Supplier: Emergent BioSolutions, Inc.
Site/Facility: Baltimore, MD, Bayview Facility, All
Address: 5901 E Lombard St, Baltimore, MD 21224
Country: USA
Purpose: Qualification Audit
Audit Date: 09 June 2020 - 17 June 2020
Auditor(s): 
Audit Participants: 
Audit Status: Approved for Use with Corrective actions indicated
cc: 
Summary and Conclusions

Scope and Purpose of Audit:

Emergent BioSolutions Bayview Facility in Baltimore, Maryland, USA, underwent a qualification audit as part of the AstraZeneca Operations GMP Audit Program on 09-17 June 2020. The purpose of the audit was to evaluate Emergent's facilities, quality systems and operations against current Good Manufacturing Practice and applicable ICH Guidance for the manufacturing and testing of bulk live virus vaccine (AZD-1222).

As agreed with Global Supplier Quality and the AZD-1222 project team, the audit was conducted remotely as a mitigation for COVID-19 facility access restrictions.

Regulatory History:

The manufacturing areas of Emergent's Bayview facility have not been inspected by a National Board of Health. The site does not hold an EU GMP Certificate.

The laboratory of the Bayview site was inspected by FDA in April of 2020 in association with a PAI of Emergent's nearby Paca Street fill/finish facility, for which they support. This inspection resulted in a 5-Item 483. A response was provided, with no further enforcement actions.

Emergent anticipates a PAI inspection of the Bayview facility in 2021 to support contract manufacturing of MAB drug substance (Raxibacumab).

Summary Statement:

The qualification audit of Emergent's Bayview facility was conducted as defined in the audit agenda. The audit was conducted over multiple sessions which occurred between 09-15 June, using tools for remote conferencing and file sharing. Virtual tours of most GMP production areas was conducted via live video. In some cases where specific areas could not be toured due to ongoing manufacturing, still pictures were provided. The closeout meeting was conducted on 17 June, 2020.

The remote nature of the audit did not result in any significant inability to evaluate Emergent's quality systems. However, it is recommended that the next routine audit of the CMO include an on-site facility tour. No acceleration of the standard 1-year audit frequency is recommended as a result of this audit.

Conclusions of Observations:

The audit of Emergent's Bayview facility resulted in three observations classified as "Major" and three observations classified as "Minor." There were no "Critical" observations made during the audit. Several recommendations as well as positive comments were also made (reference 'Highlights and Recommendations,' below).

The "Major" observations related to the following:

- Deficiencies in the systems for contamination control
- Deficiencies in document management and revision control
- Inadequate quality system design with respect to Commercial standards for GMP
The findings were shared with Emergent's Audit Management Team during the closeout, as was the process for audit report issuance, response, and documentation/closure of committed actions. Based on the findings of the audit, and contingent upon the receipt of a satisfactory audit report, Emergent's Bayview facility has been assigned a status of "Acceptable for Use with Corrective Actions Indicated" in the GAM audit management database.

**Highlights and Recommendations:**

Emergent BioSolutions (NYSE: EBS) is a publicly traded biopharmaceutical company headquartered in Gaithersburg, Maryland. In addition to manufacturing and marketing its own products (e.g., BioTrax anthrax vaccine and Narcan), the company provides contract manufacturing services for biologics and vaccine products. The company's Bayview Facility, located Southwest of Baltimore, is being considered for manufacturing of bulk vaccine and associated analytical services.

Emergent's Bayview facility was originally constructed in 1996 as a CDMO manufacturing site for Lonza. In 2009 the site was acquired by Emergent, and was subsequently renovated in 2009 to provide for 4 independent biological production suites designed for segregation and allowing for simultaneous operation for mammalian cell culture, microbial fermentation, or viral manufacturing (up to BSL-2). The approach currently being evaluated by the AZD-1222 project team would include initial production in Suite 1, with subsequent transfer of manufacturing to Suite 3 of the facility. While no significant concerns were noted regarding facility design with respect to GMP, containment, or segregation of production areas, it was noted that the purification areas of Suites 1 and 3 are classified differently (Grade C in Suite 1 vs. Grade D in Suite 2).

**Positives**

Site personnel were very forthright and presented as technically competent.

The audit management team executed the remote tours and document reviews very capably.

**Recommendations**

SOP002201 Version: 7.0 Stability Program does not require Stability protocols for studies managed by EMOB QC personnel or studies related to open containers, buffers, critical reagents, raw materials and cell bank material. It was recommended that these requirements be included in the procedure.

Records for media preparation do not track or stipulate a maximum time that media can be held prior to filtration. It was recommended that this control be added to the production process.

It was recommended that the design of calibration documentation be improved, as it is does not delineate between the calibration tolerance and the process tolerance.

**Approver:**

**Title:** Americas Hub Lead

**Date:** 22-Jun-2020
Audit Standards

The Code of Federal Regulations, Food and Drug Administration, 21 CFR
International Conference on Harmonization (ICH) Documents Q1-Q11

Critical Observations

A Critical Observation is a deficiency with Company Standards, GxPs and/or current regulatory requirements or expectations that provides an immediate and significant risk to product quality, patient safety or data integrity. A Critical Observation can also be a combination/repetition of Major Observations that indicate a critical failure of systems.

- None -

Major Observations

Major Observations are deficiencies with Company Standards, GxPs, and/or current regulatory requirements or expectations that provides a potentially significant risk to product quality, patient safety or data integrity, or could potentially result in significant observations from regulatory agency, or a combination/repetition of Other Observations that indicate a failure of system(s).

System: Documentation
Sub System: Documentation Control

Record ID: 46593

Documentation control requires improvements:

- Risk assessments have not been annually reviewed as required by SOP000263 v 3.0 Risk Management. For instance, RPT044360 v 1.0 Bayview Facility Viral Cross Contamination Risk Assessment is dated from 23/Oct/2018, prior to the construction of Area 4.

- Documents have not been updated in result of facilities/operations changes, such as the construction of Area 4, or the expansion of weigh/dispense area. For example, PLN005337 Version 6.0 Site Master File is dated from 2017, while current versions of PLN00532 Equipment, Utility and Facility Validation Master Plan and PLN000714 Site Validation Master Plan are from 2016.

- Trend reports have not been issued and approved on time as defined by SOP000291 v 11.0. For instance, RPT057097 v 1.0 (2Q 2019 EM), RPT051365 v 1.0 (3Q 2019 EM), RPT051810 v 1.0 (Utilities Q3 2019) and RPT052091 v 1.0 (Utilities Q4 2019) were approved up to 5 months after the end of the quarter. The CAPA to track the completion of the late trend reports, was extended and reports will reach seven months of delay. CAPA #1100002143, was created on 10/Mar/2020 to track completion of 2019 Annual EM and Utilities trend reports, which surpassed the period of 60 working days defined by the SOP SOP000291 v 11.0. The due date was again extended from May to July.

System: Premises & Equipment
Sub System: HVAC / Environmental Monitoring
Deficiencies were noted with the systems for Contamination Control:

- The Risk Assessment for Facility Viral Cross Contamination identifies several hazards as ‘high risk’ and defines associated mitigations. However, it does not document that the execution of mitigations have reduced the residual risk to an acceptable level.

- Rejected media was released for use lacking appropriate investigation. Water testing media, R2A, batch 284232 had failed on Growth promotion test and re-test against Pseudomonas aeruginosa on 04/Mar/2020 and 11/Mar/2020 respectively. Despite these results, the media was approved and released for use, following one single in-specification result on 19/May/2020. At the time of the audit, the associated investigation LI-20-12 was in draft.

- Spor-Klenz neutralization/inactivation was not fully performed per USP <1072>. There was no evidence of disinfectant neutralization to prove recovery of most of the strains challenged during disinfectant efficacy study RPT040471 Version: 2.0, 06/Jul/2018. The neutralization/inactivation performed by the vendor (Wuxi AppTec) was applicable for the in house strain Paecilomyces variotii only, with no further data for the remaining microorganisms, including mold and spore-forming bacteria.

- The monitoring of VHP effectiveness against virus has not been executed. The surface sampling and viral contaminant survey have not been performed as defined by the Changeover procedure SOP000277 Version: 6.2 item 6.4.9 and the associated method TMD040166 has been in draft since 2018.

- Repeat changes to the Environmental Monitoring criteria have been made to justify high trends. The recovery rates defined by the procedure SOP00291 and USP <1116> were exceeded in 1Q (11.69% - Grade D) and 2Q 2019 (5.60% - Grade C and 17.01% - Grade D), when Emergent decided to use the internal historical average instead. However, in 3Q 2019, the range obtained surpassed these new limits (Grade D- 15.67% vs. 13%) and additional assessments per intervals of recovery were performed. The trend continued to increase in 4Q 2019, reaching spikes of 8.04% in Grade C and 26.17% in Grade D, when new justifications were included. The use of continued changes to the criteria prevents holistic assessment and calls into question the effectiveness of facility and disinfectant qualification performed in 2018.

- Expectations around level 5 gowning (Aseptic gowning) were not clear. It was stated that level 5 is required in both Viral Propagation and Seed Preparation rooms from areas 1 and 2, however there is no such reference in the personnel flow diagram (1-101-A501 version 0) or the gowning procedure SOP001516 Version: 22.0.

System: Quality Management
Sub System: Quality Management System

Record ID: 46591

Quality Systems (e.g., raw material specification requirements/QC testing, bulk product expiry date assignment, cleaning qualification, continuous process verification, etc.) are designed to support
early-Phase clinical manufacturing. The site has not executed a comprehensive assessment of the
Quality System changes that will be necessary to manufacturing Phase III/Commercial product.

Minor(other) Observations

Other Observations are of a less serious or isolated nature that is not deemed Critical or Major but require correction,
or suggestions given on how to improve systems or procedures that may be compliant, but would benefit from
improvement (e.g. Good Practices seen elsewhere).

System: Premises & Equipment
Sub System: Computerized Systems

Record ID: 46594

Oversight and management of GMP computerized systems requires improvement. For example:

- The site is managing a program for Data Integrity remediation. However, the identified mitigations
  are not tracked via the site’s CAPA program. It is unclear how data integrity risks are communicated
to Management (e.g., included as part of Management Review or included in the overall site risk
mitigation program).

- The site does not have a procedure for the qualification and release of equipment-specific
  manufacturing recipes used for the production of drug substance.

System: Production
Sub System: Manufacturing Practices

Record ID: 46595

During the facility tour, multiple reusable Teflon hoses were stored in a non-free draining fashion and
on the floor in Downstream Area 3240.

System: Validation & Qualification
Sub System: Cleaning Validation

Record ID: 46596

Deficiencies were noted with the qualification of cleaning practices:

- The cleaning validation for buffer tanks (PRO048005) does not include swab sampling, only rinsate
  TOC/conductivity and visual cleanliness (swab sampling is defined in the Cleaning Validation Master
  Plan). Also, it is not clear if equipment clean hold times are qualified.

- It is unclear if the cleaning qualification/validation program addresses the re-used Teflon hoses
  associated with chromatography columns.
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