BIOPHARMACEUTICAL DEVELOPMENT PROGRAM (BDP)

ADVANCED TECHNOLOGY RESEARCH FACILITY (ATRF)

FACILITY VALIDATION MASTER PLAN

Leidos Biomedical – Government Contractor
Frederick National Laboratory for Cancer Research,
Frederick, MD 21701

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APA	Aseptic Processing Area	**MEF**	Master Equipment Files
ATRF	Advanced Technology Research Facility	**MMIC**	Materials Management and Inventory Control
BAS	Building Automation System	**MPR**	Master Production Record
BDP	Biopharmaceutical Development Program	**NCI**	National Cancer Institute
BPA	Biopharmaceutical Process Analytics	**NIH**	National Institutes of Health
BQA	Biopharmaceutical Quality Assurance	**NIST**	National Institute for Standards and Technology
BSC	Biological Safety Cabinet	**OOT**	Out-of-Tolerance
BSL	BioSafety Level	**OQ**	Operation Qualification
cGMP/CGMP	Current Good Manufacturing Practice	**PAO**	Poly-Alpha-Olefin
CS	Clean Steam	**PC**	Personal Computer
DDC	Direct Digital Control	**P&ID**	Piping and Instrumentation Diagram
DPRO	Double-Pass Reverse Osmosis	**PLC**	Programmable Logic Controller
DQ	Design Qualification	**PQ**	Performance Qualification
EHS	Environment, Health, and Safety	**PS**	Pure Steam
EM	Environmental Monitoring	**PV**	Process Validation
FAT	Factory Acceptance Test	**R&D**	Research and Development
FDA	Food and Drug Administration	**RO**	Reverse Osmosis
FME	Facilities Maintenance and Engineering	**RTS**	Return-to-Service
FMEA	Failure Modes and Effects Analysis	**SCADA**	Supervisory Control and Data Acquisition
FMECA	Failure Modes, Effects, and Criticality Analysis	**SF**	Square Feet
FTA	Fault Tree Analysis	**SIP**	Sterilize-in-Place or Steam-in-Place
GMP	Good Manufacturing Practice	**SOP**	Standard Operating Procedure
HAACP	Hazard Analysis and Critical Control Points	**SS**	Stainless Steel
HEPA	High Efficiency Particulate Air	**TOC**	Total Organic Carbon
HPLC	High Performance Liquid Chromatography	**USP**	United States Pharmacopoeia
HVAC	Heating, Ventilation, and Air Conditioning	**UV**	Ultra-violet
ICH	International Conference on Harmonization	**VHP**	Vaporized Hydrogen Peroxide
I/OQ	Installation and Operation Qualification	**VMP**	Validation Master Plan
IQ	Installation Qualification	**VPF**	Virus Production Facility
ISO	International Organization for Standardization	**WFI**	Water for Injection

1.0 INTRODUCTION

The Biopharmaceutical Development Program (BDP) Clinical Manufacturing Site is located at Frederick National Laboratory for Cancer Research (FNLCR), in Riverside Research Park, in Frederick, Maryland. [redacted]. The facility was occupied in mid-2012. The BDP is a multi-product facility for the production of biopharmaceutical products for pre-clinical testing and Phase I/II clinical trials. These products consist of monoclonal antibodies, recombinant proteins, viral vaccines, gene vectors, whole cells, cell therapies, and other protein and nucleic acid-based products. Products are prepared in conformance with the FDA regulations and guidelines for current Good Manufacturing Practice, 21 CFR Parts 210 and 211, Human Cells, Tissues, and Cellular and Tissue-Based Products, 21 CFR 1271, and Biological Products Requirements, 21 CFR Parts 600.1 and 610, as applied to the manufacture of biologics for clinical Phase I, and II use. Products may be produced, purified, vialed or otherwise final packaged, and labeled by the BDP in part or in whole as external contractors may be utilized. The facility is sited in the northeast portion of the research park (See **Appendix 13.1** – BDP Site Plan).

The objective of this Validation Master Plan (VMP) is to define the rationale and requirements for validation of the facility, equipment, and processes according to FDA regulations and guidelines, and current industry trends and standards.

The BDP uses a risk-based approach to validation. Prioritizing efforts based on risk assessment allows BDP resources to be directed to the most critical issues. Utilities, equipment, and processes are categorized into different levels of criticality based on their product quality, personnel safety, and financial impact. This Master Plan describes the risk analysis approach used by the BDP to prioritize and focus validation efforts in critical areas (such as fill/finish), and provides brief descriptions of the production areas, process equipment, and processes to be validated. More detailed descriptions of these can be found in BDP's Drug Master File[1].

2.0 DOCUMENT SCOPE

The Validation Master Plan is a "living" document subject to updates as new equipment is acquired, new facilities are commissioned, new technologies become available for monitoring utilities and processes, and regulations and guidelines are added or changed. This document includes the rationale for validation using a risk-based approach, as detailed in such documents as "Pharmaceutical cGMP's for the 21st Century - A Risk-Based Approach", ICH Q9 "Quality Risk Management", and "Guidance for Industry: Development and Use of Risk Minimization Action Plans"[2-4]. This facility Validation Master Plan describes the BDP's approach to facility, equipment, and process validation. It also identifies the systems and equipment critical to the manufacturing areas and specifies required components of Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), and Process Validation (PV) studies.

Investigational use of biopharmaceuticals requires relatively little material when compared with the demands of commercial products. Typically, Phase I/II BDP projects consist of a small number of production runs. In addition, the manufacturing processes are often optimized throughout the product lifecycle in the clinic; thus, the processes in place at the BDP may be further modified if the product lifecycle continues to Phase III. Cleaning

Validation, Analytical Method Validation, and Computer and Software Validation are addressed in separate Validation Master Plans. Non-validated quantitative equipment (i.e., pH meters, conductivity meters, gauges, etc.) is included in the Calibration Program (discussed in Section 10.0) and is not addressed in this Master Plan. The roles and responsibilities of the critical functional groups are listed to ensure the successful implementation of the Validation Master Plan. In addition, discussions of the necessary supporting programs such as calibration, preventive maintenance, change control, environmental monitoring, and training are included in this VMP.

3.0 FACILITY OVERVIEW

3.1 General Facility Description

The ATRF facility is three stories tall (not including mechanical penthouses) and includes approximately 335,000 square feet (SF). The ATRF is designed to meet applicable building codes and ordinances, and closely follows National Institutes of Health (NIH) Guidelines for Biomedical Research Facilities. The ATRF is intended to be a collaborative research and development facility focused on discovering and developing remedies for cancers. It is made up of four separate building wings or blocks including a central circulation spine. The blocks include:

(1) An administrative block that includes offices, conferencing, data center, food service, main building security and employee resource areas. BDP Management, Business Operations, Quality Assurance, and Regulatory Affairs offices are housed within the administrative block (Building E).

(2) Two research laboratory blocks (Buildings C and D) that house Advanced Technology Program laboratories and NCI Center for Cancer Research laboratories that focus on research that is intended to lead to cancer treatments and a better understanding of cancer biology. (These areas have no BDP affiliation.)

(3) A BDP block (Building A/B) that houses BDP laboratories, GMP manufacturing space, non-BDP laboratories, shared building services, and loading dock facilities.

The BDP facilities in Building A/B include:

- the BDP Early Process Sciences laboratories (Area B, Third Floor) that focus on supporting the cGMP manufacturing facility by performing process development and scale up studies,
- the BDP Process Analytics laboratories (Area B, Second Floor) that focus on providing analytical support and testing for work done in the development laboratories and from the GMP manufacturing facility,
- the BDP cGMP Manufacturing Facility (Area A, Second Floor) where material is generated, purified, and filled as needed from processes developed from various internal and external sources. Material supports studies including Phase I and II and occasionally Phase III clinical trials,
- the BDP GMP Cell Therapy Manufacturing and Support (Area B, Second and Third Floor) that focus on emergent therapies and can include the production of virus and plasmids.
- the BDP Manufacturing Support areas (Area A/B, First Floor), which include the central utility plant, cGMP warehouse, QC sampling lab, freezer farm, cold rooms, dispensary and validation lab.

3.2 CGMP Manufacturing Building Overview

The BDP manufacturing building is used to produce multiple products for pre-clinical testing and Phase I and II clinical trials. Occasionally, non-pivotal Phase III production is performed. Production areas within the facility are primarily segregated by product type, as discussed below. Classified rooms within the CGMP manufacturing areas are temperature and humidity controlled to protect the safety, quality, and purity of the product, and for operator comfort. Room classifications are correlated with the most current ISO standards, i.e., Class 100 areas meet ISO 5 specifications, Class 10,000 areas meet ISO 7 specifications, and Class 100,000 areas meet ISO 8 specifications. Active classified areas are routinely monitored for temperature, humidity, and viable and non-viable particulates to ensure compliance to air cleanliness standards and to identify trends. Detailed descriptions of the building and its environmental classifications, as well as personnel, raw material, product, component, and waste flows, can be found in BDP's Drug Master File or DMF[1].

Utility systems that support manufacturing operations include HVAC, Compressed Air, DPRO water, WFI, Clean Steam, and Pure Steam. The facility uses liquefied sources for compressed gas distribution systems (CO_2, N_2, and O_2) with final point-of-use filtration where needed. LN_2 is also distributed to select locations. Additional utility support in major manufacturing areas includes a Building Automation System (BAS), SCADA System, Uninterruptible Power Supply (UPS), Emergency Power (generator), a dedicated liquid waste decontamination system (LWDS), and a pH neutralization system. Detailed descriptions of the manufacturing support utilities can be found in BDP's Drug Master File[1].

Refer to the most recent DMF for a description of functional areas and major equipment in each area.

4.0 PROCESS DESCRIPTIONS

BDP products are produced using a variety of scientific techniques and manufacturing processes. Bacterial fermentation, cell culture, and viral vector methods are used. The facility contains the necessary equipment within the Aseptic Processing Area to vial sterile products for human administration under CGMP conditions. BDP process capabilities include bioreactor and fermentor production, virus production, cell therapy production and dosing, separation, purification, chemical modification/ conjugation, formulation, aseptic filling, and packaging/labeling.

4.1 Mammalian Cell Culture Production and Purification

Both monoclonal antibodies and viruses are produced using mammalian cells. Cells are cultured at small scale, adapted to serum- or protein-free medium, re-cloned, and subsequently scaled up to create cell banks. A vial of master or working cell bank is obtained from controlled storage. A small-scale seed culture is initiated in single use culturing containers. . The seed culture serves as inoculum for single use or SIP bioreactors scaled as required. After the production cycle is completed, the recovery and initial purification steps are performed using processes such as filtration,

centrifugation, and chromatography. Downstream purification steps and filling/labeling of the final drug product take place in downstream production suites.

4.2 Microbial Fermentation Production and Purification

Both natural products and recombinant proteins are derived from bacterial expression systems (either natural or engineered). A vial of master or working cell bank is obtained from controlled storage. A small-scale seed culture is initiated, usually in shake flasks. The seed culture serves as an inoculum to a fermentor. Subsequently, further transfer may occur to larger-scale production vessels. Harvested broth from a fermentor may be processed in the Fermentation Manufacturing Area or transferred to the Bacterial Purification Area rooms. Intermediate purified bulk product is transported, sealed and over-packaged. Final purification steps and filling/labeling of the final drug product take place in downstream production suites.

4.3 Virus Production and Purification

CGMP virus production occurs in the VPF suite. Production typically begins with establishment and characterization of master virus banks. Incoming virus preparations are re-derived and/or clonally isolated, then propagated at small scale, and subsequently scaled up to create virus banks. Material from the virus bank is used to propagate sufficient infected cell biomass, using disposable technology such as roller bottles, cell factories, or rocker platform or stirred tank bioreactors. The infected cell biomass is harvested, and the product of interest is subsequently purified and concentrated. Further processing and purification steps, filling and labeling of the final drug product take place in the VPF suite.

4.4 Cell Therapy Production and Dosing

Cell therapy production and dosing operations are carried out in one of several cell therapy suites or within the VPF on a campaign basis. Patient derived samples are processed to reduce the concentration of non-target cells and the target cells are transduced and cultivated until the desired cell concentration is reached. Production platforms utilize closed systems and aseptic processing steps. Final product is dosed to needed concentrations, formulated with cryopreservative, filled in bags, and frozen.

4.5 Semi-Automatic Filling Operation

Semi-automatic filling operations are carried out in the filling suite. Materials required for the fill are steam-sterilized or depyrogenated as appropriate or may be purchased sterile; materials pass through the autoclave and depyrogenation oven from the component prep area into the Aseptic Processing Area. All other materials are surface-decontaminated and transported to the Aseptic Processing Area. Change parts are then installed in the filling machine, and the stoppers and seals are loaded into the appropriate autoclaved bowls. The appropriate program is loaded from the PLC (indicating setup functions such as fill needle position, index speed, fill volume, tube diameter, acceleration/deceleration, etc.). A subset of vials is “run” through the machine with the fill function disabled. Vials are visually inspected for proper stopper and seal application. . The product container and dispensing tubing are aseptically connected within the ISO 5 environment. A subset of vials is filled to verify proper fill volume, by weight. Vials are filled and loaded into stainless steel trays. Manufacturing and BPA

personnel inspect filled unlabeled vials, and vial reconciliation is performed. Acceptable vials are then labeled and undergo labeled vial inspection.

4.6 Manual Filling Operation

Manual filling procedures exist for viral fills, small-volume product fills, and container closure systems not handled by the semi-automatic filling equipment. Manual fills are conducted within a BSC and typically use a peristaltic pump and filling nozzle; the container/closure system may be screw-cap cryovials or plastic or glass vials that are crimped using a semi-automatic crimper. Materials required for the fill are steam-sterilized or depyrogenated as appropriate or may be purchased sterile; all other materials, including bulk product, are surface-decontaminated and transported to the area utilizing secondary containment. The sterile product container and dispensing tubing are aseptically connected to the peristaltic pump. A subset of vials is then filled to verify proper fill volume, through weight checking. Vials are typically filled within stainless steel trays. The manual fill process uses a minimum of two operators. One operator is responsible for dispensing product into vials, the other operator applies caps or stoppers to the filled vials. Typically, a second pair of operators applies crimps to the stoppered vials and run the crimper in a separate adjoined or adjacent BSC. Manufacturing and BPA personnel inspect filled vials and perform vial reconciliation. Acceptable vials are then labeled and undergo labeled vial inspection.

5.0 VALIDATION APPROACH FOR THE BDP MANUFACTURING SITE

5.1 General Approach

Validation is the process of establishing documented evidence that provides a high degree of assurance that a specific piece of equipment or utility will consistently operate as designed and needed for processing, meeting a pre-determined set of specifications. Additionally, critical manufacturing processes, discussed in Section 8.0, are validated to ensure that these procedures are reliable and reproducible. The BDP applies the term “validation” to the process of commissioning and qualification of each equipment, utility, or process, as required by this Validation Master Plan. BDP’s validation effort consists of the following elements, as applicable:

- Design Qualification (DQ): The process of providing documented evidence that the design and purchase specifications consider applicable regulatory and operational requirements, prior to procuring the system. Typically reserved for custom or more complicated equipment to help ensure proper purchase decisions.
- Factory Acceptance Testing (FAT): Inspection and functional testing, completed at the vendor location, usually to support functional testing that would be expected as part of SAT or qualification activities at the installation. Typically reserved for custom or more complicated equipment.
- Site Acceptance Testing (SAT): Inspection and functional testing, completed at the installation site, usually to support functional testing that would be expected during qualification activities. Typically reserved for custom or more complicated equipment.
- Installation Qualification (IQ): The process of providing documented evidence that components of a utility or piece of equipment have been fabricated according to approved specifications, are installed correctly, and have support utilities that meet quality and capacity requirements.

- Cycle Development: The process of evaluating and adjusting operating parameters (i.e., time, temperature setpoints) for a cycle, so that the cycle will meet predefined criteria during qualification. This is most applicable to cleaning, washing, and sterilizing equipment such as vial washers, autoclaves, dry heat ovens, and bioreactors/fermentors with SIP capabilities. Cycle development is completed before the PQ begins.
- Operational Qualification (OQ): The process of providing documented evidence that components (including ancillaries, such as alarms) of a utility or piece of equipment operate as intended across expected operating ranges.
- Performance Qualification (PQ): The process of providing documented evidence that components of a utility or piece of equipment function together as a system for the required applications and operating ranges expected for BDP processes.
- Process Validation (PV): The process of providing documented evidence that a process will consistently produce products meeting predetermined quality attributes.
- Requalification: The process of providing documented evidence that a utility, piece of equipment, or process remained in a validated state since the last validation work was completed. Requalification occurs as a result of a set duration of time elapsing based on a higher risk assessment rating.
- Revalidation: The process of providing documented evidence that a utility, piece of equipment, or process has been maintained in a validated state since the last validation work was completed. Revalidation occurs as a result of a change-based or time-based assessment.
- Certification: The process of providing documented evidence that a system continues to perform in a manner consistent with CGMP or other standards. The BDP applies the term “certification” to the review (usually annual) of utility monitoring data to identify and resolve trends, if necessary, and to ensure that the utility performs as intended.
- Commissioning/ Commissioning Report: Testing associated with construction and renovation activities performed after installation. Commissioning is not commonly associated with the purchase of an individual piece of equipment. A final report that lists the utilities and equipment that were commissioned/qualified, the suitability for use status, and any identified operational limitations. The report includes an assessment on the readiness of the facility or area for GLP and GMP operations.

With this approach, a “validation package” for a piece of equipment might contain an FAT report, SAT report, a completed IOQ protocol, and a completed PQ protocol.

Utilities, equipment, and processes that require validation and the typical level of validation required are identified in **Appendix 13.3** to this document. Requirements for inclusion in the Validation Program are described in the SOP for the program and are based on ISPE’s “Pharmaceutical Engineering Guides for New and Renovated Facilities”[5]. Utility systems and process and analytical equipment are evaluated for direct or indirect impact on product quality. Examples of criteria that indicate direct product impact include but are not limited to: having direct product contact; having sterilization/depyrogenation functionality; producing data which is used to accept or reject product; having process control functionality; storing cell banks or final product. Utilities and equipment which meet criteria for Direct, Indirect, or No impact are summarized in the matrix shown in **Appendix 13.3**. The requirements for validation activities are based on the criticality of the system as determined from the risk assessment methods described in Section 5.2. These requirements are verified using

pre-approved written qualification protocols. Drafting and execution of protocols and execution of other validation-related activities is conducted in a manner consistent with BDP approved SOPs. Validation is conducted by appropriately trained personnel using Good Documentation Practices.

An integral part to the validation program is the drafting, approval and execution of design, installation, operational, performance, and process qualification protocols (DQs, IQs, OQs, PQs, PVs) in a logical sequence. The sequential approach requires that process parameters, operating limits and specifications be established prior to or while protocols are being drafted.

Some overlap in execution of qualification activities is permitted upon QA review and approval. QA approval requires the completion of an 'Authorization to Proceed' form that signifies that the necessary predecessor qualification activities have been successfully met prior to proceeding with the next stage of qualification. For utility systems, IQs should be substantially complete before OQ execution begins. For process equipment, IQ and OQ of the identified supporting utilities should be complete before initiating the OQ. However, cycle development (such as for sterilizing equipment) may be conducted in parallel with OQ activities, but must be complete before PQ studies begin. I/O/PQ of process equipment should be complete before related PV studies begin.

Unique protocols are drafted for a given unique piece of equipment or process. Where applicable, template protocols are used to ensure consistency of content. These are especially useful for qualification of routine equipment such as controlled temperature storage units (freezers, refrigerators, incubators, etc.), systems requalified regularly, or when replicates of a given model of equipment are in use. Each protocol is given a unique ID. In the case of a template, each template has an ID and each time an executable copy of the template is issued a unique identifier is generated. Protocols are numbered in a sequential manner with a prefix that indicates the protocol type i.e. IQ-XXX, IOQ-XXX, or PQ-XXX where X represents the sequential number associated with each prefix.

Qualification protocols list the parameters and specific acceptance requirements to be evaluated. The protocol is reviewed and approved by representatives from appropriate departments prior to initiation of validation exercises. Qualified personnel then execute and document execution of the protocol. Modifications to the system under test, discrepancies, or deviations that occur during the execution of the I/O/PQ or PV are documented and resolved before validation is considered complete. Failures during validation activities are handled as follows:

- When the failure occurs as a result of equipment or utility failure, and the cause of the failure is known: Further validation activities do not continue until resolution is complete. The number of consecutive successful replicate studies required for that system must still be met.
- When the failure occurs because of human error, either in operating the system or executing the test method, and the cause of the failure is known: That particular study may be repeated without jeopardizing the consecutive successful replicates requirement.

- When the cause of the failure is unknown: An investigation or additional cycle development may be required. The number of consecutive successful replicate studies required for that system must still be met.

Changes to the approved protocol are subject to document change control procedures. Once a protocol is executed, a validation package is created which contains the filled in protocol, raw data, electronic copies of raw data (or their network archival location), deviation reports and resolutions, a summary protocol page or separate report depending on the amount of material to be summarized with initial qualification having the potential for more information, reviews, and approvals. Once validated, equipment, utilities, and processes are maintained in a validated state by management of change, as confirmed by periodic revalidation, or more aptly termed requalification over a course of time.

Requalification due dates are determined by establishing the date of validation as the date when significant work such as a temperature mapping cycle or cleaning cycle is first performed. The requalification frequency listed in **Appendix 13.4** is extended and the due dates are scheduled as month and year and requalification completed prior to the last day of the month indicated to permit continued CGMP use. If any lapse occurs, the equipment/process is considered to be in an unvalidated state and shall be tagged accordingly until validation is successfully completed. A thorough description of the BDP's validation and revalidation approach using risk assessment is provided in Section 5.2.

5.2 Risk Assessment for Prioritizing Validation and Determining Requalification/Revalidation Frequencies

The BDP utilizes a risk-based approach to validation of utilities and equipment. This approach ensures that BDP prioritizes and focuses resources on the most critical aspects of the program. In general, utilities and equipment are categorized into different levels of criticality based on their potential impact on product quality and personnel safety. Historical information regarding failure modes of utilities, equipment and processes is available and is used as part of the risk assessment to define risk categories. These assessments are periodically re-evaluated as new data becomes available.

Risks for each system or system type that will be qualified will be evaluated based on GAMP 5 model for risk assessment. Each identified risk will be evaluated for its Severity of Impact, Likelihood of Occurrence, and Probability of Detection. Once these risks are identified, an aggregate risk factor will be assigned for each system based on the model below, which will indicate if a system or identified risk factor falls in a High, Medium, or Low risk category. A core team comprised of Quality Assurance and Validation, Manufacturing, Engineering, and Subject Matter Experts are encouraged to participate in risk reviews to establish a consistent scoring practice. **Appendix 13.5 and 13.6** are the risk assessment documents for utilities and equipment, respectively, and each assessment provides the groups that participated in or contributed to the assessment process and the date range the assessments were performed or updated.

Definitions for High, Medium, and Low risks for Severity of Impact, Likelihood of Detection, and Probability of Detection are defined below:

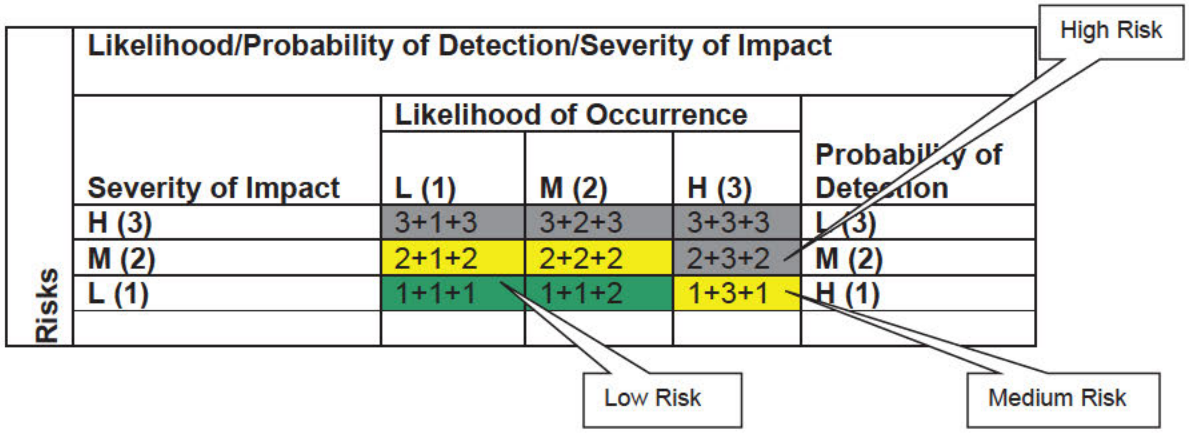
Severity of Impact
Low - Expected to have a minor negative impact. The damage would not be expected to have a long-term detrimental effect. Example - no product quality impact.
Medium - Expected to have a moderate negative impact. The impact could be expected to have short to medium term detrimental effect. Example - batch can be released, but additional testing or rework is required.
High - Expected to have a very significant negative impact. The impact could be expected to have very significant long-term and potentially catastrophic short term detrimental effect. Example - loss of batch or initiation of recall.

Likelihood of Occurrence
Low - The frequency of the event occurring is perceived to be less than once every two (2) years.
Medium - The frequency of the event occurring is perceived to be less than once every six (6) months.
High - The frequency of the event occurring is perceived to be greater than once every six (6) months.

Probability of Detection
High - Detection of the fault condition is perceived to be highly likely (e.g., direct downstream measurement of variable, or redundant monitoring using a redundant automated system, increasing the probability of detection).
Medium - Detection of the fault condition is perceived to be reasonably likely (e.g., downstream measurement or related variable is monitored, increasing the probability of detection).
Low - Detection of the fault condition is perceived to be unlikely (e.g., no effective downstream monitoring measures and no redundant monitoring).

Scoring
Once risks have been identified and risk factors assigned for each risk, an aggregate score will be computed. This risk assessment utilizes the following quantitative scores to delineate High, Medium, and Low risks for each risk identified.

High Risk - A score of greater than 6 will fall within this category
Medium Risk - A score of 5 and 6 will fall within this category
Low Risk - A score of 1-4 will fall within this category



Once the risk score is identified for each risk scenario (see **Appendix 13.5 and 13.6**) within a system, the highest risk (priority) assigned for each risk scenario within a system will be the system risk prior to mitigation.

Application to Validation
As mentioned previously, the risk assessment should provide the rationale for prioritizing validation efforts and focusing resources on the most critical aspects of the program. This allows the validation team to focus on value-added activities and avoid duplication of effort. The BDP applies the risk assessment in two ways:

1) To allow leveraging of data from commissioning, factory acceptance testing, and site acceptance testing, when appropriate, as part of the IQ and OQ protocol. For equipment and utility systems designated as High risk, full IQ/OQ testing is conducted. For equipment and utility systems designated as Medium risk and Low risk, data for some IQ and OQ test functions may be gathered from commissioning, FAT, or SAT, provided that one of the following occurs:

- the party responsible for execution of the validation protocol witnesses the execution of the test function; or
- the party responsible for execution of the validation protocol provides pre-formatted data sheets for use during the testing; conducts audits of the parties responsible for the commissioning, FAT, or SAT; and conducts “spot checks” to verify accuracy of the data

Under no circumstances may data be leveraged from commissioning, FAT, or SAT unless the level of documentation provided by the party responsible for executing the commissioning test plan, FAT, or SAT is adequate; at minimum, the documentation must include acceptance criteria, actual results, pass/fail disposition, identification of the responsible party, date of test execution, and any raw data generated during the test.

2) To allow for graded calibration and validation efforts based on the three levels of risk. Baseline requirements for different levels of risk are shown in **Appendix 13.4.** It is recognized that for some items, there are overriding regulations and/or industry standards relating to their validation. For instance, annual (or more frequent) recertification’s are compiled for utility systems to demonstrate that they remain in a trended state of control throughout the year. These recertifications are compiled regardless of whether a utility is designated as Low or Medium risk (vs. High risk) based on risk assessment. Additionally, the risk assessment is used to adjust the frequency of various revalidation efforts[6].

The risk assessment described above applies to the initial validation and revalidation/requalification of utilities and equipment that occur under normal operating conditions. It does not apply to revalidation following a failure or engineering change. In those cases, revalidation requirements are determined as described in the Engineering Event Management SOP (see Section 10.5).

5.3 Qualification Protocol Overview

Common elements to most BDP protocols are as follows:

Objective

States the objective of the protocol.

Scope and Rationale

Scope for the work is defined and relevant rationale for the validation approach is provided.

System/Equipment Description

Describes the components and use of the system.

Authority and Responsibilities

Responsibilities for all aspects of validation including generation, execution, review and approval of this protocol are as outlined in accordance with this Validation Master Plan.

Execution of Protocol

A statement about the protocol incorporating the following: "The protocol is made up of the attachment data sheets described within. The Test Description and the Acceptance Criteria are provided for each Attachment. The protocol shall be executed by trained personnel. Actual results will be completed during protocol execution. Completed attachments are reviewed by Quality Engineering or a designee other than the person who executed the Attachment. Each attachment is noted whether the acceptance criteria is met with a Yes or No. Any deviations will be addressed in the final Attachment of the protocol."

Attachment: Signature Log

The individuals participating in the execution of the protocol and/or review of individual data sheets will complete a signature reference form.

Attachment: Standard Operating Procedures

The status of the Standard Operating Procedures (SOPs) for operation, maintenance, and/or cleaning of the equipment will be recorded, along with the title, SOP number, and revision level. Relevant support SOPs may also be included.

Attachment: Validation Test Equipment

A record of test equipment used for protocol execution will be completed. Test equipment not owned by the BDP that is used during execution of the protocol will be accompanied by current calibration verification and any associated calibration record documentation. Test equipment owned by BDP that is used during execution of the protocol will be accompanied by current calibration verification and traceable back to the calibration software record.

Attachment: Manufacturer's Documentation

The manufacturer's Operation and Maintenance (O & M) manuals will be documented and their location verified. The location of the manufacturer's recommended maintenance and spare parts list for major components will be documented.

Attachment: Engineering Events

Engineering Events (i.e. Engineering Change Orders, Failure Notifications) encountered in the last validation interval or during current execution and captured and verified that the unit's operational integrity was not compromised. Some EEs may trigger additional qualification activities.

Attachment: Equipment Calibration Verification

Calibration dates for each component of the equipment/system being validated are listed.

Attachment: Authorization to Proceed

The prior protocol segment meets the criteria outlined within the protocol, and any deviations have been addressed, except for the items listed in this data sheet.

Attachment(s): Commissioning Data Sheets

Documentation of required testing performed during the construction or commissioning of the equipment/system will be recorded or referenced. This may include Cleaning, Passivation, Slope Verification, Weld Inspection and Qualification, HEPA Certification, I/O and Loop Checks, etc.

Attachment: Deviations

Lists and describes any deviations and un-expected observations that may occur during testing procedures and their corrective actions.

Qualification Summary

The Qualification Summary is a separate document or data sheets attached to the protocol that summarizes the Qualification effort and presents a conclusion as to qualification status based on the data, reconciles any corrective actions, and lists any identified limitations. For routine requalification or for simple equipment a summary sheet in the protocol is usually sufficient. For initial qualifications of complex equipment or utilities a separate validation summary may be more suitable. A separate summary report shall be given it's own protocol ID and be referenced in the protocol which it summarizes.

5.3.1 Design Qualification (DQ)

The purpose of the Design Qualification Protocol is to verify that the design and purchase specification documents for the system address regulatory and operational requirements and are found to be acceptable. DQ if required, must be performed prior to procuring equipment. Comments addressed in DQ must be incorporated to purchase specifications.

5.3.2 Installation Qualification (IQ)

During the Installation Qualification (IQ) a complete inspection of the system (utility or equipment) is performed. The protocol provides a systematic method to check the static attributes and “as found” condition of the installed utility or equipment. IQ is used to benchmark the installation of the equipment and utilities, and as a baseline for Engineering Change Control. Acceptance criteria are defined in the individual protocols.

Installation Qualification will be performed for each system, as identified in the validation matrix, to verify installation in accordance with design specifications. IQ documents may be generated and/or executed by the vendor. If this approach is taken, the BDP shall review and approve the document both prior and post execution. Testing must be witnessed by BDP staff. An internally generated document may supplement any gaps in vendor testing.

If the IQ document is generated internally, the Installation Qualification will typically include, but not be limited to, the following specific sections/topics:

Attachment: Drawing Verification

A list of the main drawings representing the system will be completed. These drawings will typically include the main P&ID drawing and the main vendor shop drawing. These and other drawings from which ‘as expected results’ were obtained may be referenced on individual data sheets. These drawings will be verified during IQ.

Attachment: Manufacturer’s Documentation

The manufacturer’s Operation and Maintenance (O & M) manuals will be documented and their location verified. The location of the manufacturer’s recommended maintenance and spare parts list for major components will be documented. Verification of data in the MEF database may also be incorporated.

Attachment(s): Component Data Sheet(s)

A data sheet for each major/critical component within the system boundaries, component labeling described on the system/equipment P&ID and/or vendor shop drawing will be completed to ensure the installed component is the specified component.

Attachment(s): Control System Hardware & Software Verification Data Sheets

Critical hardware and software components of automated portions of each system will be verified on individual data sheets, and may include the Operator Interface, the PLC configuration, the PLC software/firmware, the control system, and the environmental operating parameters. Screen prints will be utilized whenever available.

Attachment(s): Utility Data Sheets

The utilities associated with each system will be identified from an overall list of available utility systems. Confirmation of equipment utility requirements including electrical rating versus circuit rating will be performed.

Attachments: I/O Data Sheets

Inputs/Outputs from the control system(s) to equipment or systems will be verified/ referenced from commissioning documentation. See commissioning data sheets note below.

5.3.3 Operational Qualification (OQ)

The Operational Qualification (OQ) is performed upon satisfactory completion of the IQ. This completion is documented in an “Authorization to Proceed” section of the OQ protocol. The purpose of this section is to document the date of completion or acceptance of the IQ study, and to list any outstanding IQ deviations, their proposed resolutions, and the associated justifications to proceed to OQ.

The OQ describes the operational tests, measurements and control tolerances of key parameters that are critical for the proper operation of the system or equipment. Test objectives, methodologies and acceptance criteria are defined and approved prior to execution of the OQ.

Operational Qualification may typically include, but not be limited to, the following specific topics:

Attachment: Operational Parameters

The equipment/system operational parameters that will be evaluated or that may be changed by execution of the protocol will be recorded prior to protocol execution. Upon completion of testing each parameter, the parameters’ return to the original setting will be confirmed within the specific test function involved. Alternatively some parameters may be left at what is discovered as the optimal setting for intended use. The need for this attachment depends on the nature of the equipment.

Attachment: System Security

The equipment/system security features will be challenged and verified. Security features tested will include applicable access codes, user identification, passwords, and the functions available to different levels of access.

Attachment: Alarms & Interlocks

The equipment/system critical alarm and interlock conditions will be challenged and verified. Critical alarms are those that give indications of conditions that could affect product quality. Non-critical alarms may be verified as tested during commissioning and pre-commissioning activities of FAT and SAT.

Attachment: Sequence of Operation

The equipment/system sequence of operation will be challenged and verified. The sequences identified will include the startup, normal operation, and shutdown of the equipment.

Attachment: Functional Operations

The equipment/system functional operations not captured by testing of the sequence of operations will be challenged and verified – including operator controls and indicators.

5.3.4 Performance Qualification (PQ)

Upon successful completion of the IQ and OQ, a Performance Qualification (PQ) is performed for those utility systems or equipment requiring documented performance studies. In general, PQ studies are appropriate for equipment that:

- has multiple components, such as vessels, pumps, compressors, piping, etc., that must function together to create a controlled environment or make a product of specified quality
- has sterilizing/depyrogenation functionality
- requires operator interfacing during normal operation
- produces a utility of specified quality (WFI system)
- requires maintaining sterility within the system

The PQ integrates the written procedures, personnel, and materials that are encountered under normal processing conditions. Test objectives, methodologies and acceptance criteria are defined and approved prior to execution of the PQ.

A sufficient number of consecutive successful replicate studies are performed, or the system/equipment is monitored for a sufficient length of time, to demonstrate the ability of the system or equipment to achieve reproducible results and to establish a satisfactory level of confidence in the results obtained. Testing may include analysis for chemical, physical and microbiological constituents. The ability of the system or equipment to perform the intended function within the defined upper and lower process variable limits is measured. Protocols incorporate "worst case" challenges to the normal or intended operating range of the system or equipment, as appropriate. Preparation of reagents/media is documented. Performance Qualification may typically include, but not be limited to, the following specific topics:

Attachments: Performance Test Functions

The protocol consists of a sampling plan and specific tests to be performed.

5.3.5 Process Validation (PV)

The PV study integrates written procedures (which typically include Master Production Records (MPR's)), personnel, materials, equipment, utilities, and facilities in a process simulation. Test objectives, methodologies and acceptance criteria for the process are defined and approved prior to execution of the PV. The scope of process validation work at the BDP includes but is not limited to semi-automatic filling operations and manual filling operations. Processes such as formulation or manipulation of final product that is not sterile filtered may also be performed as a PV or handled as a PQ. The difference is largely based on whether actual process documents are used. (for detailed descriptions of each, see Section 8.0).

A sufficient number of consecutive successful replicate studies are performed to demonstrate the ability of the process to achieve reproducible results. This

typically includes three consecutive successful process simulations, unless otherwise justified and documented. Protocols incorporate "worst-case" challenges and typical “interventions” to the normal or intended operating state of the process. For example, worst-case challenges to a filling operation may include:

- increasing the maximum number of personnel in an area for an aseptic filling procedure;
- simulating the longest fill duration; and
- simulating the largest fill volume to maximize media exposure to environment

Typical “interventions” may include:

- simulating a spill of material from a bad dispense or damaged vial during filling validation;
- simulating vial breakage during automated filling validations; and
- simulating a vial jamming during automated filling validations

Exceptional conditions that could impact process integrity or product safety, identity, strength, quality, and purity are identified, as are failures to meet the pre-established criteria. Each exceptional condition is documented and the appropriate course of action (justification, correction) is determined and approved before validation is considered complete. The data collected are packaged and summarized for review and approval.

6.0 UTILITY SYSTEM QUALIFICATION

The utility systems installed at the BDP Manufacturing Site are qualified for installation, operation and performance as indicated in the validation matrix attached. As process requirements change, certain utilities may have to be reassessed as to criticality and the risk-assessment updated. The following sections briefly outline specific studies conducted for major utility types. The guidance would also apply for additional, or replacement systems installed at a later date in the facility.

6.1 Reverse Osmosis (RO) Water Systems

During IQ and OQ, the proper connection, installation, materials of construction and labeling/tagging of the supporting utilities (feed water, compressed air, and electricity) and components (pumps, filter modules, valves, tanks, insulation, piping, gauges, controls) are verified. Calibration of control, monitoring and recording instrumentation (e.g., pressure gauges, temperature sensors, timers) is verified. Piping and tank materials of construction are verified to match initial specifications.

RO System Piping and Instrumentation Diagrams (P&IDs), system diagrams, maintenance manuals, operating manuals and as-built drawings are identified and verified as complete and up-to-date. Relevant system operation and maintenance SOPs are identified and reviewed. The RO water system welding, cleaning and passivation reports are examined and verified as applicable for the system. The RO water system piping is confirmed to be properly supported, labeled, and sloped to drain.

Operation of the system controls, pumps, critical alarms and interlocks, temperature controls, automatic make-up, pressure controls, and output capacity are verified. The system is tested over the required operating range. System parameters are recorded as a baseline.

The OQ protocol confirms system capacity and pumping ability during a range of demand. If equipped, the system carbon filter and softener backwash are tested for correct sequencing and backwash efficacy in both manual and automatic modes. Initial Bioburden will be monitored.

For systems supplying feed water for USP utilities such as Pure Steam and WFI, the Phase I portion of the PQ protocol describes a sampling and testing plan conducted over a 10 workday period. Specifications for conductivity, total organic carbon (TOC), and Bioburden meet USP compendial standards for Purified Water. The PQ sampling is conducted on major components of the RO water system as applicable, including the feedwater system, prior to the RO membranes, , and reverse osmosis product and prior to each usage point. The sampling and testing demonstrate the performance of each system component. For example, the chlorine content of the water is monitored before and after the carbon bed filtration. Results of PQ testing are used to establish initial alert and action limits for the system.

For RO systems providing water for tasks that do not involve potential for direct product contact such as systems exclusively used for facility room surface cleaning or for supplying water for generation steam for humidification purposes (clean steam), the

Phase I portion of the PQ protocol describes a sampling and testing plan conducted over a 10 workday period. Specifications for conductivity, total organic carbon (TOC), Bioburden or other assays as needed will be established to correspond to system capabilities and requirements for the intended use.

In the Phase II portion of the PQ protocol, sampling and testing continued for 13 weeks and then for an additional 38 calendar weeks for a total of one year to demonstrate performance of the DPRO System installed in the CUP through a complete cycle of seasonal variation. These samples are taken at a reduced frequency during each consecutive stage.

The Phase II portion of a PQ for ancillary RO systems used for facility cleaning or as feed water for humidification systems may be shorter in duration. The duration utilized should be based on risk and factor in system design and intended use. Samples are taken at a reduced frequency compared to Phase I.

During annual recertification of each system, routine water monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Water Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact.

6.2 Pure Steam Systems

The Pure Steam system supplies steam for sterilization use in autoclaves and SIP culturing systems.

During IQ and OQ, the proper connections, installation, materials of construction and labeling/tagging of the supporting utilities (DPRO, plant steam, compressed air, electricity) and components (pumps, filter modules, valves, tanks, insulation, piping, gauges, controls) are verified. Calibration of control, monitoring and recording instrumentation (e.g., pressure gauges, temperature sensors, timers) is verified. Piping and tank materials of construction are verified to match initial specifications. The sanitary welding and inspection reports are identified and verified as complete and acceptable.

P&IDs, system diagrams, maintenance manuals, operating manuals and as-built drawings are identified and verified as complete and up-to-date. Relevant system operation and maintenance SOPs are identified and reviewed.

The Pure Steam System passivation and flushing reports are examined and verified. Piping is confirmed to be properly supported, labeled, and sloped to drain. Condensate removal is verified to be operational.

Operation of the system controls, critical alarms and interlocks, temperature controls, pressure controls and output capacity are verified.

The Phase I portion of the PQ protocol describes a sampling and testing plan to be conducted over a 10 workday period. Pure Steam condensate specifications for conductivity, TOC, and bacterial endotoxins meet USP compendial standards for Water

for Injection (WFI). The PQ sampling is conducted at the steam generators and at the equipment points-of-use, as specified in an approved protocol. Results of the PQ execution are used to establish initial alert and action limits.

In the Phase II portion of the PQ protocol, sampling and testing continued for one year to demonstrate performance of the Pure Steam Systems through a complete cycle of seasonal variation. These samples are taken at a reduced frequency.

Regular derouging and passivation shall be performed on the Pure Steam generators and the distribution system.

During annual recertification of the systems, routine monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Water Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact.

6.3 Clean Steam

Clean Steam is used to supply humidification steam to air handlers that supply classified spaces.

During IQ and OQ, the proper connections, installation, materials of construction and labeling/tagging of the supporting utilities (feed water for clean steam generator, plant steam, compressed air, electricity) and components (pumps, valves, tanks, insulation, piping, gauges, controls) are verified. Calibration of control, monitoring and recording instrumentation (e.g., pressure gauges, temperature sensors, timers) is verified. Piping and tank materials of construction are verified to match initial specifications. The welding and inspection reports are identified and verified as complete and acceptable.

P&IDs, system diagrams, maintenance manuals, operating manuals and as-built drawings are identified and verified as complete and up-to-date. Relevant system operation and maintenance SOPs are identified and reviewed.

Piping is confirmed to be properly supported, labeled and sloped to drain. Condensate removal is verified to be operational.

Operation of the system controls, critical alarms and interlocks, temperature controls, pressure controls and output capacity are verified.

The Phase I portion of the PQ protocol describes a sampling and testing plan to be conducted over a shorter duration of at least 10 workdays. Clean Steam condensate specifications for conductivity, TOC, and bacterial endotoxins meet established criteria which may be less stringent than USP Pure Steam for TOC based on equipment design and risk. The PQ sampling is conducted at the air handling equipment points-of-use at a minimum, as specified in an approved protocol. Results of the PQ execution are used to establish initial alert and action limits.

In the Phase II portion of the PQ protocol, sampling and testing continues for a duration to demonstrate performance of the Clean Steam Systems through a seasonal variation. These samples are taken at a reduced frequency.

During annual recertification of the systems, routine monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Water Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact.

6.4 Water for Injection (WFI) System

During IQ and OQ, the proper connections, installation, materials of construction and labeling/tagging of the supporting utilities (plant steam, compressed air, process chilled water, electricity) and components (pumps, filter modules, valves, tanks, coils, insulation, piping, gauges, controls) are verified. Calibration of control, monitoring and recording instrumentation (e.g., pressure gauges, temperature sensors, timers) is verified. Piping materials of construction are verified to match initial specifications. Tank vent filter locations are documented as accessible for integrity testing. The WFI piping sanitary welding and inspection reports are reviewed and verified as complete and acceptable.

The WFI System P&IDs, system diagrams, maintenance manuals, operating manuals and as-built drawings are identified and verified as complete and up to date. Relevant system operation and maintenance SOPs are identified and reviewed.

The WFI System cleaning, passivation, and sanitization reports are examined and verified. The WFI System piping is verified to be properly supported, labeled, and sloped to drain.

Operation of the system controls, pump, critical alarms and interlocks, temperature controls, automatic make-up, pressure controls and output capacity are verified.

The OQ protocol confirms system capacity and pumping ability during minimum and maximum demand. The return distribution loop flow velocities under minimum and maximum demand are confirmed to meet the specified values.

During OQ and PQ, WFI loop temperature and pressure control are observed to maintain temperature and pressure settings during system operation. Any adjustments or limitations are noted.

The Phase I portion of the PQ protocol describes a sampling and testing plan to be conducted over a 10 workday period. Specifications for conductivity, TOC, bioburden, and bacterial endotoxins meet USP compendial standards for WFI. The PQ sampling is conducted on major components of the WFI System, including the feedwater system, condenser and WFI storage/re-circulation tank, and on the drops/ points-of-use specified in an approved protocol. Results of the PQ execution validate the temperature control capability and the on-demand cooling. The data is used to establish initial alert and action limits.

In the Phase II portion of the PQ protocol, sampling and testing continues for one year to demonstrate performance of the WFI System through a complete cycle of seasonal variation. These samples are taken at a reduced frequency.

Regular passivation and derouging as needed shall be performed on the WFI still, storage tank, and distribution loops.

During annual recertification of the system, routine water monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Water Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact.

6.5 Liquid Waste Decontamination System

During IQ, design documentation, manufacturers' manuals, spare parts lists, certification documentation and drawings are identified and verified where applicable. The proper connection and installation of the supporting utilities (plant steam, electricity, compressed air) and components (valves, gauges, displays, sensors) are verified. Calibration is verified. Alarms are tested to ensure proper operation. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the process-critical controls operate as expected, including access security, hatch interlocks (if applicable), alarms, cycle sequencing and timing of cycle steps and cycle reports. Pressure hold tests are verified as complete to confirm pressurization is maintained per criteria established in the protocols. A thermal mapping study is conducted to verify setpoint acquisition. Temperature probe placement is documented.

During PQ, the performance of the system is verified by operating it with the worst case established tank volume. Three consecutive successful loads must be run. Heat penetration studies include probing the vessel with temperature sensors and using biological indicators of *Geobacillus stearothermophilus* to demonstrate acceptable lethality. The worst case established tank volume is identified prior to execution of the PQ. The test process is described in detail, minimally including temperature sensor placement locations and volume of effluent undergoing decontamination.

Revalidation occurs every two years. Relevant Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Calibration is verified. The performance of the system is verified by conducting a single, worst case, heat penetration study by probing each vessel with heat distribution temperature sensors and using biological indicators of *Geobacillus stearothermophilus* to demonstrate acceptable lethality. The test process is described in detail, minimally including temperature sensor placement locations and volume of effluent undergoing decontamination.

6.6 pH Neutralization System

During IQ, the proper connection, installation, materials of construction and labeling/tagging of the components (valves, piping, gauges, controls) are verified.

Calibration of control, monitoring and recording instrumentation (e.g., pressure gauges) is verified. Field components are compared to initial specifications. Piping materials of construction are verified to match specifications.

The P&IDs, system diagrams, maintenance manuals, operating manuals and as-built drawings for the pH neutralization systems are verified as complete and up-to-date. Relevant system operation and maintenance SOPs are identified and reviewed. The piping of the pH neutralization systems is confirmed to be properly supported, and labeled.

Operational tests are conducted during OQ to determine that the process-critical controls operate as expected, including access security, alarms, cycle sequencing and timing of cycle steps.

This system is a shared building utility and not GMP in nature. The system is designed to ensure discharge into the sanitary sewer meets pH requirements of Frederick. The system is controlled by ATRF FME staff.

6.7 Building Automation System

The Building Automation System provides monitoring and control of the HVAC System. The BAS system is commissioned to verify proper installation and functionality. The BAS system is non-GMP and controlled by FME. The SCADA system is the GMP system that monitors that the BAS controls HVAC to the proper pressure, temperature, and humidity.

6.8 SCADA System

The Supervisory Control and Data Acquisition (SCADA) system provides Part 11 compliant data monitoring of environmental conditions for temperature, humidity, and differential pressure of the GMP areas. . The system provides monitoring for Controlled Temperature Units (CTUs) such as refrigerators, freezers, cold rooms, and some utility systems. SCADA provides monitoring and system control for water system distribution and storage. SCADA also provides monitoring of environmental conditions such as room temperature and humidity, room differential pressures, and specialized alerts for select equipment. The system has the capability to store data, trend, alarm, and generate reports to support GMP operations.

During IQ and OQ, the proper connection, installation, and tagging of the supporting utilities (electricity, compressed air) and components (solenoids, panels, transducers, programmable logic controllers, communication lines, interface modules, gauges, controls, workstation) are verified. Calibration of instrumentation (e.g., pressure gauges, temperature sensors, differential pressure sensors) is verified.

System diagrams, maintenance manuals, operating manuals and as-built drawings are identified and verified as complete and up-to-date. Relevant system operation and maintenance SOPs are identified and reviewed.

Operation of the system controls, alarms and interlocks and outputs are verified. The SCADA workstation is tested for security, operating commands to change setpoints and screen setups, input/output signals, digital input/output signals and control loop operation. The SCADA control panels are tested for operational and functional integrity. The SCADA (workstation and field controllers) software backup function is verified and tested for system backup to a disk-based file for archiving. The report outputs are tested for various displays and printouts of system status and analysis.

No annual recertification is required. Engineering Events are utilized to track system changes or failures. SCADA data is utilized during power outage or monitored equipment failure events to help assess time and mode of failure and impact to product or materials.

6.9 Heating, Ventilation and Air Conditioning (HVAC) Systems

HVAC systems listed in the validation matrix – **Appendix 13.3**, will be qualified. During IQ, the proper connection, installation, materials of construction and labeling/tagging of the supporting utilities (water, electricity, clean steam) and major components (filter modules, coils, fans, dampers, insulation, humidifiers, de-humidifiers, ductwork, air handling units, gauges, controls) are verified. Calibration of control, monitoring and recording instrumentation (e.g., pressure gauges, temperature sensors, timers) is verified. HEPA filter integrity test reports are reviewed. Field components are compared to design specifications. Relevant standard operating procedures (SOPs) for system operation and maintenance are identified and reviewed. The HVAC system P&IDs, system diagrams, maintenance manuals, operating manuals, and as-built drawings are identified and verified as complete and up-to-date.

During the OQ, temperature, airflow, differential pressures, and air directionality in the ISO classified clean rooms of the BDP are measured. Localized directional airflow is assessed at critical sites, such as in the filling suite, using a smoke generator to visualize airflow. The number of air changes in each room is calculated from air balance reports.
Critical alarm, monitoring and control instrumentation is challenged by simulation of appropriate conditions to verify that the systems operate as intended.

The Phase I portion of the HVAC PQ describes a sampling and testing plan to be conducted over a 10 workday period including 5 days static and 5 days of dynamic monitoring. The test conditions and acceptance criteria are detailed for each controlled and critical area (including number of sampling points and locations) using the current ISO standards for air cleanliness. Environmental monitoring data for the PQ is collected during static and dynamic (operational) conditions. The environmental monitoring parameters include temperature, humidity, differential pressures, non-viable and viable airborne particulates, and surface viable particulates.

In the Phase II portion of the PQ protocol, sampling and testing continued for one year to demonstrate performance of the HVAC System through a complete cycle of seasonal variation. These samples are taken at a reduced frequency. For renovation and expansion areas the Phase II portion duration may be shortened. Risk should be the basis of the chosen duration and capturing a seasonal change to see different

contaminant profiles and control differences between humidification and dehumidification seasons is suggested.

During annual recertification of the system, routine environmental monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Environmental Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Non-conforming air change rates and HEPA filter integrity tests performed since the last qualification/recertification are included. Room differential pressures are reviewed to ensure that no unintentional changes or trends have occurred.

6.10 Emergency Power Systems

During IQ and OQ the proper connection, installation, and tagging of the supporting services (electricity and fuel source) and components are verified. Field components are compared to initial specifications and verified for compliance to local codes and electrical requirements.

The Emergency Power System P&IDs, system diagrams, maintenance manuals, operating manuals and as-built drawings are identified and verified as complete and up-to-date.

The emergency generator is tested to document running modes, critical alarms and interlocks, automatic transfer switching, automatic shutdown and manual override capabilities. Any recording devices are tested. A power outage is simulated and the emergency generator load capability tested by energizing and operating supported equipment.

The emergency generator and critical switchgear are on preventive maintenance programs to ensure operational reliability. The equipment is under FME control. No annual requalification is required. Changes or failures are captured via relevant Engineering Events.

6.11 Compressed Air System

During IQ and OQ, the proper connection, installation, materials of construction and labeling/tagging of the supporting utility (electricity) and components (compressors, filter modules, valves, air dryers, insulation, piping, gauges, controls) are verified. Calibration of control, monitoring and recording instrumentation (e.g., pressure gauges, timers) is verified. Field components are compared to design specifications. Piping materials of fabrication are verified to match initial specifications. Relevant system operating and maintenance SOPs are identified and reviewed. The P&IDs, system diagrams, maintenance manuals, operating manuals and installation as-built drawings for each system are identified and verified as complete and up-to-date. The cleaning, drying, and pressure test reports for each system are reviewed for completion. The piping for each system is verified to be properly supported and labeled.

Operation of the system valves, controls, compressors, critical alarms and interlocks, pressure cutoffs, and output capacities are verified. The automatic regenerating,

sequencing and alarm mechanisms of the dryers are tested. The systems are tested over the required operating range.

The protocols outline tests to study the capacity and pressure during the estimated minimum and maximum use for each system. Pressure hold tests are verified as complete to confirm pressurization is maintained per criteria established in the protocols.

The Compressed Air System PQ describes a sampling and testing plan. Phase 1 is conducted over a 10 workday period. Specifications are derived from current ISO standards for air cleanliness at the intended points-of-use. Testing includes total particulate counts, viable counts, dew point (moisture content) and hydrocarbon analysis. Phase 2 of the PQ sampling and testing continued for one year to demonstrate performance of the HVAC System through a complete cycle of seasonal variation. These samples are taken at a reduced frequency.

For renovation and expansion areas that tap into the existing system the expanded areas are addressed via an IOQ. The quality of the gas is verified by a PQ sampling strategy requiring shorter duration than qualification of a complete system. Rational for the sampling approach shall be included in the qualification protocol and should factor in the nature and scope of the expansion and risk associated with the planned usage.

During annual recertification of the system, routine air quality monitoring results for Pharmaceutical Air, any Compressed Air used in an ISO 5 environment, and any 0.2 micron filtered air supporting GMP manufacturing areas are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Utility Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact.

6.12 Compressed & Liquefied Gas Distribution Systems

During IQ and OQ, the proper connection, installation, materials of construction and labeling/tagging of the components (gases, filter modules, valves, piping, gauges, controls) are verified. Calibration of control, monitoring and recording instrumentation (e.g., pressure gauges, timers) is verified. Field components are compared to initial specifications. Piping materials of construction are verified to match specifications.

The P&IDs, system diagrams, maintenance manuals, operating manuals and as-built drawings for the gas distribution systems are verified as complete and up-to-date. Relevant system operation and maintenance SOPs are identified and reviewed. The piping of the gas distribution systems is confirmed to be properly supported, cleaned, dried, and labeled. Proper connection of the gases to the process equipment is verified, including presence of appropriate point-of-use filters. Operation of the system controls, critical alarms and interlocks, and delivery pressures are verified.

The PQ protocol describes a complete sampling and testing plan to verify that the system reliably provides compressed gas, which meets the current ISO standards for air cleanliness for its intended use. Testing includes total particulate counts, dew point (moisture content), hydrocarbon analysis and viable particle counts. Systems are not sampled in their liquid form.

For renovation and expansion areas that tap into the existing system the expanded areas are addressed via an IOQ. The quality of the gas is verified by a PQ sampling strategy requiring shorter duration than qualification of a complete system. Rational for the sampling approach shall be included in the qualification protocol and should factor in the nature and scope of the expansion and risk associated with the planned usage.

During annual recertification of the system, routine gas quality monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Utility Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact.

6.13 Portable Clean Rooms and Downflow Booths

During IQ, the proper connection, installation, materials of construction and labeling/tagging of the components (filter modules, fans, gauges, controls) are verified. Calibration of control, monitoring and recording instrumentation is verified. Field components are compared to design specifications. Relevant standard operating procedures (SOPs) for system operation and maintenance are identified and reviewed. The P&IDs, system diagrams, maintenance manuals, operating manuals and as-built drawings are identified and verified as complete and up-to-date.

During the OQ, airflow, differential pressures, and air directionality are measured. The number of air changes is calculated from air balance reports. Critical alarm, monitoring and control instrumentation is challenged by simulation of appropriate conditions to verify that the systems operate as intended.

Environmental monitoring data for the PQ is collected during static and dynamic (operational) conditions. The environmental monitoring parameters include temperature, humidity, differential pressures, non-viable and viable airborne particulates, and surface viable particulates. The OQ protocol verifies the appropriate air change rate in the room, and linear velocity across the HEPA filters. Additionally, the room differential pressures and directional air flows are verified, as appropriate.

The PQ protocol consists of environmental monitoring (room temperature, relative humidity, non-viable and viable airborne particulates, and surface viable particulates). The test conditions and acceptance criteria are detailed (including number of sampling points and locations) using the current ISO standards for air cleanliness.

During annual recertification of the system, environmental monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Environmental Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Non-conforming air change rates and HEPA filter integrity tests performed since the last recertification are included. Room differential pressures are reviewed to ensure that no unintentional changes or trends have occurred. This is typically performed as part of the HVAC annual recertification as this category of equipment is most easily treated as any other room for recertification.

6.14 Purified Water Generation Units

During IQ, the installed purified water generation units for the PA laboratories are reviewed against the appropriate purchase orders. Design documentation, manufacturers' manuals, spare parts lists, certification documentation and drawings are identified and verified where applicable. System attributes, such as materials of construction and temperature/ pressure ratings are documented. The equipment is checked for connection to proper support utilities. Calibration is verified where applicable. Relevant system operation and maintenance SOPs are identified and reviewed.

During the OQ, operational tests are conducted to determine that the process-critical controls and alarms operate as expected.

The PQ describes a sampling and testing plan to be conducted over a 20 workday period. Specifications for conductivity, TOC, and bioburden meet USP compendial standards for Purified Water.

During annual recertification of the systems, water quality monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events and Water Monitoring Excursion Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of each system is intact.

6.15 Vaporized Hydrogen Peroxide Decontamination System

During IQ, the installed system is compared to specifications listed on purchase orders. Design documentation, manufacturers' manuals, spare parts lists, certification documentation and drawings are identified and verified where applicable. The system connections to proper support utilities are verified. System attributes are documented and calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

During OQ, operation of the system, controls, critical alarms and interlocks and outputs are verified. Room leak tests are performed during OQ testing to verify safe levels of VHP outside of the rooms during decontamination, and to ensure evacuation of VHP from rooms after decontamination.

Cycle development studies will be performed.

During the PQ, three successful consecutive decontamination cycles are run and documented. Decontamination is determined by biological indicators of *Geobacillus stearothermophilus* to demonstrate acceptable lethality. Room sampling points are documented. Temperature, relative humidity, and VHP concentration data are monitored. Critical cycle parameters are documented.

During annual requalification, relevant Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. One successful decontamination cycle is run and documented. Decontamination is determined by biological indicators of *Geobacillus*

stearothermophilus to demonstrate acceptable lethality. Room sampling points are documented. VHP concentration data is monitored. Critical cycle parameters are documented.

6.16 Warehouse (MMIC)

During IQ, relevant HVAC system operation and maintenance SOPs are identified and reviewed. The Warehouse HVAC P&IDs, and as-built drawings are identified and verified as complete and up to date.

During OQ, controlling and monitoring systems are tested, alarm functionality verified, and access controls challenged. During PQ, temperature and humidity will be verified to be within acceptable limits. Temperature uniformity will be tested for a minimum of 7 days during warm weather and 7 days minimum during cold weather. Summer and winter conditions will be monitored to ensure that the environmental conditions can be maintained within acceptable limits for temperature and humidity, during the two extreme weather conditions.

Annual recertification consists of a review of any Relevant Engineering Events and SCADA temperature and humidity trending. This may be included as part of the Annual HVAC Certification. If any unresolved trends are detected that show a shift in performance, a revalidation is required. Revalidation shall be for 5 days during seasonal conditions that will adequately evaluate the performance condition. Fewer sensors than were used during the original validation may be used, but SCADA locations and high and low study locations will be included.

7.0 PROCESS EQUIPMENT QUALIFICATION

The process equipment installed at the BDP Manufacturing Site is to be qualified for installation, operation, and performance as indicated by its criticality score from the master risk assessment. As process requirements change, certain equipment may have increased or decreased criticality (for instance, a freezer that once stored only raw materials may have increased criticality if used to store final vialed product), and the risk-assessment is appropriately updated. The following sections briefly outline specific studies to be conducted for major equipment types.

7.1 Controlled Temperature Units

Controlled temperature units include refrigerators, freezers, ultra-low freezers, walk-in cold rooms and freezers, and controlled temperature incubators.

During IQ, the installed units are reviewed against manufacturers' documentation and approved specifications for suitable materials and installation. The equipment is checked for proper connection and installation of the support utility (electricity) and alarms/monitoring devices. System attributes are documented. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed. Operational tests are conducted during OQ to determine that the process-critical controls and alarms operate as expected. An empty chamber thermal mapping study is

conducted for at least 24 hours to verify that the chamber temperature is uniform and within specifications.

Open door studies are conducted to demonstrate the equipment's ability to maintain temperature during normal operating conditions. Power failure studies are conducted to understand chamber temperature trajectories in the event of power loss or unit failure. A trend report from the SCADA system is generated. These tests are for information only, with no acceptance criteria. Datalogger placement for OQ mapping studies is documented.

For controlled temperature units that store final product or are otherwise deemed critical, a PQ will be conducted. Loaded thermal mapping for 24 hours will be performed during this PQ and may use actual materials or an analog. For controlled rate freezers, the media used during the PQ is an analog for product or formulation buffer without product to ensure the process is representative. Datalogger placement is documented.

Requalification of controlled-temperature storage units is based on the equipment risk assessment. Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Revalidation may be needed following unit modification, relocation, or failure. In these cases, the equipment is checked for proper connection and installation of the support utility (electricity) and alarms/monitoring devices. Calibration is verified. For revalidation, operational tests are conducted to determine that the process-critical controls and alarms operate as expected. A thermal mapping study is conducted for at least 24 hours to verify that the chamber temperature is uniform and within specifications. The unit may be mapped empty or full if materials are not easily relocatable. The reason for this is that empty mapping is usually the worst case as there is no load mass to dampen thermal shifts. Datalogger placement is documented.

7.2 Temperature- and Humidity-Controlled Carbon Dioxide Incubators

During IQ, the installed incubators are reviewed against manufacturers' documentation and approved specifications for suitable materials and installation. The equipment is checked for proper connection and installation of the support utilities (electricity, CO_2) and alarms/monitoring devices. System attributes are documented. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the process-critical controls and alarms operate as expected. An empty chamber thermal mapping study is conducted for at least 24 hours to verify that the chamber temperature is uniform and within specifications. Mapping also documents CO_2 and humidity RH% against unit or owner specifications. For units with no relative humidity control RH% data is collected and documented. Additional mapping studies may be conducted if the equipment owner anticipates operating the incubator at several temperature setpoints. Datalogger placement is documented.

Open door studies are conducted to demonstrate the equipment's ability to maintain temperature during normal operating conditions. Power failure studies are conducted to

understand chamber temperature trajectories in the event of power loss. Datalogger placement during both information only studies is documented.

For incubators with sterilization cycles, if the sterilization cycle is to be used, an empty chamber thermal mapping is completed. Datalogger placement is documented.

Requalification of incubators is based on the equipment risk assessment. Risk level 1 (High) require requalification every 5 years. In general, these units include those in QC service for EM and may include units used for critical growth such as cell banks or viral production. As incubators used for culture growth have the feedback of growth parameters, requalification is not typically required. During requalification, Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Revalidation may be needed following unit modification, relocation, poor growth performance, or failure. In these cases, the equipment is checked for proper connection and installation of the support utilities and alarms/monitoring devices as relevant for the cause of the revalidation. Calibration is verified. For revalidation, operational tests are conducted to determine that the process-critical controls and alarms operate as expected. An empty chamber thermal, CO_2, and relative humidity map are collected for at least 24 hours at each temperature setpoint in active use as applicable for the unit. For self-sterilizing incubators, an empty chamber thermal map verifies acceptable lethality. Datalogger placement is documented.

7.3 Autoclaves

Autoclaves at the BDP are classified either as sterilizing autoclaves or decontamination autoclaves. BDP's policy is to fully validate sterilizing autoclaves that support CGMP production operations. In addition, decontamination autoclaves will typically have and IQ and OQ performed and a PQ when dealing with BL3 or other processes with higher safety concerns. All decontamination autoclaves must follow institutional environmental health and safety protocols and are monitored monthly while in use for proper operation.

During IQ, design documentation, manufacturers' manuals, spare parts lists, certification documentation and drawings are identified and verified where applicable. The proper connection and installation of the supporting utilities (clean steam, plant steam, electricity, compressed air) and components (valves, gauges, displays, sensors) are verified for both sterilizing and decontaminating autoclaves. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the process-critical controls operate as expected, including access security, door interlocks (if applicable), alarms, cycle sequencing and timing of cycle steps and cycle reports. For sterilization autoclaves, a leak test is conducted on the chamber (Bowie-Dick test). For each cycle, a thermal mapping study is conducted to verify setpoint acquisition and empty chamber temperature uniformity for the duration of the sterilization period. Temperature probe placement is documented.

During PQ, the performance of the autoclaves is verified by operating the autoclaves with various approved worst case load configurations to ensure steam penetration. Both

sterilizing capability and decontamination capability are demonstrated, as appropriate. Three consecutive successful loads must be run. Load items must reach ≥121.5°C for a minimum of 20 minutes. Additional time should be added, especially for decontamination units, to provide additional safety margin. Heat penetration studies typically include thermal mapping of each package type, probing the chamber and load items with temperature sensors and use biological indicators of *Geobacillus stearothermophilus* to demonstrate acceptable lethality. The worst case load configurations are identified prior to execution of the PQ. The load configurations are photographed and described in detail, minimally including temperature sensor placement locations, load item descriptions, tubing lengths if applicable, package wrapping materials of applicable sizes and layers, and orientation of containers/vessels.

Revalidation occurs annually for CGMP sterilizing autoclaves and every two years for decontamination autoclaves in the validation program. Relevant Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Calibration is verified. Critical alarm of low sterilization temp is tested to ensure proper operation as cycles are primarily controlled by temperature. The performance of the autoclaves is verified by conducting a single heat penetration study for each cycle, including a thermal map of each worst case load type, probing the chamber and load items with temperature sensors and using biological indicators of *Geobacillus stearothermophilus* to demonstrate acceptable lethality. The thermal maps are assessed against acceptance criteria and if approaching or outside the criteria are compared to those from previous validation studies to identify trends. The worst case load configurations are described in detail, minimally including temperature sensor placement locations, tubing lengths if applicable, package wrapping materials of applicable sizes and layers, and orientation of containers/vessels.

7.4 Culturing Systems (including Bioreactors & Fermentors both SIP and Single Use)

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. The proper connection and installation of the supporting utilities and components (valves, gauges, displays, sensors, and filters) are verified for the system. Field components are compared to design specifications. Calibration is verified. The system software is reviewed against the approved specifications. The equipment is checked for proper connection to and installation of any hardware and software. Relevant system operation and maintenance SOPs are identified and reviewed. Materials of construction are verified to match specifications, with particular attention to product-contact surfaces. For SIP systems, piping and vessel material certs and welding documentation and slope are verified.

Operational tests are conducted during OQ to verify that the process-critical controls operate as expected. These may include temperature, agitator or rocker speed, pH, dissolved oxygen, pressure, and gas flow. The control system architecture and security are verified. Testing of instrument/PC communication, software version, and access security occurs. Alarm conditions are simulated to verify proper alarm and interlock functionality. For SIP systems and single use systems where applicable, a culturing vessel pressure hold test is conducted. Temperature mapping is performed for at least 24 hours to demonstrate that equipment can achieve critical temperature requirement(s). For some single use systems, traditional mapping may not be feasible

i.e. Miltenyi Prodigy. In addition, for single use systems the temperature mapping may be performed after the PQ execution as mapping does not require a sterile vessel.

For traditional stainless steel systems, sterilize-in-place (SIP) functionality is verified through triplicate sterilization runs. These include a thermal map to verify setpoint acquisition and temperature uniformity and using biological indicators of *Geobacillus stearothermophilus* to demonstrate acceptable lethality. Datalogger placement is documented.

Performance tests are conducted during PQ to demonstrate the capability of the units to remain sterile during typical unit operations such as seeding, sampling and harvesting. During a sterility run, general growth medium such as animal free TSB is used. The run conditions are based upon parameters that are very favorable for contaminating organisms such as low pressure, high aeration, and high agitation and should reflect practical process limits. Successful runs will maintain sterility for the duration and the test medium will adequately support growth at completion of the run as verified by growth promotion. In addition, the ability of the units to support adequate growth of selected cell cultures may be demonstrated.

For SIP systems, PQ testing includes SIP sterilization followed by a process simulation of the longest duration expected during routine operation, using microbiological growth medium. Typical PQ testing for SIP systems will require three consecutive successful runs.

PQ for single use culturing systems will be conducted through execution of a single media hold study, demonstrating ability to perform expected operations such as feeds and collect samples aseptically which will ensure that equipment and utilities will consistently operate as designed when operating in its routine environment under normal operating conditions. PQ sterility hold run would be performed based on the maximum interventions to demonstrate that that equipment can maintain the sterility in a normal operating environment. Since all the single use components (vessels, bags, associated tubing, filters, and fittings) are qualified by the vendors for initial sterility and typically include a vendor maximum approved duration, the PQ run will be focused on maximum intervention available from the worst-case recipe available at BDP. If any future process requires a duration exceeding the vendor-approved sterility hold duration, then extra samples will be tested for purity of culture during the batch process.

If the single use culturing system are used with different sizes of vessels/bags, rationale should be provided in the protocol to justify the worst-case vessel/bag or utilize a bracketing approach.

There is no formal requalification for single use systems. However, significant process changes, Engineering Events that involve failures or system changes, single use component changes not qualified by the vendor, or process failures may trigger additional qualification activities especially if negative trends are identified or operational integrity may be compromised. Events are reviewed to ensure that they don’t reflect a trend in the type of failure occurring and that the operational integrity of the system is intact.

During requalification of SIP systems once every two years, relevant Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Critical alarms may be tested to ensure proper operation. Performance is verified through one temperature stability run of not less than 12 hours, one thermal map of the SIP cycle with biological indicators (BIs) and temperature probes, and one sterile hold process simulation.

7.5 CIP Skids

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities (electricity, WFI, pharmaceutical compressed air) and components (valves, gauges, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the process-critical controls operate as expected, including access security, interlocks (if applicable), alarms, cycle sequencing and timing of cycle steps. For each recipe, process parameters, such as WFI volume, detergent selection and concentration, wash temperature, wash times, rinse conductivity, and drying steps are verified.

Cleaning efficacy is verified during PQ studies for each connected vessel/system in conjunction with the validation of that system. Vessels are visually inspected for cleanliness. Rinse samples are evaluated against established criteria.

Annual requalification is limited to verifying that the cycle parameters match what is in the SOP, and a review of relevant Engineering Events to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. A test wash cycle is not required as the BDP relies on cleaning verification for critical wash steps as cleaning validation is not practical given the multi-product nature and typically low replicates of process runs.

7.6 Vial Washer

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities (electricity, WFI, pharmaceutical compressed air) and components (valves, gauges, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the process-critical controls operate as expected, including access security, interlocks (if applicable), alarms, cycle sequencing and timing of cycle steps. For each vial size, process parameters, such as WFI spray and air blow times, and line speed, are verified. Cleaning efficacy is verified for each vial size during the OQ using a riboflavin or similar challenge solution.

Cleaning efficacy is verified during PQ studies for each vial size, using a typical number of vials per load. Washed vials are visually inspected and checked for damage. Washed vials are also aseptically reconstituted with WFI and tested for particulates, TOC, conductivity, endotoxin, and bioburden according to compendial standards for WFI listed in the current USP.

During annual requalification, relevant Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Performance is verified through verification of wash parameters, washing at least 1000 vials of each format currently in use and inspecting them before and after washing for damage, noting operational alarms, and submitting vials reconstituted with WFI and tested for particulates, TOC, conductivity, endotoxin, and bioburden according to compendial standards for WFI listed in the current USP.

7.7 Parts Washer (Glassware, Fittings, Equipment)

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities (electricity, steam, WFI, pharmaceutical compressed air) and components (valves, gauges, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the process-critical controls operate as expected, including access security, interlocks (if applicable), alarms, cycle sequencing and timing of cycle steps. For each cycle, process parameters, such as prewash, wash, circulated rinse, WFI rinse, Dry, and cooldown time, temperatures, and setpoints for detergents are verified. Cleaning efficacy is verified for each cycle during the OQ using a riboflavin or similar challenge solution.

Cleaning efficacy is verified during PQ studies for each pre-defined wash cycle and each load rack. Load items are coated with a simulated soil such as Soytone or TSB and allowed to dry. Washed load items are visually inspected and a rinse sample is sent for analysis of TOC ≤ 5 ppm, Conductivity ≤ 5 µS/cm, Bacterial Endotoxin (LAL) ≤ 0.25EU/mL, Bioburden ≤ 10CFU/100mL, and Particulates meet USP <788>.

During annual requalification, relevant Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Performance is verified through verification of wash parameters, performing one run of each cycle and rack in a matrix approach, and submitting a rinse sample for each run for analysis of TOC ≤ 5 ppm, Conductivity ≤ 5 µS/cm, Bacterial Endotoxin (LAL) ≤ 0.25EU/mL, Bioburden ≤ 10CFU/100mL, and Particulates meet USP <788>.

7.8 Stopper Washer

As standard practice the BDP uses prewashed and treated stoppers. As such there is no requalification procedure prescribed for this equipment type.

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities (electricity, steam, WFI, pharmaceutical compressed air) and components (valves, gauges, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the process-critical controls operate as expected, including access security, interlocks (if applicable), alarms, cycle sequencing and timing of cycle steps. For each stopper cycle, process parameters, such as WFI spray and air blow times, detergent dispensing (if used), and line speed, are verified. Cleaning efficacy is verified for each cycle during the OQ using a riboflavin or similar challenge solution.

Cleaning efficacy is verified during PQ studies for each cycle, using a predefined stopper cycle. Washed stoppers are visually inspected and checked for damage.

7.9 Depyrogenation Oven

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities (compressed air, chilled water, electricity) and components (valves, gauges, filters, displays, recorder) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the controls operate as expected, including access security, door interlocks (if applicable), cycle sequencing and timing of cycle steps, critical alarms and interlocks.

Non-viable particulate monitoring of the empty chamber during ramping, soaking, and cooling is conducted according to the current ISO standards for air cleanliness. For each cycle, a thermal mapping study is conducted to verify setpoint acquisition and empty chamber temperature uniformity for the duration of the depyrogenation period. Thermocouple placement is documented.

During PQ, the performance of the depyrogenation oven is verified by operating the oven with various load configurations to ensure heat penetration. Once the hardest-to-heat load is determined, three consecutive successful cycles using that load must be run. During these cycles, heat penetration is verified by probing the wrapped pans containing vials with thermocouples, and endotoxin reduction is verified using endotoxin challenge vials. The load configurations are described in detail, minimally including thermocouple placement locations, package wrapping materials and sizes of containers.

Revalidation occurs annually for depyrogenation ovens. Relevant Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Calibration is verified. The performance of the ovens is verified by conducting a single non-viable particulate monitoring run of the chamber during ramping, soaking, and cooling, according to the

current ISO standards. Additionally, a single heat penetration study/endotoxin challenge is performed for the hardest-to-heat load configuration. These results are compared to those from the previous year's validation study to identify trends. The load is described in detail, minimally including thermocouple placement locations, package wrapping materials and sizes of containers.

7.10 Preparative Chromatography Skids

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities and components (pumps, valves, regulators, recorders, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Testing is conducted during OQ to determine that instrument/PC communication, access security, and alarms function as expected. Power loss recovery is verified.

Testing is conducted to ensure that operating parameters are monitored and controlled, such as valve positioning, system pressure, and flow rates. When applicable, the UV, conductivity, temperature, and pH monitoring systems are tested for proper operation. The gradient functions and fraction functions are tested. The assembled system is checked for leaks using a backpressure equal to or greater than the expected process backpressure with a minimum of at least 70% of the system's maximum operating pressure.

7.11 Homogenizers

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities and components (pumps, valves, regulators, recorders, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Testing is conducted during OQ to determine that instrument/PC communication, software versions, access security, and alarms function as expected. Testing is conducted to ensure that operating parameters are monitored and controlled, such as valve positioning, system pressure, and flow rates. Any sequences or additional cycles to perform SIP or sanitization will be tested during OQ.

7.12 Process Centrifuges (excludes bench and floor bottle units)

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities and components (pumps, valves, regulators, recorders, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Testing is conducted during OQ to determine that instrument/PC communication, access security, and alarms function as expected. Testing is conducted to ensure that operating parameters are monitored and controlled, such as valve positioning, system pressure, speed, and flow rates.

7.13 TFF Skids

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities and components (pumps, valves, regulators, recorders, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Testing is conducted during OQ to determine that instrument/PC communication, software version, access security, and alarms function as expected. Testing is conducted to ensure that operating parameters are monitored and controlled, such as valve positioning, system pressure, and flow rates. When applicable, conductivity, temperature, and pH monitoring systems are tested for proper operation. The gradient functions and fraction functions are tested. The assembled system is checked for leaks using a backpressure of equal to or greater than the expected process backpressure with a minimum of at least 70% of the system's maximum operating pressure.

7.14 Biological Safety Cabinets (BSCs)

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities and components (pumps, valves, regulators, recorders, sensors) are verified. Calibration/certification is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Testing is conducted during OQ to determine that system operates, and alarms function as expected. Power loss recovery is verified. Testing is conducted to ensure that operating parameters are monitored and controlled, Air flow velocity, patterns, temperature and humidity (if applicable), HEPA filter integrity, etc., are verified from BSC certification.

During PQ, viable, non-viable, surface sampling studies will be performed for at least 10 days to ensure that BSC meets user specifications and that cleaning program is effective. Trend reports for environmental conditions will also be included in the PQ to ensure that environmental conditions are maintained during the study and meet acceptance criteria. The PQ testing may be conducted as part of area HVAC testing.

BSC certification will occur at least annually with critical units, those used for filling, cell banking, and virus production, may be certified on a 6-month schedule. Recertification of BSCs typically occurs as part of the HVAC system annual certification, unless a failure has occurred. Environmental monitoring results are graphed to identify and resolve trends, if necessary. Relevant Engineering Events are reviewed to ensure that

they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. BSC certification reports are reviewed.

7.15 Semi-automatic Vial Filling Machines

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities (electricity, compressed air) and components (valves, regulators, recorders, sensors, change formats) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the controls operate as expected, including access security, cycle sequencing and timing of cycle steps, alarm functions, and interlocks. Testing is conducted to ensure that operating parameters are controlled, such as line speed, rotational speeds, and filling nozzle modes and fill volume adjustment and accuracy. Proper operation of the stopper and crimp cap vibrator bowls & chutes and vial application is verified.

During PQ, the performance of the semi-automatic filling machines is verified by performing at least three consecutive successful process simulations using various vial sizes and fill volumes. For a given vial format i.e., 13 or 20 mm, a matrix approach may be utilized that covers the full operating range of fill volumes and vial sizes. This approach reduces the number of required fills while still mitigating risks. Filled vials and the surrounding filling station area are checked for the absence of splashed medium. Vials are also inspected for significant foaming. Filling accuracy is verified. If applicable, the vial counter should be assessed with manual counts from pans of processed vials.

Filled vials are visually inspected for particulates, improper seals, and damage to the stopper, seal, and glass. The percentage of rejected vials must meet predetermined acceptance criteria. Filled vials are tested for liquid particulate matter according to the most recent USP for injectables and potentially for other product types and are subjected to a container/ closure integrity test.

Environmental monitoring within the filling machine cabinet is conducted continuously from setup through completion of filling (non-viable and viable) and throughout the validation for areas outside the filling machine but within the ISO 5 environment.

The vial size/fill volume combinations for the PQ are derived from a matrix, as discussed in Section 8.1 for process validation. If microbiological growth medium is used for PQ testing, the PQ may occur simultaneously with the PV, as both require process simulation.

Revalidation for semi-automatic filling machines occurs at least annually. This consists of one successful PQ type run rotating through the vial size/fill volume combinations discussed in Section 8.1 for process validation. During requalification, relevant Engineering Events are reviewed to ensure that they don't reflect a trend in the type of failure occurring, and that the operational integrity of the system is intact. Critical alarms that could result in product loss are tested to ensure proper operation.

7.16 Vial Labelers

During IQ, manufacturers' as-built drawings, diagrams and material lists are identified and verified. Field components are compared to design specifications. The proper connection and installation of the supporting utilities (electricity, pharmaceutical compressed air) and components (gauges, sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Operational tests are conducted during OQ to determine that the process-critical controls operate as expected, including access security, interlocks (if applicable), alarms, cycle sequencing and timing of cycle steps. For each vial/label size process parameters, such as lot number, label application, and line speed, are verified. Labeled vials are visually inspected and checked for damage.

During PQ studies define an appropriate sample size of vials to label and perform the PQ runs, with pre-defined reject rate acceptance limits. Labeled vials should be visually inspected for acceptable label placement and checked for damage.

7.17 Analytical HPLCs (Manufacturing Support)

During IQ, manufacturers' diagrams and material lists are identified and verified. Field components and materials of construction are compared to design specifications. The proper connection and installation of the supporting utilities and components (valves, regulators, recorders, and sensors) are verified. Calibration is verified. Relevant system operation and maintenance SOPs are identified and reviewed.

Testing is conducted during OQ to determine that instrument/PC communication, access security, and alarms (when applicable) function as expected. Testing is conducted to ensure that operating parameters are monitored and controlled, including flow rates, and column and vial compartment temperatures. When applicable, the UV, conductivity, and pH monitoring systems are tested for proper operation. Noise and temperature stability, injection precision, and gradient composition are verified. Testing is also conducted to verify proper operation of the auto sampler, if one is present.

8.0 PROCESS VALIDATION

8.1 Semi-Automatic Filling Operations

During process validation, semi-automatic filling operations are simulated with microbiological growth medium (media fills). The media fills expose the growth medium to the same conditions seen by the product (i.e., delivery system, container closure systems, critical environments, and process manipulations) to evaluate likelihood of contamination during actual operations[7]. Media fills are specific to the container/closure system (vial closure size and vial volume range), range of fill volumes, filling process, filling equipment, and location. Operators are trained and qualified following applicable SOP's. The qualified operator pool is considered interchangeable, however as aseptic manipulations are involved the operator must participate in a successful validation media fill of any vial size or format as part of initial qualification and then remain qualified by participation in a successful media fill validation run within 12 months of a process fill. Participation should be consistent with the nature of each operator's or

participants duties during routine production. One technician performs critical primary aseptic tasks and interventions. Other technicians perform other filling operation tasks and assist the critical technician to ensure hands only touch critical surfaces. Roles are further defined by the validation protocol and applicable SOP's. Different roles have varying degrees of impact to the process validation.

The PV protocol incorporates "worst case" challenges to the normal or intended operating state of the process, for example, increasing the typical number of personnel in an area, or extending the duration of a filling procedure. During PV, the number of personnel in the filling area and their activities (i.e., one person loading vials into the machine and performing aseptic steps, and two to three staff performing other support activities) are representative of a production run. The process simulation includes normal and non-routine interventions as follows:

- Crimp bowl addition
- Stopper bowl addition
- Vial jam in feed mechanism actual/simulation
- Fallen vial actual/simulation
- Stopper stuck in bowl actual/simulation
- Crimp stuck in bowl actual/simulation
- Adjusting position of non-viable particle counter nozzle
- Adjusting position of filling cannula/needle
- Replace the tubing set
- Crimp head adjustment actual/simulation
- Outfeed rail width adjustment actual/simulation
- Clean machine after actual or simulated broken vial
- Clean/lubricate the crimp head jaws

Interventions demonstrate that these events may be performed during actual processing without significant risk for product contamination. Simulation in the context of an intervention means that the steps and tools used to correct the problem are used just as they would be in an actual event. The process medium is tested for growth promotion before and after use in the media fills. Environmental monitoring within the filling machine cabinet is conducted continuously from aseptic setup through completion of filling (non-viable and viable), at the beginning, middle, and end of filling for areas outside the filling machine but within the ISO 5 environment. Pre and Post EM is also collected per the governing SOP.

Fill accuracy is verified periodically during production. One hundred percent (100%) of the filled vials are visually inspected for turbidity, particulates, improper seals, and damage to the stopper, seal, and glass. The inspection is first performed by manufacturing and then a second 100% inspection is performed by Quality Control/Process Analytics. The percentage of rejected vials must meet predetermined acceptance criteria. The number of vials missed by manufacturing must also meet acceptance criteria as QC/PA only inspects 10% of the vials during production runs. Rejected vials with defects that do not compromise the integrity of the seal are sent for incubation for sterility assessment. Only weight check vials and vials that lack integrity may be excluded from incubation. For batch sizes of less than 5000 vials, one or more contaminated vials, cause the validation to fail. For a batch size of 5000-10,000 vials, one contaminated vial results in an investigation followed by a repeat of the media fill, and 2 or more contaminated vials results in a failure of the media fill.

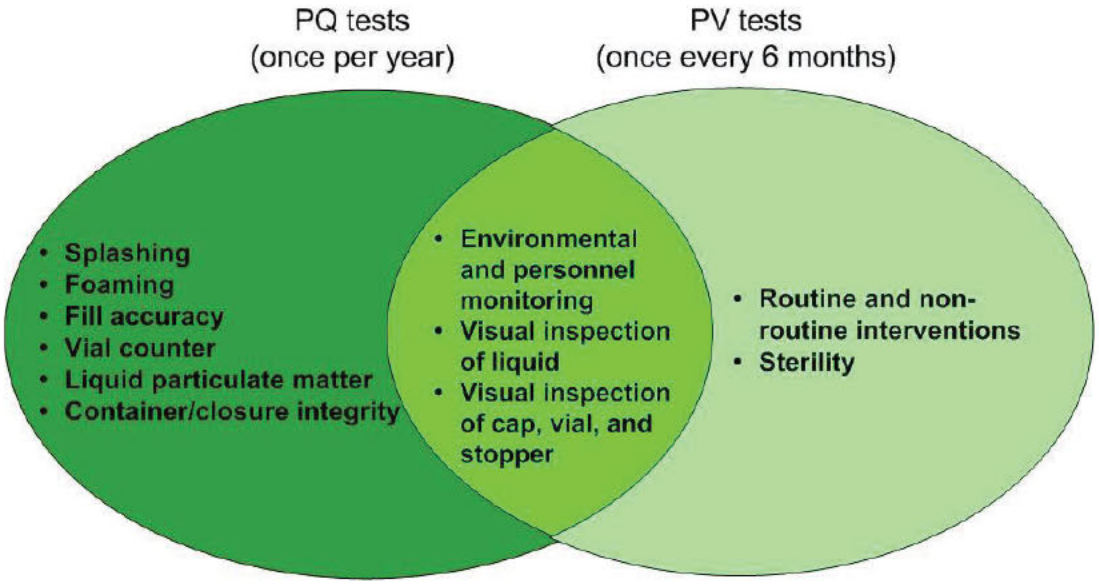
8.1.1 Initial Validation

Initial process validation consists of at least five consecutive successful media fills of at least 5,000 acceptable inspected vials each run. A bracketing approach for fill volume and vial size is used as all vials use the same closure specifically the stopper and crimp. In addition, all the vial handling equipment is fundamentally the same including infeed belt system, filling apparatus/pump, stopper applicator, crimp applicator, and crimper. Only the scroll wheel (if present) and the star wheel are changed. The height adjusts as well to account for the variance in vial height. As the fundamental differences between vials are minimal the matrix shown in the graphic covers all vial formats, all tubing sizes, and the full range of fill volumes.

	Vial sizes			
	10 mL	5 mL	3 mL	
Fill volumes	8 mL	4 mL	2.5 mL	1 x 5000-vial runs required for 8 and 2.5 mL volume
	3 mL	2 mL	0.25 mL	1 x 5000-vial runs required for 3 and 0.25 mL volume
	2 x 5000-vial runs required for this vial size	1 x 5000-vial run required for this vial size using intermediate volume	2 x 5000-vial runs required for this vial size	

8.1.2 Revalidation

As discussed in Section 7.14, there is significant overlap in the test methods used in the PQ for the vial filling machine, and the PV for the process. This overlap is illustrated in Venn diagram below. It is reasonable to combine the PQ and PV revalidation efforts to comply with the yearly requirement for the filling machine, and the biannual requirement for the process.



8.1.2.1 Process Revalidation

Under normal operation, should no changes be made to the container/closure system, fill volumes, filling process, and location, then the aseptic media fill process is considered to maintain its "validated" status if at least one successful process validation run was performed within the last six months rotating through each vial size format utilizing a fill volume indicative of the format i.e. large for 10 mL vial (8.0 mL), small for 3 mL vial (0.25 mL), and intermediate for the 5 mL vial (3.0 mL). Each fill size should use different proportional tubing diameter. If any of these aspects change, revalidation is necessary and requirements are evaluated based on the scope of the change. Typically change to a single variable requires only a single run and the revalidation run incorporating this documented change can fulfill the revalidation requirement.

8.1.2.2 Container/Closure System Revalidation

For an individual container/closure system (vial, stopper, and seal) to be considered "validated", at least one successful process validation run must be made within 6 months of a process fill. This approach allows three vial sizes, utilizing the same stopper and seal, to remain validated by cycling through the three vial sizes in series. Typical progression will result in each vial size/fill combination being performed roughly every 18 months. If the time since the last validation media fill exceeds 12 months, functional verification of critical machine functions shall be performed before execution of the revalidation to ensure risk of validation failure is not increased due to mechanical issues.

8.2 Manual Filling Operations

During process validation, manual filling operations are simulated with microbiological growth medium (media fills). These hand fills are conducted with at least as many vials as are expected in the maximum batch size. The hand fills will expose the growth medium to the same conditions seen by the product (i.e., delivery system, container closure systems, critical environments, and process manipulations) to evaluate likelihood of contamination during actual operations[7]. Manual filling operations of filling and stoppering are highly-critical; therefore, unlike semi-automatic filling processes the validation of those operations are directly linked to the operators performing those tasks. Hand fills are specific to a container/closure system, filling process, range of fill volumes, set of locations, and set of filling and stoppering operators.

Validation of crimping operation occurs as part of the manual filling process. However, crimping operators are not validated and are instead qualified via training. If crimping operations are conducted to qualify a new operator in that role, they may be conducted with empty vials or WFI fills, as an alternative to microbiological growth medium. Crimped vials are visually inspected for improper seals, and damage to the stopper, seal, and glass. The percentage of rejected vials must meet predetermined acceptance criteria.

The PV protocol incorporates "worst case" challenges to the normal or intended operating state of the process, for example, pausing operations, or extending the duration of a filling procedure. During PV, the number of personnel in the filling area and their activities (i.e., filling, capping, crimping, assisting, and performing environmental monitoring) are representative of a production run. The process medium is tested for growth promotion before and after use in the media fills. Environmental monitoring within the Biological Safety Cabinet (BSC) and adjacent room is conducted continuously and at critical points during the validation.

Filling accuracy is verified for the range of fill volumes expected during production. One hundred percent (100%) of filled vials are visually inspected for particulates, improper seals, and damage to the stopper, seal, and glass. The percentage of rejected vials must meet predetermined acceptance criteria. Vials that have only cosmetic defects (that do not compromise the integrity of the seal) are returned to the batch of filled vials and sent for incubation for sterility assessment. Only fill check vials and vials that lack integrity may be removed prior to incubation. One or more contaminated vials results in a failure of the media fill.

In addition to sterility, filled vials are tested for particulate matter and bacterial endotoxins according to the most recent USP, and are subjected to a container/ closure integrity test.

Subsequent to aseptic media fill validation for manual filling operations, the maximum number of vials filled during product runs may not exceed the number of vials filled or stoppered per operator during the media fill validation.

8.2.1 Initial Validation

Initial process validation consists of three consecutive successful media fills of the largest batch size expected. A bracketing approach for fill volume may be taken for a given container/closure system. For example, if the smallest and largest fill volumes are included in the validation for a given container/closure system, fill volumes in between those are also considered validated. Thus, since three runs are typically required for validation, two may be done using the largest fill volume (representing the worst case for sterility if the product exposure duration is longest) and one may be done using the smallest fill volume (representing the worst case for filling accuracy). In this way, one set of media fill runs allows a range of fill volumes to be validated for a given container/closure system.

Operators maintain validation for a period of 1 year and therefore must participate in each activity within that interval to maintain validated status. Operator validation is limited to the tasks they maintain validation in and the number of vials they filled or stoppered. New operators must initially participate in 3 runs of any size/format and in any manual fill suite location. After initial validation, participation in a single validation run within 12 months of a process run is required.

8.2.2 Revalidation

Under normal operation, should no changes be made to the container/closure system, range of fill volumes, filling process, or location, the aseptic media fill

process is considered to be “validated” if at least one successful validation run is performed within six months of the process fill for the given vial size/fill volume combination. If process aspects change, revalidation is necessary and requirements are evaluated based on the scope of the change.

Under these same conditions, an operator remains validated if he or she participates in at least one successful validation run per year. Additionally, a location for performing the fill remains validated if one successful validation run occurs in that area within the last year.

For an individual vial size or type fill to be considered “validated”, at least one successful qualifying validation run must be made within a year of the process run . As the 2 and 3 mL vials are dimensionally similar and the 5 and 10 mL vials are dimensionally similar a format within each group with any fill volume needs to be performed for that category to be “validated”. The 2/3 mL and the 5/10 mL groups all share the same 13 mm closure system. Validation status may be allowed to lapse based on production requirements. Novel container or vial sizes will be evaluated on a case by case basis as volume and closure type must be evaluated for risk and will require from 1 to 3 runs for validation. Careful consideration to upcoming projects and their fill requirements should be given to ensure needed formats, areas, and operators needed for a given fill are validated when required.

8.3 Sterile Transfer Operations and Aseptic Manipulations

Sterile transfer validation is used to verify that a process fluid remains sterile during transport from one location to another. This usually applies in the case of media transfer and inoculation of large-scale fermentors and bioreactors. Process fluid transfer is facilitated by making aseptic connections to the process reservoir, making aseptic connections to the receiving reservoir (often a fermentor or bioreactor) and transporting the fluid between the two (usually by pumping).

Aseptic manipulation validation is used to verify that operations done to products after final filtration or to products that cannot be sterile filtered can be performed maintaining sterility of the process fluid. This usually applies to final filtration, formulation steps after final filtration or to cell therapy products as they cannot be sterile filtered. In a validation all the steps are performed in a way that replicates the process, or the worst-case approach for a grouping of related processes, performing all aseptic manipulations using growth medium.

The process is simulated three consecutive times using microbiological growth medium. Media and reagent preparation are documented. Acceptance criteria include medium sterility and growth promotion. This process operation may be integrated into other equipment validations. Typical term for requalification is annually for processes involving final product. Routine requalification only requires a single run.

8.4 Airflow Visualization Studies

Airflow visualization or smoke studies are a tool to complement aseptic operations. Studies are generally for critical operations such as filling performed within ISO 5 environments of rooms or within BSCs. The process can be valuable in detecting

undesirable airflow including swirling, eddies, or other turbulent forms of airflow. All open containers and critical surfaces should follow the principle of “first air” meaning that air that contacts critical areas should originate from the HEPA filters without first contacting any other surfaces.

Testing evaluates airflow during static and dynamic processing conditions. The smoke source should not be heavier than air and should not be directed forcefully from the source as this could obscure subtle issues with the airflow. Studies should be captured with a camera from angle(s) that definitively depicts critical airflow.

Complete studies are performed initially incorporating both the equipment and the process. This includes static and dynamic testing in the critical and immediately adjacent areas. The studies should evaluate the actual equipment and process steps and operator techniques to be used. Changes to a process, equipment, or room require supplemental studies to evaluate the effects of the changes. These supplemental studies are only required for the areas/steps impacted.

Airflow studies may also be valuable as part of a contamination investigation. Trending of low return airflow volumes is also a good practice. A room could maintain the same ACH, but changes in the magnitude of area return volumes could alter the direction of the airflow thereby altering the risk associated with process steps. If shifts are detected, airflow values should either be returned to levels consistent with the time of testing or airflow visualization studies repeated to the extent necessary to determine that principles of first air are adequately maintained.

8.5 Gowning Validation/Qualification

Gowning qualification is used to document the effectiveness of the sterile gowning procedure for individuals entering an Aseptic Processing Area (APA). Individuals whose jobs require them to enter an APA during CGMP production operations or for the purpose of performing validation and/or maintenance work while the area is in service must be qualified according to the gowning qualification SOP, and requalified yearly.

Environmental monitoring is conducted at the beginning of the qualification before gowning occurs, and at the end of the qualification, to verify that the environment maintains acceptable air cleanliness levels for the duration of the study. The purpose of this is to ensure that the environment has not compromised the study, and to aid in interpretation of results.

During gowning qualification, the test subject applies gowning according to the approved gowning procedure for the area. A Quality Control technician tests the gowning efficacy by sampling the gown and glove for viable organisms. Initial gowning qualification is performed 3 times, subsequent requalification requires only a single performance.

9.0 ROLES AND RESPONSIBILITIES OF VALIDATION PARTICIPANTS

The participants in the execution of this Validation Master Plan have as their common objective the accurate execution of the qualification/validation of the BDP Manufacturing Site. To accomplish this objective, the anticipated roles and responsibilities of the

participants from FNLCR, their contractor Leidos Biomedical, and qualified validation contractors are outlined below.

Group	Roles/Responsibilities
Validation Contractors	• Manage contractor validation resources to attain successful completion of validation scope • Maintain and communicate validation schedule • Prepare and execute DQ, IQ, OQ and PQ protocols as defined in the contract • Document and communicate to BDP any deviations/exceptional conditions encountered during the qualification studies and propose corrective actions • Write validation final reports as defined by contract and procedures • Participate in investigations, as applicable
BDP Production Group	• Assist the validation department in drafting, reviewing and executing validation protocols and reports, so that they reflect production processes and needs • Provide technical and process-related input regarding the content of the qualification protocols, including acceptance criteria • Draft and implement equipment and process SOPs • Provide personnel to assist in the operation of equipment during validation testing • Provide operators to assist in PQ work and execute PV studies • Review and approve validation protocols and reports • Review deviations/exceptional conditions and propose corrective actions • Assist with scheduling and coordination of material, information and availability of equipment and personnel

Group	Roles/Responsibilities
Biopharmaceutical Quality Engineering (BQE) Group	• Draft and revise Master Plan documents • Provide technical and process-related input regarding the content of the qualification protocols, including acceptance criteria • Draft, review, execute, and approve validation protocols and reports • Review and approve utility and equipment SOPs • Verify that results are within acceptable limits • Review deviations/exceptional conditions and propose and approve corrective actions • Oversee investigations, as applicable
Biopharmaceutical Process Analytics (BPA) Group	• Participate in setting acceptance criteria for validation protocols • Provide laboratory and testing support to validation effort • Coordinate testing of validation samples by contract laboratories • Perform environmental, water, and utility monitoring • Verify scientific validity of BPA test results • Provide personnel to assist in the operation of equipment during BPA-related validation testing
BDP Engineering Group and Facilities Maintenance and Engineering (FME)	• Provide technical and process-related input regarding the content of the qualification protocols as requested • Advise on exceptional conditions, and propose and execute corrective actions • Provide engineers or issue work orders for FME staff to assist in the operation of utility equipment during validation testing • Write and implement utility and equipment preventive maintenance SOPs • Ensure calibration of specified instrumentation and ensure that it remains in a calibrated state throughout the calibration period • Perform Preventive Maintenance on utilities; assist in performing Preventive Maintenance on equipment as applicable

10.0 SUPPORTING PROGRAMS

This section provides descriptions of the supporting programs to ensure continued operation of the BDP Manufacturing Site in a validated state, in compliance with current Good Manufacturing Practice (CGMP).

10.1 Documentation Programs

Documentation programs have been developed to ensure that quality standards are met, operations are consistently performed, and data and records are credible, well organized, retrievable, and securely stored. The types of documents in the documentation programs include but are not limited to: validation records; standard operating procedures; test protocols and results; equipment files (see Section 10.4); and master and batch production records.

The documentation programs themselves are described in SOPs. Written and approved procedures are established for writing, reviewing, approving, distributing and revising documents encompassed by the documentation programs. The documentation programs are administered by BQA.

10.2 Instrument Calibration Program

Regular calibration of quantitative instruments is necessary to generate scientifically-sound data and to comply with CGMPs. Components or instruments that require calibration are identified and the frequency of calibration determined. Written and approved procedures have been developed for performing and documenting instrument calibration (including use of qualified contractors), and for evaluating the cause and impact of out-of-tolerance conditions and failed calibrations.

Calibration activities are scheduled to ensure they are appropriate and timely and are performed using NIST-traceable or other approved standards. Calibration records are reviewed by BQE. Physical forms are filed by BQA documentation. BQE and BDP Engineering jointly administer this program.

10.3 Preventive Maintenance Program

As required by the CGMP regulations, a preventive maintenance program is in place that addresses the frequency and scope of maintenance for process and analytical equipment and process-critical utility systems. Preventive maintenance activities are scheduled to ensure they are timely and are performed in accordance with engineering recommendations, production requirements and recognized trade practices. Written and approved procedures have been developed for scheduling, performing and documenting preventive maintenance, and for evaluating the work's impact on current validation status if appropriate. A system has been developed to maintain preventive maintenance plans.

The Preventive Maintenance Program is typically administered by Facilities, Maintenance, and Engineering (FME) for utility-oriented equipment while analytical equipment is handled by the BDP and relies on vendor service.

10.4 Master Equipment Files

Centralized Master Equipment Files (MEF) are established for utility systems, subsystems and process and analytical equipment. A unique identification number is assigned to each individual piece of utility equipment or process equipment and are used as the basis for the MEF.

These files constitute the equipment history for both critical and non-critical equipment in BDP areas, and the contents of the MEF are described in written, approved procedures. Maintenance work, both scheduled and unscheduled, is documented in these centralized files, which also include repair/service records, purchasing records, equipment manuals, engineering specifications, spare parts lists, calibration records, validation records, cleaning records, retired equipment logs, and other information, as appropriate. Active MEF's are on-site and are administered by BQA. Access to the files is limited to authorized individuals. Most FME performed maintenance work is maintained in an FME software platform.

10.5 Engineering Event Management

An Engineering Event is established to document failures and changes to utility systems and process and analytical equipment. Engineering event management will start upon the execution of initial validation of the ATRF facility. Deviation management procedures will be used to track and close any deviations that occur during validation activities.

This Engineering Event Management SOP describes the procedure for managing "engineering events" that have the potential to remove GMP systems, equipment, buildings and areas from an "In-Service" status. Events include, but are not limited to, changes, failures, and calibration Out-of-Tolerance (OOT) events. This and related SOPs also describes the procedure for returning equipment, systems, buildings and areas to an in-service status after the engineering event has been resolved (return-to-service (RTS)).

Engineering Events are evaluated by BQA for their potential impact on product and are filed as instructed in the SOP.

10.6 Environmental, Water, and Utility Monitoring Program

Environmental monitoring occurs within CGMP manufacturing and other areas of BDP as defined in EM SOP. The environmental parameters monitored include non-viable particulates, airborne and surface viable organisms, temperature, and relative humidity. BSCs and Portable Clean Rooms if used are treated as other rooms for this purpose.

In addition, the process-critical utility systems are routinely monitored for quality. These include Clean Steam, Pure Steam, Water for Injection, DPRO Water, Purified Water Generation Systems, Compressed Air, and Compressed Gas Distribution Systems.

Written and approved procedures describe the responsibilities for environmental monitoring, the sampling points, sampling frequency, sampling methods and

instruments, methods of evaluation, acceptable limits, recordkeeping, and responses to excursions or out-of-specification results.

Data gathered from environmental monitoring programs are used to evaluate the effectiveness of controls, such as preventive maintenance and housekeeping/ sanitation, and to monitor activities that may affect product/process integrity and personnel protection. Alert and action levels are established for critical parameters of routine points using regulatory guidelines and design specifications where appropriate. These levels are evaluated annually and recalculated as necessary.

10.7 Changeover and Decontamination Procedures

Since the BDP Manufacturing Site is designed to manufacture numerous drug substances on a campaign basis, changeover from one product/process to the next is controlled and documented. Changeover activities include removal and reconciliation of product from the previous campaign; documented disinfection/cleaning of the production areas, and equipment; monitoring and reporting of environmental quality; and final changeover review and area clearance by BQA.

The Virus Production Facility (VPF) is designed for paraformaldehyde, vaporized hydrogen peroxide (VHP), and chemical decontamination following the manufacture of products from BL-2 and BL-3 level agents. The decontamination is part of the changeover procedure and is conducted according to written and approved procedures. Paraformaldehyde decontamination is only applicable to BSCs as required for select maintenance. VHP or chemical decontamination may be used interchangeably for suite decontamination for BL-2 and VHP required after initial chemical decontamination for BL-3 organisms. Final release of the decontaminated suite requires BQA approval.

10.8 Training Program

A Training Program is established to ensure new and current BDP employees receive applicable training in CGMP, job skills, and procedures (SOPs) associated with manufacturing and facility practices. The training objectives are met by various training methods, such as academic courses, seminars, tutorials, on-the-job training, etc. Training is documented. The Training Program is administered by BQA. Some specific safety, biosafety, and occupational health training not associated with CGMP operation is provided and administered by Leidos Biomedical Environmental Health and Safety personnel.

10.9 Pest Control

To further minimize the potential for product contamination, BDP employs a pest control system characterized in a written procedure. The system may utilize contractors or FME staff. The exterior of the ATRF is managed by the landlord.

11.0 CITATIONS

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[5] ISPE, “Pharmaceutical Engineering Guides for New and Renovated Facilities”, Volume 5, *Commissioning and Qualification*, First Edition, March 2001.

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13.0 APPENDICES

Appendix 13.1: BDP Site Plan
Appendix 13.2: Functional Area Descriptions and Major Equipment
Appendix 13.3: Validation Matrix
Appendix 13.4: Risk-Based Calibration and Validation Requirements Matrix
Appendix 13.5: Risk Assessment – Utilities
Appendix 13.6: Risk Assessment – Equipment

VMP-003 Appendix 13.1
BDP Site Plan - ATRF

Appendix 13.2
Functional Area Descriptions and Major Equipment

A listing is available in the facility Drug Master File (DMF). Refer to the most recent DMF maintained by BQAD for these documents. Referring to the DMF avoids the risk of inconsistencies between the two documents and the DMF is reviewed on an annual basis.

Appendix 13.3
Validation Approach Matrix

Table shows typical approach to consider when purchasing and maintaining equipment.
The approach used initially for the ATRF for each new piece of equipment is in VMP-003 REV 00

Equipment or Process Category	Direct/Indirect/ No impact	SAT	IQ	OQ	PQ	PV	Requal/ Cert Interval Years	Notes
Utility System	Direct/Indirect	X*	X	X	X		**	1
Utility System	No impact	X*						1
Autoclave (Decon)	Indirect		X	X	X		1 or 2	1
Autoclave (Sterilizing)	Direct	X*	X	X	X		1	1
Backup Power System	Indirect	X*	X	X				
Biological Safety Cabinet	Direct		X	X	X[2]		1, HVAC	
Centrifuge (Specialty)	Varies		X	X				4
Cold Room	Direct/Indirect		X	X	X		3 or NA	5
Compressed Gas System	Direct		X	X	X		1	
Chromatography System	Direct		X	X				
CIP Skid	Direct	X	X	X	X			
Culture System, SIP Fermentor/Bioreactor	Direct	X*	X	X	X		2	
Culture System, Single Use	Direct		X	X	X		EE	
Decontamination System	Indirect	X*	X	X	X		2	
Depyrogenation Oven	Direct	X	X	X	X	X	1	
Freezer	Direct		X	X	X[3]		3 or NA	
Homogenizer	Direct	X*	X	X				
Incubator	Direct		X	X			5 or NA	
Parts/Glassware Washer	Direct	X*	X	X	X		1	
POU Water System	Indirect		X	X	X		1	
Refrigerator	Direct		X	X	X[3]		3 or NA	
SCADA	Direct	X*	X	X	X			1
Vial Crimper Manual	Direct		X			X	0.5	
Vial Crimper Automatic	Direct		X	X	X	X	0.5	
Vial Filler Manual	Direct		X			X	0.5	
Vial Filler Automatic	Direct	X*	X	X	X	X	0.5	1
Vial Labeler	Direct	X*	X	X	X			
Vial Washer	Direct	X*	X	X	X	X	1	1

Only systems or equipment with direct or indirect impact potential used for GMP are validated.
Direct indicators include: direct product contact, sterilization/depyrogenation functionality, producing data used to accept/reject product, process control, and critical storage.
* Depends on vendor and complexity of system
** Varies from annual, to on demand with EE, to not required. Refer to body of VMP.
1, May include DQ, FAT, or Commissioning
2, Typically handled as part of HVAC/Room qualification
3, Need for PQ depends on use, required when units hold final product
4, Standard floor or bench units require calibration but not validation
5, Units that do not stored final product or otherwise deemed critical do not require PQ

Appendix 13.4
Revalidation Matrix

Criticality Levels and Codes for Qualification and Associated Process and Frequency

Risk Level:	High (1 most critical)	Medium (2 intermediate)	Low (3 least critical)
Autoclaves	Calibration annually	Calibration annually	Calibration annually
	Requalification Annually	Requalification every 2 years	Initial qualification only
Controlled Temperature Equipment	Calibration annually	Calibration annually	Calibration annually
	Requalification every 3 years, 5 years for incubators	Initial qualification only*	
Culturing Systems: SIP Bioreactors and Fermenters	Calibration annually	Calibration annually	
	Requalification every 2 years	Initial qualification only*	
Culturing Systems: Single Use	Calibration annually		
	Initial qualification only*		
Utility Systems	Calibration annually	Calibration annually	Calibration annually
	Requalification Annually (or every 2 years in the case of biowaste)	Initial qualification only*	No qualification
Aseptic Processes	Requalification Annually (filtration, post filtration formulation, cell therapy final dosing)	Initial qualification only* (cell therapy aphesis processing)	
Miscellaneous	Calibration annually	Calibration annually	Calibration annually
	Requalification Annually	Initial qualification only*	No qualification

*Requalification results from Engineering Change, including failure, relocation, and change to intended use/setpoint. The Engineering Event procedure will determine what is required.

Appendix 13.5
Risk Assessment for Utilities

Project and System: ATRF - Buildings A and B Utilities
Assessor(s): The following groups participated in development of the risk assessment: Quality Engineering and Validation, Late Process Sciences, and Process Analytics.
Assessment Dates: March-September of 2022

						Before Mitigation							Remarks
Row #	ATRF #	System Name	Location and/or Spec Reference	Risk Scenario	Consequence	Relevance (Business, GMP)	Severity of Impact (High, Medium, Low)	Likelihood of Occurance (High, Medium, Low)	Probability of Detection (Low Medium, High)	Risk Score	Priority (High, Medium, Low)	Risk Mitigation (Testing scenario, Procedural control, Requirements, Design or Configuration Change)	
		Utilities											
1	WWFI001A	Water for Injection (WFI) Generation Storage and		Pump Failure	Loss of WFI	Direct	High-3	Low-1	High-1	6	Low	Spare pump is kept on hand	
3				[illegible] failure	of WFI			1	High-1	5	Low		
4				Plant St	Loss of WFI		Medium-2	Low-1	High-1	4	Low	None Required	
5				[illegible] Fa	s of WFI			1	High-1	5	Low		
6				DPRO Supply Failure	Loss of WFI			Low 1	High-1	5	Medium	None Required	
				Pipe or Pressure Failure on Distribution Loop	Loss of WFI		Medium-2	Medium-2	High-1	5	Medium	Interlock point of use valves to limit use and maintain flow and [illegible] re	Typically flow due to power interruptions
8	DPRO001A	Dou Osmosis (DPRO) Generation, Storage and [illegible]		TOC/Conductivity Sensor Failure	Loss of WFI, low quality product collected		High-3	Low-1	High-1	6	Low	None Required	Risk depends on whether controlling or non-controlling [illegible]
				Pump Failure	Loss of RO Generation	Direct	High-3	Low-1	High-1	5	Low	None Required	
9							Medium-2	Low-1	High-1	4	Low	None	
10				F	s of R tion			Low-1	High-1	5	Medium	Maintain energy	
11				Heat Exc Failure	Loss of RO Generation		Low-1	Low-1	High-1	3	Low	None Required	
12					of R tion		Medium-2	Low-1	High-1	6	Low	None Required	
13	BLER001A	Plant Steam System (3 [illegible]		Pump Failure	Loss of line and could lead to [illegible]	In-Direct	Medium-2	Low-1	High 1	4	Low	None Required	
14				PLC failure	Loss of line and could lead to [illegible] uct loss		Medium-2	Low-1	High-1	4	Low	None Required	
15				Loss of Utaly (Gas & Electric)	Loss of line and could lead to product loss		High-3	High-3	High-1	7	Medium	UPS power to controller system being considered as most outages are less than 10 [illegible]	
15	PSGR001/002A	Pure Steam Generation and Distribution		System leak	Loss of pure steam	Direct	Medium-2	Low 1	High 1	4	Low	None Required	We have 2x systems and can maintain processes on a single PSG
16				PLC failure	Loss of pure steam		Medium-2	Low-1	High 1	4	Low	None Required	We have 2x systems and can maintain processes on a single PSG
17				Plant Steam Failure	Loss of pure steam		High-3	Low-1	High 1	5	Low	None Required	We have 2x systems and can maintain processes on a single PSG
18				DPRO Supply Failure	Loss of pure steam		High-3	Low-1	High-1	5	Low	None Required	We have 2x systems and can maintain processes on a single PSG
19				TOC/Conductivity Sensor Failure	Loss of pure steam		Medium-2	Low-1	High-1	4	Low	Steam samples routinely analyzed	We have 2x systems and can maintain processes on a single PSG
	ECSG001A [illegible]	Clean Steam Generation and Distribution		System leak	Loss of clean steam	In-Direct	Medium-2	Low-1	High-1	4	Low	None Required	
21					Loss of clean steam			Low-1	High-1	5	Low	None Required	
22					s of			1	High-1		Low		
23				Failure	Loss of clean steam			Low-1	High 1	5	Low	None Required	
24	CHLR005A	Process Chilled Water Generation and Distribution System		ure	Loss of process chilled water	In-Direct	Low-1	Low 1	High-1	3	Low	None Required	
25							1	1	High-1	3	Low	Redundancy	
26				R rant loss	Loss of process chilled water		Low-1	Low 1	High 1	3	Low	None Required	
				F			Low-1	1	High-1	3	Low	None Required	
28				Loss of utilities	Loss of process chilled water		Low-1	Low-1	High 1	3	Low	None Required	

Project and System: ATRF - Buildings A and B Utilities
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Assessment Dates: March-September of 2022

							Before Mitigation							Remarks
Row #	ATRF #	System Name	Location and/or Spec Reference	Risk Scenario	Consequence	Relevance (Business, GMP)	Severity of Impact (High, Medium, Low)	Likelihood of Occurrence (High, Medium, Low)	Probability of Detection (Low, Medium, High)	Risk Score	Priority (High, Medium, Low)	Risk Mitigation (Testing scenario, Procedural control, Requirements, Design or Configuration Change)	
29	SAHU001A/002A	Heating Ventilation and Air Conditioning (HVAC) System	Roof	Failure BAS	Loss of EnvControl	Direct	Medium-2	Medium-2	High-1	5	Medium	SCADA system maintains records. Affects production schedule - handled procedurally	Serving Cell Culture & Purification ISO 7 and 8 Spaces. Built with redundant fans running on VFD - normally at 75%. AHU 1 and 2 supply main header feeding CC & Purification
30				Loss of Power	Loss of EnvControl		Medium-2	High-3	High-1	6	Medium	SCADA system maintains records. Affects production schedule - handled procedurally.	
31				Control valve failure	Loss of EnvControl		Medium-2	Medium-2	Medium-2	6	Medium	SCADA system maintains records. Affects production schedule - handled procedurally	
32				Motor failure	Loss of EnvControl		Low-1	Low-1	High-1	3	Low	None Required	2 fan motors and isolation damper. Single motor provides about 70% airflow and will maintain airflow direction
33				Cooling/Heating Coil Failure	Loss of EnvControl		Low-1	Medium-2	High-1	4	Low	None Required	
34				Failure of VFD	Loss of EnvControl		Low-1	Medium-2	High-1	4	Low	Changes made to	
35				HEPA Filters not sealing either frames	Loss of EnvControl		Medium-2	Medium-2	Medium-2	6	Medium	Smoke studies to verify tight seal	
36				Exhaust Fan-Motor & belt failure	Loss of pressurization		Low-1	Low-1	High-1	3	Low	None Required	Exhaust fans are designed with N+1 redundancy and are on E-Power
37				Clogged drains on cooling coils	Loss of time		Low-1	Medium-2	High-1	4	Low	None Required	
38	SAHU003A	Heating Ventilation and Air Conditioning (HVAC) System - Viral Production Facility	Roof	Failure BAS	Loss of EnvControl	Direct	High-3	Medium-2	High-1	6	Medium	SCADA system maintains records. Affects production schedule - handled procedurally.	
39				Loss of Power	Loss of EnvControl		Medium-2	High-3	High-1	6	Medium	SCADA system provides alarm notification and maintains records. System on Standby power Affects production schedule - handled procedurally.	
40				Control valve failure	Loss of Env Control		High-3	Medium-2	Medium-2	7	Medium	SCADA system provides alarm notification and maintains records. Affects production schedule - handled procedurally.	
41				Motor failure	Loss of Env Control		High-3	Low-1	High-1	5	Medium	Motors redundant run unit PM SCADA monitors differential pressure providing detection of significant failure. Pressure trends also reviewed periodically	2 fan motors and isolation damper. Single motor provides about 70% airflow and will maintain airflow direction
42				Cooling/Heating Coil Failure	Loss of EnvControl		High-3	Medium-2	High-1	6	Medium	Maintain spares and or service contracts	
43				Failure of VFD	Loss of Env Control		High-3	Low-1	High-1	5	Low	None Required	
44				HEPA Filters not sealing either frames	Loss of EnvControl		Medium-2	Medium-2	Medium-2	6	Medium	Smoke studies to verify tight seal	
45				Exhaust Fan-Motor & belt failure	Loss of pressurization		Low-1	Medium-2	High-1	4	Low	None Required	Exhaust fans are designed with N+1 redundancy and are on E-Power
46				Clogged drains on cooling coils	Loss of time		Low-1	Medium-2	High-1	4	Low	None Required	
47	SAHU004A	Heating Ventilation and Air Conditioning (HVAC) System Filling Area		Failure BAS	Loss of Env Control leading to loss of time or loss of product depending on timing of event	Direct	High-3	Medium-2	High-1	6	Medium	SCADA system provides alarm notification and maintains records. Affects production schedule - handled procedurally	ISO 5 inside a ISO 7 area

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48				Loss of Power	Loss of Env Control, leading to loss of time or loss of product depending on timing of event		High-3	High-3	High-1	7	Medium	SCADA system provides alarm notification and maintains records. Affects production schedule - handled procedurally	
49				Control valve failure	Loss of Env Control, leading to loss of time or loss of product depending on timing of event		Medium-2	Medium-2	Medium-2	6	Medium	SCADA system provides alarm notification and maintains records. Affects production schedule - handled procedurally	
50				Motor failure	Loss of Env Control, leading to loss of time or loss of product depending on timing of event		High-3	Low-1	High-1	5	Low	Motors receive routine PM. SCADA monitors differential pressure providing detection of significant failure. Pressure trends also reviewed periodically	2 fan motors and isolation damper. Single motor provides about 70% airflow and will maintain airflow direction
51				Cooling/Heating Coil Failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
52				Failure of VFD	Loss of Env Control		Low-1	High-3	High-1	5	Low	None Required	
53				HEPA Filters not sealing in their frames	Loss of Env Control		Medium-2	Medium-2	Medium-2	6	Medium	Smoke studies to verify tight seal	
54				Clogged drains on cooling coils	Loss of time		Low-1	Medium-2	High-1	4	Low	None Required	
55	SAHU005A	Heating Ventilation and Air Conditioning (HVAC) System, A2 ISO 8 Hallways, Mat Inspection, and storage	Mezz	Failure BAS	Loss of Env Control	Direct	Medium-2	Medium-2	High-1	5	Medium	SCADA system maintains records. Affects production schedule - handled procedurally	
56				Loss of Power	Loss of Env Control		Medium-2	High-3	High-1	6	Medium	SCADA system maintains records. Affects production schedule - handled procedurally	
57				Control valve failure	Loss of Env Control		Medium-2	Medium-2	Medium-2	6	Medium	SCADA system maintains records. Affects production schedule - handled procedurally	
58				Motor failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
59				Cooling/Heating Coil Failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
60				Failure of VFD	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
61				HEPA Filters not sealing in their frames	Loss of Env Control		Medium-2	Medium-2	Medium-2	6	Medium	Smoke studies to verify tight seal	
62				Clogged drains on cooling coils	Loss of time		Low-1	Medium-2	High-1	4	Low	None Required	
63	SAHU019A	Heating Ventilation and Air Conditioning (HVAC) System, first floor ISO 8 dispensing/sampling and storage	[illegible]	Failure BAS	Loss of Env Control	Indirect	Low-1	Medium-2	High-1	4	Low	None Required	Critical area is the downflow booth which operates independently and proper function is easy to determine.
64				Control valve failure	Loss of Env Control		Medium-2	Medium-2	Medium-2	6	Medium	None Required	
65				Motor failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
66				Cooling/Heating Coil Failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
67				Failure of VFD	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
68				Clogged drains on cooling coils	Loss of time		Low-1	Medium-2	High-1	4	Low	None Required	
69	SAHU006A	Heating Ventilation and Air Conditioning (HVAC) System, A2 CNC Area		Failure by any means leading to loss of enough airflow to impact adjacent classified CGMP space via airflow reversal	Loss of Env Control	Indirect	Low-1	High-3	High-1	5	Low	None Required	Power interruption is the most frequent cause. Other causes would be low occurrence.
70	SAHU007A	Heating Ventilation and Air Conditioning (HVAC) System first floor GMP warehouse MMC, QC sampling, and corridors	Mezz	Failure BAS	Loss of Env Control	Indirect	Low-1	Medium-2	High-1	4	Low	None Required	eCMD Warehouse, MMC, QC sampling, and CNC corridors
71				Control valve failure	Loss of Env Control		Medium-2	Medium-2	Medium-2	6	Medium	Maintain spares and/or service contracts	

Project and System: ATRF - Buildings A and B Utilities
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72				Motor failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
73				Cooling/Heating Coil Failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
74				Failure of VFD	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
75				Exhaust Fan-Motor & belt failure	Loss of pressurization		Low-1	Medium-2	High-1	4	Low	None Required	Exhaustfans are designed with N+1 redundancy and are on E-Power
76				Clogged drains on cooling coils	Loss of time		Low-1	Low-1	High-1	3	Low	None Required	
77	SAHU009A	Heating Ventilation and Air Conditioning (HVAC) System, first floor Chiller Room		Failure by any means leading to Chiller malfunction from extreme temperture	Loss of Env Control	Indirect	Low-1	Low-1	High-1	3	Low	None Required	
78	SAHU010A	Heating Ventilation and Air Conditioning (HVAC) System, A2 Manufacturing Administrative area and hall		Failure by any means leading to loss of enough airflow to impact adjacent CGMP space via airflow reversal	Loss of Env Control	Indirect	Medium-2	Medium-2	High-1	5	Low	None Required	Reversals impact VPF material airlock and directionally the men's and women's main manufacturing area gowning rooms
79	SAHU01 1B/012B	Heating Ventilation and Air Conditioning (HVAC) System, Quality Control, Development, B231 0 GMP Area, and non-BDP labs		Failure BAS	Loss of Env Control	Indirect	Low-1	Medium-2	High-1	4	Low	Critical areas monitored by SCADA for differential pressure making detectability of most failure modes High	
80				Control valve failure	Loss of Env Control		Medium-2	Medium-2	Medium-2	6	Medium	Maintain spares and/or service contracts	
81				Motor failure	Loss of Env Control		Low-1	Low-1	High-1	3	Low	None Required	2 air handlers and isolation dampers. Single unit supplies about 70% output to maintain airflow direction
82				Cooling/Heating Coil Failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
83				Failure of VFD	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
84				Exhaust Fan-Motor & belt failure	Loss of pressurization		Low-1	Medium-2	High-1	4	Low	None Required	Exhaust fans are designed with N+1 redundancy and are on E-Power
85				Clogged drains on cooling coils	Loss of time		Low-1	Medium-2	High-1	4	Low	None Required	
86	SAHU014B/015B	Heating Ventilation and Air Conditioning (HVAC) System, Quality Control, Development, B231 0 GMP Area, and non-BDP labs		Failure BAS	Loss of Env Control	Indirect	Low-1	Medium-2	High-1	4	Low	Critical areas monitored by SCADA for differential pressure making detectability of most failure modes High	
87				Loss of Power	Loss of Env Control leading to loss of time or loss of product depending on timing of event		Medium-2	Le Lde-	High-1	4	Low	Air handler on UPS power and SCADA system provides alarm notification and maintains records	
88				Control valve failure	Loss of Env Control		Medium-2	Medium-2	Medium-2	6	Medium	Maintain spares and/or service contracts	
89				Motor failure	Loss of Env Control		Low-1	Low-1	High-1	3	Low	None Required	2 air handlers and isolation dampers. Single unit supplies 100% output to maintain airflow supply and direction
90				Cooling/Heating Coil Failure	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
91				Failure of VFD	Loss of Env Control		Low-1	Medium-2	High-1	4	Low	None Required	
92				Exhaust Fan-Motor & belt failure	Loss of pressurization		Low-1	Medium-2	High-1	4	Low	None Required	Exhaust fans are designed with N+1 redundancy and are on E-Power
93				Clogged drains on cooling coils	Loss of time		Low-1	Medium-2	High-1	4	Low	None Required	
94	GASB-N2, GASB-CO2, GASB-02	Nitrogen, Carbon Dioxide, Oxygen Storage and Distribution (Liquid and Gas)		Mechanical Failures	Leakage, Loss of pressure	Direct	High-3	Low-1	High-1	5	Low	None Required	
95				Controller or tank level/temp failure	Loss of supply		Low-1	Low-1	High-1	3	Low	None Required	

Project and System: **ATRF - Buildings A and B Utilities**
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Assessment Dates: **March-September of 2022**

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Row #	ATRF #	System Name	Location and/or Spec Reference	Risk Scenario	Consequence	Relevance (Business, GMP)	Severity of Impact (High, Medium, Low)	Likelihood of Occurrence (High, Medium, Low)	Probability of Detection (Low, Medium, High)	Risk Score	Priority (High, Medium, Low)	Risk Mitigation (Testing scenario, Procedural control, Requirements, Design or Configuration Change)	
96	EGEN001A	Standby Power System for Building A and B		Mechanical Failures	Loss of time, loss of stored product, loss of production	In-Direct	High-3	Low-1	High-1	5	Medium	Routine system PM	
97				Transfer Switch Failure	Loss of time, loss of stored product, loss of production		High-3	Low-1	High-1	5	Medium	Routine system PM	
98	UPSP001A	Uninterruptible Power Supply System		Mechanical Failures	Loss of time	In-Direct	High-3	Low-1	High-1	5	Medium	None Required	SCADA is most critical system on UPS
99				Battery replacement and inverter maintenance	Loss of time		High-3	Low-1	High-1	5	Medium	Process is scheduled to minimize downtime.	
100	DECO001A	Liquid Waste Decontamination		PLC Failure or Power interruption causing control	Loss of time	In-Direct	Low-1	Low-1	High-1	3	Low	Back up PLC modules	
101				Pump Failure	Loss of time		Low-1	Low-1	High-1	3	Low	None Required	
102				Instrument Failure	Loss of time		Low-1	Low-1	High-1	3	Low	None Required	
103				Utility failure	Loss of time		Low-1	High-3	High-1	5	Low	None Required	Electric accounts for nearly all loss of utility events and require user to reset
104				Vent Fiter failure	Loss of time		Low-1	Low-1	Medium-2	4	Low	None Required	
105	SCADA001A	Supervisory Control and Data Acquisition System (SCADA)		Power Failure	E Gen and UPS Backup	Direct	Low-1	Low-1	High-1	3	Low	None Required	
106				Controller or Sensor Failure	Loss of data		High-3	Low-1	High-1	5	Low	None Required	
107	BAS1001A001B	Building Automation System (BAS)		Power Failure	loss of control	Direct	Low-1	Low-1	High-1	3	Low	System is on UPS and Generator Back-up	
108				Computer or Sensor Failure	Loss of data		Medium-2	Medium-2	High-1	5	Low	SCADA monitors critical aspects of BAS like differential pressure and room temperature and humidity	
109	3601CHLR	Cooling Water Generation and Distribution System		Failure of mechanical components	Loss of cooling utility	no impact	Low-1	Medium-2	High-1	4	Low	None Required	These are not on E-power. Additional chiller and cooling tower designed to provide some redundancy

Appendix 13.6
Risk Assessment for Equipment

Project and Systems **ATRF - Buildings A and B Process Equipment**
Assessor(s): **The following groups participated in development of the risk assessment: Quality Engineering and Validation, Late Process Sciences, and Process Analytics.**
Assessment Dates: **March-September of 2022**

						Before Mitigation							Remarks
Row#	ATRF #	System Name	Usage Type	Risk Scenario	Consequence	Relevance (Business, GMP)	Severity of Impact (High, Medium, Low)	Likelihood of Occurrence (High, Medium, Low)	Probability of Detection (Low, Medium, High)	Risk Score	Priority (High, Medium, Low)	Risk Mitigation (Testing scenario, Procedural control, Requirements, Design or Configuration Change)	
					Process Equipment								
200	AUTO005A, AUTC011A	Autoclave GMP Sterilizing	Sterilizing with Pure Steam	PLC Failure	Loss of time, and raw materials	Direct	High-3	Low-1	High-1	5	Low	None Required	
201				Door - Mechanical Defects	Loss of time, and raw materials		Low-1	Medium-2	High-1	4	Low	None Required	
202				Loss of Utility	Loss of time, and raw materials		Low-1	Low-1	High-1	3	Low	None Required	
206	AUTC006A, AUTC007A, AUTC016B	Autoclave GMP Decon	Decon with Plant Steam	PLC Failure	Loss of time	Direct	Low-1	Low-1	High-1	3	Low	None Required	
207				Door - Mechanical Defects	Loss of time		Low-1	Low-1	High-1	3	Low	None Required	
208				Loss of Utility	Loss of time		Low-1	Low-1	High-1	3	Low	None Required	
209	AUTC009A	Autoclave GMP Virus Decon	Decon with Plant Steam	PLC Failure	Loss of time	Direct	Low-1	Low-1	High-1	3	Low	None Required	
210				Door - Mechanical Defects	Loss of time		Medium-2	Medium-2	High-1	5	Low	None Required	
211				Loss of Utility	Loss of time		Low-1	Low-1	High-1	3	Low	None Required	
212	IRAD001A	Vaporized Hydrogen Peroxide (VHP) Decontamination System	Cuto decontamination	Failure to control humidity	Ineffective de-contamination	Direct	Medium-2	Low-1	High-1	4	Low	System monitors humidity and will not allow cycle to proceed if out of range	
213				Uniform distribution of Vapor	Ineffective de-contamination		Medium-2	Low-1	Medium-2	5	Medium	Verified using Chemical Indicators and Biological Indicators	
214				Does not achieve concentration in set time	Ineffective de-contamination		Low-1	Low-1	High-1	3	Low	Redundant room H2O2 concentration monitors allow monitoring and trending	
215				Failure of humidity sensor	Ineffective de-contamination		Low-1	Low-1	Medium-2	4	Low	None Required	
216	COLD 007A/009A/009A/110A	Controlled Temperature Storage - Cold Room	Mixed Use (raw materials, intermediate product)	Compressor Failure	Loss of raw material, samples, or product	Direct	Low-1	Low-1	High-1	3	Low	Systems have dual compressors	Loss of cell culture harvest is higher impact than loss of fermentation harvest
217				Controller Failure	Loss of raw material, samples, or product		Low-1	Low-1	High-1	3	Low	None Required	
218				Loss of chilled water from power outage or other reason will inhibit operation of water cooled compressors	Loss of raw material, samples, or product		Low-1	Medium-2	High-1	4	Medium	COLD007A had an air cooled backup system installed on one compressor	
219	COLD017B/018B	Controlled Temperature Storage - Cold Room	Final Product	Compressor Failure	Loss of product	Direct	High-3	Low-1	High-1	5	Low	None Required	
220				Controller Failure	Loss of product		High-3	Low-1	High-1	5	Low	None Required	
221	OVEN003A	Depyrogenation Oven	Depyrogenation and sterilization of glass vials and other filling instruments	PLC Failure	Loss of time and raw materials	Direct	Low-1	Low-1	High-1	3	Low	None Required	
222				Particulate Generation	Loss of time and raw materials		Medium-2	Low-1	Low-3	6	Medium	Vials are covered during cycle, particulates menitored at least every 6 months	
223	SWSH001A	Stopper Washer	Washing of vial stoppers	PLC Failure	Loss of time	Direct	Low-1	Low-1	High-1	3	Low	None Required	Stoppers are rarely washed as pre-washed and treated stoppers are typically used
224				Instrument Failure	Loss of time		Low-1	Low-1	Medium-2	4	Low	None Required	Stoppers are rarely washed as pre-washed and treated stoppers are typically used
225	VWSH001A	Vial Washer	Washing of glass vials	PLC Failure	Loss of time	Direct	Low-1	Low-1	High-1	3	Low	None Required	
226				Instrument Failure	Loss of time		Low-1	Low-1	Medium-2	4	Low	None Required	
227	73660	Vial Filler Stopper Capper (Automated)	Aseptic filling, stoppering and crimping of glass vials	Alignment Issues	Jamming, Vial Breakage, Crimp integrity, higher rejects, product loss	Direct	High-3	Medium-2	Medium-2	7	High	Procedure runs test vials prior to product vials. Interventions covered under validation. System training	
228				Wear and Tear related mechanical failures	Loss of time		Medium-2	Low-1	Medium-2	5	Medium	None Required	
229		Vial Filler (Manual)	Peristaltic pump used for product filling	Fill Accuracy		Direct	High-3	Low-1	Medium-2	6	Medium	Procedure requires at least one check weight vial per vial pan	
230		Vial Capper (Manual)	Crimp sealing on glass vials	Variance in operability	breakage of vials, crimp quality, loss of product	Direct	High-3	Medium-2	High-1	6	Medium	Establish procedural controls and monitor program	
231				particulate generation during crimping	Loss of product		Low-1	Low-1	High-1	3	Medium	Airflow studies illustrate this is not a concern. Crimping is done in separate BSC or area where vials are fully stoppered	
232	Multiple	Chromatography System	Column purification	Pump Failure	Loss of Product and time	Direct	Medium-2	Low-1	High-1	4	Low	None Required	
233				High Pressure Failure	Loss of Product and time		High-3	Low-1	High-1	5	Low	None Required	
234				pH or conductivity sensor failure	Loss of Product and time		Medium-2	Low-1	Medium-2	5	Low	None Required	
235				Mechanical Integrity - Leakage	Loss of Product and time		Medium-2	Medium-2	High-1	5	Low	None Required	
236				PLC Failure	Loss of Product and time		High-3	Low-1	High-1	5	Low	None Required	
237	DFBH003B/004B	Downflow Booth	Raw material sampling or powdered material	Mechanical failure of blower	Loss of Air/Velocity	Direct	Low-1	Low-1	High-1	3	Low	None Required	Raw Material Sampling DFBH003B
238	BSCB056A-60A	Biological Safety Cabinet (BSC) - Virus Production Facility	Aseptic processing with containment	Mechanical failure of blower	Loss of Air/Velocity	Direct	High-3	Low-1	High-1	5	Low	Units monitor proper operation and provide alarm if outside range	Type B2 BSCs also must work with building exhaust
239				Elevated EM Viable	contamination		Medium-2	Low-1	Low-3	6	Medium		There is a delay in obtaining viable results due to incubation

Project and Systems **ATRF - Buildings A and B Process Equipment**
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Assessment Dates: **March-September of 2022**

						Before Mitigation								Remarks
Row #	ATRF #	System Name	Usage Type	Risk Scenario	Consequence	Relevance (Business, GMP)	Severity of Impact (High, Medium, Low)	Likelihood of Occurrence (High, Medium, Low)	Probability of Detection (Low, Medium, High)	Risk Score	Priority (High, Medium, Low)	Risk Mitigation (Testing scenario, Procedural control, Requirements, Design or Configuraton Change)	
240		Biological Safety Cabnet (BSC) - Fill/Finish	Aseptic processing with containment	Mechanical failure of blower	Loss of Air/Velocity	Direct	Medium-2	Low-1	High-1	4	Low	None Required	
241				Elevated EM Viable	contamination		High-3	Low-1	Low-3	7	Medium	Cleaning addressed in SOP and EM results are trended	There is a delay in obtaining viable results due to incubation
242		Biological Safety Cabnet (BSC) - Cell Therapy	Aseptic processing with containment	Mechanical failure of blower	Loss of Air/Velocity	Direct	Medium-2	Low-1	High-1	4	Low	Units monitor proper operation and provide alarm if outside range	Type B2 BSCs also must work with building exhaust
243				Elevated EM Viable	contamination		High-3	Low-1	Low-3	7	Medium	Cleaning addressed in SOP and EM results are trended	There is a delay in obtaining viable results due to incubation
244		Biological Safety Cabnet (BSC) - Cell Banking	Aseptic processing with containment	Mechanical failure of blower	Loss of Air/Velocity	Direct	Medium-2	Low-1	High-1	4	Low	None Required	
245				Elevated EM Viable	contamination		Medium-2	Low-1	Low-3	6	Medium	Cleaning addressed in SOP and EM results are trended	There is a delay in obtaining viable results due to incubation
246		Biological Safety Cabnet (BSC) - General	Aseptic processing with containment	Mechanical failure of blower	Loss of Air/Velocity	Direct	Medium-2	Low-1	High-1	4	Low	None Required	
247				Elevated EM Viable	contamination		Medium-2	Low-1	Low-3	6	Medium	Cleaning addressed in SOP and EM results are trended	There is a delay in obtaining viable results due to incubation
248	VLAB101A, 79670	Vial Labeller	Label application to product vials	Alignment or misfeed related failures	alignment related crasses reducing label readability, require removal and reapplication of new label - loss of	Direct	Low-1	Low-1	High-1	3	Low	None Required	Quality of print is related to printer. Labels manually checked prior to inserting printed rolls into the
249	CIPS001A/002A	Clean in Place System: Cell Culture A2317 and Fermentation A2310	A2506, A2317 CIPS001A, A2310 CIPS002A	PLC Failure	Loss of time	Direct	Low-1	Low-1	High-1	3	Low	None Required	
250				Pump Failure	Loss of time		Low-1	Low-1	High-1	3	Low	None Required	
251				Instrument Failure	Loss of time		High-3	Low-1	Medium-2	6	Medium	Maintain spares, rinse samples sent to QC for cleaning verification	
252				Utility failure	Loss of time		Low-1	Medium-2	High-1	4	Low	None Required	
253	WASH005A	Glassware (Parts) Washer - Wash Area	Automated cleaning of parts and containers	PLC Failure	Loss of time	Direct	Low-1	Low-1	High-1	3	Low	None Required	
254				Instrument Failure	Loss of time		Low-1	Low-1	Medium-2	4	Low	None Required	
255				Cross Contamination - due to multi product use	Cross contamination - loss of produc and time		High-3	Low-1	Medium-2	6	Medium	Procedural controls to segregate processes during wash cycles. Rinse water testing performed by QC	
256	Multiple	Bioreactor Single Use	Culturing of organisms	Instrument and Probe Failure	Possible Loss of Product	Direct	Medium-2	Medium-2	High-1	5	Medium	Maintain spares and/or service contracts	Rocker, stirred tank, and unique systems like the Prodigy used
257				PLC Failure	Possible Loss of Product		Medium-2	Low-1	High-1	4	Low	None Required	
258				Sterile Integrity with mechanical connections or vessel itself	Loss of product		High-3	Medium-2	Medium-2	7	High	Establish procedural controls	
259				Loss of Gas (DO, N1, O2, etc) Supply	Possible Loss of Product		Medium-2	Low-1	Medium-2	5	Low	None Required	
260	BIOR004B, 76100	Bioreactor SIP	Culturing of eukaryotic organisms	Instrument and Probe Failure	Possible Loss of Product	Direct	Medium-2	Medium-2	High-1	5	Low	None Required	
261				PLC Failure	Possible Loss of Product		Medium-2	Low-1	High-1	4	Low	None Required	
262				Sterile Integrity with mechanical connections	Loss of product		High-3	Low-1	Medium-2	6	High	Establish procedural controls and monitor program	
263				Loss of Gas (DO, N1, O2, etc) Supply	Possible Loss of Product		Medium-2	Low-1	Medium-2	5	Low	None Required	
264				Loss of Pure Steam Pressure	Mechanical damage of agitator or loss of batch/product		Medium-2	Low-1	Medium-2	5	Medium	Redundancy in Pure Steam Generator and alarm for low pressure for Pure Steam and for seal pressure on unit	
265				Loss of facility power	This will impact ability to supply Pure Steam for seal and Plant Steam for maintaining culture temperature		High-3	Medium-2	High-1	6	Medium		
266	FERM002A/003A/004B	Fermentor SIP	Culturing of prokaryotic organisms	Instrument and Probe Failure	Possible Loss of Product	Direct	Medium-2	Medium-2	High-1	5	Low	None Required	
267				PLC Failure	Possible Loss of Product		Medium-2	Low-1	High-1	4	Low	None Required	
268				Sterile Integrity with mechanical connections	Loss of product		Medium-2	Low-1	Medium-2	5	Medium	Establish procedural controls and monitor program	
269				Loss of Gas (DO, N1, O2, etc) Supply	Possible Loss of Product		Medium-2	Low-1	Medium-2	5	Low	None Required	
270				Loss of Pure Steam Pressure	Mechanical damage of agitator or loss of batch/product		Medium-2	Low-1	Medium-2	5	Medium	Redundancy in Pure Steam Generator and alarm for low pressure for Pure Steam and for seal pressure on unit	
271	Multiple	Incubator - CO_2 - Production or QC		Temperature - Lack of uniformity	Decrease in product yield.	Direct	Medium-2	Low-1	Low-3	6	Medium	Test during OQ	
272				Control of Humidity, Loss of CO2	Decrease in yield or Loss of product or assay		Medium-2	Low-1	High-1	4	Low	None Required	
273				Microbial contamination - due to inadequate maintenance of humidification system	Loss of product		High-3	Low-1	Medium-2	6	High	Establish procedural controls.	

Project and Systems Assessor(s): **ATRF - Buildings A and B Process Equipment**
The following groups participated in development of the risk assessment: Quality Engineering and Validation, Late Process Sciences, and Process Analytics.
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274	Multiple	Incubator Shaker - Production		Temperature - Lack of uniformity	Decrease in product yield	Direct	Low-1	Low-1	Low-3	5	Medium	Test during OQ	
275				Failure of shaker	Decrease in yield or Loss of product		Low-1	Low-1	High-1	3	Low	None Required	
276	Multiple	Incubator		Temperature - due to fault/failure	Validity of EM samples	Direct	Medium-2	Low-1	High-1	4	Low	None Required	
277		Homogenizer		Loss of Efficiency - due to pressure loss or degradation of orifice plate	Loss of time	Direct	Low-1	Low-1	Medium-2	4	Low	None Required	
278				Pump Seal Failure due to WFI loss or other causes	Loss of Mechanical equipment - time loss		Low-1	Low-1	High-1	3	Low	None Required	
279				Loss of Power	Loss of time		Low-1	Low-1	High-1	3	Low	None Required	
280	Multiple	Centrifuge - Floor, fixed or swing		Failure of Temp Control	Loss of product	Direct	Medium-2	Low-1	High-1	4	Low	None Required	Only calibration for most bottle centrifuges
281				Off-Balance	Loss of time, spillage		High-3	Low-1	High-1	5	Low	None Required	
282	Multiple	Centrifuge - Benchtop		Failure of Temp Control	Loss of product	Direct	Medium-2	Low-1	High-1	4	Low	None Required	Only calibration for bottle centrifuges
283				Off-Balance	Loss of time, spillage		Medium-2	Low-1	High-1	4	Low	None Required	
284	Multiple	Centrifuge single use		Failure of Temp Control	Loss of product	Direct	Medium-2	Low-1	High-1	4	Low	None Required	
285				Off-Balance	Loss of time, spillage		Medium-2	Low-1	High-1	4	Low	None Required	
286	86480	Centrifuge disc stack		Failure of Temp Control	Loss of product	Direct	Medium-2	Low-1	High-1	4	Low	None Required	
287				Failure of system control	Loss of product		Medium-2	Low-1	Medium-2			None Required	
288				Off-Balance	Loss of time		Low-1	Low-1	High-1	3	Low	Detection and safety mechanism built in	
289	Multiple	Purified Water Generation Unit	Lab water usage	System failure to meet required water quality	Invalidation of assay, loss of time	Direct	Low-1	Low-1	High-1	3	Low	Most assays have controls, units are on PM plan and	
290		CTU, -80C Freezer - Final Product		Compressor Failure	Loss of product	Direct	High-3	Medium-2	High-1	6	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
291				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
292		CTU, -80C Freezer - Raw Materials		Compressor Failure	Loss of product	Direct	Low-1	Medium-2	High-1	4	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
293				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
294		CTU, -80C Freezer		Compressor Failure	Loss of product	Direct	Low-1	Medium-2	High-1	4	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
295				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
296		CTU, Freezer - Final Product		Compressor Failure	Loss of product	Direct	High-3	Low-1	High-1	5	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
297				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
298		CTU, Freezer - Raw or in process materials		Compressor Failure	Loss of product	Direct	Low-1	Low-1	High-1	3	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
299				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
300		CTU, Freezer -		Compressor Failure	Loss of product	Direct	Low-1	Low-1	High-1	3	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
301				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
302		CTU, Refrigerator -		Compressor Failure	Loss of product	Direct	Low-1	Low-1	High-1	3	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
303				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
304		CTU, Refrigerator -		Compressor Failure	Loss of product	Direct	Low-1	Low-1	High-1	3	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
305				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
306		CTU, Refrigerator -		Compressor Failure	Loss of product	Direct	Low-1	Low-1	High-1	3	Low	Procedure to respond to a failure - to move product GMP units tied to SCADA alarm	
307				Controller Failure	Loss of product	G	Low-1	Low-1	High-1	3	Low	GMP units tied to SCADA	
308		Controlled Rate Freezer	Bacterial & Mamalian	LN2 delivery failure	Loss of product	Direct	High-3	Low-1	High-1	5	Low	None Required	Cell banks
309				Controller Failure	Loss of product		High-3	Low-1	High-1	5	Low	None Required	
310		Controlled Rate Freezer	Cell Therapy	LN2 delivery failure	Loss of product	Direct	High-3	Low-1	High-1	5	Low	None Required	Final Product
311				Controller Failure	Loss of product		High-3	Low-1	High-1	5	Low	None Required	