AUDIT EXERCISE PART III

Report Date: 24th April 2019

Audit Date: 28th March 2019

Audit Scope: Some of the North Carolina State University's BTEC Standard Operating Procedures and Executed Batch Records were Desk Audited.

Auditor: Yash Chaturvedi

Objective: To find non – compliances in the Standard Operating Procedures and Batch Production Records provided by BTEC and in the BTEC facility during the physical inspection.

This Report has Four parts

Part I: Report Describing Non – Compliances

Part II: Appendix I: Desk Audit Non – Compliances

Part III & Part IV: Appendix II & III: Facility Audit Non – Compliances

This Report is for the fulfillment of Audit Activity Part II and will be added to the Final Written Report as Appendices.

Part I: Explanation of Non - Compliances

April 24th, 2019

Krisstina Burgess, Ph.D.
Biomanufacturing Training and Education Center (BTEC)
North Carolina State University

Dear Dr. Krisstina Burgess

The BEC 575 Student group B conducted an inspection of BTEC: The Golden Leaf Biomanufacturing Training and Education Center of North Carolina State University situated at 850 Oval Dr, Raleigh 27606 on March 28th, 2019. The team specifically inspected **Facility Warehouse** managed by **Eric**, **Utilities Chamber** managed by **Jason**; **Production Laboratory** managed by **Krisstina Burgess**, **Staging Room** and **Buffer Prep Room** managed by **Suleiman**. During the inspection, our team documented deviations from current good manufacturing practices (cGMPs) in the facility, which is meant to be a place of manufacturing of different drugs and biologics. Deviations from cGMPs include non-compliance with the Title 21, Code of Federal Regulations (21 CFR) Part 211. The documented observations, which described several significant objectionable conditions relating to your facility's compliance with cGMP. These significant deviations observed during the inspections include, but were not limited to, the following. Also, for each of the non – compliance a corrective action has been proposed which can be followed to successfully comply with the cGMPs:

1. You failed to investigate that the appropriate written procedures designed in **SOP GL008** titled '**Material Control**' to have operational processes for cGMP material Control, Inventory Maintenance and Issuance of Materials for Manufacturing and disposition of returned materials were not followed. The team found various traces of wrong material placement and mixing of personal materials with the facility materials. It must be noted that to preserve and store the material in its pure form, it must be isolated from any type of external interference. Moreover, the mixing of items can lead to the wrong issuance of the materials in some cases. These items are labeled after careful inspection according to your designed procedures and wrong placement in their designated area may cause the issuance of defective material and eventually impact the final product. Such procedures include validation of control of components and drug products

containers and closures in 21 Code of Federal Regulations (21 CFR) **Part 211. 80 (b)** and 21 CFR part **211.80 (d)**. These non-compliances have been listed in **Appendix II: Facility Audit Serial Number 1; 3; 4; and 7 – 11.**

Corrective Action: There can be several corrective actions that can be taken to mend this situation, but I would like to suggest that you can employ another well-trained personnel along with the warehouse manager to verify each process that has been completed. This could help eliminate the mixing of received, released, rejected and the leftover raw materials for disposal. Additionally, this would help in organizing the warehouse more effectively for better material flow.

2. You failed to assure that the appropriate written procedures designed in **SOP GL022** titled '**BTEC Operations Room Cleaning**' to have cleaning procedures for all the Operations Labs in the facility were not followed. The team noted various deviation from these written procedures during their investigation. They found several dirt patches and spills across the facility. The presence of these patches must be justified as sanitation is one of the predominant aspects of Good Manufacturing Practices. All these dirt patches and oil spills may be the cause of contamination in the final product while compromising its integrity, purity, strength, and effectiveness. Apart from dirt, pollen was also detected, which can be a major allergen and a dominating factor of microbial infection among biologics. These factors prevent you to have a clean and aseptic manufacturing facility. Additionally, this also includes infrastructure conditions. While investigating the team found paint coming off the walls, stickers chipped off the walls and stains on walls, which assumingly contribute to rising in Particulate Matter (PM). Such procedures indirectly and directly violate 21 CFR part **211.56** and 21 CFR Part **211.67** for sanitation of facilities and the cleaning of equipment which is in direct contact of the materials being used respectively. These non – compliances have been listed in **Appendix II, Serial Number 16; 18; 35; 37 and 39.**

   Corrective Action: As a cGMP facility these are major flaws that must be avoided. Although all these cleaning and sanitation tasks are validated but not followed. I would recommend acting immediately by establishing stringent cleaning and sanitation procedures including regular checks for sanitation. Conducting internal audits routinely will also an option which will help to bolster workers' commitment to keeping the workspace clean and sanitized.

3. The facility failed to commit to the established written procedures to have every released item in the facility tagged and labeled. The team found tools and items in service without any identification or items with plucked labels. This can be extremely dangerous to the final product as many other products are also manufactured in the same facility and using instruments without labels may end up into mixing of the devices. This may cause product failure due to cross – contamination and huge monetary losses for the facility. So, it is very essential to keep a track of instruments used in the manufacturing of a specific product and dispose it safely. Such procedures violate 21 CFR Part **211.68.** These non-compliances are listed in **Appendix II: Serial Numbers 3; 4; 5; 6; 28; and 36.**

Corrective Action: You must act immediately as it is an imminent flaw in the facility. I would suggest performing an internal audit to locate such items with no label or identification. Dispose these items according to your standard operating procedures and employ new and labeled instruments and keep a track of their service life to dispose them timely.

4. During the facility and desk investigation process, the team found large deviations from the facility's established operating procedures designed in document **GL009** titled '**BTEC Documentation Practices**' to define how to document tasks in forms and task sheets. These procedures are made so that every document in the facility is standard and easy to understand even after the specified limit of the document archive time. Such practices violate 21 CFR Part **211.22** which recommends the facility to follow all the guidelines or procedures prepared by quality personnel. The non-compliances can be found in the attached **Appendix I** and **Appendix II, Serial Number 15; 20 – 24; 29; 30; 33 and 38.**

   Corrective Action: I would suggest retraining the employees to follow documentation practices and other procedure in the facility. Also, conduct internal audits timely to find non – compliances in the facility.

5. You failed to establish an appropriate written procedure to perform timely calibration of several essential metrological instruments. These instruments may have a direct impact on the final product. It is very crucial to have calibrated measuring instruments so that the components or raw materials for a product are weighed and mixed accurately. This will help in keeping the complex combination of the product in its pure and original form that was validated and approved for manufacturing. Such procedures include validation of automatic, mechanical and electronic

equipment in 21 CFR Part **211.68 (b)** and 21 CFR Part **211.160 (b)(4)**. These non – compliances are listed in **Appendix III**.

Corrective Action: I would suggest to setting up a panel of quality personnel to prepare standard operating procedures for the calibration of the measuring instruments. Try to perform calibration of the instruments immediately even before the committee is setup.

Part II: Appendix I

Desk Audit

This Appendix enlists the non-compliances found in the Batch Production Records. The Non-compliances are listed in the second column while not following the facilities standard operating procedures.

S.No	Non-Compliance	SOP and Step	21 CFR Part 211.xx
1	Batch Record **MR006 Step 2.1**: The Weigh Boat, Analytical Balance and the plastic container has no cleaning record available	Step 7.1.3 of SOP CS005	21 CFR Part 211.67(a)
2	Batch Record MR006 Step 2.1: The Weigh Boat and the plastic container were not labeled	Step 7.1.1 of SOP GL008	21 CFR Part 211.105(a)
3	Batch Record BR003 Step 2.1: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
4	Batch Record BR003 Step 2.2: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
5	Batch Record BR003 Step 3.20: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
6	Batch Record BR003 Step 3.30: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)

7	Batch Record BR003 Step 3.40: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
8	Batch Record BR003 Step 3.50: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
9	Batch Record BR008 Step 2.1: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
10	Batch Record BR008 Step 2.2: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
11	Batch Record BR008 Step 3.10: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
12	Batch Record BR008 Step 3.20: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
13	Batch Record BR008 Step 3.30: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
14	Batch Record BR008 Step 3.40: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
15	Batch Record BR008 Step 3.50: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
16	Batch Record BR008 Step 3.70: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
17	Batch Record BR008 Step 3.80: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)

18	Batch Record BR008 Step 3.90: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
19	Batch Record BR008 Data Sheet: Entry was filled using gel ink pen	Step 7.1.1 of SOP GL009	21 CFR Part 211.22(d)
20	Batch Record BR003 Step 2.2: Material ID for BL21 (DE3) (pAD1) GFP Working Cell Bank was not available	Step 7.1.1 of SOP GL008	21 CFR Part 211.105(a)
21	Batch Record SR018 Step 2.1: Correction made does not indicate reason, date and initials for it	Step 7.1.7 of SOP GL009	21 CFR Part 211.22(d)
22	Batch Record BR003 Step 2.2: The blank has been left incomplete without any data	Step 7.1.3 of SOP GL009	21 CFR Part 211.22(d)
23	The form FCS011: The date entered by the checker does not follow the format stated in SOP	Step 7.1.5 of SOP GL009	21 CFR Part 211.22(d)
24	The form FCS012: The date entered by the checker does not follow the format stated in SOP	Step 7.1.5 of SOP GL009	21 CFR Part 211.22(d)

Part III: Appendix II

Facility Audit

The Appendix enlists the non-compliances found during the Facility Audit

S.NO.	Description	Personnel	SOP Violated	21 CFR Part 211 References
1.	A box containing L-Shaped cell spreader was lying in the quarantine with a release sticker on it in the Warehouse (Room 023)	Eric	Step 7.2.5 of SOP GL-008	211.80(b)
2.	FIFO for material ID# L-023 has not been followed. Box with date 071817 was opened before the box dated 092515 in the Warehouse (Room 023)	Eric	Step 7.3.3 of SOP GL-008	211.86 (a)
3.	An unlabeled box was found in the quarantined area of the Warehouse (Room 023)	Eric	Step 7.2.2 of SOP GL-008	211.82 (b)
4.	An unlabeled box was lying over the cabinet with flammable materials in it (on the left side of the entrance.) of the Warehouse (Room 023)	Eric	Step 7.2.2 of SOP GL-008	211.80 (d)

5.	Material ID# E-022 Lot 011411 with a scratched released label in the Warehouse (Room 023)	Eric	Step 7.2.5 of SOP GL-008	211.80 (d)
6.	Chipped / distorted label on the (no rinse sanitizer container) lot #022310 (Lysol), shelf HO4 (Room 023)	Eric	Step 7.2.5 of SOP GL-008	211.80 b
7.	A released material box from VWR International found in the rejected area in the Warehouse (Room 023)	Eric	Step 7.2.5 of SOP GL-008	211.80 (d)
8.	A Quarantined box found in released area dated: - 010319 in the Warehouse (Room 023)	Eric	Step 7.2.3 of SOP GL-008	211.80 (d)
9.	A rejected material / box found in freezer (dated: - 110315) in the Warehouse (Room 023)	Eric	Step 7.2.6 of SOP GL-008	211.80 (b)
10.	Quarantine box was found in flammable area of the Warehouse (Room 023)	Eric	Step 7.2.3 of SOP GL-008	211.80(d)
11.	Unlabeled box on the flammable container in the Warehouse (Room 023)	Eric	Step 7.2.2 of SOP GL-008	211.80 d

12.	Quarantine item found in refrigerator RF 0230 in the Warehouse (Room 023)	Eric	Step 7.2.3 of SOP GL-008	211.80(d)
13.	The Warehouse Manager was not wearing appropriate PPE (no glasses)	Eric	Step 7.5.2.1 of SOP GL-002	211.28(a)
14.	Box required to be refrigerated located outside of refrigerator in the Warehouse (Room 023)	Eric	Step 7.3.7 of SOP GL-008	211.142 b
15.	Blank space in comments of form FGL-005, was not N/A, initialed and dated	Eric	Step 7.1.3 of GL-009	211.22 (d)
16.	Personal Items found in the refrigerator RF-030 (Room 023)	Eric	Step 5.1 of SOP GL022	211.28 b
17.	Incorrect entry Yankee Doodle of material ID R-089 in Form FGL-005, was neither crossed with single line nor explained, initialed and dated	Eric	Step 7.1.7 of GL-010	211.22 (d)
18.	Found personal items in the warehouse (Room 023)	Eric	Step 5.1 of SOP GL022	211.28 b
19.	Incorrect entry BEC 480, in Form FGL-005 was not explained, initialed and dated	Eric	Step 7.1.7 of GL-011	211.22 (d)

20.	Form FGL-005, Blank space in incorrect class No. BEC 480 was not N/A, initialed and dated (Room 023)	Eric	Step 7.1.3 of GL-009	211.22 (d)
21.	Form FGL-005, Date for material ID L-370 and class no. Yankee Doodle was not recorded calendar date format in the Warehouse (Room 023)	Eric	Step 7.1.5 of GL-009	211.22 (d)
22.	Form FGL-005, Date for material ID R-009 and class no. BEC 463 was not recorded calendar date format in the Warehouse (Room 023)	Eric	Step 7.1.5 of GL-009	211.22 (d)
23.	Form FGL-005, Date for material ID R-009 and class no. BEC 463 was not recorded calendar date format (Room 023)	Eric	Step 7.1.5 of GL-009	211.22 (d)
24.	Document UML-004 from compressed air log book was not up to date (No entries) (Room 013)	Jason	Step 7.1.9 of SOP GL-009	211.22 (d)
25.	Waste treatment tank, instruction sheet was not legible, extremely dirty (housekeeping) (Room 013)	Jason	Step 7.19.1 of SOP EN-001	Part 211.67. a
26.	Water storage tank not clean (Housekeeping) (Room 013)	Jason	Step 7.19.1 of SOP EN-001	Part 211.67. a
27.	All the sensors giving output on the Water purification control panel is out of calibration which was due March 2015 (Room 013)	Jason	Step 7.19.1 of SOP EN-001	211.68 a

28.	Unidentified probe in function near the deionization sensor gauges was not labeled and had no identification/calibration sticker on it (Room 013)	Jason	Step 7.19.1 of SOP EN-001	211.68 a
29.	Form FEN-001, Date for safety shower of was not recorded in calendar date format (Room 013)	Jason	Step 7.1.5 of GL-009	211.22 d
30.	Form FEN-001, Incorrect entry in initial and date was not explained, initialed and dated (Room 013)	Jason	Step 7.1.7 of GL-009	211.22 d
31.	Used gowns in the gowning area were left unattended (Room 137)	Krisstina Burgess	Step 7.4 of SOP GL-004	211.56 a
32.	No gloves in gown in area (Room 140)	Krisstina Burgess	Step 7.8.1.6.3 of SOP GL-002	211.28 b
33.	EHL 001 Dates were not in the correct format. (Room 143D)	Krisstina Burgess	Step 7.1.5 of SOP GL-009	211.22 d
34.	An HPW water container was in use even after being expired on 120518 (Room 142)	Krisstina Burgess	Step 7.19.1 of SOP EN-001	211.84 e

35.	Mop and bucket lying in the Airlock room between the production facility and hallway (Room 142)	Krisstina Burgess	Step 7.1.16 of SOP GL-022	211.56b
36.	A thermocouple probe in the facility with no ID# and out of calibration since 070909 (Room 142)	Krisstina Burgess	Step 7.1.1 of SOP GL008	211.68 a
37.	Door in the solution preparation hallway was not clean (Room 142)	Krisstina Burgess	Step 5.5 of SOP GL022	211.56 a
38.	FGL-030 entry date not verified for March 4th, 2019 (Room 160)	Suleiman	Step 7.1.10 of SOP GL-009	211.194 (a) (2)
39.	Oil spills were found on the window panes in Room 160	Suleiman	Step 5.5 of SOP GL022	211.56 (b)

Part IV: Appendix III

This Appendix enlists all those non - compliances found during inspection for which specific SOPs have not been established but are a matter of concern for the facility and require immediate action.

S. No	Description	Personnel	21 CFR 211 Ref.
1.	The temperature monitoring system had two electronic monitors with no physical system. And both were incoherent in Room 023	Eric	211.42 (c) (10) (iv)
2.	A weight balance was due to be calibrated on March 2013 (Room 023)	Eric	211.68 a
3.	Warehouse was not regulated (no electronic system to control temperature and humidity in the warehouse 023)	Eric	211.42. c.10.ii
4.	PHC-1633 probe had no log or calibration label in Room 159	Suleiman	211.68 a
5.	No calibration tag on pH probe in Room 163	Suleiman	211.68 a
6.	No clear calibration date on the CCAA30 and CCA100 air hoses in Room 163	Suleiman	211.68 a
7.	No calibration date on HPW hose in Room 163	Suleiman	211.68 a
8.	No calibration tag on vacuum pump in Room 163	Suleiman	211.68 a