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1.0 PURPOSE:

- 1.1 To describe a general procedure to ensure that HVAC Units serving the Clinical Manufacturing Facility (CMF) Cleanrooms at 128 Sidney Street Premises is appropriately operated and suitably maintained as per applicable recommendations.

2.0 SCOPE:

- 2.1 The HVAC for the Cell Culture 2 Room 111 is being controlled by a primary rooftop air handling unit (AHU) manufactured by Venmar, CES Inc. The Cleanroom HVAC (PRTU-1) System (Asset #1046) consists of 5 main groups of components. These include:
 - 2.1.1 One Air Handling Unit (AHU)
 - 2.1.2 One Electric Steam Humidifier (H-1)
 - 2.1.3 Two Exhaust Fans (PEF)
 - 2.1.4 Two Hot Water Reheat Coils (RHC)
 - 2.1.5 Fan Powered HEPA (FPH)
- 2.2 The HVAC for the Cell Culture 1 Room 107 is being controlled by a primary rooftop air handling units (AHU) manufactured by Venmar, CES Inc. The Cleanroom HVAC (PRTU-2) System (Asset #1063) consists of 3 main groups of components. These include:
 - 2.2.1 One Air Handling Unit (AHU)
 - 2.2.2 One Electric Steam Humidifier (H-2)
 - 2.2.3 One Hot Water Reheat Coil (RHC)

- 2.3 The HVAC for the Purification 1 Room 115 is being controlled by a primary rooftop air handling unit (AHU) manufactured by Venmar, CES Inc. The Cleanroom HVAC (PRTU-3) System (Asset #1061) consists of 5 main groups of components. These include:
 - 2.3.1 One Air Handling Unit (AHU)
 - 2.3.2 One Electric Steam Humidifier (H-3)
 - 2.3.3 One Hot Water Reheat Coil (RHC)
 - 2.3.4 Eight Fan Powered HEPA (FPH)
 - 2.3.5 One Exhaust Fan (PEF)
- 2.4 The HVAC for the Purification 2 Room 117 is being controlled by a primary rooftop air handling units (AHU) manufactured Venmar, CES Inc. The Cleanroom HVAC (PRTU-4) System (Asset #1062) consists of 4 main groups of components. These include
 - 2.4.1 One Air Handling Unit (AHU)
 - 2.4.2 One Electric Steam Humidifier (H-4)
 - 2.4.3 One Hot Water Reheat Coil (RHC)
 - 2.4.4 Four Fan Powered HEPA's (FPH)
- 2.5 The HVAC for critical area adjacent to CMF is being controlled by a primary rooftop air handling unit (AHU) manufactured by Trane. The Critical HVAC (RTU-4) System (Asset #1473) consists of 5 main groups of components. These include
 - 2.5.1 One Air Handling Unit (AHU)
 - 2.5.2 One Exhaust Fan (PEF)
 - 2.5.3 Seven Fan Powered Boxes (FP)
 - 2.5.4 Three Variable Air Volume Boxes (VAV)
 - 2.5.5 One Unit Heater (UH)

- 2.6 The HVAC for critical area adjacent to CMF is being controlled by an AC system manufactured by Trane. The Critical HVAC System (RTU-7, consisting of Asset #1474 and #1475) consists of 2 main groups of components. These include
 - 2.6.1 One Indoor Evaporator Unit
 - 2.6.2 One Outdoor Condenser Unit
- 2.7 The HVAC for critical area adjacent to CMF is being controlled by a primary air handling unit (AHU) manufactured by Sanyo. The Critical HVAC (AC-1) System (Asset #1476) consists of 2 main groups of components. These include
 - 2.7.1 One Air Handling Unit (AHU)
 - 2.7.2 One Condenser (Condenser)
- 2.8 The HVAC for critical area adjacent to CMF is being controlled by a primary air handling unit (AHU) manufactured by Sanyo. The Critical HVAC (AC-2) System (Asset #1478) consists of 2 main groups of components. These include
 - 2.8.1 One Air Handling Unit (AHU)
 - 2.8.2 One Condenser (Condenser)
- 2.9 This document will cover the following aspects for all the HVAC Units
 - 2.9.1 Operation
 - 2.9.2 Preventive Maintenance
 - 2.9.3 Calibration

3.0 REFERENCE:

- 3.1 Execution of this SOP assures compliance with the requirements of:
 - 3.1.1 21 CFR 211.46 Ventilation, air filtration, air heating and cooling
 - 3.1.2 21 CFR 211.67 Equipment cleaning and maintenance.
 - 3.1.3 21 CFR 211.105 Equipment Identification.
 - 3.1.4 21 CFR 211.160 General requirements, section (b)(4).
 - 3.1.5 ICH Q7 4.2
- 3.2 Installation Operation and Maintenance Manual by Trane on file with Engineering.
- 3.3 Installation, Operation and Maintenance Instructions by Venmar CES, Inc on file with Engineering.
- 3.4 09047-IOQ Installation and Operation Qualification for the Cleanroom HVAC System PRTU-1, Asset # 1046
- 3.5 09050-IOQ Installation and Operation Qualification for the Cleanroom HVAC System PRTU-2, Asset # 1063
- 3.6 09054-IOQ Installation and Operation Qualification for the Cleanroom HVAC System PRTU-3, Asset # 1061
- 3.7 09055-IOQ Installation and Operation Qualification for the Cleanroom HVAC System PRTU-4, Asset # 1062
- 3.8 FM107 Quarterly PM of Cleanroom HVAC System PRTU-1
- 3.9 FM108 Semi-Annual PM of Cleanroom HVAC System PRTU-1
- 3.10 FM109 Quarterly PM of Cleanroom HVAC System PRTU-2
- 3.11 FM110 Semi-Annual PM of Cleanroom HVAC System PRTU-2
- 3.12 FM112 Quarterly PM of Cleanroom HVAC System PRTU-3
- 3.13 FM113 Semi-Annual PM of Cleanroom HVAC System PRTU-3
- 3.14 FM114 Quarterly PM of Cleanroom HVAC System PRTU-4

- 3.15 FM115 Semi-Annual PM of Cleanroom HVAC System PRTU-4
- 3.16 FM161 Quarterly PM of Critical HVAC System RTU-4
- 3.17 FM162 Quarterly PM of Critical HVAC System RTU-7
- 3.18 FM163 Quarterly PM of Critical HVAC System AC-1
- 3.19 FM164 Quarterly PM of Critical HVAC System AC-2
- 3.20 FM168 Semi-Annual PM of Critical HVAC System RTU-4
- 3.21 FM169 Semi-Annual PM of Critical HVAC System RTU-7
- 3.22 FM170 Semi-Annual PM of Critical HVAC System AC-1
- 3.23 FM171 Semi-Annual PM of Critical HVAC System AC-2
- 3.24 QA011 Electronic Deviation Program

4.0 ATTACHMENTS:

- 4.1 N/A

5.0 DEFINITIONS:

Term	Definition
HVAC	Heating, Venting and Air Conditioning
PM	Preventive Maintenance <ul style="list-style-type: none">• PM-3: Quarterly Preventive Maintenance• PM-6: Semi-annual Preventive Maintenance

6.0 SAFETY:

- 6.1 Any operation or maintenance of the Air handling Units should be performed only by trained Acceleron personnel and/or outside HVAC technicians and extreme caution should be taken while doing so.
- 6.2 When servicing or repairing an electrical component of the HVAC systems, the potential exists for serious and even fatal injury. Use extreme care when working on live electrical circuits – lethal voltage potentials do exist.

- 6.3 Whenever possible, disconnect power by shutting off the main power switch before working on the unit. Advise all operation personnel of the shutoff, and lock the main distribution center supply switch if possible.

NOTE: It may be necessary to disconnect more than one power source. Before work begins, verify that ALL power to the unit has been disconnected.

7.0 RESPONSIBILITY:

Role	Responsibility
Acceleron Pharma Personnel	<ul style="list-style-type: none">• Appropriately trained Acceleron Pharma personnel or a qualified contractor are responsible for performing repair and preventive maintenance.
Engineering	<ul style="list-style-type: none">• Engineering is responsible for ensuring Differential Pressure Monitors associated with the HVAC systems are calibrated according to schedule• Engineering is responsible for filing completed maintenance and calibration forms associated with this document, in the appropriate Asset folders• Engineering is responsible for completing, reviewing and filing the maintenance forms associated with this document

8.0 EQUIPMENT AND SUPPLIES:

- 8.1 General Mechanics Tools
- 8.2 Heavy Duty Vacuum Cleaner
- 8.3 Ammeter
- 8.4 Digital Voltmeter
- 8.5 Replacement/Spare Parts such as Filters and Belts

9.0 PROCEDURE:

9.1 The following procedure should be followed for all the HVAC Systems:

9.1.1 Operation

9.1.1.1 The HVAC Systems are integral components of the production process. The system is shutdown only during the PM work by the outside vendor technician or appropriately trained Acceleron Pharma personnel. A shutdown performed for any other reason, should be documented with the appropriate reason only after, notifying Manufacturing, Facilities, QA, and the outside HVAC contractor.

9.1.1.1.1 Do not start up any system components without first determining the reason for the shut down and verifying that all issues have been addressed.

9.1.1.2 Refer to Installation, Operation and Maintenance Instructions by Venmar CES, Inc., Operation and Maintenance Manual by Trane, and the BMS Documentation on file with Engineering for any questions related to the operation and maintenance of the HVAC system.

9.1.2 Preventive Maintenance (PM)

9.1.2.1 Preventive Maintenance for the HVAC units and attached components is done primarily on two schedules. These schedules are based upon manufacturer and service vendor recommendations, also considering the intended usage rates. Historic PM and Unit performance data, has demonstrated acceptable performance with the schedule presented. If the performance of the unit is less than satisfactory, maintenance and schedules will be assessed for revision. At a minimum, a quarterly and semi-annual schedule should be maintained.

9.1.2.1.1 PM-3: A basic PM is performed quarterly.

9.1.2.1.2 PM-6: A complete PM is performed semi-annually.

- 9.1.2.2 The PM performed by Outside Vendor will be checked and verified for frequency and tasks as per the checklist provided in the Forms associated with this procedure.
- 9.1.2.3 The following steps should be followed by Facilities while reviewing the PM Worksheet submitted by the Vendor.
 - 9.1.2.3.1 Confirm the Asset Numbers, Model and Serial Numbers as specified on the form.
 - 9.1.2.3.2 Confirm the Maintenance Frequency as specified on the form.
 - 9.1.2.3.3 Check the maintenance history. Make sure that the scheduled frequency has been met and that there are no gaps.
 - 9.1.2.3.3.1 Confirm completion of specified tasks against checklist provided on the Form.
 - 9.1.2.3.4 Sign and date upon approval.
- 9.1.2.4 Completed Forms should be filed by Engineering in the individual Asset File.
- 9.1.2.5 Quarterly PM forms do not need to be filled out when the semi annual PM is due. The work done for the semi annual PM encompasses the quarterly PM work.

9.1.3 Calibration

- 9.1.3.1 Calibration is required for the following instruments associated with the Cleanroom HVAC System PRTU-1 Unit, PRTU-2 Unit, PRTU-3 Unit, PRTU-4 Unit:
 - 9.1.3.1.1 Differential Pressure Monitors: They are calibrated on a semi-annual schedule.
 - 9.1.3.1.2 Temperature and Relative Humidity Monitors: They are calibrated on a semi-annual schedule.

9.1.4 Cleanroom Certification and HEPA Filter Integrity Verification will occur on a semi-annual basis

9.1.4.1 Verification is required for air changes per hour, airborne particle count, room pressurization and velocity across filter, as specified in ISO 14644, and HEPA filter integrity as specified in IEST-RP-CC006.3 (Testing Cleanrooms) associated with the CMF Cleanroom area and the QC Sampling Room 253.

9.1.4.1.1 Air changes per hour, airborne particle count, room pressurization, and velocity across filter are trended and compared to previous tests. A trend in any of these that may indicate the HVAC system is operating sub-optimally will be investigated.

9.1.4.1.2 HEPA filter integrity will be reported as Pass/Fail as dictated by guidelines and vendor tests.

9.1.4.2 The Cleanroom certification and HEPA filter integrity reports done by the outside vendor will be reviewed by Engineering

9.1.4.2.1 Engineering will review the reports and ensure that all testing has been done as required and turn the completed reports into Engineering Document Control.

9.1.5 Temperature and Relative Humidity

9.1.5.1 Monitors for temperature and relative humidity are maintained on a calibration schedule to ensure that each PRTU is operating within engineering design specifications.

9.1.5.2 In order to maintain an ideal environment within each PRTU space, when the relative humidity level exceeds engineering design specifications the room temperature must be adjusted to ensure the environment remains within the design specification.

NOTE: Please refer to the Installation and Operation Qualification for each PRTU specifications.

9.1.5.3 Temperature and Relative Humidity Adjustment Procedure.

- 9.1.5.3.1 The desired limit for Relative Humidity (RH) within the Clinical Manufacturing Facility desired range of 10 and 65 percent RH. The RH set point for the humidifiers within the CMF will be 40%.
- 9.1.5.3.2 In the event of a RH excursion that lasts 24 hours or longer, Facilities / Engineering will adjust the temperature set point of the HVAC Unit that controls the room that is out of range.
- 9.1.5.3.2.1 If the RH exceeds 65% for 24 hours or longer, adjust temperature set point by adding 0.5° C. Continue to adjust set point by 0.5° C every 24 hours until relative humidity is within range. Do not adjust above 22.0° C.
- 9.1.5.3.2.2 If it becomes necessary to adjust temperature above 22.0° C, first inspect the components of the HVAC equipment to determine if all pieces are functioning as expected.
- 9.1.5.3.2.3 After RH is within range for 24 hours or greater, temperature may be adjusted by lowering set point.
- 9.1.5.3.3 Should the excursion continue to last 48 hours, Facilities / Engineering will provide a memo to Quality informing each department of the event. If necessary, an investigation will be initiated to explore other corrective measures.

Signature Manifest

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Final Approval

Name/Signature	Title	Date	Meaning/Reason
Jacob Miller (JMILLER)	Process Engineer II	02 Jul 2018, 04:23:46 PM	Approved

QA Final Approval

Name/Signature	Title	Date	Meaning/Reason
Martin Carvalho (MCARVALHO)	Associate Director of QA	05 Jul 2018, 04:48:51 PM	Approved

MFG Manager Final Approval

Name/Signature	Title	Date	Meaning/Reason
Jacob Miller (JMILLER)			
Mauricio Barraza (MBARRAZA)	Associate Director Tech Ops	28 Jun 2018, 05:16:49 PM	Approved