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1.0 Purpose

This SOP describes the procedure for managing and relaying the status of the manufacturing areas and the utilities that support them. This SOP may also be used to handle the status of an individual piece of equipment.

2.0 Scope

This SOP applies to process and production areas that support CGMP activities for the BDP and utility systems (and their points of use).

Area status placarding requirements do not apply to Process Analytics\Quality Control or Development areas.

3.0 Authority and Responsibility

3.1 The Director, Biopharmaceutical Quality Assurance (BQA), Biopharmaceutical Development Program (BDP) has the authority to define this procedure.

3.2 BDP Personnel are responsible for:

3.2.1 Relaying the production scheduling needs for areas and utilities.

3.2.2 Adhering to Status Placarding and Area Status Update communications.

3.2.3 Adjusting active EM monitoring locations and frequencies according to the present status.

3.3 BDP QA is responsible for:

3.3.1 Requesting as needed an updated area status as part of pre-production clearance by BQA per ***SOP 21104, Pre-Production Clearance*.**

3.4 The BQA Quality Engineering and Validation Manager is responsible for:

3.4.1 Updating the Area Status whenever dictated by needs, utility changes, or updated monitoring data.

3.4.2 Specifying gowning, cleaning, and monitoring requirements that currently applies.

4.0 Status Designations and Placarding

4.1 Status designation and placarding through the Area Status Update (Attachment 1) serve to summarize the status of production areas by functional zones and utilities.

4.2 Processing areas and utility systems that support CGMP activities for the BDP are maintained in a service status commensurate with processing needs. The facility is divided into general and dedicated processing regions.

4.3 General Areas

4.3.1 The general areas are managed as In-Service and active unless otherwise noted.

4.3.2 These areas include all main corridors on [redacted], clean staging [redacted], cold room [redacted] and [redacted], Buffer Prep [redacted], Inspection and labelling areas [redacted] and [redacted], and ISO 8 storage areas [redacted] and [redacted].

4.3.3 During the default active state Gowning, Cleaning, and Routine EM per ***SOP 22315, Environmental Monitoring in BDP GMP Areas at the ATRF*** are performed.

4.3.4 The status will be noted and color-coded for easy assessment on the Area Status Update.

4.4 Dedicated process areas or Suites

4.4.1 Dedicated process areas may switch between an active and inactive state as dictated by production needs.

4.4.2 Active suites must have full Gowning, Cleaning, and Routine EM per governing SOPs performed.

4.4.3 For a suite to be considered inactive any required cleanings following processing to clear the area from potential product contamination must first be performed.

4.4.4 Inactive suites do not undergo routine EM.

4.4.5 Inactive suites may reduce the gowning requirements to ISO 8, the same level as the adjacent corridors. Gowning requirements may not be removed altogether for any area that is not fully segregated; this specifically applies to the main processing area on A2.

4.4.6 Routine cleaning shall be performed in an inactive state. Requirements for the cleaning of the ceilings or walls are not enforced while in an inactive state.

4.4.7 A suite may also be listed as Limited Use or Out of Service. These status levels are distinct from inactive as there are other conditions preventing or inhibiting

the area from achieving an active state. The Virus Production Facility, [redacted] Suite, B3 Suites, PA\QC sampling lab A1306 or the first floor B1 weigh out and storage areas may be Out of Service without impacting the use of the main processing area of A2. Cleaning and gowning requirements will be specified when in a Limited Use or Out of Service state.

4.5 Utilities

4.5.1 For utilities, the default mode is to keep the utility systems themselves in an In-Service state. However, POU (Points of Use) for some systems may be in an active or inactive state or affected by an Engineering Event.

4.5.2 Utilities that are tracked for status are: Clean Steam, Compressed Gases, DPRO, Pure Steam, and WFI. Compressed gases include CA (Compressed Air), PA (Pharmaceutical Air), N2 (Nitrogen both liquid and gas), O2 (Oxygen), and CO2 (Carbon Dioxide). They may be listed collectively unless a distinction between services must be made.

4.5.3 HVAC is not directly tracked as a utility for the purpose of this SOP. HVAC is tracked under processing areas through the EM results. Issues with any HVAC system will be addressed via an EE per ***SOP 21526, Engineering Event Management and Status Placarding*** and noted on the Area Status Update.

4.5.4 Active utilities and POU are acceptable for use when the systems are running as intended, routinely sampled per EM procedures ***SOP 22314, Monitoring of BDP GMP Compressed Gases*** and ***SOP 22316, Water Monitoring in BDP GMP Areas at the ATRF***, and the sampling results are within specifications.

4.5.5 The status will be noted and color-coded on the Area Status Update.

4.6 Generation and Review of Monitoring Data

4.6.1 Data is generated from the EM database which is accessed through the BDP App.

4.6.2 Export the data selecting the required date range.

4.6.3 Sort data and flag any failure, action, or alert results. Elevated or non-conforming results may impact use status.

4.6.4 Look for trends in the data, which could include: changes in performance of area or system, a pattern of elevated results, high activity in a given area, and be indicative of a larger problem rather than an isolated event.

4.6.4.1 Utilize the Trending Report function in the BDP App to generate graphs to assist in determination of a trend. Select a date range sufficient to see the required data.

4.6.4.2 Periodic trending of data, attached as part of the Area Status Update, is a useful tool to monitor steam, water, and functional area performance in between the annual certification. Any trends identified during this exercise should be noted and resolved as needed. There is no specified interval for this trending, but it is recommended to be generated several times per year.

4.6.4.3 Note that any results that require an EM investigation per ***SOP 22313, Environmental and Utility Monitoring – Excursions Event Initiation and Investigation*** may already have associated trending completed.

4.6.5 Any results that indicate loss of control of an area or a negative trend requires justification for a “Green” “Released” designation.

4.7 Status Designations and Associated Color Code

4.7.1 Released (Color Code Green)

This designation denotes that the utility or area is available to support GMP activities and that on-going requirements for use continue to be met.

4.7.2 Inactive (Color Code Yellow)

This designation denotes that the utility or area is functionally available to support GMP activities but that some aspect, typically EM or gowning, is not at the level required for Release of the Area for In-Service/Active status.

4.7.3 Limited Use (Color Code Yellow)

This designation denotes that the equipment, utility, building, or area is functional but that the system or unit is operating at less than validated or qualified operation. Examples include:

- Reducing environmental monitoring in an area.
- Putting a use point out-of-service in a system where the validated state includes the use point.
- Allowing reduced use of a utility that is not fully released. A specific example would be the making of R&D buffers with WFI without sufficient data following return to service.

Note: Some Limited Use conditions may be suitable to support GMP activities. Placards documenting a Limited Use designation will specify the condition causing the limited use and include associated use limitations and restrictions. Use of an area for GMP activity requires a preproduction clearance by Quality Assurance per ***SOP 21104*, *Pre-Production Clearance***.

4.7.3.1 Limited Use designations will be specifically called out on the Area Status Update.

4.7.4 Out-of-Service/Shutdown (Color Code Red)

This designation denotes that the equipment, utility, or area is not functional. This status can result from a failure, but can also result from changes, upgrades, preventive maintenance, or planned shutdowns. Depending on the event, most requirements for use (for example, gowning or cleaning) may be significantly reduced or eliminated during periods of Shutdown.

4.7.5 Return-to-Service (Color Code Yellow)

This designation denotes that the equipment, utility, or area is undergoing activities to return it to an “In-Service” or “Inactive” status. For example, these activities may include enabling the utility (if it was disabled), cleaning activities, re-establishment of gowning requirements, and monitoring activities to confirm environmental control.

4.7.6 Conditionally Released (Color Coded Green with term “Conditionally Released” and potentially other detail added.)

This designation may be used during the Return-to-Service period and denotes that the equipment, utility, building, or area has demonstrated compliance with preliminary Return-to-Service monitoring requirements and has been conditionally authorized by BQA Engineering for use. The decision to allow a conditional release is dependent on the criticality of the event that caused the condition, BDP experience with the equipment, utility, building, or area in similar situations, and the nature of the activities that will immediately follow the conditional return to service.

Note: In addition, use of an area for GMP activity requires a preproduction clearance by BQA per ***SOP 21104*, *Pre-Production Clearance***.

4.8 Communication of Area Status

4.8.1 Frequency

4.8.1.1 There is no set frequency for updating the area status. However, the status should be updated based on the following guidelines. An update should be made based upon availability of updated monitoring data, utility status changes, or processing needs.

4.8.1.2 An update should be issued as soon as knowledge of an adverse condition, which places an area or utility out of service or limits its use.

4.8.2 Email

4.8.2.1 The update will be sent via email to relevant persons within the BDP. At a minimum distribution will include staff involved in production, QA, environmental monitoring, and the facility.

4.8.3 Placarding

4.8.3.1 A copy of the current Area Status Update should be posted by production staff at the entrance to the VPF ([redacted]) and the Production Facility ([redacted]).

4.8.3.2 Copies may also be posted at other locations as needed.

4.8.3.3 Present and previous copies of the Area Status Update may be retrieved from **H:\6QA\Area Status Update** where a folder for each year may be found and each update has the date of issue in the file name.

4.8.3.4 Active GMP production areas will be posted with Form 21104-02, BQA Pre-Production Clearance Qualification Checklist and Approval.

4.8.4 Equipment/Utility Use Point Placards

4.8.4.1 Equipment that is found to be out of calibration and cannot be brought into calibration must be placarded or tagged to prevent inadvertent use. Refer to ***SOP 21508, Equipment Calibration Program*** Form 21508-03.

4.8.4.2 Equipment or utility use points that are out-of-service, but still operational, must be placarded or tagged to prevent inadvertent use. At a minimum, tags/ placards need to include the date the unit or use point went out of service, who is tagging the unit or use point out of service, and the event (EE) tracking number if applicable.

4.8.4.3 The following tag/placard is recommended.

(Side 1)

(Side 2)

5.0 References and Related Documents

SOP 21104	*Pre-Production Clearance*
SOP 21508	*Equipment Calibration Program*
SOP 21526	*Engineering Event Management*
SOP 22313	*Environmental and Utility Monitoring – Excursions Event Initiation and Investigation*
SOP 22314	*Monitoring of BDP GMP Compressed Gases*
SOP 22315	*Environmental Monitoring in BDP GMP Areas at the ATRF*
SOP 22316	*Water Monitoring in BDP GMP Areas at the ATRF*

6.0 Attachments

6.1 **Attachment 1** Sample Area Status Placard

7.0

[redacted]

Attachment 1
Sample Area Status Placard

Area Status Update for ATRF (Date Issued) per SOP 21554

GOWNING REQUIRED AS NOTED

Routine cleaning is in effect.

(Special notation or considerations such as EE's, status changes, etc. communicated here)

Filling Area and Component Prep (Rooms [redacted]

[redacted] Fill Area released for use based on EM data through MM/DD/YY.

Component Prep released for use based on EM data through MM/DD/YY.

Gowning: Effective (gowning qualification required for fill area) ..... EM: Active

General Areas/Corridors and Buffer Prep ([redacted]

[redacted]

Areas released for use based on EM data through MM/DD/YY.

Gowning: Effective ..... EM: Active

Upstream Areas

Cell Culture Area acceptable for validation and non-GMP work.

Gowning: Effective (ISO 8 all areas) ..... EM: Inactive

Fermentation Area conditionally released for use.

Gowning: Effective (ISO 8 all areas [redacted] not needed) ..... EM: Active

Purification Areas

Acceptable for validation and non-GMP work.

[redacted] Gowning: *(ISO 8 gowning permitted all areas with coveralls added during active processing)* ..... EM: Inactive

VPF

Area is out of service. Gowning and cleaning requirements removed until RTS initiated. Adhere to signage posted at the door for updates.

Gowning: Suspended ..... EM: Inactive .....

First Floor Weighout and Support

Released for use based on monthly EM data through MM/DD/YY.

Gowning: Effective for [redacted] only. ..... EM: Active for B1305/B1306 only

PA Sampling Lab (A1305, A1306, A1307)

Area is in standby for a backup to [redacted] Cleaning and Sampling needed prior to use.

Gowning: Suspended ..... EM: Inactive ..... Cleaning: inactive

B2310 Cell Therapy

Acceptable for validation and non-GMP work.

Gowning: Reduced to shoe covers only ..... EM: Inactive

Utilities: Compressed Gases (CA, PA, O2, CO2, N2) ..... EM: Active

Released for use based on recent CO2, N2 and PA testing through MM/DD/YY.

Utilities: Water and Steam (PS, CS, DPRO, WFI)

CS released based on EM data through MM/DD/YY.

PS released based on EM data through MM/DD/YY.

WFI is in a limited use state based on EM data through MM/DD/YY. WFI POU AXXX-X is currently in a limited use state and should not be used for GMP activities. All other points acceptable for GMP use.

DPRO is released based on EM data through MM/DD/YY.

Lab Water Systems ([redacted]) Acceptable per monthly EM through MM/DD/YY.

..... EM: Active.

Update completed and authorized by (name of staff, can be different for completed and authorized)