SOP Title:	**Policies for Operation, Cleaning, and Routine Maintenance of Controlled Temperature Equipment**
SOP Number:	**21533**
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1. PURPOSE

This procedure describes Biopharmaceutical Development Program (BDP) policies for operating and maintaining controlled-temperature equipment units.

2. SCOPE

This procedure applies to BDP personnel who are responsible for any part of the operation, cleaning, and/or routine maintenance of controlled-temperature units (CTUs). This Standard Operating Procedure (SOP) applies to free-standing and walk-in refrigerators, freezers, and controlled room temperature units. This SOP does not specify procedures for calibration or unplanned maintenance required on these units. Refer to **SOP 21508 Equipment Calibration Program** for those procedures. Refer to **SOP 19102 Routine Use and Disinfection of Biological Safety Cabinets, Incubators, Shakers, and Centrifuges** for operation and maintenance requirements for incubators.

3. RESPONSIBILITIES

3.1 Area Supervisor / BDP

- Trains personnel

3.2 Laboratory and Manufacturing Personnel

- Performs procedure

3.3 Biopharmaceutical Quality Assurance (BQA)

- Provides quality oversight

4. MATERIALS AND REAGENTS

Part Number	Description	BDP Approved Substitution Permitted?
10167	Dispatch	☐ YES ☒ NO
10168	Cavicide	☐ YES ☒ NO
30129	70% Isopropyl Alcohol (Decon-Ahol)	☐ YES ☒ NO

5. GENERAL POLICIES FOR CTUS

5.1 Usage guidance.

5.1.1 Use protective gloves to protect hands when handling ultra-low frozen materials.

5.1.2 Material stored in cold rooms should be kept at least 6" from the walls and floors, and 12" from the ceiling. Floor restriction does not apply to drums which are to be placed on drum dollies. In freezers and refrigerators, do not store GMP materials on the base (floor) of the unit. Only shelf racks should be used. This guidance helps to maintain proper storage temperatures.

5.2 Operating ranges and setpoints.

5.2.1 The BDP does not specifically have controlled room temperature chambers, but most GMP rooms maintain a temperature of 16 to 22°C.

5.2.2 BDP has controlled temperature equipment for the following temperatures.

Name	Temperature Range in °C
Refrigerator or Cold Room	2-8
Freezer	-10 to -30
Freezer	-20 to -40
Ultra Low Freezer	-70 to -90
Liquid Nitrogen (LN_2) Vapor Phase	≤ -130

5.2.3 For controlled temperature units (CTUs) considered part of a Good Manufacturing Practices (GMP) area or that stores GMP components or materials, the setpoints are established by the validation of that unit and stored as part of the validation protocol. Validated setpoint values are reflected in the calibration system for single point calibration of the unit and may be posted on the unit itself. Setpoint changes are managed through the engineering change system.

5.2.4 For CTUs not considered part of a GMP area and does not store GMP components or materials, the following setpoints are recommended:

- To maintain +2 to +8°C, use a setpoint of +4°C
- To maintain -10 to -30°C, use a setpoint of -20°C
- To maintain -90 to -70°C, use a setpoint of -80°C
- Performance of individual controlled-temperature storage equipment will vary and depends on variables such as load and external ambient temperature. Thus, setpoints should be adjusted if alarms occur routinely indicating temperatures out of range or adjusted as part of the validation or revalidation process.

Contact Quality Engineering about changing setpoints.

5.2.5 Operating ranges for incubators should not exceed +2°C from setpoint for GMP cell growth operations. Alternative ranges may be acceptable for specific operations as required by the process. If a tighter process tolerance is required, contact Quality Engineering.

5.2.6 Validation status including validated setpoint, the date validation was performed, and the frequency of revalidation is displayed on each validated unit with a label. Equipment should not be relocated or adjusted without consultation with Quality Engineering. An example label is shown.

Equipment Validation Status	
MEF # **91100**	Protocol # **PQ-154**
Setpoint: **-82°C**	LN2 levels if applicable: NA
Frequency/ Period: **3Yr**	Risk Level: **2**
Done Date: **06/26/2023**	Location: [redacted]

5.3 Alarm setpoints (Local and SCADA).

5.3.1 Low temperature alarm setpoints should be 1 to 2 degrees above the low limits of the acceptable temperature ranges. For example, if the acceptable temperature range is 2 to 8°C, an effective low alarm setpoint is 3°C. The Supervisory Control and Data Acquisition (SCADA) system also uses a LoLo alarm in addition to the Lo alarm. The LoLo should be the low point of the acceptable temperature range.

NOTE: It may not be possible to set the low temperature alarm above the lower limit of the range due to normal operation of the unit. In this case, the low temperature alarm setpoint must not be less than the lower limit of the range.

5.3.2 High temperature alarm setpoints should be 1 to 2 degrees below the high limits of the acceptable temperature ranges. For example, if the acceptable temperature range is 2 to 8°C, an effective high alarm setpoint is 7°C. **The SCADA system also uses a HiHi alarm in addition to the Hi alarm. The HiHi should be the high point of the acceptable temperature range.**

NOTE: It may not be possible to set the high temperature alarm below the upper limit of the range due to normal operation of the unit. In this case, the high temperature alarm setpoint must not exceed the upper limit of the range.

5.3.3 Probes controlling alarm response, both local and through SCADA, may be placed within a tube (typically a 15 or 50 mL centrifuge tube) containing air or liquid to dampen alarm response. Placing the probe in an air-filled tube should be the first option. If the delay is insufficient, a 50/50 mix of glycol and water may be used. The liquid volume should be minimized such that the delay only prevents the triggering of an alarm during typical opening durations needed for use. Excessive liquid volumes will mask critical alarms.

5.3.4 Alarm setpoints should consider the tightness of the control range of the unit and should not be set to alarm routinely. If alarms setpoints cannot fall within the guidance above without nuisance alarms, consult with Quality Engineering.

5.3.5 For CTUs considered GMP, alarm setpoints are established by the validation of that unit and stored as part of the validation protocol. Alarm setpoint changes shall be addressed by Quality Engineering and tracked in the CTU equipment and SCADA equipment logbooks as applicable.

5.3.6 For CTUs not part of a GMP area and not storing GMP components or materials, local alarm setpoints may be adjusted by the equipment owner. Record any adjustment to setpoints in the equipment logbook.

5.4 Temperature monitoring

5.4.1 The following table illustrates temperature monitoring requirements and suggestions for various applications of CTUs.

		Controlled-Temperature Unit Application		
		Final product storage	Part of GMP area or storage of GMP components/materials	Not part of a GMP area and does not store GMP components/materials
Temperature Monitoring Method/Device	Local alarm or external temperature controller/alarm	R	R	S
	Alarm connection to Building Alarm System (SCADA)	R	R Any exceptions evaluated on a case-by-case basis	S

5.4.2 Temperatures for GMP units are monitored using SCADA.

5.4.3 Any unit not connected to SCADA used for GMP requires a daily check while the unit contains material.

The daily check relies on using the calibrated digital display on the unit at least daily when the equipment is in operation, excluding weekends, holidays, and facility closures. This information is recorded in the equipment logbook.

5.4.4 SCADA failure or otherwise offline

5.4.4.1 If failure does not impact data/archival capture, just monitor local equipment for the presence of alarm conditions until resolved.

5.4.4.2 If failure is isolated to a single/limited number of points, monitor temperature using daily check method in equipment log until resolved. Consider more frequent monitoring based on the unit's contents or transfer contents to another unit. An external monitoring device may be used.

5.4.4.3 If failure is widespread, a separate document may be used to monitor temperature of all active GMP equipment using a daily check method. This form should be attached to the EE/change control for the SCADA failure event. Consider more frequent monitoring based on risk/value of contents. External monitoring devices may be used, especially for critical units.

5.5 Safety

- Do not store dry ice or packages which contain dry ice as the refrigerant in walk in controlled-temperature equipment. This presents an oxygen depletion risk.

6. ROUTINE MAINTENANCE FOR CONTROLLED-TEMPERATURE EQUIPMENT

6.1 The following routine maintenance items should be performed by the equipment owner or designee as a part of routine use for most CTUs.

6.1.1 Check alarm back-up battery by looking for corresponding alarm or indicator.

6.1.2 Check the door gasket for leaks as indicated by ice buildup at the leak for freezers. Check the gasket for cuts, cracks, separation of gasket from the door or unit frame, and holes. If the gasket is damaged, place a trouble call.

6.1.3 Check the inside of the freezer for frost buildup.

6.1.3.1 If the frost buildup is one inch thick or greater, defrosting is required. Failure to perform a timely defrost will place additional load on compressor(s) and negatively impact temperature stability.

6.1.3.2 Relocate the contents. The freezer must have the same range and validation status and alarm connections of equal or better. Record the relocation in each equipment logbook.

6.1.3.3 Defrost per manufacturer's recommendations. -80°C defrosting should be at least 48 hours to ensure not only the chamber, but the refrigeration system is defrosted. Once defrosted, wipe down the inside with an approved disinfectant listed in Section 4.1. After wipe down, allow to dry, and then restore power to the unit.

6.1.3.4 Allow the freezer to return to proper operational range before returning contents.

6.1.3.5 Record activities in the equipment log.

6.1.3.6 Note that no change to Freezerworks software inventory is required provided that the move is temporary while a unit is being defrosted, repaired, or validated, the move is captured in the equipment log, and items are returned to the original shelf location. The equipment log shall list the new temporary location and freezer MEF number, the dates, and times of transfer to and from (returning contents to original freezer), and a statement that the entire contents had been transferred (and any exceptions).

6.1.4 Check for unusual noise or vibration.

6.1.5 Check the air filter. If the filter is dirty, clean or replace the filter or place a trouble call.

6.1.6 The listed checks, themselves, do not require documentation in the logbook. The fact that there was a routine maintenance check of the equipment and the actions taken as a result of the checks should be recorded in the equipment log.

6.2 Cold Rooms will be maintained by FME following an established Preventative Maintenance schedule managed by the Maximo program.

7. CLEANING OF CONTROLLED-TEMPERATURE EQUIPMENT

7.1 For routine cleaning, wipe down the interior and exterior of the CTU with an approved disinfectant listed in Section 4.1, as necessary.

7.2 In the event of a biological spill inside or on the exterior of one of the units, follow **SOP 17109 Procedures for Safe Handling, Decontamination, and Spill Cleanup of Infectious or Potentially Infectious Materials** or **SOP 26106 Spill Control and Clean-up in the BDP Production Areas of the ATRF** to disinfect and clean the spill.

8. DOCUMENTATION AND RECORDS

8.1 Document routine monitoring, maintenance, and cleaning of CTUs on **Form 21533-01** in the equipment logbook.

8.2 **Form 21533-01** will be populated with the logbook ID, the MEF number of the equipment, the equipment name or 'Description', and the page numbers. The fields for 'Range' (should match those established in Section 5.2 or a range approved by BQA), 'Building', and 'Room' may be customized at the time of request so that these fields are hard coded in the issued logbook.

8.3 Routine usage, the placement and withdrawal of materials, does not require a logbook entry in most cases. An entry should be made under the following conditions:

8.3.1 Placement or removal of high value materials or intermediate or final product.

8.3.2 When routine usage such as placing a large thermal mass results in a system or SCADA alarm. The log entry can then be used to determine the reason for related SCADA alarms.

8.4 Facilities, Maintenance, and Engineering (FME) personnel will document maintenance or calibration performed in the equipment logbook for all GMP equipment and non-GMP equipment where a log was issued.

8.5 See **SOP 21531 Equipment Logs**, for instructions on keeping equipment logbooks.

9. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
17109	Procedures for Safe Handling, Decontamination, and Spill Cleanup of Infectious or Potentially Infectious Materials
19102	Routine Use and Disinfection of Biological Safety Cabinets, Incubators, Shakers, and Centrifuges
21508	Equipment Calibration Program
21531	Equipment Logs
21533-01	Controlled-Temperature Equipment Logbook Template
26106	Spill Control and Clean-up in the BDP Production Areas of the ATRF