTROL RECORDS OR OTHER RECORDS ARE INSTITUTED ONLY BY AUTHORIZED PERSONNEL.

SPECIFICALLY,

A. THE QUALITY UNIT FAILED TO ENSURE THAT ELECTRONICALLY HELD DATA GENERATED DURING ANALYTICAL TESTING OF DRUG SUBSTANCE, DRUG PRODUCT, AND STABILITY SAMPLES, WAS PROTECTED FROM DELETION OR MANIPULATION, AND/OR REVIEWED FOR ACCURACY AND COMPLETENESS. THE QUALITY UNIT ALSO FAILED TO REVIEW AUDIT TRAILS OF VARIOUS DATA ACQUISITION SOFTWARE PLATFORMS, IN SUPPORT OF GENERATED ANALYTICAL RESULTS. AT THE TIME OF THIS INSPECTION, NO INVESTIGATIONS HAD BEEN PERFORMED TO ASSESS THE IMPACT OF THE DATA DELETIONS, MODIFICATIONS OR THE FAILURE TO REVIEW SYSTEM AUDIT TRAILS ON DRUG SUBSTANCE AND DRUG PRODUCT ANALYZED UNTIL APPROXIMATELY, DECEMBER 2019.

FOR EXAMPLE, (b) (4) ***, DATA ACQUISITION SOFTWARE, WAS USED FOR ANALYTICAL TESTING OF DRUG SUBSTANCE AND DRUG PRODUCT FROM APPROXIMATELY*** (b) (4) ***TO*** (b) (4) ***. AN AUDIT TRAIL REVIEW IDENTIFIED*** (b) (4) ***DELETIONS, AND*** (b) (4) ***REPROCESSED FILES. NO INVESTIGATION TO THE NATURE OF THE DELETIONS OR REPROCESSED FILES, OR ASSESSMENT OF THE IMPACT TO REPORTED DRUG SUBSTANCE AND DRUG PRODUCT ANALYSIS, WAS PERFORMED.***

B. ANALYTICAL BALANCES USED IN THE ANALYSIS OF DRUG SUBSTANCE AND DRUG PRODUCT, SAMPLE RECEIPT, AND SAMPLE PREPARATION, HAVE NO MECHANISM BY WHICH TO PREVENT USERS FROM CHANGING THE DATE AND TIME PRESENT ON PRINTED RECORDS.

C. THE WINDOWS OPERATING SYSTEM INSTALLED ON THE FIRM'S COMPUTERS, DO NOT FULLY PREVENT USERS FROM CHANGING THE SYSTEM DATE AND TIME. DURING THE BIOCHEMISTRY LABORATORY WALK-THROUGH, IT WAS OBSERVED THAT THE PRESET TIME-ZONE AND

SUBSEQUENTLY, THE DATE AND TIME WAS ABLE TO BE MODIFIED.

Response:

Emergent is committed to improving control of data generated and stored by electronic systems. The execution of PLN040233, Data Integrity Site Assessment Project Master Plan, is currently in progress and was provided to the investigator during the inspection [Attached]. Controls are in place and in use to ensure data integrity for all data generated to support commercial product (i.e. (b) (4)) testing by the Quality Control laboratory. Interim controls have been established to ensure data integrity for QC instruments that have yet to be mapped to folders on a secure network targeted to be complete by (b) (4) Retrospective data review for all batch testing performed between (b) (4) will be completed by (b) (4)

Commercial product ((b) (4)):

A. (b) (4) was not utilized for release or stability testing of (b) (4) . (b) (4) software was replaced with (b) (4) software at our Bayview site, prior to performing release and stability testing of (b) (4) . A comprehensive assessment was completed to evaluate the integrity of all data generated, by computerized electronic systems to support (b) (4) drug product (DP) release testing and stability testing prior to the FDA submission to support the transfer of the DP manufacturing process to Emergent Camden and analytical transfer to Emergent Bayview from (b) (4) (b) (4)

The assessment included data generated on the following computerized systems: (b) (4) (b) (4) and (b) (4) and included the execution of instrument and system audit trail reviews to confirm integrity of the data. The assessment did not identify any instances of data deletions. All data reprocessing was performed per the appropriate and approved test procedures. Retroactive review of audit trails was performed as part of the assessment. Based on review of the audit trails, the data to support (b) (4) DP lots was deemed acceptable and integral. There were no observations made that would have affected the legitimacy of the data. Reference Deviation# 3100007949.

Non-commercial products:

(b) (4) was not utilized for release or stability testing of (b) (4) and has since been decommissioned. An audit trail review of (b) (4) data acquisition software was presented during the inspection; it identified (b) (4) deletions from (b) (4) to (b) (4) There were (b) (4) file records deleted and (b) (4) system records deleted. The audit trail reason for the deleted File Records ((b) (4) total) was "deleted file transfer verification", these files were related to the stand-alone system which was not on the (b) (4)) and the data was being stored on the network drive ((b) (4)). The (b) (4) files were transferred by the system administrator to the (b) (4) for storage. Since the system was not configured for the (b) (4), it was unable to verify the transfer. However, the data was manually uploaded

successfully to the (b) (4), as confirmed by the audit trail. The remaining (b) (4) deleted File Records were deleted in (b) (4) by (b) (4) during the initial installation of the HPLC system.

The deleted System Records (b) (4) total) were deleted commands from the (b) (4) Queue as opposed to raw data files. Table 1 below summarizes the deleted queue commands.

Table 1 Deleted Queue Commands

Description	Reason	# of Records
Deleted Document Audit command with description "Executed import on an existing file"	(b) (4)	(b) (4)
Deleted Commit command for upload	(b) (4)	(b) (4)
Deleted Import command for upload	(b) (4)	(b) (4)
Total Records		(b) (4)

Audit command was flagged when trying to upload and "Import" an (b) (4) version that already existed or trying to do a "Commit" with no existing versions.
The following files were provided during the inspection, and are also attached for your review:

- (b) (4) Deleted Files. pdf"
- (b) (4) Audit Trail Memo.pdf
- Delete files (b) (4) .pdf and
- Deleted System Records Audit Trail.pdf"

In addition, (b) (4) " [Attached] confirms the number of system record deletions (b) (4). No testing data files were deleted.

All batches manufactured and/or tested at the Bayview site prior to (b) (4) were intended for clinical supply. To ensure data integrity of previously generated data and reported results, CAPA# 1100002231 was initiated to assess data integrity for data generated to support drug substance, and drug product testing for other products previously tested at our Bayview facility. All clinical supply batches currently within expiry will be prioritized for assessment. Protocol PRO48450 was generated for the assessment: targeted to be completed by (b) (4) , to evaluate the integrity and validity of the data for all drug substances and products manufactured under GMP conditions and tested prior to 01 October 2019.

As a preventative action, SOP000299, *Review of Quality Control (QC) Data*, was revised to

include instructions and requirements for the review of audit trails, for the data generated by electronic computerized systems. The revised SOP000299, version 8.0, became effective on 23 January 2020 [Attached].

Computerized systems supporting (b) (4) DP testing have been mapped (per specification documents) and confirmed through the respective test methods (TMD) to secure network data storage folders and user access verified to ensure that only users with the appropriate permissions can delete, modify, rename, or move stored data and according to approved procedures (tested under test protocol).

All remaining QC computerized systems will be evaluated per CAPA# 1100002248 to ensure instruments are mapped to folders on the secure network and that only users with proper permissions can delete, modify, rename or move stored data files. The targeted completion date is (b) (4)

SOP001708, *Development of Validation Protocols and Final Reports*, was revised (v.11.0 - effective 11 February 2020) to include secure network data storage mapping and user group access as part of its requirements for new computerized systems [Attached].

To ensure computerized system integrity, CAPA# 1100002246 was opened. SOP043816, *Performance Monitoring of Computerized Systems*, has been created [Attached] to include the requirement of periodic review of all applicable computerized systems.

B. These QC balances were previously not secured to prevent users from changing the date and time present on printed records. Analytical balances are used in the quality control laboratories for reagent preparation. The printed weights obtained from the balances after chemical weigh out are used to confirm the weight that was entered into the test or reagent preparation forms. Deviation# 3100008802 has been opened to assess any potential impact to analytical data generated resulting from the lack of administrative control of the balances. In response to this observation, we have since secured all analytical balances in the quality control laboratories to prevent users from changing date and time present on printed records.

   As a preventive action, CAPA# 1100002247 was opened. SOP000508, *Calibration of Weight Indicating Instruments* was revised to include requirements for new analytical balances to be secured, prior to the initial equipment calibration, to prevent users from changing time and date. [Attached].

C. In response to this observation, all existing computers in the quality control laboratories were secured to prevent users from changing the time zone. Deviation# 3100008803 has been opened to assess impact on analytical data generated resulting from the ability to change time zones on the computer workstations in the QC laboratory. Internal procedures (provided during the inspection) SOP004678 (v 5.0), *Generation, Review and Approval of User Requirement Specifications*, and FRM005120 (v 3.0), *21 CFR Part 11/Annex 11 Master Test*

Script, were updated to ensure installation of new computers will also secure the time-zone function to prevent users from changing it [Attached].

Observation 2.

2 ESTABLISHED SPECIFICATIONS, TEST PROCEDURES AND LABORATORY CONTROL MECHANISMS ARE NOT FOLLOWED AND DOCUMENTED AT THE TIME OF PERFORMANCE.

SPECIFICALLY,

A. SAMPLE IDENTIFICATION NUMBERS ARE INCONSISTENT AND WERE OBSERVED TO BE MANUALLY CORRECTED, MULTIPLE DAYS AFTER DATA ACQUISITION. NO INVESTIGATION WAS PERFORMED, NOR WAS ANY DOCUMENTED JUSTIFICATION PROVIDED FOR THE CHANGES TO SAMPLE IDENTIFICATION NUMBERS. FOR EXAMPLE,

ANALYSIS NUMBER (b) (4) (b) (4) ***, TEST METHOD*** (b) (4) ***, STEP 6.8.6 DIRECTS THE ANALYST TO*** (b) (4) ***URING REVIEW OF THE*** (b) (4) ***, THE FOLLOWING MANUAL EDITS TO THE SAMPLE ID NUMBERS*** (b) (4) ***) WERE OBSERVED.***

- (b) (4) ***#QC19-0549A, ACQUIRED ON*** (b) (4) ***, WAS CHANGED TO QC19-0549B ON 11/18/2019.***
- (b) (4) ***#QC19-0352A, ACQUIRED ON*** (b) (4) ***WAS CHANGED TO QC19-0553A THEN QC19- 0552A, ON 11/19/219.***
- (b) (4) ***#QC19-0352B, ACQUIRED ON*** (b) (4) ***, WAS CHANGED TO QC19-0552B ON 11/19/2019.***
- (b) (4) ***#QC19-0353A, ACQUIRED ON*** (b) (4) ***, WAS CHANGED TO QC19-0553A ON 11/19/2019.***
- (b) (4) ***#QC19-0553B, ACQUIRED ON*** (b) (4) ***, WAS CHANGED TO QC19-0553B ON 11/19/2019.***
- (b) (4) ***#QC19-0354A, ACQUIRED ON*** (b) (4) ***, WAS CHANGED TO QC19-0554A ON 11/19/2019.***
- (b) (4) ***#QC19-0354B, ACQUIRED ON*** (b) (4) ***, WAS CHANGED TO QC19-0554V ON 11/19/2019.***
- (b) (4) ***#QC19-0355A, ACQUIRED ON*** (b) (4) ***, WAS CHANGED TO QC19-0555A ON 11/19/2019.***
- (b) (4) ***#QC19-0355B, ACQUIRED ON*** (b) (4) ***, WAS CHANGED TO QC19-0555B ON 11/19/2019.***

THE PRINTOUT OF THE SEQUENCE, HOWEVER, WAS NOT MANUALLY CORRECTED TO ALIGN WITH THE CHANGE IN THE SAMPLE (b) (4) ***NOTATED ON THE PRINTED*** (b) (4) ***. NO SUPPORTING DATA OR DOCUMENTED JUSTIFICATION FOR THE CHANGE IN SAMPLE*** (b) (4) ***ON THE*** (b) (4) ***WAS PROVIDED, AND NO INVESTIGATION INTO THE*** (b) (4) ***DISCREPANCIES WAS PERFORMED BY THE QUALITY CONTROL UNIT.***

B. DEVIATIONS FROM TEST METHODS ARE NOT INVESTIGATED, AND ARE MANUALLY CORRECTED, DAYS AFTER PERFORMANCE, WITH NO SUPPORTING DATA OR DOCUMENTED JUSTIFICATION FOR THE CHANGES. FOR EXAMPLE,

(b) (4)
HE SAMPLE INCUBATION
(b) (4) ***) WAS ORIGINALLY DOCUMENTED AS PERFORMED ON*** (b) (4) ***AT*** (b) (4) ***FROM*** (b) (4) ***TO*** (b) (4) ***WITH*** (b) (4) ***INCUBATION*** (b) (4) ***TREATMENT) PERFORMED AT*** (b) (4) ***FROM*** (b) (4) ***TO*** (b) (4) ***PER TEST METHOD*** (b) (4) ***ANALYSTS SHALL '*** (b) (4)

ON 15AUG2019, THE INCUBATION TEMPERATURE AND TIMES FOR THE (b) (4) ***WERE MANUALLY CORRECTED AND EXCHANGED WITH THE INCUBATION TEMPERATURE AND TIMES OF THE*** (b) (4) ***TREATMENT, WITHOUT ANY DOCUMENTED EVIDENCE, OR JUSTIFICATION SUPPORTING THE CHANGE, OR INVESTIGATION INTO THE APPARENT DEVIATION FROM THE TEST METHOD.***

C. DOCUMENTATION OF STABILITY SAMPLE ANALYSES DOCUMENTATION FOR APPEARANCE, (b) (4) ***DETERMINATION AND*** (b) (4) (b) (4) ***PER*** (b) (4) ***, "VISUAL INSPECTION (APPEARANCE) OF*** (b) (4) ***USING THE*** (b) (4) ***METHOD" ARE DEFICIENT; THE LOT NUMBER OF THE*** (b) (4) (b) (4) ***GLASS TUBES USED IN ANALYSIS ARE NOT RECORDED, GLASS TUBES ARE*** (b) (4) ***WITH*** (b) (4) (b) (4) ***WHICH IS NOT***

FILTERED FOR RESIDUE, PARTICULATES OR OIL, AND AFTER DETERMINATION OF (b) (4)***, THE SAMPLE*** (b) (4) ***DOES NOT HAVE TO BE IMMEDIATELY USED, HOWEVER THERE IS NO DOCUMENTATION REGARDING THE SAMPLE STORAGE BETWEEN ANALYSES. FOR EXAMPLE,***

(b) (4) **,** (b) (4) ***DETERMINATION OF SAMPLES WAS PERFORMED ON*** (b) (4) ***, AND*** (b) (4) ***ANALYSIS WAS PERFORMED ON*** (b) (4) ***HOWEVER, RO RECORDS COULD BE PROVIDED, DOCUMENTING WHERE THE SAMPLES WERE STORED BETWEEN ANALYSES, DESPITE THE REQUIRED*** (b) (4) ***°C SAMPLE STORAGE CONDITION.***

Response:

Our initial review of the observed deficiencies did not identify these events as deviations. Upon re-evaluation of these events, a deviation was initiated per our internal procedures to address any potential impact. Additionally, the Quality unit views data integrity as an important component of our responsibility to ensure the quality of products and any deficiency to the integrity of the data is of critical importance. Therefore, as part of Deviation# 3100008697, all (b) (4) drug product release and stability data was evaluated for adherence to ALCOA principles which included:

Principal	Evaluation
Attributable	1. QA reviewed each data collection form to ensure a "Performed by" and "Reviewed by" signature and date was present. 2. Any corrections that were made by the analyst were checked to ensure the person who entered the data, initialed and dated the correction with an explanation code. 3. All pages marked "COPY" were checked for initial and date. 4. Any related reports (deviations, etc.) referenced were checked for initials/date. 5. Operative audit trails reviewed
Legible	1. All data entries were reviewed to ensure they were readable. 2. All entries were reviewed to ensure they were made in blue or black ink only.
Contemporaneous	1. All data collection forms were reviewed to ensure the "reviewed by" signature occurred within the allowable time period (as stated in the SOP) from the "performed by" signature.

	2. QA reviewer ensured that any justification for missed signatures or dates was documented with initials and date. 3. All data (including attachments/printouts) was checked against the forms to ensure timely documentation (the data was generated at the right time and not after the form was reviewed).
Original	1. All forms were checked to ensure that data was generated on the current version of the form at the time of use. 2. Forms were checked to ensure any forms in "Draft" version had an explanation with initials and date. 3. Page numbers were checked in every data packet to ensure no pages were missing or duplicated. 4. All forms were confirmed to be original. 5. Assessed associated audit trails and storage locations
Accurate	1. Calculations were checked where possible (ex: calculating the amount of time passed for incubation/reading of plates) 2. Dates and times were checked on all performed work to ensure a timely, sequential flow of work. 3. Expiration/Calibration dates were checked to ensure all reagents/chemicals/equipment documented were within expiration/calibration at time of use.

This assessment concluded that the test data as reported adheres to ALCOA principles and the reported data is considered accurate and valid. To reinforce these principles with the Quality Control staff,(b) (4) counseling sessions were held on (b) (4) with all laboratory personnel to ensure an understanding and application of the principles defined in the following SOPs: SOP000299, *Review of Quality Control Data*, SOP029029, *Bayview Data Integrity Procedure*, and SOP041954, *Good Documentation Practices – Bayview* [Training Report Attached].

A. In response to this observation, Deviation# 3100008697 was opened. The root cause was identified to be a typographical error made during the entry of the sample IDs into the sequence table. As the sample IDs can be confirmed from the data capture form, FRM042039, *Data Capture form for Reducing* (b) (4) (b) (4) there is no apparent impact to the integrity of the data and the results are acceptable. The sequence printout included with the (b) (4) was amended to correct the sample IDs.

   To ensure future corrections to data are properly documented and include supporting justification for change, SOP000299, *Review of Quality Control Data*, was revised to include detail on how corrections to data are to be performed [Attached]. Specifically, the SOP requires all raw data corrections to reference documentation supporting the correction or

change. All laboratory personnel were trained on the updated procedure as part of the counseling sessions that were held on (b) (4).

B. Deviations from test methods are required to be documented per our internal procedure, SOP000261, *Deviation Investigation Process*. In response to this observation, Deviation# 3100008697 was opened. The root cause was determined to be the design of the data capture form, FRM042039 which recorded the (b) (4) and (b) (4) treatment incubation temperatures (b) (4) providing the potential of recording information into the wrong section. To mitigate the risk of recording the incubation parameters in the wrong section, data capture form FRM042039 was revised to have the incubations recorded in a (b) (4), reducing the potential for transposition of entries. The deviation concluded that there is no supporting documentation to confirm that the proper incubation temperatures were performed, and therefore the integrity of the data cannot be confirmed. The results for (b) (4) (b) (4)) were invalidated.

Although the (b) (4) timepoint for lot (b) (4) was invalidated, the purity of lot (b) (4) by (b) (4) was demonstrated to meet specification at (b) (4) and (b) (4). Additionally, there have been no missed timepoints or data invalidated for the other (b) (4) drug product lots: (b) (4) and (b) (4). Therefore, there is no impact to the demonstrated stability of (b) (4) drug product due to the invalidating of the (b) (4) data for the (b) (4) timepoint. (see attached (b) (4) stability trends: including and excluding the (b) (4) timepoint for lot (b) (4) stored at (b) (4) °C and (b) (4) °C/ (b) (4) %RH).

Additionally, there was no impact to the conclusion of the (b) (4) for (b) (4) drug product, (b) (4) (b) (4) (b) (4) as the invalidated date was not used to support this study. To ensure continued confirmation of (b) (4) drug product stability, the first drug product campaign of (b) (4) using (b) (4) bulk drug substance will be put on stability as per the proposed post approval stability commitment.

C. In response to this observation, Deviation# 3100008697 was opened. The root cause was determined to be method as (b) (4) *Visual Inspection (Appearance) of* (b) (4) *using the* (b) (4), did not provide instructions as to when the sub-sections of the method should be completed (b) (4). Discussion with performing analyst indicated that the samples were most likely stored at (b) (4) °C between analyses, however, storage cannot be confirmed as no entry was made on the data capture form or the associated Controlled Temperature Unit (CTU) logbook. The samples in question were found to pass sample acceptance criteria per (b) (4) as well as specification per (b) (4) (b) (4) (b) (4)), despite the un-documented storage. In the worst case, had the samples not been stored at (b) (4) °C between analyses, stability of (b) (4) drug product has been demonstrated at (b) (4) and (b) (4)

months when stored at (b) (4) °C/ (b) (4) % RH. There have been no out of specification or aberrant trends observed for appearance of (b) (4) drug product. Therefore, the deviation concluded there is no apparent impact and the data will be reported as is.

Change Control# 2100004801 was opened to revise method (b) (4) . The (b) (4) and (b) (4) sub-sections of the method will be performed in (b) (4) to ensure integrity of the sample is always maintained. (b) (4) will be added to replace the (b) (4) . Sections to record the lot number of the (b) (4) and (b) (4) glass tubes, as well as the lot of the (b) (4) will be added to data capture form FRM042231, *Appearance Evaluation for* (b) (4) Change Control# 2100004801 is targeted to close by (b) (4) ahead of the (b) (4) drug product stability timepoint for lots (b) (4) , and (b) (4) scheduled on (b) (4) (b) (4) .

Observation 3.

3 THE RESPONSIBILITIES AND PROCEDURES APPLICABLE TO THE QUALITY CONTROL UNIT ARE NOT IN WRITING AND FULLY FOLLOWED.

SPECIFICALLY,

A. SOP042317, "QC INVESTIGATIONS AND INVALID EVENTS", DOES NOT PRECLUDE THE ANALYST WHO PERFORMED THE ANALYSIS WHICH GENERATED AN INVALID EVENT, FROM PERFORMING AN INDEPENDENT INVESTIGATION INTO THE INVALID EVENT. (b) (4) OF (b) (4) INVALID EVENTS SINCE JANUARY 21, 2020 WERE INVESTIGATED BY THE SAME ANALYST WHO PERFORMED THE ORIGINAL ANALYSIS. THE WRITTEN PROCEDURE STATES THAT "VERBAL APPROVAL CAN BE USED IN ORDER TO MOVE FORWARD WITH A REPEAT TEST". AS SUCH, SAMPLE RETEST, PER THE WRITTEN PROCEDURE, IS POSSIBLE PRIOR TO A DOCUMENTED SECONDARY REVIEW AND APPROVAL OF THE ACCURACY AND COMPLETENESS OF THE INVALID EVENT INVESTIGATION.

B. DATA GENERATED FROM LABORATORY ANALYSES IS NOT REVIEWED IN A TIMELY MANNER, OR IN ACCORDANCE TO THE WRITTEN PROCEDURE. SOP000299, "REVIEW OF QUALITY CONTROL (QC) DATA", STEP 6.1.2.1, ESTABLISHES THAT QC DATA SHALL BE REVIEWED WITHIN (b) (4) (b) (4) . HOWEVER, IT WAS REPEATEDLY OBSERVED THAT DATA IS ROUTINELY REVIEWED OUTSIDE OF THE (b) (4) WINDOW, WITHOUT COMMENT, JUSTIFICATION OR INVESTIGATION.

Response:

A. SOP042317, *Documentation and Investigation of Invalid Events in Quality Control Laboratories*, [Attached] was modified to preclude the analyst who generated the invalid event from investigating the event. The verbal approval option for retesting was removed and now states, "written approval must be obtained from a supervisor or designee prior to repeat testing". In addition, Form FRM044390, *Invalid Event Documentation and Investigation Form*, [Attached] was revised to include a confirmation indicating the test record and invalid assay laboratory investigation was evaluated and approved by an independent reviewer not responsible for the invalid event prior to initiating a re-assay and/or retest. As of 08May2020, all QC personnel have completed training on the updated versions of SOP042317 and notified of the updated revision of Form FRM044390.

B. Emergent recognizes the importance of timely data review and will continue to improve our cycle time for review. SOP000299, *Review of Quality Control (QC) Data*, [Attached] was revised to include a (b) (4) quality control data review and additional (b) (4) for quality assurance data review. Any data reviewed outside of targeted review period will require documented justification. Corrective action will be taken to assure adherence to the review timing requirements. To assure that QC data review cycle times remain under control, performance against this metric will be measured as part of Quality Management Review. As of 08May2020, all QC personnel have completed training on the updated version of SOP000299.

Observation 4.

4 EMPLOYEES ARE NOT GIVEN TRAINING IN THE PARTICULAR OPERATIONS THEY PERFORM AS PART OF THEIR FUNCTION AND CURRENT GOOD MANUFACTURING PRACTICES.

SPECIFICALLY,

ON 04/09/2020 DURING A WALKTHROUGH OF THE BIOCHEMISTRY LABORATORY, (b) (4) ***STORAGE SOLUTIONS,*** (b) (4) (b) (4) ***WERE OBSERVED CONNECTED TO AN HPLC. UPON REQUEST, IT WAS DETERMINED THAT THE PREPARER DID NOT DOCUMENT PREPARATION OF THE*** (b) (4) ***SOLUTIONS, PER THE FIRM'S WRITTEN PROCEDURE, SOP002191, "SOLUTION PREPARATION". ADDITIONAL REQUEST FOR THE PREPARER'S TRAINING RECORD RESULTED IN DETERMINATION THAT TRACEABILITY OF THE PREPARER TO TRAINING RECORDS WAS NOT POSSIBLE, AS THE PREPARER WAS NOT PRESENT ON THE FIRM'S EMPLOYEE SIGNATURE LOG. THERE IS NO DOCUMENTED EVIDENCE THE PREPARER HAS BEEN TRAINED ON THAT RELEVANT PROCEDURE(S). ADDITIONAL INQUIRY IDENTIFIED*** (b) (4) ***OTHER PEOPLE WHO PARTICIPATE IN ANALYSIS OR PERFORM ACTIONS IN THE FIRM'S***

ANALYTICAL LABORATORIES, ARE SIMILARLY NOT IDENTIFIED ON THE EMPLOYEE SIGNATURE LOG, PREVENTING TRACEABILITY TO THEIR RELATIVE TRAINING AND QUALIFICATIONS. AT THE TIME OF THIS INSPECTION, NO ASSESSMENT HAD BEEN MADE TO THE IMPACT ON ANALYSIS PERFORMED, OR IMPACTED, BY PERSONNEL WHO DO NOT HAVE DOCUMENTED EVIDENCE OF TRAINING ON THE FIRM'S WRITTEN PROCEDURES OR TEST METHODS.

Response:

Emergent is dedicated to ensuring our employees remain current on training requirements and that these requirements are met prior to execution of GxP tasks. Our Training Program defines the requirements for all training activities supporting GxP operations required to maintain employee qualification and compliance. This program is applicable to all permanent employees and contingent workers, (temporary employees, consultants, contractors, vendors), involved in support of the development, manufacture, testing and distribution of all products produced at the Emergent Bayview site. Department Managers are responsible for ensuring that all direct reports have the training, education and experience necessary to perform their assigned functions/duties and duties/responsibilities are aligned with assigned training curriculum. Employees/contingent workers are responsible for completing training requirements in a timely fashion and prior to performing the applicable operation/function. Per SOP001653, *Training Program*, all employees/contingent workers are required to have training completed prior to performing a task or procedure. As of 08 May 2020, all employees/ contingent workers performing activities, are confirmed to be trained on the task they are performing. This program utilizes both paper and electronic systems to document, monitor and assess training compliance. A revision to SOP001653 (v 14.0), *Training Program*, expanded the use of Emergent's (b) (4) to include all contingent workers (as defined above) where previously applicable consultant, contractor and vendor training records were all paper based. Training completion in (b) (4) is documented electronically and authenticated via a network username and password. Training metrics obtained from (b) (4) are reported to the site (b) (4) and a (b) (4) review is subsequently performed as part of the Quality Management Review.

Emergent Bayview's Good Documentation Practices (GDP) procedure is a part of our Training Program; and is maintained in line with current GMP and regulatory standards and is periodically reviewed as per internal procedures. SOP041954, *Good Documentation Practices - Bayview*, was recently revised and made effective on 30 December 2019. This revision included an update to the associated form, FRM042261, *Signature Registration Form - Bayview*, and inclusion of the completion requirement in (b) (4) for new employees/contingent workers and the (b) (4) review for current employees/contingent workers. SOP041954 instructs all employees and contingent workers to ensure a current signature sample is on file by completing and/or updating FRM042261, (b) (4) , at (b) (4) , or upon (b) (4) , and prior to signing or initialing any Emergent Controlled Document. To facilitate obtaining a current

signature registration documented on FRM042261 (v 2.0) in (b) (4), all employees and contingent workers as of (b) (4) were assigned a task for completion in (b) (4) with a Due Date of (b) (4). This date was assigned under the assumption that a signature registration using FRM042261 (v 1.0) was already on file per procedure.

Upon notification that the contingent worker cited in the observation did not have a completed signature registration in (b) (4), further investigation was performed into pending completion of signature registration forms sitewide and that number was provided to the Inspector. The number provided was not specific to personnel in the analytical laboratories only. Many of those pending completion of the signature registration form were either new employees/contingent workers needing to complete this for the first time or already had a signature registration previously documented on FRM042261 (v 1.0). Missing signature registration forms have been obtained for all active employees/contingent workers performing GxP work.

In addition, an internal deviation, Deviation# 3100008666, was initiated to document the event, and determine the impact to GMP data and documentation associated with any outstanding signature registrations. The root cause was determined to be Method, due to (1) missing instructions in SOP001653 for use of FRM001597, *New Hire Training Checklist*, and (2) Human as the employees/contingent workers and Department Managers did not respond to the (b) (4) notifications for overdue assignments. CAPA(s) resulting from that deviation will implement systemic changes to prevent recurrence including revision to SOP001653. Revisions include details for usage of FRM001597 as a new hire onboarding packet that specifies items for completion within a reduced timeframe due to potential GxP impact. This includes having all new personnel record their signature on FRM042261 within (b) (4) from date (b) (4) and prior to performing any GxP task, as required per SOP001653. Alignment of required due dates will be completed in (b) (4) for new employees and for the (b) (4) signature review/update. The training department will run a report of overdue learnings (b) (4) which will be provided to Department Heads and escalated to the Bayview Leadership Team if unresolved by the (b) (4). The revised procedure, SOP001653 (v 15.0), and form, FRM001597 (v 9.0), [Attached] are provided for your review. All employees and contingent workers performing GxP work for the site will be counseled to ensure they understand the requirements and how to meet the requirements. A majority of the training has been completed, with the remainder to be performed by (b) (4). [Training Report Attached].

In reference to the contingent worker cited in the observation, training on the respective procedure, SOP002191, *Solution Preparation*, was completed in Emergent's (b) (4) prior to the Contingent Worker executing the applicable task [Attached]. The associated training document was provided to the Inspector. The employee was, however, missing the signature registration form at the time of the Inspector's request to see it. This has since been obtained and documented in (b) (4). A review of the contingent worker's training curriculum was checked against their training records and it is confirmed that they have been properly trained in accordance with SOP001653 prior to task execution. See below for a high-level summary of the contingent worker's training for the task observed by the Inspector:

- Date of Hire: (b) (6)
- Training documented in (b) (4) for SOP002191: (b) (6)
- Task execution of SOP002191: (b) (6)
- Signature Registration form FRM042261 Completion: (b) (6)

Observation 5.

5 SEPARATE OR DEFINED AREAS TO PREVENT CONTAMINATION OR MIX-UPS ARE DEFICIENT REGARDING OPERATIONS RELATED TO THE HOLDING OF REJECTED COMPONENTS BEFORE DISPOSITION.

SPECIFICALLY,

(b) (4) (b) (4) ***OF*** (b) (4) ***, LOT NO.*** (b) (4) ***AND*** (b) (4) (b) (4) ***CONTAINING A*** (b) (4) ***. LOT NO.*** (b) (4) ***WERE OBSERVED IN THE REJECT CAGE. UPON INQUIRY, IT WAS DETERMINED THAT THERE WAS NO ASSOCIATED NON-CONFORMING MATERIAL REPORT INITIATED FOR THE*** (b) (4) (b) (4) (b) (4) ***, INDICATING THE RATIONALE FOR REJECTION, AS PER WRITTEN PROCEDURE, SOP001965, " NON-CONFORMING MATERIAL PROCESS". ADDITIONALLY, IT WAS DETERMINED THAT, THE*** (b) (4) (b) (4) ***, LOT NO.*** (b) (4) ***, WAS PREVIOUSLY REJECTED AND DISPOSITIONED FOR DISPOSAL WITHIN*** (b) (4) ***ON*** (b) (4) ***. NEITHER MATERIAL WAS LABELED WITH REJECT LABELS AS PER SOP001965.***

Response:

Deviation# 310008644 was initiated to capture the event of the late initiation of the Non-Conforming Material Report (NCMR) for the (b) (4) (b) (4). Upon investigation, it was determined that the deviation is a result of a failure in the method. Method was determined to be a root cause because SOP001965 "Non-Conforming Material Process", does not provide a timeframe to initiate a NCMR. Furthermore, it does not provide a clear process to notify QA of the non-conforming material to allow for proper labeling. As a result, SOP001965 [Attached] has been revised as detailed below.

- Immediately contact Quality Assurance to properly label the material.
- Within (b) (4) initiate creation of the NCMR upon observance or notification of a non-conformance of materials, which do not meet specifications or in-process limits.
- Transfer the storage location of the non-conforming material to the Reject/QA Hold cage
- Perform periodic reviews of the Reject /QA Hold storage location.

Deviation# 310008643 has been initiated to investigate the reason the (b) (4) was rejected during Quality inspection. Upon investigation, it was determined that the deviation is a result of a failure in the method. Method was determined to be a root cause because SOP001692, Receipt and Inspection of Incoming Materials, does not include instruction to verify storage conditions against the material specification of Quality Managed materials. The (b) (4) (b) (4) arrives as ambient but requires (b) (4) °C storage. SOP001692, Section 6.1.3.5 states to expedite processing of temperature sensitive materials; however, this material was not deemed to be temperature sensitive at the time of delivery. Pursuant to CAPA# 1100001920, which was already in place, SOP001692 will be made obsolete and replaced with SOP043593, *Receiving and Distributing Purchased Materials*. SOP043593 was updated to include a section to specifically outline the transfer of material to an appropriate bin location based on storage conditions and that the storage conditions are defined on the material specification for Quality Managed Materials. In addition, SOP043593 [Attached] was updated to include steps to use the End of Day report to verify materials are stored in the correct location and under the proper storage conditions. The changes to SOP043593 reduces the likelihood of a repeat occurrence of improperly storing a material that is delivered at one temperature but requires storage at a different temperature.

SOP000279, *Inspection and Disposition of Incoming Raw Materials and Components*, [Attached] has been revised to clarify labeling requirements for nonconforming or potentially nonconforming material while pending investigations are in-process. Investigations for non-conforming material must be completed before the material is dispositioned.

SOP043817, *Material and Product Status Labeling*, [Attached] has been made effective to define the material labels within the facility.

SOP027884, *Quality Hold and Reject Procedure for Product and Intermediates*, [Attached] was revised to include reference to SOP043817 for labeling nonconforming or potentially nonconforming product with a QA Hold label while pending further disposition.

(b) (4) Notification 10161056 has been created to establish a (b) (4) PM to perform a (b) (4) review of the Reject / QA Hold storage location. This review will be both physical and electronic systematical to ensure materials are properly labeled and stored as they await disposition. This review will also ensure materials have been properly disposed upon completion of the NCMR investigation and the associated material disposition.