IMA LIFE
Aseptic Processing and Freeze Dryer Solutions

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Functional Specification

Machine Model : Lyomax 3

Serial No. : 900EEF1114

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Revision Table			
Revision	Change Request No.	By/Initial	Date
Revision Description			
0	N/A	DDL	06 JAN 2017
Initial release			
1	N/A	DDL	06 MAR 2017
• Entire document: Update typos and formatting issues. • Section 2.1.1: Update electrical codes, unloading type, control instrumentation, and add sterility monitoring as special requirement. • Section 2.1.2.2: Update shelf heat up rate. • Section 2.1.2.3: Add condenser capacity. • Section 2.2.2: Add note for door locking. • Section 2.2.4: Update type of loading system and add note for operation in a freeze drying step. • Section 2.2.10.1 item 3.e: Add TE204, TE205 and TE206. • Section 2.2.13: Add note for description of the unloading pusher. • Section 3.1.3.2: Remove note for decontamination override. • Section 3.1.4: Add functions 18 and 19. • Section 3.2: Add note for item 11 and remove note about sequential functions. • Section 3.2.5.1.1 and 3.2.5.9.1: Update section for loading system being provided on this project. • Section 3.2.5.9: Update steps 6 and 7 with unloading pusher operation. • Section 3.2.6.3: Update step 3 to drain through FV1650. • Section 3.2.6.5: Update valve opening sequence for steam inlet. Add note to close FV38 on signal loss. • Section 3.2.6.8: Remove reference to jacket cooling. • Section 3.2.6.10: Remove iClient (not part of the scope of the project). • Section 5.1.1.2: Update color display on alarms.			
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• Section 1.2: Update URS date. • Section 2.1.1, 2.2.10.5.3, 3.2.18, 3.2.25: Add Unloading pusher bellows integrity test. • Section 2.2.4: Add intermediate plate information. • Section 2.2.4.2: Reword “intermediate plate.” • Section 2.2.5.1: Add item 2.j. • Section 2.2.9: Update position of ice condenser, update number of cooling circuits. • Section 2.2.10.1: Add note for PSH41 alarm. • Section 2.2.13: Update entire section. • Section 2.3.2.2: Add slot door components. • Section 3.1.4: Update items 8, 9, 18 and 19. • Section 3.2.5.1.1: Add item 6.			

• Section 3.2.5.3, 3.2.5.6, 3.2.5.8: Add unloading pusher bellows evacuation. • Section 3.2.5.9.1: Add item 5.			
3	N/A	DDL	06 JUL 2017
• Section 2.1.1: Update condenser section for type of defrost, update number of condenser coil temperature probes. • Section 2.2.3: Update setpoint name for item 2.g. • Section 2.2.4: Remove interlock for shelves if bridge plate is not retracted. • Section 2.2.4.8: Remove note for “if automatic cycle is active” for item 3.h. • Section 2.2.4.9: Update setpoint name for item 1.e. Add item 3.c. Remove item 4. • Section 2.2.5.1: Remove item 2.j. • Section 2.2.8: Add PSH250 to item 1.e. • Section 2.2.10.1: Update SV309 tag number for item 2.c and 3.c, add TE205 and TE206 to item 2.e and 7.d, remove alarm action for PSH41. • Section 2.2.10.5.2: Update heading for items 1 and 3. • Section 2.2.14: Remove item 1, update heading for item 2, update setpoint name for items 2 and 3, remove FV29 from item 4. • Section 3.1.4: Update/add function items 18-22, add status items 8, 14 and 15, update pushbutton tag for status item 12. • Section 3.2.2: Remove heat exchanger outlet temperature average, update for redundant shelf inlet temperature probes, update item 1.d, add item 1.e. • Section 3.2.3: Update entire section. • Section 3.2.5: Add note for availability of manual functions after item 4. • Section 3.2.5.1: Add item 4. • Section 3.2.5.1.1: Remove section. • Section 3.2.5.4: Remove item 1. • Section 3.2.5.8: Update aeration description and section reference. • Section 3.2.5.9: Remove items 3 and 4, update slot door opening description for operator positioning. • Section 3.2.5.9.1: Remove section. • Section 3.2.6: Update decontamination interlock criteria, remove parameter *Decon temp stabilization time (min).* • Section 3.2.6.1: Update item 3. • Section 3.2.6.2: Update item 1. • Section 3.2.6.3: Update item 1 to aerate with air, update draining sequence in item 2, remove drain through FV1650. • Section 3.2.6.4: Update item 2. • Section 3.2.6.5: Update items 2, 3, 4, 5, 8 and 9. • Section 3.2.6.6: Update items 1 and 3 for main isolation valve sequencing. • Section 3.2.6.7, 3.2.6.8: Update to keep main isolation valve open. • Section 3.2.6.9: Update main valve bellows evacuation, aeration and valve sequencing. • Section 3.2.6.10: Add “prior to decontamination” to item 1.b. Add item 1.h, remove “primary” from item 1 and 2 headings, specify chamber pressure *“or”* condenser pressure probe fail for item 2, update abort criteria for item 2, update item 2 decontamination abort note criteria, add hold mode display to item 4, update item 4 hold criteria, update			

decontamination override function description, remove note for requirement of CIP and SIP after decontamination override. • Section 3.2.10: Add note for availability of manual functions, update recipe parameters. • Section 3.2.10.3: Add FV1050, FV1128 and FV1129 to item 1, update item 2. • Section 3.2.10.6: Update item 1. • Section 3.2.10.7.1: Add note for valves to close if not already open. • Section 3.2.10.7.3: Remove FV29 closes. • Section 3.2.10.7.5: Add FV1050 to item 1, add bypass rinse cycle parameter to item 2. • Section 3.2.10.8: Add FV1050, add clearing if CIP interlock. • Section 3.2.10.9: Add FV1050 to item 1 and remain open in item 2. • Section 3.2.10.12: Add abort without draining note to item 2, remove failure of the CIP supply pressure transducer from item 2, add items 2.i and 2.j. • Section 3.2.14.2.1: Add SV42 to item 1. • Section 3.2.14.2.2: Remove SV42 from item 2. • Section 3.2.14.3: Update item 1. • Section 3.2.14.4: Update valve sequencing, update discharge pressure, clear interlock for SIP. • Section 3.2.14.6: Update valves to *remain* open. • Section 3.2.14.7: Add TE205 and TE206. • Section 3.2.14.11: Update heading for item 1, add item 1.a, update item 1.b for condenser pressure *"and"* chamber pressure probes, update alarm condition for item 1.g. • Section 3.2.15.1: Update item 2. • Section 3.2.15.3: Update valve sequencing for items 2 and 3. • Section 3.2.17.1: Update heading title. • Section 3.2.24.4: Remove loading door closed failure. • Section 3.2.5: Add freeze drying to cycle queue. • Section 5.1.1: Remove load/unload manual intervention screen. • Section 6.1.2.4: Update parameter type for items 2 and 3, remove item 6. • Section 6.1.2.7: Update parameter type for item 1.			
4	N/A	DDL	29 NOV 2017
• Section 3.1.4: Add notes to display for HMI panel items 14 and 15. • Section 3.2.5: Update decontamination interlock start time. • Section 3.2.10.12: Add items 1.h and 2.k.			

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APPENDICES

No appendices exist for this Functional Specification document.

1 Introduction

1.1 Purpose

IMA Life is producing **1** freeze dryer for the end user, **Sanofi Pasteur**.

This is the functional specification document for the IMA Life **SA35-00116** pharmaceutical freeze dryer. The specifications in this document are used as a base for the development and qualification of the freeze dryer. The mechanical, electrical and process related information shall be taken into account when the freeze dryer is designed. The system functionality has been subdivided into system units and this document clarifies the functionality of each unit.

The purpose of this functional specification is to provide a detailed description of the technical solution that will meet the requirements of the end user.

1.2 Reference Documents

This functional specification is based on the requirements in the following specifications:

REF.	ITEM	IDENTIFICATION	REV.	DATE	SOURCE
1	User Requirements Specification	Q_0544166_ SPECIFICATION	2.0	02-Aug-2016	Sanofi Pasteur
2	IMA Life Deviation List	15A155fd_DEV_04 Exceptions_Comments to URS	4.0	05-Apr-2016	IMA Life

1.3 Glossary

The following acronyms and terms may be used throughout this document:

Acronym/Term	Description
Audit Trail	An MS SQL database that stores freeze dryer alarms/messages, iFIX system messages, and user actions such as login/logout and setpoint/parameter changes (including electronic signatures).
CIP	Clean In Place cycle
FAT	Factory Acceptance Test using IMA Life test documentation
iFIX	GE's 64-bit Fully Integrated Control System (iFIX) software, which is installed on the PC and provides the PC HMI to the control system
HMI	Human-Machine Interface
I/O	Input/Output
Index	Shelf ram movement to the next loading or unloading position.
Jog	Incremental device movement while a button is pressed
LRP	Liquid Ring Pump
MS SQL	Microsoft Structured-Query-Language
PC	Personal Computer
PC HMI	The iFIX SCADA
PDF	Adobe Acrobat File
PLC	Programmable Logic Controller
SCADA	Supervisory Control And Data Acquisition
SIP	Sterilization In Place cycle
URS	User Requirements Specification

2 Overview

2.1 General Functional Description

The freeze dryer is capable of freeze drying liquid products. The freeze dryer consists of a chamber, product shelves, an ice condenser and functional sub-systems.

Each freeze dryer is supplied on a carbon steel frame finished in an industrial grade paint onto which the various components of the machine are mounted.

Having all the components (the chamber, hydraulic group, condenser, refrigeration groups, vacuum group and power cabinet) installed on frames and tested prior to shipment will reduce installation and commissioning of the equipment on site, and will ensure optimal layout for ease of maintenance. An integrated Power / Control cabinet and network of junction boxes house the electrical and instrumentation components.

The freeze dryer control system consists of two levels of control: the Personal Computer (PC HMI) as the higher level control and the Programmable Logic Controller (PLC) as the lower level. Field-mounted equipment (e.g. instrumentation and actuators) are integrated into the system to control the freeze dryer. The freeze dryer chamber is a pressure vessel containing temperature-controlled shelves. The shelves are loaded with product from the facility production area. The shelves can be cooled and heated using refrigeration circuits and an electrical immersion heater as required by the shelf temperature control.

The chamber normally operates under a vacuum, which is achieved using vacuum pumps. During the sublimation process, large volumes of vapor are released from the product and these vapors are condensed on the refrigerated condenser coils. Condensable vapors are pumped to the condenser via the desublimation of vapor onto the condensing elements. Non-condensable vapors are pumped by mechanical vacuum pumps. Controlled clean air or nitrogen bleeds into the chamber to control the vacuum level during the drying steps of the freeze drying cycle. Nitrogen or clean air is also used during the initial vacuum release (pre-aeration) and clean air is used during the final vacuum release (aeration) stages of the freeze drying cycle.

An automatic CIP cycle is provided to wash to drain the particulate matter and dried water soluble stains that reside inside of the chamber and condenser.

An automatic SIP cycle is provided to steam-sterilize the freeze dryer. Steam sterilization of the freeze dryer will cause the internal surfaces of the freeze dryer to be heated to a maximum temperature of 130 °C.

The freeze dryer is capable of using steam to defrost the condenser coils and melting the ice that has formed during the drying steps of the freeze drying cycle.

2.1.1 Project Configuration

No.	General
1	Model: Lyomax 3
2	1 freeze dryer
3	Unit Tag: FD EF1114
4	Split frame construction
5	Imperial units of measurement (°C, micron, PSI)

No.	Codes and Standards
1	Electrical standard per NFPA 79A, CSA, NEC
2	Pressure vessel code per ASME Section VIII Div 1, CRN
3	Clean piping and vessel practices per ASME BPE 2012* *exceptions per IMA Life standard
4	Pharmaceutical standards per 21 CFR Parts 210 & 211, WHO
5	Manufacturing standards per cGMP, 21 CFR Part 211 Subpart D
6	Potent processing per IMA Life Design Guideline
7	Documentation and Software development per GAMP V
8	Software per 21CFR Part 11

No.	Electrical
1	Power Supply: 3P/208V/60Hz, Control Power: 24V DC (partial)
2	15 meters of control cabinet interconnecting cabling
3	15 minute UPS
4	Electrical enclosures are CUL with ESA certification

No.	Chamber
1	Chamber main door located opposite the loading door
2	Automatic chamber main door locking
3	Loading door (non-tilting)
4	Loading door located on the chamber wall opposite the main door
5	Chamber pressure transducer
6	Sight glass in door: 1 150mm (6") remotely illuminated
7	Sight glass in chamber: 1 150mm (6") illuminated
8	Integration with an isolator

No.	Shelves
1	Number of product shelves: **4** +1 temperature compensation shelf
2	Basic interdistance: **110** mm
3	Hydraulic stoppering
4	Stoppering pressure control: pressure transducer
5	Shelf ram bellows with integrity test
6	Constant level loading (CLL)

No.	Loading/Unloading System
1	Manual loading through a loading door on the loading side
2	Semi-automatic unloading through the loading door on the loading side
3	Unloading pusher bellows with integrity test

No.	Main Isolation Valve
1	Hydraulic mushroom
2	Main isolation valve bellows with integrity test

No.	Condenser
1	Defrost / decontamination cycle using steam
2	Defrost decontamination cycle per IMA Hazardous Product Design Specification Decontamination of Freeze Dryers: HPDSdecontamination.doc
3	Condenser pressure transducer
4	Sight glass: 1 150mm (6") illuminated

No.	Shelf and Condenser Cooling
1	Liquid nitrogen cooling (LN_2)
2	Redundant circulation pumps
3	Shelf fluid inlet temperature probe
4	Shelf fluid outlet temperature probe
5	External outlet manifold temperature probes
6	Backup shelf fluid inlet temperature probe
7	Shelf fluid hx outlet temperature probe
8	Condenser cooling via direct expansion of nitrogen gas
9	4 Condenser coil temperature probes

No.	Heat Exchange System
1	5.0 cSt silicone oil
2	Molecular sieve moisture trap

No.	Vacuum System
1	Oil-Sealed Rotary Vane vacuum pump
2	Redundant primary vacuum pump
3	Modulating vacuum control valve
4	Vacuum pump group vacuum gauge (Pirani)

No.	Sanitization and Cleaning Systems
1	Sterilization in Place (SIP) cycle with control based on sterilization pressure
2	Media fill
3	2 sterile filters with manual integrity test

No.	Sanitization and Cleaning Systems
4	Sterilizable Recirculation Clean in Place (CIP)

No.	Control and Instrumentation
1	Allen Bradley PLC
2	Ethernet IP fieldbus network
3	Loading HMI panel
4	Maintenance HMI panel

No.	SCADA
1	iFIX HMI software
2	Language:: English
3	7 Security levels
4	General overview screen
5	Historical trending screen
6	Engineering parameter screens
7	Maintenance screen
8	Device Mode
9	Batch reports (standard)
10	21CFR part 11 compliance with SQL audit trail database
11	e-Signatures

No.	Special Requirements
1	Potent product processing
2	Sterility monitoring

2.1.2 Performance

The minimum freeze dryer performance specifications are contained in the following subsections.

2.1.2.1 Vacuum Performance

	Vacuum Performance	Value	Comments
1	System leak rate	0.01 mbar l/sec	Clean, dry, empty
2	Evacuation Time	20 min or less	To 0.1mBar
3	Ultimate vacuum	5 micron	oil sealed pumps

2.1.2.2 Shelf Performance

	Shelf Performance	Value	Comments
1	Shelf heat up rate	1°C/minute average	Clean, dry, empty, -40°C to +20°C
2	Shelf maximum temperature	80 °C	
3	Shelf minimum temperature	-55 °C	LN_2 Cooling
4	Shelf cooling (+20 to -40°C)	20 min or less	LN_2 Cooling, Clean, dry, empty, +20°C to -40°C
5	Shelf uniformity across the shelf stack (-40 to +20°C) at steady state under vacuum	Min and Max are within 2.0 °C of each other	LN_2 Cooling
6	Shelf control (+40 to -40°C)	+/-1.0 °C	Shelf temperature control +/- from setpoint, steady-state

2.1.2.3 Condenser Performance

	Condenser Performance	Value	Comments
1	Condenser Cooling (+20 to -40°C)	30 min or less	LN_2 Cooling
2	Condenser Ultimate Temperature	-75 °C	LN_2 Cooling
3	Condenser Capacity	75 kg	Ice at 12.7mm thick

2.2 Freeze Dryer Sub-Systems

2.2.1 Chamber

The freeze dryer chamber is a pressure vessel that houses the product shelves. The chamber is rectangular and made from AISI 316L stainless steel. The floor of the chamber is pitched to ensure drainage. Horizontal nozzles within the chamber are also pitched to ensure drainage of liquids.

The periphery of the chamber opening has a bezel to enable the equipment to be sealed into the wall of a clean room. The chamber is equipped with a main door such that the chamber opens into the maintenance room. The chamber main door has a solid silicone seal, located around the periphery of the door, suitable for vacuum and pressure applications. The door is closed manually and two hydraulically-actuated closing pins are extended when the close door button is pushed on the HMI.

The door is locked automatically by the insertion of multiple hydraulically-actuated locking pins once the chamber is under vacuum. Door closed status is indicated by a position switch. Door locked and unlocked statuses are each indicated by limit switches.

2.2.2 Locking / Unlocking Chamber Main Door

The chamber main door is located opposite the loading door and will remain locked at all times unless required by the scenarios below.

1. Locking/unlocking the chamber main door is performed:
   a. During automatic cycles as required.
   b. Manually by selecting the Chamber Main Door Lock/Unlock button on the maintenance HMI panel.

2. Locking / unlocking interlocks:
   a. PT105 chamber pressure and PT203 condenser pressure <= 3 psia. The chamber and condenser must be evacuated to ensure that the door gasket is compressed and the door locking / unlocking pins are free of the door.
   b. The chamber main door is closed per section 2.2.3.
   c. The loading door is closed as indicated by XS178 / XS179 proximity switches.
   d. PT105 chamber pressure and PT203 condenser pressure probe fail alarms inactive.

3. Locking / unlocking sequence during an automatic cycle:
   a. If PT105 chamber pressure and PT203 condenser pressure are > 3 psia, LRP1 liquid ring pump evacuates the chamber through the condenser drain line per section 2.2.10.4.
   b. When PT105 and PT203 <= 3 psia, HYD1 hydraulic pump starts.
   c. If locking is required:
      i. After HYD1 has been running for 5 seconds, SV203 chamber main door lock valve opens to extend the locking pins and lock the door.
      ii. When the PLC receives feedback that the chamber main door is locked from the door locked limit switches ZS100-107, then after 15 seconds, SV203 is de-energized, HYD1 is de-energized per section 2.2.7 and, if evacuation was required, LRP1 is de-energized per section 2.2.10.4.
   d. If unlocking is required:
      i. After HYD1 has been running for 5 seconds, SV202 door unlock valve opens to retract the locking pins and unlock the door.
      ii. When the PLC receives feedback that the chamber main door is unlocked from the door unlocked limit switches ZS120-123, then after 15 seconds, SV202 is de-energized, HYD1 is de-energized per section 2.2.7 and, if evacuation was required, LRP1 is de-energized per section 2.2.10.4.

4. Locking / unlocking sequence using the Chamber Main Door Lock/Unlock button on the HMI panel:
   a. Select Manual Mode per section 3.1.3.2.
   b. Close the chamber main door if locking, and also the loading door.
   c. Evacuate the chamber using Manual Function *System LRP Evacuation* per section 3.1.3.2.
   d. PT105 chamber pressure and PT203 condenser pressure are <= 3 psia, select the Manual Function *Chamber Main Door Lock or Unlock button* per section 3.1.4.
   e. HYD1 hydraulic pump starts.
   f. If locking is selected:
      i. After HYD1 has been running for 5 seconds, SV203 chamber main door lock valve opens to extend the locking pins and lock the door.
      ii. When the PLC receives feedback that the chamber main door is locked from the door locked limit switches ZS100-107, then after 15 seconds, SV203 is de-energized, HYD1 is de-energized per section 2.2.7.
   g. If unlocking is selected:
      i. After HYD1 has been running for 5 seconds, SV202 door unlock valve opens to retract the locking pins and unlock the door.
      ii. When the PLC receives feedback that the chamber main door is unlocked from the door unlocked limit switches ZS120-123, then after 15 seconds, SV202 is de-energized, HYD1 is de-energized per section 2.2.7.

2.2.3 Opening and Closing Chamber Main Door

1. Opening / closing the chamber main door is performed:
   a. Manually by the user using the maintenance HMI panel.

2. Opening interlocks:
   a. The HMI panel is enabled per section 3.1.3.2.
   b. Manual Mode is active per section 3.1.3.2:
   c. The chamber main door is unlocked per section 2.2.2.
   d. The chamber main door is closed as indicated by the XS140 door closed position switch.
   e. The loading door is closed as indicated by XS178 / XS179 proximity switches.
   f. The chamber is not pressurized, as indicated by the PSH11 chamber pressure switch.
   g. PT105 chamber pressure and PT203 condenser pressure are <= 15.2 psia and >= System Engineering Parameter *Aeration setpoint* (typically 14.2 psia) minus 0.15 psia AND PT105 chamber pressure and PT203 condenser pressure probe fail alarms inactive.
   h. The main isolation valve is closed per section 2.2.8.

3. Closing interlocks:
   a. The HMI panel is enabled per section 3.1.3.2.

b. Manual Mode is active per section 3.1.3.2
c. The chamber main door is closed as indicated by XS140 door closed proximity switch. This requires the user to swing the door closed and hold it shut.
d. The shelf ram is in the home position (shelf ram retracted).
e. PT105 chamber pressure and PT203 condenser pressure probe fail alarms inactive.

4. Opening sequence:
   a. HYD1 hydraulic pump starts.
   b. After HYD1 has been running for 5 seconds, SV212 retract primary pins valve opens for 20 seconds to retract the primary pins. The timed delay is to ensure that the pins are fully retracted and that they will not interfere with the opening of the chamber main door.
   c. After the 20 second delay, HYD1 stops per section 2.2.7.

5. Closing sequence:
   a. HYD1 hydraulic pump starts.
   b. After HYD1 has been running for 5 seconds, SV213 extend primary pins valve opens for 20 seconds to extend the primary pins. The timed delay is to ensure that the pins are fully extended to secure the door.
   c. After the 20 second delay, HYD1 stops per section 2.2.7.

2.2.4 Constant Level Loading / Unloading

The freeze dryer is configured to allow constant level loading for manual loading. Constant level loading is a method by which each of the shelves to be loaded (or unloaded) will always be at the same height relative to an absolute position.

To facilitate constant level loading and to minimize the exposure of the internals of the freeze dryer during loading and unloading, the freeze dryer will be equipped with a slot-type loading door.

The loading door opens upward. Loading door closed status is indicated by proximity switches XS178 and XS179 mounted at the bottom of the left and right sides of the door.

The door is positioned to accommodate a loading / unloading height suitable for the loading system to be used.

In Manual Mode or loading/unloading step in a freeze drying cycle, the door can be jogged open/closed from the HMI panel by the user.

The loading door has the ability to move to a maintenance position, which provides clearance for gasket replacement.

The loading door is designed to integrate with a manually operated intermediate plate. When the slot door is open, the intermediate plate can be extended into position to facilitate the loading of vial trays to a shelf.

If the intermediate plate is not fully retracted (tilted away from the slot door), slot door movement will be disabled.

2.2.4.1 Reserved

2.2.4.2 Manual Constant Level Loading/Semi-automatic Unloading

The loading door is operated by jog open and close manual push buttons. The shelves are indexed to the loading or unloading position, level with an intermediate plate located within the door opening, by selecting shelf index up or down manual push buttons. The manual controls are located on an HMI panel adjacent to the door. The loading door is located in the back wall of the chamber, opening into the isolator, with a maintenance door located in the machinery area.

During loading, once a shelf is in position, the operator will manually push the vials on to the shelves. During unloading, once a shelf is in position, the unloading pusher integrated with the freeze dryer will push the vials off the shelf towards the unloading area.

2.2.4.3 Reserved

2.2.4.4 Reserved

2.2.4.5 Reserved

2.2.4.6 Reserved

2.2.4.7 Integration with an Isolator

The loading / unloading side of the freeze dryer interfaces with an isolator. The isolator limits access to the door's moving parts and prevents injury to personnel and damage to plant and equipment. Whenever the personnel door of the isolator is not closed or the glove ports are in use, loading door movement is stopped and, if the loading door is not closed, the shelf ram movement is also stopped. The loading door is designed with an open construction to allow penetration of VHP sterilizing agents into the mechanism of the loading door.

2.2.4.8 Loading Slot Door Gasket System

1. The loading door utilizes dual gaskets mounted in the chamber loading door flange to form a reliable seal between the door and the flange. The gaskets are used to provide seals for containing both pressure and vacuum.
   a. The inner gasket:

   i. Is a silicone rubber “O” ring that provides a vacuum seal between the chamber loading door flange and the loading door when PT105 chamber pressure < atmospheric pressure.

b. The outer gasket:
   i. Seal prevents air from the isolator from entering the chamber during initial evacuation from atmospheric pressure to 11 psia and during the final stages of aeration from 11 psia to atmospheric pressure
   ii. Seal prevents water and steam from leaking out of the freeze dryer into the isolator during CIP/SIP cycles.
   iii. Is pressurized by energizing loading door gasket latching solenoid valves SV1103 and SV1104A.
   iv. Is vented by energizing loading door gasket latching solenoid valves SV1103A and SV1104.
   v. Uses PSL37 loading door gasket pressure switch to determine pressurized / vented state.

2. Loading door outer gasket pressurization interlocks:
   a. The loading door is closed as indicated by XS178 / XS179 proximity switches.

3. Loading door outer gasket system operation:
   a. Freeze drying cycle:
      i. The loading door outer gasket is pressurized when the evacuation step starts and remains pressurized until PT105 chamber pressure is < 11 psia. Then, the gasket is vented.
      ii. The loading door outer gasket is again pressurized when PT105 chamber pressure is >= 11 psia until the another function in this section changes its status. (Pressurization can start at the pre-aeration step or the aeration step depending on pre-aeration pressure).
      iii. If the loading door outer gasket is pressurized at the start of unloading, it will be vented before the loading door is opened.
   b. SIP and Defrost/Decontamination cycle:
      i. The loading door outer gasket is pressurized at the start of the cycle and remains pressurized until drying has completed. Then, the gasket is vented.
      ii. If an SIP or Defrost/Decontamination cycle has ended before drying has completed, the loading door outer gasket will remain pressurized until an SIP drying phase completes, the door is commanded to open or until PT105 chamber pressure is < 11 psia. Then, the gasket is vented.
   c. CIP cycle:
      i. The loading door outer gasket is pressurized at the start of the cycle and remains pressurized until drying has completed. Then, the gasket is vented.
      ii. If a CIP cycle has ended before drying has completed (aborted or zero drying time), the loading door outer gasket will remain pressurized until a CIP/SIP drying phase completes, the door is commanded to open or until PT105 chamber pressure is < 11 psia. Then, the gasket is vented.
   d. Leak Test Cycle:

i. The loading door outer gasket is pressurized when evacuation starts and remains pressurized until PT105 chamber pressure is < 11 psia. Then, the gasket is vented.

e. Manual functions (Main Vacuum Valve, System LRP Evacuation):
   i. The loading door outer gasket is pressurized when the evacuation step starts and remains pressurized until PT105 chamber pressure is < 11 psia. Then, the gasket is vented.

f. Manual functions (Chamber Main Door Open):
   i. The loading door outer gasket is pressurized while the chamber main door is opening and remains pressurized while the door is opened. From this point on, the gasket will remain pressurized until an SIP drying phase completes, the door is commanded to open or until PT105 chamber pressure is < 11 psia. Then, the gasket is vented.

g. Isolator VHP Cycle:
   i. The loading door outer gasket is pressurized when the evacuation step starts and remains pressurized until PT105 chamber pressure is < 11 psia. Then, the gasket is vented.

h. Sterility Monitoring
   i. The loading door outer gasket is pressurized and PT105 chamber pressure is > 11 psia and Chamber not sterile alarm is active.
   ii. The loading door outer gasket is pressurized if the isolator on the loading side is not sterile.

2.2.4.9 Loading Slot Door Interlocks

1. Loading door movement interlocks:
   a. No loading door drive inverter alarms are active.
   b. The Shelf/Door Stop function is not active (per section 3.1.4).
   c. The loading isolator door is closed and the glove ports are not in use.
   d. The chamber is not pressurized, as indicated by PSH11 chamber pressure switch (door open / air damp only).
   e. PT105 chamber pressure is <= 15.2 psia and >= System Engineering Parameter *Aeration setpoint* (typically 14.2 psia) minus 0.15 psia AND PT105 chamber pressure probe fail alarm inactive (door open / air damp only).
   f. The chamber main door is closed as indicated by XS140 door closed proximity switch. For freeze dryers that have the main door on the non-sterile side (e.g., the machine room), this condition maintains the sterility of the isolator.
   g. Software travel limit not reached during jogging.
   h. Software travel target within software travel limits during positioning movements.
   i. Additional position-specific interlocks below.

Note that the loading door gasket must be de-pressurized per section 2.2.4.8 before the door can be open. This is not listed as an interlock because the gasket may be de-pressurized when the door is requested to open.

2. Loading door open-specific interlocks:

a. The main isolation valve is closed per section 2.2.8.
b. In manual mode the chamber not sterile alarm is active.

3. Loading door close-specific interlocks:
   a. All applicable axes of any automated loading/unloading equipment (e.g., compact loader pusher-bar, transporter transfer frame and vial platform) docked to the freeze dryer must be homed.
   b. In manual mode the chamber not sterile alarm is active (jog door open or homing only).
   c. Unloading pusher retracted.

2.2.5 Shelves

The shelf stack consists of 4 product shelves and one (1) compensation shelf, of the same dimension as the other shelves. The interdistance space between the shelves is 110 mm.

The shelves are constructed of AISI 316L stainless steel in a hollow construction that provides channels through which a heat transfer fluid passes. A top compensating (radiation) shelf is provided to ensure that product, on the uppermost product shelf, is exposed to the same thermal conditions as on the lower shelves.

2.2.5.1 Hydraulic Shelf Movement

A hydraulic cylinder, with a ram, is mounted on the top of the chamber. The piston passes through vacuum seals into the chamber and is attached to the pressure plate. The product shelves are each suspended by four vertical stainless steel rods located at the sides of the shelf. A hydraulic power unit is supplied, mounted on the main support frame of the equipment (see section 2.2.7). This provides the force to move the piston and raise or lower the shelves.

The system may be used to move the shelves to ease the cleaning of the chamber and loading/unloading of the product. Systems equipped with a loading door will also be equipped with constant level loading (see section 2.2.4).

The system may also be used to insert stoppers into vials at the end of the freeze drying process. Pressure plate and counter-pressure plates are located at the top and bottom of the chamber. The system is designed to produce and withstand sufficient force for the shelves to be pressed together and insert stoppers into the vials. The maximum operational stoppering pressure, across the shelves, is 1.0kg/cm^2 (14.2lb/in^2).

It is possible to remotely adjust the shelf stoppering pressure via the PC HMI. The hydraulic system pressure may be adjusted up to a pressure equivalent to the maximum operational stoppering pressure stated above.

A flexible stainless steel bellows is fitted to isolate the hydraulic ram from the drying chamber. The bellows is provided to prevent any possible contamination of the chamber by hydraulic oil that may

leak through the hydraulic ram seals. The bellows is evacuated per section 2.2.10.5.1. The bellows is provided with a vent dryer and an automatic vacuum integrity test per section 3.2.16.

1. Shelf movement is controlled:
   a. Automatically by the PLC during automatic cycles when required to move the shelf ram to the desired position without involvement by the user.
   b. Manually from the HMI panel by the user during Manual Mode and during the Loading and Storage/Unloading steps of the freeze drying cycle to jog the shelf ram up or down.

2. Shelf movement interlocks (conditions that do not apply to jogging have been noted):
   a. The Shelf/Door Stop function is inactive per section 3.1.4.
   b. ZT1 shelf ram position sensor has not failed. Once the sensor fails, the condition remains active until the failure is reset by the user from the PC HMI Alarms screen. (not applicable to jogging)
   c. To move the ram down, the chamber main door must be closed. This condition prevents injuries by eliminating exposure to the pinch points that result as the shelf stack collapses.
   d. If the chamber main door on the maintenance room side of the freeze dryer is open, then the loading panel on the clean room side of the freeze dryer de-activates.

      These conditions prevent the situation where a person in the clean room can move the ram up while an open chamber door on the maintenance room side allows entry into the chamber (and vice versa).
   e. The unloading pusher is home.
   f. The loading door is closed or:
      i. The isolator guarding is not breached and all relevant axes for any docked automated loading/unloading equipment are home.
   g. The main isolation valve must be closed except when re-homing if the shelves drift during the Freeze Drying Cycle. If CIP is active, shelf movement is allowed if the main isolation valve is in the CIP position.
   h. Shelf ram failed to reach position alarm is active. Once this failure occurs, the condition remains active until the failure is reset by the user from the PC HMI Alarms screen.
   i. Shelf ram movement over pressure alarm inactive. Once this failure occurs, the condition remains active until the failure is reset by the user from the PC HMI Alarms screen.

3. Manual or automatic shelf movement sequence:
   a. HYD1 hydraulic pump starts.
   b. After HYD1 has been running for 5 seconds, SV220 shelf ram movement enable valve and FV214 shelf ram movement speed/direction valve discrete output is energized. SV220 is normally de-energized (i.e. closed). This state prevents the ram from drifting downward. Once energized, FV214 receives an analog signal from the PLC to move the ram up or down at a specific speed.

c. When ZT1 position transmitter attached to the ram indicates that the ram is in position or the shelf ram pressure / home position is reached (depending on active function), SV220, FV214, and HYD1 de-energize per section 2.2.7 and the analog signal to FV214 is reset.
d. If the ram position drifts by more than 0.5 mm from setpoint, then HYD1, SV220, and FV214 are energized as stated above to correct the position of the ram. When the ram is again in position, the valves and pump are de-energized as stated above.

2.2.6 Heat Exchange System

The heat exchange system is comprised of cooling and heating exchangers in series through which heat transfer fluid is circulated by a pump. The heat transfer fluid is circulated through the shelves to affect heat transfer to/from the product.

1. Cooling exchangers:
   a. The cooling exchangers are of a brazed stainless steel plate construction and each one is cooled by direct expansion of LN_2.

2. Electrically immersion heat exchanger (shelf circuit):
   a. Cylindrical AISI 304 stainless steel vessel fitted with multiple heating elements with stainless steel external protection
   b. Two thermostatic switches are provided to avoid overheating the heat transfer fluid:
      i. TSH25 temperature limit switch is attached to the external body of the heater (set at 100°C). This switch will automatically reset when the temperature < 100°C.
      ii. TSH25A thermostatic safety switch is embedded within the heater elements (set at 120°C). This safety switch must be manually reset at the device unless an SIP Cycle is running. If an SIP cycle is running, the switch is reset via a discrete PLC output.
   c. HTR1 Shelf fluid heater interlocks (to prevent a possible fire hazard and/or unexpected operation):
      i. CP1 or CP2 circulation pump is running for a delay.
      ii. Both TSH25A thermostatic safety switch and TSH25 secondary temperature limit switch do not indicate high temperature (Shelf fluid temp > safety setpoint alarm not active).
      iii. TE201 shelf fluid inlet temperature probe or TE201A redundant shelf fluid inlet temperature probe not failed.

3. Heat transfer fluid is circulated by means of a centrifugal pumping system:
   a. Shelves:
      i. Two pumps are provided but only one pump is required to circulate the heat transfer fluid through the system.
      ii. The pumping duty is alternated between the two pumps every time an automatic freeze drying cycle is initiated. In the event one pump fails, or there is a drop in discharge pressure, that pump will turn off and the other pump will turn on. In the event that the second pump fails to develop discharge pressure, this pump will also shut off.

iii. CP1/CP2 Circulation pump interlocks:
1. TE201 shelf fluid inlet temperature probe and TE201A redundant shelf fluid inlet temperature probe not failed.
2. DPS1 shelf fluid circulation pump low pressure alarm not reset by the user from the PC HMI Alarms screen.

b. Expansion tank to accommodate volume changes caused by temperature changes during various cycles
i. Fluid level indicator (sight glass).
ii. Fitted with a molecular sieve moisture trap to prevent water being absorbed by the heat exchange medium.

2.2.7 Hydraulics

1. The hydraulic system is used for:
a. Shelf ram movement per section 2.2.5.1 and stoppering described below.
b. Operation of the chamber main door primary pins per section 2.2.3.
c. Operation of the chamber main door secondary pins per section 2.2.2.
d. Opening / closing the main isolation valve per section 2.2.8.

2. The hydraulic system contains:
a. Automatic adjustment for stoppering pressure. Safety devices prevent excessive force being generated and to prevent the shelf stack collapsing.
b. A counterbalance valve mounted directly to the bottom of the ram cylinder eliminating piping to the valve to increase system safety.
c. Pressure regulated valves for operating the chamber main door primary pins and secondary pins located at the hydraulic pump.
d. A hydraulic pump.
i. HYD1 Hydraulic pump interlocks:
1. Hydraulic pump not over pressure. If the PSH9 safety switch is tripped, then the pump stops. Once the pump is stopped by the switch, it has to be reset by the user from the PC HMI Alarms screen.
ii. HYD1 Hydraulic pump shutdown:
1. When the hydraulic pump is no longer required to run, it stops after System Engineering Parameter *Hydraulic pump shutdown delay* (typically 60 seconds) has elapsed. Keeping the hydraulic pump running for a minimum time period prevents unnecessary wear and possible damage to the hydraulic circuit, which could occur if the hydraulic pump were allowed to turn on and off repeatedly and in rapid succession.

3. Automatic stoppering sequence during the freeze drying cycle:
a. The shelf ram is extended, collapsing the shelves.

b. When shelf movement downward is inhibited, the hydraulic pressure builds.
c. When PT306 stoppering pressure >= Recipe Step Setpoint *Ram pressure* then a hold timer, defined by Recipe Step Setpoint *Stoppering dwell time*, starts.
d. When the hold timer expires, the hydraulic ram is fully retracted.

4. Manual Mode ram extend sequence:
   a. When the user extends the hydraulic ram and the shelf movement downward is inhibited, the hydraulic pressure builds.
   b. When PT306 stoppering pressure >= PC HMI Manual Control Screen *Stoppering pressure* then a 10 sec hold timer starts.
   c. When the hold timer expires, the ram can no longer be extended. The user must release the jog button to reset the hold timer and to allow for the ram to be extended once again.

2.2.8 Main Isolation Valve

The main isolation valve is a hydraulic mushroom style valve with a plate which contains a trapezoidal gasket which is compressed against the condenser wall. The valve opens into the chamber. The valve enables the chamber and condenser to be isolated from one another, in order for product dryness to be assessed and to allow defrost of the condenser without wetting of the chamber.

The shelf ram must be fully-retracted before the main isolation valve can be opened.

1. Main isolation valve open sequence:
   a. When the main isolation valve is required to open, the pressure differential between the chamber and condenser is compared. If the pressure differential |PT105-PT203| > 2.0 psia then FV8 condenser inlet valve and FV29 chamber inlet valve 1 open to equalize the pressure.
   b. HYD1 hydraulic pump starts.
   c. After the HYD1 hydraulic pump has been running for 5 seconds, SV1A (main isolation valve open) energizes to extend the piston. HYD1 hydraulic pump and SV1A remain energized until the XS164 main valve cylinder not extended and XS165 main valve cylinder not retracted limit indicate that the main isolation valve is fully open.
   d. Once the switch is activated, SV1A and HYD1 hydraulic pump per section 2.2.7 de-energize.
   e. If XS164, XS165 or PSH250 indicate a loss of position, then HYD1 hydraulic pump and SV1A energize until the switch indicates that the main isolation valve is in the open position.
2. Main isolation valve close sequence:
   a. The HYD1 hydraulic pump starts.
   b. After the HYD1 hydraulic pump has been running for 5 seconds, SV1 (main isolation valve close) energizes to retract the piston. The HYD1 hydraulic pump and SV1 remain energized until the PSH250 pressure switch, XS164 main valve cylinder not extended and XS165 main valve cylinder not retracted switches indicate that the main isolation valve is fully closed.
   c. Once the pressure switch is activated, SV1 and HYD1 hydraulic pump per section 2.2.7 de-energize.

d. If the PSH250 pressure switch, XS164 or XS165 limit switch indicate a loss of position, then the HYD1 hydraulic pump and SV1 energize until the switch indicates that the main isolation valve is in the closed position.

3. Main isolation CIP sequence:
   a. The main valve is opened as described above.
   b. SV1 (main isolation valve close) energizes to retract the piston. The hydraulic pump and valve remains energized until XS164, XS165 and XS167 main valve cylinder in CIP position limit switches indicates that the main isolation valve is in the CIP position.
   c. Once the CIP position switch is activated, the valve and hydraulic pump per section 2.2.7 de-energize.
   d. If the limit switches indicate a loss of the CIP position, then the CIP cycle aborts.

2.2.9 Ice Condenser

The ice condenser is located below the chamber and is is integral to the vessel.

The condensing surface within the condenser body comprises a number of polished stainless steel tubes. A series of tubes are manifolded in order to form a refrigeration circuit. Each circuit is cooled by the direct expansion of LN_2 and cold N_2 gas. The system consists of 4 circuits.

Each condenser cooling circuit is monitored by an RTD temperature probe, which is mounted in a thermal well, located approximately at the mid-point distance along one tube section of each circuit, to enable its removal without the need to enter the condenser.

A platinum resistance thermoelement, contained in a thermowell welded at the middle of each coil, is used to measure coil temperature.

A platinum thermoelement will provide the coil temperature information to the PLC.

2.2.10 Vacuum System

The vacuum system is used for:

1. Automatic freeze drying
2. Leak test
3. Bellows test cycles
4. Bellows evacuation
5. Various manual functions

During a freeze drying cycle the vacuum system is used to evacuate the chamber and condenser. This reduces the pressure within the chamber, aiding the sublimation of the frozen portion of the product, which is essential to the freeze drying process.

2.2.10.1 Vacuum Group

The vacuum necessary for the freeze drying process is created by using a vacuum group mounted on a machine frame.

1. The vacuum configuration consists of:
   a. Two two-stage, oil sealed, rotary vane vacuum pumps equipped with an oil mist filter and gas ballast.
   b. AISI 304 stainless steel pipework that connects each vacuum pump to the condenser.
   c. An automatic, spring return, pneumatically actuated butterfly valve (FV2 main vacuum valve) located close to the connection to the condenser to isolate the vacuum group from the freeze dryer. In the event of a power failure this valve closes (fails closed) automatically to prevent contamination of the condenser from the vacuum group.
   d. Two-pump installations have individual automatic butterfly isolation valves FV11 and FV12 installed on the inlet of each pump, allowing each to be isolated when acting as standby pumps or if the primary pump should fail.

2. Defrost / Decontamination initial evacuation sequence:
   a. Condenser cooling per section 3.2.3 starts so that any water in the condenser or chamber will freeze on the condensing surface and not contaminate the vacuum system.
   b. The pumping system is sized such that all pumps are required to satisfy the standard evacuation time. VP1 vacuum pump 1 starts and VP2 vacuum pump 2 starts.
   c. SV308 vacuum pump 1 nitrogen purge valve opens and SV309 vacuum pump 2 nitrogen purge valve opens.
   d. Reserved
   e. When either vacuum pump is running, and the lowest functional condenser coil temperature of TE203, TE204, TE205 and TE206 is <= -40°C for 10 minutes, then the rest of the vacuum group starts as described in the next step.
   f. After VP1 vacuum pump and VP2 vacuum pump have been confirmed running for 10 sec, FV11 vacuum pump 1 isolation valve and FV12 vacuum pump 2 isolation valve open.
   g. Once PT301 vacuum pump group vacuum <= chamber vacuum or if the vacuum system has been evacuated for 5 minutes, then FV2 main vacuum valve opens.

3. Automatic freeze drying and Leak Test initial evacuation sequence:
   a. Condenser cooling per section 3.2.3 starts so that any water in the condenser or chamber will freeze on the condensing surface and not contaminate the vacuum system.
   b. The pumping system is sized such that all pumps are required to satisfy the standard evacuation time. VP1 vacuum pump 1 starts and VP2 vacuum pump 2 starts.
   c. SV308 vacuum pump 1 nitrogen purge valve opens and SV309 vacuum pump 2 nitrogen purge valve opens.
   d. Reserved

e. When either vacuum pump is running, and the lowest functional condenser coil temperature of TE203, TE204, TE205 and TE206 is <= -40°C for 10 minutes, then the rest of the vacuum group starts as described in the next step.
f. After VP1 vacuum pump and VP2 vacuum pump have been confirmed running for 10 sec, FV11 vacuum pump 1 isolation valve and FV12 vacuum pump 2 isolation valve open.
g. After the vacuum group is running, the main isolation valve opens.
h. Once PT301 vacuum pump group vacuum <= chamber vacuum or if the vacuum system has been evacuated for 5 minutes, then FV2 main vacuum valve opens.

4. Freeze drying evacuation once the chamber vacuum setpoint is reached:
   a. One vacuum pump stops and becomes the reserve pump. This reserve pump will restart in the case of a vacuum alarm or a failure as described in item c below.
   b. The energized vacuum pump will be used to maintain the vacuum setpoint. Every time an automatic freeze drying cycle is initiated the duty will alternate between the two vacuum pumps.
   c. If the primary vacuum pump should stop (due to over current or other failure) or if the corresponding pump isolation valve should fail, then FV2 main vacuum valve closes and the active vacuum group stops. The reserve vacuum pump will start, and after 10 seconds the corresponding pump isolation valve will open. Once PT301 vacuum system pressure <= chamber vacuum or if the vacuum system has been evacuated for 5 minutes, then FV2 main vacuum valve re-opens.

5. Manual mode evacuation sequence:
   a. The user can start the following functions from the manual controls screen (see section 3.1.3.2) in the following order:
      i. Condenser cooling
      ii. Vacuum Pump 1 and / or Vacuum Pump 2
      iii. Main isolation valve
      iv. Main vacuum valve with vacuum setpoint

6. Bellows evacuation sequence:
   a. The active vacuum pump is used to evacuate the bellows. If no vacuum pump is running when bellows evacuation is required, the last active vacuum pump is used:
      1. The vacuum pump starts.
      2. SV308 vacuum pump 1 nitrogen purge valve and SV309 vacuum pump 2 nitrogen purge valve opens.
      3. 10 seconds after the pump starts, the vacuum pump isolation valve opens.

7. Media fill evacuation sequence:
   a. Condenser cooling per section 3.2.3 starts so that any water in the condenser or chamber will freeze on the condensing surface and not contaminate the vacuum system.

b. A vacuum pump starts (last one used for freeze drying cycle).
c. SV308 vacuum pump 1 nitrogen purge valve and SV309 vacuum pump 2 nitrogen purge valve opens.
d. When the vacuum pump is running, and the lowest functional condenser coil temperature of TE203, TE204, TE205 or TE206 is <= -40°C for 10 minutes, then after 10 seconds, the vacuum pump isolation valve opens and FV2 main vacuum valve opens and the main isolation valve opens per section 2.2.8.
e. The energized vacuum pump will be used to maintain the vacuum setpoint.

2.2.10.2 Vacuum Measurement and Control

The chamber is supplied with a heated capacitance manometer PT101.

PT301 Pirani gauge is supplied on the vacuum pump group, fitted downstream of FV2 main vacuum valve.

Automatic vacuum control is achieved by the admission of gas (clean air or nitrogen, the appropriate valve is selected via the PC HMI) into the chamber at a rate controlled by cycling FV66, an automatic modulating needle valve. The valve is controlled by the PLC logic**.** The PLC uses the chamber vacuum gauge as the process variable. During this time, the aeration valves into the chamber also open. The supply of nitrogen or clean air into the system is used to counteract the vacuum created by the vacuum pump group and condensing water vapor.

In the event that PT101 fails, FV66 is closed until the failure no longer exists.

2.2.10.3 Media Fill Pressure Measurement and Control

The chamber is supplied with a pressure transducer PT105.

Chamber pressure is achieved via the actuation of FV2 main vacuum valve to evacuate the chamber to the media fill cycle pressure set point. Should the PT105 chamber pressure rise above the media fill cycle set point plus the media fill pressure deviation set point, FV2 main vacuum valve will open to return the PT105 to the media fill pressure set point. Should the PT105 fall below the media fill cycle set point minus the media fill pressure deviation set point, FV5 gas bleed bypass valve will open to return PT105 to the media fill pressure set point.

2.2.10.4 Liquid Ring Pump (LRP)

1. LRP1 is used to pull vacuum:
   a. To evacuate the chamber and condenser so that the chamber main door can be locked/unlocked.
   b. To evacuate the condenser prior to and during the steaming phase of the defrost cycle.
   c. To evacuate the system prior to the steam purge phases of the SIP cycle.

d. To dry the system at the end of the CIP and SIP cycle.

2. LRP1 interlocks:
   a. FV16 main drain valve is closed.
   b. FV48 main drain bypass valve is closed.
   c. Once LRP1 is running for 15 sec, if FSL1 LRP low flow switch indicates that the flow is low for 10 seconds, then the LRP stops. This alarm must be reset by the user from the PC HMI Alarms screen.

3. The following evacuation startup sequence is followed:
   a. FV16 main drain valve is closed.
   b. LRP1 starts and SV17 LRP seal water supply valve opens after 15 seconds.
   c. If LRP1 is confirmed on for 5 seconds and FSL1 LRP low flow switch indicates water flow for 5 seconds, then FV15 LRP isolation valve opens
   d. When FV15 is confirmed open for 5 seconds, then the required drain valve(s) can be open to start evacuation.
   e. If evacuation of both the chamber and condenser is required, the main isolation valve opens per section 2.2.8, 5 seconds after FV15 is confirmed open and then FV9 condenser drain valve is opened.

4. Reserved

5. The following evacuation shutdown sequence is followed:
   a. The drain valve(s) close.
   b. The main isolation closes per section 2.2.8 if evacuation on both the chamber and condenser was required.
   c. After 5 seconds, FV15 LRP isolation valve closes.
   d. After 5 seconds, LRP1 stops and SV17 closes.

2.2.10.5 Bellows Evacuation

The pressure in the bellows must be consistent with the pressure in the chamber/condenser when the bellows is moved. Bellows evacuation prevents bellows deformation caused when the air space enclosed by the bellows is of a greater pressure than the air space of the chamber/condenser. It also minimizes the risk of bellows leakage into the chamber/condenser.

2.2.10.5.1 Shelf Ram Bellows

1. When either a Freeze Drying cycle is active, or no cycle is active:
   a. When PT105 chamber pressure <= 12.5 psia:
      i. Vacuum pump group starts per section 2.2.10.1 item 6.

ii. SV54 bellows vent valve closes.
iii. After 5 seconds, SV55 bellows evacuation valve opens.

b. No cycle active with no active manual functions requiring a vacuum pump group (to limit vacuum pump group running time):
   i. When PT304 shelf ram bellows vacuum is <= 200 micron for 2 minutes
      1. SV55 bellows evacuation valve closes.
      2. Vacuum pump group stops.
   ii. When PT304 shelf ram bellows vacuum is >= 999 micron
      1. Vacuum pump group starts per section 2.2.10.1 item 6.
      2. SV55 bellows evacuation valve opens.
   iii. Items 1.b.i and ii above are repeated based upon bellows pressure until PT105 > 12.5 psia for 2 minutes.
   iv. If PT304 fails, the bellows is continuously evacuated until PT105 > 12.5 psia for 2 minutes.
c. When PT105 > 12.5 psia for 2 minutes:
   i. Vacuum pump group stops (if not required for purposes other than bellows evacuation).
   ii. SV55 bellows evacuation valve closes.
   iii. 5 seconds after SV55 is commanded closed, SV54 bellows vent valve opens. This allows the air inside the bellows to escape when the bellows is retracting, and allows dried air into the bellows when the bellows is extending.
d. If PT105 fails, the bellows is continuously evacuated until the failure no longer exists.

2. During the bellows integrity test:
   a. When the bellows is tested:
      i. Vacuum pump group starts per section 2.2.10.1 item 6.
      ii. SV54 bellows vent valve closes.
      iii. After 5 seconds, SV55 bellows evacuation valve opens.
   b. After the bellows is tested:
      i. Vacuum pump group stops.
      ii. SV55 bellows evacuation valve closes.
      iii. 5 seconds after SV55 is commanded closed, SV54 bellows vent valve opens.

2.2.10.5.2 Main Isolation Valve Bellows

1. When Leak Test Cycle not active:
   a. When PT203 condenser pressure <= 12.5 psia:
      i. Vacuum pump group starts per section 2.2.10.1 item 6.
      ii. SV77 bellows vent valve closes.
      iii. After 5 seconds, SV78 bellows evacuation valve opens.

b. For no cycle active with no active manual functions requiring a vacuum pump group CIP, or SIP active (to limit vacuum pump group running time):
   i. When PT307 MIV bellows vacuum is <= 200 micron for 2 minutes
      1. SV78 bellows evacuation valve closes.
      2. Vacuum pump group stops.
   ii. When PT307 MIV bellows vacuum is >= 999 micron
      1. Vacuum pump group starts per section 2.2.10.1.
      2. SV78 bellows evacuation valve opens.
   iii. Items 1.b.i and ii above are repeated based upon bellows pressure until PT203 > 12.5 psia for 2 minutes.
   iv. If PT307 fails, the bellows is continuously evacuated until PT203 > 12.5 psia for 2 minutes.
c. When PT203 > 12.5 psia for 2 minutes:
   i. Vacuum pump group stops (if not required for purposes other than bellows evacuation).
   ii. SV78 bellows evacuation valve closes.
   iii. 5 seconds after SV78 is commanded closed, SV77 bellows vent valve opens. This allows the air inside the bellows to escape when the bellows is retracting, and allows dried air into the bellows when the bellows is extending.
d. If PT203 fails, the bellows is continuously evacuated until the failure no longer exists.

2. During the bellows integrity test:
   a. When the bellows is tested:
      i. Vacuum pump group starts per section 2.2.10.1 item 6.
      ii. SV77 bellows vent valve closes.
      iii. After 5 seconds, SV78 bellows evacuation valve opens.
   b. After the bellows is tested:
      i. Vacuum pump group stops.
      ii. SV78 bellows evacuation valve closes.
      iii. 5 seconds after SV78 is commanded closed, SV77 bellows vent valve opens.

3. During the Leak Test cycle:
   a. Prior to closing the main isolation valve:
      i. The vacuum pump group starts per section 2.2.10.1 item 6.
      ii. SV77 bellows vent valve closes.
      iii. After 5 seconds, SV78 bellows evacuation valve opens.
   b. After final aeration:
      i. The vacuum pump group stops.
      ii. SV78 bellows evacuation valve closes.
      iii. 5 seconds after SV78 is commanded closed, SV77 bellows vent valve opens.
   c. If PT203 fails, the bellows is continuously evacuated until the failure no longer exists.

2.2.10.5.3 Unloading Pusher Bellows

1. When either a Freeze Drying cycle is active, or no cycle is active:
   a. When PT105 chamber pressure <= 12.5 psia:
      i. Vacuum pump group starts per section 2.2.10.1 item 6.
      ii. SV1001 bellows vent valve closes.
      iii. After 5 seconds, SV1000 bellows evacuation valve opens.
   b. No cycle is active with no active manual functions requiring a vacuum pump group (to limit vacuum pump group running time):
      i. When PT501 unloading pusher bellows vacuum is <= 200 microns for 2 minutes
         1. SV1000 bellows evacuation valve closes.
         2. Vacuum pump group stops.
      ii. When PT501 unloading pusher bellows vacuum is >= 999 microns
         1. Vacuum pump group starts per section 2.2.10.1 item 6.
         2. SV1000 bellows evacuation valve opens.
      iii. Items 1.b.i and ii above are repeated based upon bellows pressure until PT105 > 12.5 psia for 2 minutes.
      iv. If PT501 fails, the bellows is continuously evacuated until PT105 > 12.5 psia for 2 minutes.
   c. When PT105 > 12.5 psia for 2 minutes:
      i. Vacuum pump group stops (if not required for purposes other than bellows evacuation).
      ii. SV1000 bellows evacuation valve closes.
      iii. 5 seconds after SV1000 is commanded closed, SV1001 bellows vent valve opens. This allows the air inside the bellows to escape when the bellows is retracting, and allows dried air into the bellows when the bellows is extending.
   d. If PT105 fails, the bellows is continuously evacuated until the failure no longer exists.

2. During the bellows integrity test:
   a. When the bellows is tested:
      i. Vacuum pump group starts per section 2.2.10.1 item 6.
      ii. SV1001 bellows vent valve closes.
      iii. After 5 seconds, SV1000 bellows evacuation valve opens.
   b. After the bellows is tested:
      i. Vacuum pump group stops.
      ii. SV1000 bellows evacuation valve closes.
      iii. 5 seconds after SV1000 is commanded closed, SV1001 bellows vent valve opens.

2.2.11 Refrigeration System

The refrigeration system contains:

a. One low temperature liquid nitrogen CUMULUS® cooling unit. The CUMULUS® cooling system utilizes a liquid nitrogen supply as the refrigeration source. A nitrogen/heat transfer fluid heat exchanger is utilized to cool the shelf heat transfer fluid.
b. Separate low temperature cryogenic modulating control valves for temperature control on the exhaust of the shelf and condenser circuits.
c. Separate heat exchangers for shelf cooling using direct expansion of LN_2 to cool the heat transfer fluid as it is circulated through the plate heat exchanger.
d. Separate heat exchangers for condenser cooling using gaseous nitrogen to cool the coils.

2.2.11.1 Reserved

2.2.12 Reserved

2.2.13 Unloading Pusher Movement

The unloading pusher movement is controlled by the freeze dryer PLC. During manual mode or an unloading step of a freeze drying cycle, there are a series of interlocks and sequences that will be initiated by the operator pressing the unloading pusher functions on the HMI. When the freeze dryer requires the unloading pusher to extend or retract during loading/unloading, unloading pusher bellows test or CIP, the freeze dryer PLC will send a request to move. The unloading pusher is always sealed unless movement is required. When movement is required during a freeze drying cycle or CIP cycle, the unloading pusher is unsealed prior to extending and sealed once retracted if no additional movement is required. When movement is required during the unloading pusher bellows test, the unloading pusher is unsealed prior to extending and sealed once extended; the unloading pusher is then unsealed prior to retracting and sealed once retracted.

The unloading pusher must be sealed when the unloading pusher bellows is evacuated. If the unloading pusher bellows is being evacuated, unloading pusher movement is disabled.

2.2.14 Chamber and Condenser Aeration

1. Removed
2. Chamber Aeration:

   The chamber is aerated with clean air by opening FV4, FV5, FV7, FV3, until PT105 chamber pressure >= System Engineering Parameter *Aeration setpoint* (typically 14.2 psia) for the System Engineering Parameter *Chamber aeration time* (typically 60 seconds) or until PT105 >= 15.2 psia for 2 sec.
3. System Aeration:

The chamber and condenser are aerated with clean air by opening FV4, FV5, FV7, FV3, FV29 chamber inlet valve 1, and FV8 condenser inlet valve, until PT105 chamber pressure and PT203 condenser pressure >= System Engineering Parameter *Aeration setpoint* (typically 14.2 psia) for the System Engineering Parameter *Chamber aeration time* (typically 60 seconds) or until PT105 or PT203 >= 15.2 psia for 2 sec.

4. Freeze Drying Cycle Pre-aeration:

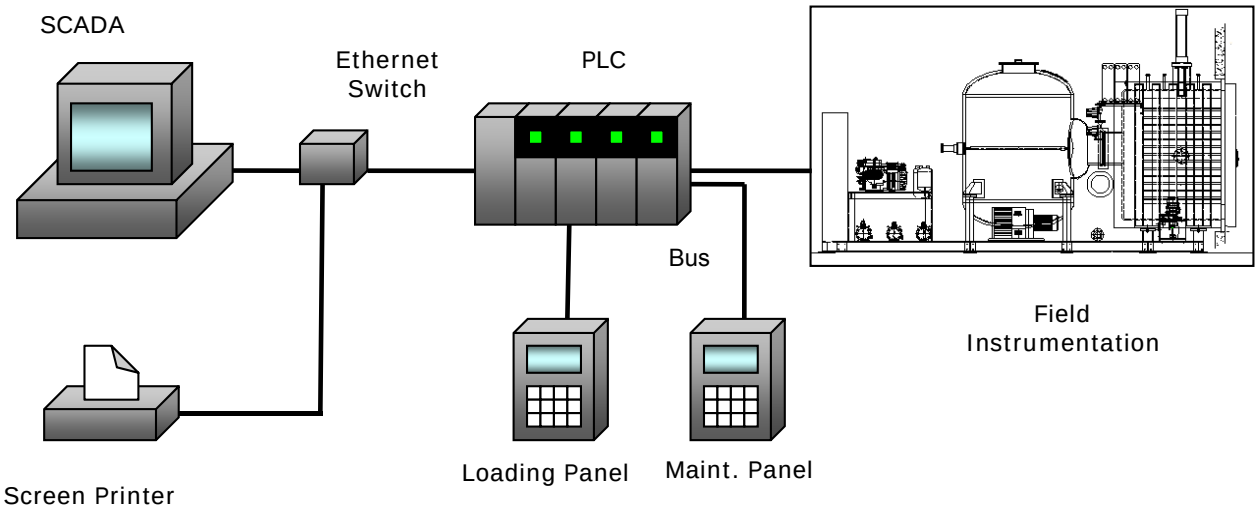
   The chamber is aerated until PT105 chamber pressure >= Recipe Parameter *Pressure* by opening FV4, FV5, FV3 and FV6 nitrogen supply valve for nitrogen if Recipe Parameter *Gas* is set to N2 or FV7 for air if *Gas* is set to Air.

5. Pre-aeration (Manual Mode):

   The chamber is pre-aerated until PT105 chamber pressure >= the manual pre-aeration *setpoint* entered by opening FV4, FV5, FV3, and FV6 for nitrogen if the Air/N2 selection is set to N2 or FV7 for sterile air if it is set to Air.

2.3 Base eLyomaster Control System

The following block diagram illustrates the components of the control system.



1. All of the required electrical, instrumentation, and control devices are installed in either a power or control cabinet.

2. The control system includes:
   a. Rockwell ControllogixPLC
   b. iFIX SCADA
   c. 1 remote HMI panel
   d. Screen printer with Ethernet port
   e. 1 Ethernet switch (and all associated CAT6 patch cables) for the SCADA and PLC network

2.3.1 Electrical and Power Distribution System

The power and control cabinet are used to distribute the required electrical signaling throughout the freeze dryer.

2.3.1.1 Power Cabinet

The power cabinet is mounted on the refrigeration skid. The power cabinet includes a main disconnect switch where customer supplied three phase power is connected. The power cabinet includes all alternating current power distribution equipment only.

2.3.1.2 Control Cabinet

The control cabinet includes all PLC, instrumentation, signaling and Network distribution equipment. A network of electrical junction boxes are located throughout the freeze dryer which are connected to the control cabinet.

2.3.2 Instrumentation and Control System

A single PLC system is used for analog and discrete inputs and outputs.

Analog signaling controlled devices are connected to the PLC via transmitters or direct connection.

2.3.2.1 Programmable Logic Controller (PLC)

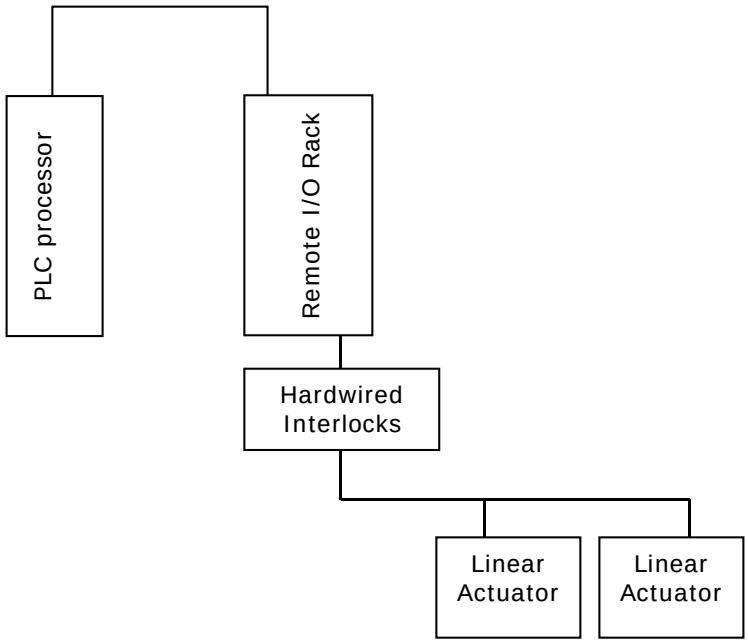
A Rockwell Controllogix PLC communicates with the SCADA via Ethernet.

The PLC controls all machine functions, performs all interlock checks, and generates all process/device alarms. In conjunction with analog and discrete inputs from the field devices, the PLC program uses control loops and other calculations to control machine systems via analog and discrete outputs to field devices. Examples of these systems include shelf temperature control, vacuum control, and pressure control.

2.3.2.2 Screen Printer

A color printer is connected to the SCADA network.

2.3.2.3 Loading Slot Door Control Components



3 Functions

3.1 Manual Functions and Interventions

3.1.1 Power Cabinet

	Function
1.	The door of the power cabinet contains a main disconnect switch that removes power from the freeze dryer from any devices that are not powered from the UPS.

3.1.2 Control Cabinet Switches

The following switches are available on or in the control cabinet.

	Pushbutton or Handswitch
1.	**Control Power Stop** function removes control power from any devices that are not powered from the UPS.
2.	**Control Power Reset** function restores control power.
3.	**Alarm Silence** function silences the alarm horn on the control cabinet until the next safety alarm occurs.
4.	**Shelf Heater Over Temp Reset** function resets thermostatic safety switch TSH25A per section 2.2.6 item 2.b.ii.

3.1.3 PC HMI

3.1.3.1 Cycle-Related Pushbuttons

1. The following pushbuttons are available at the PC HMI on the Freeze Drying Recipe screen and apply to the freeze drying cycle only:
   a. Select Hold / De-Select Hold
   b. Step Advance

2. The following pushbuttons are available at the PC HMI on the Recipe screen for each cycle and apply to all cycles, with exceptions as noted:
   a. Start Cycle
   b. Abort Cycle
   c. Cycle Reset (not applicable for the Freeze Drying cycle because recipe download provides this function)

3.1.3.2 PC HMI Manual Controls

The following manual functions are available at the PC HMI. Any functions marked with an asterisk (*) require Manual Mode to be active.

	Function
1.	**Control Select** function is used to change the mode of the freeze dryer to Auto or Manual.
2.	***Device Mode** function changes the mode of the freeze dryer to Device Mode (a subset of manual mode).
3.	**Loading Panel Enable** function enables the loading panel.
4.	**Maintenance Panel Enable** function enables the maintenance panel.
5.	***Shelf Temperature Control (including setpoint entry)** function controls shelf temperature to the setpoint entered via the heating and refrigeration systems.
6.	***Condenser Cooling Control (including setpoint entry)** function cools the condenser via the refrigeration system.
7.	***Vacuum Pump 1** function runs VP1 vacuum pump 1 and opens FV11 vacuum pump 1 isolation valve.
8.	***Vacuum Pump 2** function runs VP2 vacuum pump 2 and opens FV12 vacuum pump 2 isolation valve.
9.	***Main Isolation Valve** function opens the main isolation valve per section 2.2.8.
10.	***Main Vacuum Valve (including setpoint entry)** function opens FV2 main vacuum valve and controls the vacuum to the setpoint entered if the setpoint > 0 and the proper manual functions are active. The loading door gasket is operated per section 2.2.4.8 item e.i.
11.	**Air/N2** function changes the bleed gas between air and nitrogen for manual vacuum control and manual chamber pre-aeration.
12.	***Chamber Pre-Aeration (including setpoint entry)** function pre-aerates the chamber per section 2.2.14 item 5.
13.	***Chamber Aeration** function aerates the chamber per section 2.2.14 item 2.
14.	***System Drain** function aerates the chamber and condenser per section 2.2.14 item 3.Then the main isolation valve opens per section 2.2.8 and FV9 condenser drain valve open to drain the chamber and condenser.
15.	***System LRP Evacuation** function evacuates the chamber and condenser via the LRP per section 2.2.10.4 item 3. The loading door gasket is operated per section 2.2.4.8 item e.i.
16.	**Stoppering Pressure Setpoint** for manual shelf jog down function.
17.	**Decontamination Override** function disables all interlocks for decontamination. This includes manual operations and auto cycle sequencing. This function is only available to a high-level user. Available on alarms screen.

3.1.3.3 Device Mode

Device Mode can be enabled from the PC HMI manual controls screen when the freeze dryer is in Manual Mode. Using the unit graphic screen at the PC HMI, individual devices can be controlled by the user with minimal interlocking imposed by the PLC logic. Control of the freeze dryer using Device Mode is intended for maintenance purposes only. When Device Mode is exited, all devices return to their de-activated state.

1. The following interlocks will be active for Device Mode to maintain a minimal measure of protection for personnel, plant, and equipment:
   a. All hardwired interlocks will remain operational.
   b. Device Mode can only be activated when no manual functions are active.
   c. Device Mode cannot be activated if any of the HMI panels are enabled from the manual controls screen.
   d. There will be no provision to activate the doors or extend/retract door pins.
   e. There is no provision to move the shelf ram.
   f. There is no provision to inflate the loading door gasket.
   g. Device Mode cannot be used to create a stored energy situation. This means placing the freeze dryer in a state of stored energy that it could not have reached during its normal idle state. The following devices cannot be activated in Device Mode because they are sources of stored energy:
      i. The shelf fluid heater.
      ii. Valves that allow air, nitrogen, or other vacuum control/aeration/pre-aeration gas into the sterile filter lines.
      iii. Valves that allow CIP water, SIP steam, defrost water into the system.
      iv. Valves that allow LN_2 into the system.
   h. If a vacuum pump is running in Device Mode, then its respective motor cooling valve is automatically opened.
   i. Automatic routines such as vacuum pump shutdown/cooling and bellows evacuation will overrule selections made in Device Mode.
   j. The main isolation valve cannot be opened if the bellows vent valve is closed and bellows evacuation is inactive.
   K. The hydraulic pump will automatically start when the main isolation valve is opened or closed in Device Mode.
   L. If the liquid ring pump or the CIP recirculation pump is activated in Device Mode and low flow has been detected, then the pump will automatically de-activate. In this case, the pump must be reset by the user from the PC HMI alarms screen.

3.1.4 HMI Panels

The loading panel is installed near the loading door of the freeze dryer.
The maintenance panel is installed near the chamber main door of the freeze dryer. Each panel is enabled from the PC HMI Manual Controls screen. Any functions marked with an asterisk (*) require the panel to be enabled. Any functions marked with a double asterisk (**) are provided via hardwired pushbuttons.

The following functions are available at the panels:

Table: Panels

	Function	Loading Panel	Maintenance Panel
1.	***Chamber Pre-Aeration (including setpoint entry from Manual Controls Screen)** function pre-aerates the chamber per section 2.2.14 item 5.	x	
2.	***Chamber Aeration** function aerates the chamber per section 2.2.14 item 2.	x	x
3.	***Shelf Jog Down** function extends the shelf ram per section 2.2.7 item 4 and 2.2.5.1 item 3.	x	x
4.	***Shelf Jog Up** function retracts the shelf ram per section 2.2.5.1 item 3.	x	x
5.	***Shelf Index Down** function extends the shelf ram to the next unloading position per section 2.2.5.1 item 3.	x	
6.	***Shelf Index Up** function retracts the shelf ram to the next loading position per section 2.2.5.1 item 3.	x	
7.	***Loading Door Close** function jogs the door closed.	x	
8.	***Loading Door Open** function jogs the door until the fully-open position is reached.	x	
9.	***Home Load Door** function homes the loading door to the fully open position.	x	
10.	***Chamber Main Door Close** function extends the pins to close the door per section 2.2.3 item 5.		x
11.	***Chamber Main Door Open** function retracts the pins to allow the door to be pulled open per 2.2.3 item 4. The loading door gasket is operated per section 2.2.4.8 item f.i.		x
12.	***Chamber Main Door Lock** function extends the pins to lock the door per section 2.2.2 item 4.		x
13.	***Chamber Main Door Unlock** function retracts the pins to unlock the door per section 2.2.2 item 4.		x
14.	****Shelf/Loading Door Stop** function stops/prevents shelf and loading door movement.	x	x
15.	***Shelf/Loading Door Reset** function resets the Shelf/Loading Door Stop function to allow shelf ram and loading door movement.	x	x

	Function	Loading Panel	Maintenance Panel
16.	**Chamber Sight Glass Light** function illuminates the chamber sight glass light.	x	x
17.	**Loading/Unloading Complete** ends the Loading step and advances the cycle to the next step of the recipe. It also ends the freeze drying cycle when selected during unloading.	x	
18.	**Unloading Pusher Extend** function will jog the unloading pusher out on the shelf towards the loading door. Note: This function will be disabled during a freeze drying cycle.	x	
19.	**Unloading Pusher Retract** function will jog the unloading pusher back towards the home position. Note: This function will be disabled during a freeze drying cycle.	x	
20.	**Unloading Pusher Index** function will extend the unloading pusher to the next position. These positions will correspond to a position suitable to remove the next vial tray. There are a total of 6 positions including home. Note: These positions will be set from the engineering parameters screen.	x	
21.	**Unloading Pusher Home** function will retract the unloading pusher to the home position.	x	
22.	**Unloading Pusher Reset** function will reset an unloading pusher hard stop alarm.	x	

The following will be displayed on each panel:

	Status
1.	**Panel enabled / disabled**
2.	**Chamber pressure**
3.	**Shelf fluid inlet temperature**
4.	**Active cycle/mode message:** If a cycle is active, then either the name of the cycle or ‘Cycle complete - generating end report’ is displayed. If Auto mode is active but all cycles are inactive, then ‘no cycle active’ is displayed. If Manual mode is active, then ‘Manual Mode’ is displayed. If Device mode is active, then ‘Device Mode’ is displayed.
5.	**Shelf ram status:** ‘Shelf ram homed’ is displayed when the shelf ram is fully retracted. Otherwise ‘Shelf ram not homed’ is displayed.
6.	**Shelf position**
7.	**Shelf number**
8.	**Shelf interdistance**
9.	Loading door home status: ‘Loading door homing required’ is displayed when Loading door homing required alarm active (Loading panel only)
10.	Guarding status: ‘Guarding breached’ is displayed when Guarding breached loading door alarm is active.
11.	Hyd/loading dr abort load side selected status is displayed when PB73 is pressed.

	Status
12.	Hyd/loading dr abort maint side selected status is displayed when PB75 is pressed
13.	Waiting for chamber main door to close timer is displayed on the panel that operates the main door after **Close Chm Door** button is pressed.
14.	Unloading index position: The home position will be displayed as “0” and the corresponding positions will be displayed as the appropriate number. Note: This is displayed only on the loading panel.
15.	**Unloading pusher position (in mm)** Note: This is displayed only on the loading panel.

3.2 Automatic Functions

This section contains automatic functions including automatic cycles. The following is a list of automatic cycle-start interlocks:

1. Automatic mode active
2. No automatic cycles active
3. Chamber main door closed
4. Control power on
5. All valves in de-energized state
6. Main isolation valve closed
7. Cycle end report generation inactive
8. Facilities alarms inactive
9. Fieldbus fail alarm inactive
10. Various cycle-specific interlocks
11. Decontamination not required

    NOTE: Item 11 does not apply to Defrost / Decontamination cycle. A Freeze Drying cycle can also be restarted.

3.2.1 Temperature Control

1. The shelf temperature control system consists of:
   a. Liquid nitrogen cooling heat exchangers and associated supply and control valves
   b. A heater
   c. Two shelf fluid circulation pumps. The primary circulation pump is rotated at the start of each automatic freeze drying cycle.

2. The condenser cooling system consists of:
   a. Liquid nitrogen cooling heat exchangers and associated supply and control valves

3.2.2 Shelf Temperature Control

Heating and cooling of the shelves is controlled by PID loops in the PLC. One of two platinum resistance thermoelements, contained in a thermowell welded at the inlet of the shelf manifold, is used to measure fluid inlet temperature. The shelf fluid inlet temperature is used as the process variable to which the temperature of the shelf heat transfer fluid can be controlled. Shelf temperature control is disabled if TE201 shelf fluid inlet temperature probe and the redundant TE201A shelf fluid inlet temperature probe has/have failed.

A single platinum thermoelement will provide TE202 shelf fluid outlet temperature information to the PLC and chart recorder.

1. In Manual or Auto Mode when **only** shelf temperature control is active and <u>when condenser cooling is not active</u>, the following control is initiated:
   a. Circulation pump CP1 or CP2 starts per section 2.2.6.
      i. Whenever the LN_2 system is stopped, the shelf fluid circulation pump remains running for 10 minutes to avoid heat transfer fluid from freezing in the heat exchanger.
   b. There are two control loops running concurrently:
      i. The shelf fluid heat exchanger LN_2 exhaust cooling control loop: The process variable is TE460 LN_2 shelf cooling exhaust temperature and the setpoint is set to System Engineering Parameter *Shelf ht ex outlet cool PID sp*.
      ii. The shelf fluid inlet cooling control loop: The process variable is the shelf fluid inlet temperature and the setpoint is set to the shelf fluid inlet temperature setpoint.
      iii. FV1461 cold box LN_2 supply valve opens to allow nitrogen to flow into the heat exchangers. The lesser of the two control outputs described above is used as the TCV460 LN2 shelf temperature control valve output.
   c. If SIP is not active and the shelf fluid inlet temperature is <= the setpoint, the shelf fluid heater SCR is enabled until the shelf fluid inlet temperature is > the setpoint plus 4 °C. The heater % output = heater PID loop output minus shelf cooling PID output. The heater stops if vacuum

high deviation or vacuum failure alarm occurs during the freeze drying cycle or if any interlocks per section 2.2.6 item 2.c become active.

d. If TE460 LN_2 shelf cooling exhaust temperature is < -140 °C, then an alarm is generated and the associated FV1461 cold box LN_2 supply valve closes and the associated TCV460 LN_2 shelf temperature control valve is open a fixed 15%. These conditions remain until TE460 is greater than the low temperature alarm value, at which point the system returns to normal control.

e. If DPT481 shelf cooling differential pressure cold box is low, then an alarm is generated and the associated TCV460 LN_2 shelf temperature control valve closes. These conditions remain until DPT481 pressure is above the alarm reset pressure, at which point the system returns to normal control.

2. When neither shelf nor condenser cooling has been requested for a continuous 10 minutes the CUMULUS® cooling units go into the following shutdown sequence:
   a. FV1461 cold box LN_2 supply valve closes and the associated TCV460 LN_2 shelf temperature control valve and TCV468 LN_2 condenser temperature control valve opens a fixed 15%. After 60 seconds both valves close.

3.2.3 Condenser Cooling

1. In Manual or Auto Mode when **only** condenser temperature control is active, and <u>when shelf cooling is not active</u>, the following control is initiated:
   a. There are two control loops running concurrently:
      i. The condenser fluid heat exchanger LN_2 exhaust cooling control loop: The process variable is TE704 condenser coil #4 exhaust temperature and the setpoint is set to System Engineering Parameter *Cond ht ex outlet cool PID sp*.
      ii. The condenser cooling control loop: The process variable is the average of TE203, TE204, TE205, TE206 condenser coil temperatures. The setpoint is set to the condenser temperature setpoint.
      iii. FV1465 cold box LN_2 supply valve is open to allow nitrogen to flow into the heat exchangers. The lesser of the two control loop outputs described above is used as the TCV468 LN_2 condenser temperature control valve output.

   b. If TE704 condenser coil LN_2 outlet temperature is < -140 °C then an alarm is generated, the associated FV1465 condenser cold box LN_2 supply valve closed and the associated TCV468 LN_2 condenser temperature control vale is open to a fixed 15%. These conditions remain until TE704 is greater than the low temperature alarm value, at which point the system return to normal control.

2. When condenser cooling has not been requested and TCV468 has been closed for a continuous 10 minutes the CUMULUS® cooling units go into the following shutdown sequence:
   a. FV1465 condenser cold box LN_2 supply valve closes and the associated TCV468 LN_2 condenser temperature control valve opens a fixed 15%. After 60 seconds both valves close.

NOTE: Condenser cooling is disabled if the chamber main door is *not* closed as indicated by the XS140 door closed position switch.

3.2.4 Concurrent Shelf Temperature Control and Condenser Cooling

1. In Manual or Auto Mode, when both condenser cooling and shelf cooling are active, the following controls are initiated:
   a. The shelf and condenser temperature can be controlled concurrently as described in sections 3.2.2 and 3.2.3.

3.2.5 Freeze Drying Cycle

The Freeze Drying cycle operates according to step functions, which are built and executed in a recipe format on the PC HMI. Once a cycle initiates, because the PLC stores the active recipe and controls cycle sequencing, the cycle will continue without interruption in the case of a PC HMI failure.

IMA recommends regular use of a leak test prior to the start of a Freeze Drying Cycle. This will ensure the integrity and safety of the system.

1. The freeze drying cycle recipe:
   a. May contain up to 50 steps. The recipe is built by the user to meet the requirements of the pharmaceutical product using the following step types:
      i. Loading
      ii. Freezing
      iii. Evacuation
      iv. Drying
      v. Pressure Rise Test
      vi. Pre-Aeration
      vii. Stoppering
      viii. Aeration
      ix. Storage/Unloading

Each freeze drying step will include standard parameters. The user can change the value of these parameters. Examples of step parameters are the shelf temperature, chamber vacuum, and step time.

2. When building a recipe the following conditions apply:
   a. A maximum of one Loading step is allowed and it must reside in step 1.
   b. A Freezing step can follow only a Loading step or another Freezing step or reside in step 1.
   c. A maximum of one Evacuation step is allowed, and it must follow a Freezing step.
   d. A Drying step can follow only the Evacuation step, a Pressure Rise Test step, or another Drying step.
   e. A Pressure Rise Test step can follow only a Drying step and is not performed on media fill cycles.
   f. A maximum of one Aeration step is allowed, and it must follow a Drying step, a Pressure Rise Test step, or a Stoppering step.
   g. A maximum of one Pre-aeration step is allowed, and it must follow a Drying step, or a Pressure Rise Test step.
   h. A maximum of one Stoppering step is allowed and it must follow a Drying step, Pressure Rise Test step, or Pre-Aeration step.
   i. A maximum of one Storage/Unloading step is allowed and it must follow a Loading step, Aeration step, or Stoppering step or reside in step 1.

A freeze drying recipe will also contain text fields for product notes and a recipe name.

3. The following Freeze Drying General Recipe Parameters are available to the user:

Description
Vacuum high deviation sp (micron)
Vacuum fail sp (micron)
Media Fill (Yes/No)
Vac cntrl (Air; N2)

4. The following Freeze Drying Engineering Parameters are available to the user:

Description
Max ramping shelf temp dev (°C)
Max step end shelf temp dev (°C)
Step end low vacuum dev (micron)
Step end high vacuum dev (micron)

The main door must be locked in order to start a Freeze Drying cycle.

Once condenser cooling is enabled, it will remain active until a Decontamination cycle introduces steam into the system.

A Freeze Drying cycle MUST be followed by a Decontamination cycle. However, the Freeze Drying cycle may be restarted if needed for error recovery.

Once the loading door is opened, a *'decontamination required'* software interlock will be enabled.

The Decontamination cycle MUST be followed by CIP and SIP cycles. After completion of a decontamination cycle, manual functions will be allowed, but no other automatic cycles are available.

A System Leak Test cycle and bellows integrity tests should be run before a Freeze drying cycle has started. This will verify system integrity and ensure a high level of containment.

The following sections provide a general description of the steps of the freeze drying cycle.

3.2.5.1 Loading

Typically this is the first step of the freeze drying cycle.

Loading Step Parameters:

Description
Shelf temperature (°C)

	Action
1.	The shelf fluid inlet temperature is controlled to the step setpoint, Recipe Parameter *Shelf temperature*, as described in section 3.2.2 item 1.
2.	The user opens the loading door and positions each shelf for loading using the loading panel.
3.	When the user has completed loading the freeze dryer, they will jog the shelves to the home position and close the loading door. Then, the user selects either *Loading/Unloading Complete* from the loading panel or *Step Advance* on the PC HMI Freeze Drying Recipe screen to end the Loading step and advance the cycle to the next step of the recipe. Selection of *Loading/Unloading Complete* and *Step Advance* is permitted only if the shelf ram is home and the loading door is closed.
4.	A *'decontamination required'* software interlock is set once the loading door is open and remains active until the decontamination step of a Decontamination cycle is successfully completed or a Decontamination override is selected.

3.2.5.1.1 Removed

3.2.5.2 Freezing

This step is used to freeze the product that has been loaded onto the shelves during the Loading step.

Freezing Step Parameters:

Description
Shelf temperature (°C)
Step time (HH:MM)

	Action
1.	This function ramps the shelf temperature from the step end setpoint of the previous step to the setpoint of the current step, Recipe Parameter *Shelf temperature*, at a rate determined by the Recipe Parameter *Step time*. The step time starts when the step starts.

If the freezing function is the first step programmed in the recipe then the ramp starts from the current shelf fluid inlet temperature.

	Action
2.	The shelf temperature is controlled as described in section 3.2.2 item 1.
3.	When the step time expires, if the shelf fluid inlet temperature is within +/- Engineering Parameter *Max step end shelf temp dev* (typically 1°C) deviation from the step setpoint, then the cycle advances to the next step of the recipe.

3.2.5.3 Evacuation

The purpose of this step is to evacuate the chamber to the chamber vacuum or media fill chamber pressure setpoint.

Evacuation Step Parameters:

Description
Chamber vacuum (micron)
Condenser temperature (°C)
Media fill chamber prs (psia)

	Action
1.	The loading door gasket is operated per section 2.2.4.8 item a.i. The vacuum / pressure setpoint is achieved without ramping. The General Recipe Parameter *Media Fill* determines whether the step evacuates to the Chamber vacuum or Media fill chamber prs setpoint. Evacuation to the Recipe Parameter *Chamber vacuum* setpoint occurs as described in section 2.2.10.1 item 3. Evacuation to the Recipe Parameter *Media fill chamber prs* setpoint occurs as described in section 2.2.10.1 item 7. Shelf ram bellows evacuation starts per section 2.2.10.5.1 item 1. Main isolation valve bellows evacuation starts per section 2.2.10.5.2 item 1. Unloading pusher bellows evacuation starts per section 2.2.10.5.3 item 1.
2.	The shelf temperature is controlled to the step end setpoint specified in the previous step of the recipe as described in section 3.2.4.
3.	The condenser is cooled to the Recipe Parameter *Condenser temperature* setpoint as described in section 3.2.4. **NOTE: Once condenser cooling is enabled, it will remain active until a Decontamination cycle introduces steam into the system.**
4.	For non-media fill cycles when the chamber vacuum < step setpoint and the shelf fluid inlet temperature is within +/- Engineering Parameter *Max step end shelf temp dev* (typically 1°C) deviation from the previous step end setpoint, then the cycle advances to the next step of the recipe.
5.	For media fill cycles, when PT105 chamber pressure is <= the setpoint and the shelf fluid inlet temperature is within +/- Engineering Parameter *Max step end shelf temp dev* (typically 1°C) deviation from the step setpoint, the cycle advances to the next step of the recipe.

3.2.5.4 Drying

This step is used to dry the product.

Drying Step Parameters:

Description
Shelf temperature (°C)
Chamber vacuum (micron)
Step time (HH:MM)
Condenser temperature (°C)
Media fill chamber prs (psia)

	Action
1.	For non-media fill cycles, this function will ramp the chamber vacuum from the setpoint of the previous step to the setpoint of the current step, Recipe Parameter *Chamber vacuum*, at a rate determined by the Recipe Parameter *Step time*. The chamber vacuum is controlled as described in sections 2.2.10.2 and 2.2.10.1 item 4. For media fill cycles, the chamber pressure is controlled as described in section 2.2.10.3. General Recipe Parameter *Media Fill* determines whether the step evacuates to the Chamber vacuum or Media fill chamber prs setpoint.
2.	This function will also ramp the shelf temperature from the step end setpoint of the previous step to the setpoint of the current step, Recipe Parameter *Shelf temperature*, at a rate determined by the Recipe Parameter *Step time*. The shelf temperature is controlled as described in section 3.2.4.
3.	The condenser is cooled to the Recipe Parameter *Condenser temperature* setpoint as described in section 3.2.4.
4.	For non-media fill cycles when chamber vacuum <= step setpoint + Engineering Parameter *Step end high vacuum dev* (typically 20 micron) and chamber vacuum >= step setpoint - Engineering Parameter *Step end low vacuum dev* (typically 50 micron) and the shelf fluid inlet temperature is within +/- Engineering Parameter *Max step end shelf temp dev* (typically 1°C) deviation from the step setpoint, then the cycle advances to the next step of the recipe.
5.	For media fill cycles, when the shelf fluid inlet temperature is within +/- Engineering Parameter *Max step end shelf temp dev* (typically 1°C) deviation from the step setpoint, the cycle advances to the next step of the recipe.

3.2.5.5 Pressure Rise Test

The Pressure Rise Test step closes the appropriate valves to isolate the chamber from the condenser and sterile filter lines, and then examines the pressure rise in the chamber. A large pressure rise indicates that too much moisture remains in the product.

Pressure Rise Test Step Parameters:

Description
Pressure rise (micron)
Test time (sec)
Test repeat time (min)

	Action
1.	The shelf temperature is controlled per section 3.2.4 to the step end setpoint specified in the previous step of the recipe.
2.	The condenser is cooled to the Recipe Parameter *Condenser temperature* setpoint per section 3.2.4.
3.	To isolate the chamber and limit the pressure reduction in the condenser, the main isolation valve closes per section 2.2.8, and FV2 main vacuum valve, FV29 chamber inlet valve and FV66 gas bleed valves are closed to test the pressure rise.
4.	The test criterion is determined by adding the pressure rise setpoint to the current chamber vacuum. The test passes if the chamber vacuum rise < Recipe Parameter *Pressure rise* for the Recipe Parameter *Test time*. Should the chamber vacuum rise >= Recipe Parameter *Pressure rise* within the Recipe Parameter *Test time*, then the test fails and an alarm is annunciated. The valves open to control the chamber vacuum to the setpoint specified in the previous step of the recipe for the duration of Recipe Parameter *Test repeat time*. The chamber vacuum is controlled as described in sections 2.2.10.2 and 2.2.10.1 item 4. The bleed gas to counteract the vacuum created by the vacuum system is defined by Freeze Drying General Recipe Parameter *Vac cntrl*. After the repeat time has elapsed, the test restarts. The test repeats until it passes or the user selects *Step Advance* at the PC HMI.

3.2.5.6 Pre-Aeration

The Pre-Aeration step is used to pre-aerate the chamber and condenser after the product is dry, prior to the Stoppering step.

Pre-Aeration Step Parameters:

Description
Gas (Air/N2)
Pressure (psia)

	Action
1.	The main isolation valve closes per section 2.2.8. The condenser is cooled, per section 3.2.4, to the setpoint specified in the last drying step of the recipe.
2.	The shelf temperature is controlled, per section 3.2.2 item 1 to the step end setpoint specified in the last drying step of the recipe.
3.	The chamber is pre-aerated per section 2.2.14 item 4. Shelf ram bellows evacuation may stop per section 2.2.10.5.1 item 1.c (setpoint dependent). Main isolation valve bellows evacuation may stop per section 2.2.10.5.2 item 1.c (setpoint dependent). Unloading pusher bellows evacuation may stop per section 2.2.10.5.3 item 1.c (setpoint dependent). The loading door gasket is operated per section 2.2.4.8 item a.ii (setpoint dependent).

3.2.5.7 Stoppering

The stoppering step is used to stopper the vials.

Stoppering Step Parameters:

Description
Stoppering dwell time (sec)
Ram pressure (psig)

	Action
1.	If pre-aeration was not selected, the main isolation valve closes per section 2.2.8. The condenser is cooled, per section 3.2.4, to the setpoint specified in the last drying step of the recipe. The shelf ram extends to stopper the vials. Once PT306 >= Recipe Parameter *Ram pressure*, which indicates that the stoppers have been compressed into the vials, the shelf ram is held in position for the duration of the Recipe Parameter *Stoppering dwell time*.
2.	After expiration of the dwell time, the shelf ram retracts to the home position.
3.	The shelf temperature is controlled, per section 3.2.2 item 1 to the step end setpoint specified in the last drying step of the recipe.

3.2.5.8 Aeration

The Aeration step is used to aerate the chamber and condenser prior to the Storage/Unloading step.

Aeration Step Parameters:

Description
N/A

	Action
1.	If pre-aeration and stoppering were not selected, the main isolation valve closes per section 2.2.8. The condenser is cooled, per section 3.2.4, to the setpoint specified in the last drying step of the recipe.
2.	The shelf temperature is controlled, per section 3.2.2 item 1 to the step end setpoint specified in the last drying step of the recipe.
3.	The chamber is aerated per section 2.2.14 item 2. Shelf ram bellows evacuation stops per 2.2.10.5.1 item 1.c if not already stopped in Pre-Aeration (setpoint dependent). Main isolation valve bellows evacuation stops per section 2.2.10.5.2 item 1.c if not already stopped in Pre-Aeration (setpoint dependent). Unloading pusher bellows evacuation may stop per section 2.2.10.5.3 item 1.c (setpoint dependent). The loading door gasket is operated per section 2.2.4.8 item a.ii (setpoint dependent).

3.2.5.9 Storage/Unloading

Typically this is the last step of the freeze drying cycle.

Storage/unloading Step Parameters:

Description
Shelf Temperature (°C)

	Action
1.	The shelf temperature is controlled to the step setpoint, Recipe Parameter *Shelf temperature* as described in section 3.2.2 item 1.
2.	The condenser is cooled, per section 3.2.4, to the setpoint specified in the last drying step of the recipe.
3.	The user opens the loading door and positions each shelf for loading using the loading panel.
4.	The operator presses the unloading pusher extend button on the clean room HMI to unload product from the shelf. After the unloading stroke has been completed, the operator presses the unloading pusher retract button on the clean room HMI.
5.	Once the shelf has been unloaded, when the unloading pusher is confirmed retracted, the user will press the index shelf down button on the clean room HMI to unload the next shelf. Steps 6 and 7 will be repeated until all shelves are unloaded.

	Action
6.	When shelf unloading is complete, the operator will close the loading door. Once the loading door is confirmed closed, the operator will press the load/unload complete button. NOTE: the operator must ensure that nothing remains on the shelf stack as this could cause damage to the shelves.
7.	The shelf ram homes, and the cycle ends. The cycle batch report is created.

3.2.5.9.1 Removed

3.2.5.10 Freeze Drying Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are listed in EF1114_AL (alarm list).

1. The following conditions cause the cycle to abort:
   a. The user selects Abort at the PC HMI.

2. The following conditions cause the cycle to hold (Freeze drying in hold mode message on the PC HMI). Holding pauses all temperature/vacuum control ramps, pauses the step timer, and prevents advancing to the next step in the recipe:
   a. The shelf fluid inlet temperature probe and redundant shelf fluid inlet temperature probe fail.
   b. The shelf fluid inlet temperature is not within +/- Engineering Parameter Max ramping shelf temp dev (typically 4 °C) of the ramping setpoint. The cycle is held until the shelf fluid inlet temperature is within +/- 1 °C of the ramping setpoint.
   c. The step time has expired (if applicable) and the shelf fluid inlet temperature is not within +/- Engineering Parameter *Max step end shelf temp dev* (typically 1 °C) of the step setpoint.
   d. The drying step time has expired and the chamber vacuum > step setpoint + Engineering Parameter *Step end high vacuum dev* (typically 20 micron) OR chamber vacuum < step setpoint - Engineering Parameter *Step end low vacuum dev* (typically 50 micron).
   e. If the chamber vacuum is > than the ramping setpoint by more than the amount specified by General Recipe Parameter *Vacuum high deviation sp*, the cycle is held until the chamber vacuum is <= active setpoint. While the step is held, the following also occur depending on which step type is active:
      i. During a Drying step: both vacuum pumps are used, FV6 nitrogen supply valve or FV7 sterile air supply valve and FV66 gas bleed valve closes, and if the active ramping temperature setpoint is > 20°C then the heater is disabled.
      ii. During a Pressure Rise Test step: both vacuum pumps are used, FV6 nitrogen supply valve or FV7 sterile air supply valve close and FV66 gas bleed valve closes (if open), the remaining gas bleed lines open (if closed), the main isolation valve opens per section 2.2.8 (if closed) and FV2 main vacuum valve open (if closed), and the step enters the repeat stage (refer to section 3.2.5.5 and remains there until the repeat time expires and the step returns from hold.
   f. The chamber vacuum is > General Recipe Parameter *Vacuum fail sp*, the cycle is held until the chamber vacuum is <= active setpoint. While the step is held, the following also occur depending on which step type is active:

i. During a Drying step: both vacuum pumps are used, FV6 nitrogen supply valve or FV7 sterile air supply valve close and FV66 gas bleed valve closes, the shelf fluid heater disables, and the active temperature setpoint is set to -70 °C. When the step returns from hold, the previous temperature setpoint is used again.

ii. During a Pressure Rise Test step: both vacuum pumps are used, FV6 nitrogen supply valve or FV7 sterile air supply valve close and FV66 gas bleed valve closes (if open), the remaining gas bleed lines open (if closed), the main isolation valve opens per section 2.2.8 (if closed) and FV2 main vacuum valve open (if closed), and the step enters the repeat stage (refer to section 3.2.5.5) and remains there until the repeat time expires and the step returns from hold.

g. The chamber vacuum low deviation from the setpoint is >= 100 micron. The cycle is held until the chamber vacuum is within this deadband.

h. The user selects *Hold* from the PC HMI Freeze Drying Recipe screen.

i. Control power is lost.

3. The following conditions cause the cycle to pause during loading and stoppering until the condition is corrected:
   a. Shelf failed to reach position or hydraulic stoppering position probe fail.

4. Upon returning from a power failure the cycle will resume where it was interrupted.

3.2.6 Defrost / Decontamination Cycle

If a freeze drying cycle is run and the *'decontamination required'* software interlock is active, a successful Defrost / Decontamination cycle, another freeze drying cycle or a decontamination override must be completed to have full access to automatic and manual functions.

In this cycle, steam is used to defrost the condenser at the end of the freeze drying cycle. The contaminated effluent will be drained to the customer's processing facility for deactivation. Once this is completed, the chamber, condenser and transitional piping between the freeze dryer and the customer drain connection are decontaminated with steam.

The interlocks with the customer's drain connection will have to be satisfied before this cycle can start. This is accomplished through an interface system with the freeze dryer.

Defrost / Decontamination Recipe Parameters
Defrost time (min)
Drying time (min)
Decontamination pressure (psia)
Decontamination temp (°C)
Decontamination time (min)
Condensate drain time (min)
Defrost / Decontamination Engineering Parameters
Maximum time to achieve decon temp (min)
Maximum time below decon temp (sec)
Steam pressure offset (psia)
Condenser cooling time (min)
Shelf cooling time (min)
Shelf cooling temp. setpoint (°C)

When activated, the Defrost / Decontamination cycle operates as follows:

3.2.6.1 Evacuate

	Action
1.	The loading slot door gasket is pressurized per section 2.2.4.8 item 3.b.
2.	The main isolation valve is opened per section 2.2.8. The chamber and condenser are evacuated using the vacuum pumps per 2.2.10.1 section 2 and condenser cooling remains enabled.

	Action
3.	When the lowest functional condenser coil temperature is ≤ -50°C and the chamber vacuum is < 1000 micron, the main door is locked if not already locked, the main vacuum valve closes and the vacuum pumps are stopped. The main isolation valve is closed per section 2.2.8. Condenser cooling is stopped.

3.2.6.2 Defrost

	Action
1.	FV20 steam defrost valve opens to admit steam into the condenser until the lowest functional condenser coil temp probe is >= 50°C for the duration defined by the Defrost Recipe Parameter *Defrost time.* If PT203 condenser pressure > 11.6 psia, FV20 will be closed. It will re-open when PT203 < 8.7 psia. When the Defrost Recipe Parameter *Defrost time* expires, the cycle will advance to the next step.

3.2.6.3 Aerate and drain

	Action
1.	The chamber and condenser are aerated with air per section 2.2.14 item 3.
2.	The freeze dryer will enable the **drain request** signal to the customer to indicate that condensate is present in the drain line and is ready to be recovered. The cycle will wait until the **drain ready** signal is received from the customer. When the **drain ready** signal from the customer is received, confirming the system is at or below atmospheric pressure and ready to receive the contaminated effluent, the **drain active** signal is sent from the freeze dryer to the customer's drain system. The condenser is drained through FV1650 potent product process drain valve for the time specified in recipe parameter *Condensate drain time*. During this step, the chamber and condenser will be aerated continuously per section 2.2.14 item 3.
3.	All valves return to their no-cycle active state. After this timer, the draining active signal is disabled.

3.2.6.4 Second Evacuation

	Action
1.	The main isolation valve is opened per section 2.2.8. The chamber and condenser are evacuated using the vacuum pumps per 2.2.10.1 section 2.
2.	When the lowest functional condenser coil temperature is ≤ -50°C and the chamber vacuum is < 1000 micron, then condenser cooling and the vacuum pumps are stopped.

3.2.6.5 Decontamination

	Action
1.	The main isolation valve remains open. The freeze dryer will enable the **drain request** signal to the customer to indicate that decontamination will be sending hot condensate to the customer potent drain. The cycle will wait until the **drain ready** signal is received from the customer. When the **drain ready** signal from the customer is received, confirming the system is at or below atmospheric pressure and ready to receive the condensate, then the **drain active** signal is sent from the freeze dryer to the customer's drain system. FV1650 potent product process drain valve, FV1128 chamber low pressure relief isolation valve and FV1129 condenser low pressure relief isolation valves open. FV1651 potent process drain steam trap bypass valve is closed. The freeze dryer is pressurized with steam through FV38 steam supply valve, FV29 chamber inlet valve and FV8 condenser inlet valve. The steam pressure is controlled to Recipe Parameter *Decontamination pressure* using the steam supply valve as the control output and the primary chamber or primary condenser pressure as the process variable. FV38 opens when PT105 and PT203 ≤ (Recipe Parameter *Decontamination pressure* - Engineering parameter *Steam pressure offset*) and close when PT105 or PT203 > Recipe Parameter *Decontamination pressure*. NOTE: If the **drain ready** signal from the customer is lost for any reason, FV38, FV1650, FV1128 and FV1129 will close until the signal is restored.
2.	When TE1650 potent process drain temperature and all functional condenser coil temperatures are ≥ Recipe Parameter *Decontamination temp,* the decontamination timer starts. Decontamination will continue for the time specified by Recipe Parameter *Decontamination time.* NOTE: If the time to reach *Decontamination temp* exceeds the *Maximum time to achieve decon temp,* a message for *Decontamination time excessive* is annunciated.
3.	The decontamination timer holds if TE1650, TE203, TE204, TE205 or TE206 fall < Recipe Parameter *Decontamination temp*.
4.	If the decontamination timer is held longer than the time period defined by Decontamination Engineering Parameter *Maximum time below decon temp*, then the decontamination timer resets. It restarts when all decontamination temperatures are above the *Decontamination temp*.
5.	The decontamination timer expires when it reaches Recipe Parameter *Decontamination time*. **The *'decontamination required'* software interlock is cleared.**
6.	FV38, FV29 and FV8 close.
7.	FV1651 opens to allow the steam to discharge down the drain.
8.	Steam is discharged down the drain until the chamber pressure is <= 15.2 psia and a 1 minute timer expires.
9.	FV1650, FV1128 and FV1129 close and FV1651 is opened.
10.	If CIP follows Decontamination in Cycle Queue, then the cycle is complete and the freeze dryer advances to the CIP cycle. Interlock requiring CIP cycle is set. Manual mode is now available. Otherwise, the cycle then advances to the next step.

3.2.6.6 Dry System

	Action
1.	The main isolation valve remains open and the chamber and condenser are evacuated using the liquid ring pump for the duration defined by Decontamination Recipe Parameter *Drying time* section 2.2.10.4 item 3. Main isolation valve bellows evacuation per section 2.2.10.5.2 item 1.
2.	The liquid ring pump shuts down per section 2.2.10.4 item 5.
3.	The main isolation valve closes.

3.2.6.7 Cool Condenser

	Action
1.	The main isolation valve remains open and the condenser coils are cooled, as described in section 3.2.3, for the time period defined by Decontamination Engineering Parameter *Condenser cooling time*.

3.2.6.8 Cool Shelves

	Action
1.	The main isolation valve remains open and the shelves are cooled as described in section 3.2.2 to Decontamination Engineering Parameter *Shelf cooling temp. setpoint*. The shelf fluid heater is disabled.
2.	Once the shelf fluid inlet temperature is <= Decontamination Engineering Parameter *Shelf cooling temp. setpoint*, the shelf fluid inlet temperature is controlled at this setpoint for the duration defined by Decontamination Engineering Parameter *Shelf cooling time*.
3.	The PLC automatically resets the internal thermostatic safety switch on the shelf fluid heater via a discrete output from this point on until the end of the cycle. The automatic reset is performed to preclude the user from having to locally reset the switch after every Decontamination cycle.

3.2.6.9 Aerate System

	Action
1.	Main isolation valve bellows evacuation starts per section 2.2.10.5.2 item 3a. When PT307 MIV bellows vacuum < 999 micron or 5 minutes has elapsed, the main isolation valve is closed per section 2.2.8.
2.	When the main isolation valve is confirmed closed, the chamber and condenser are aerated per section 2.2.14 item 3.
3.	The main isolation valve bellows evacuation stops per section 2.2.10.5.2 item 3.b.
4.	FV16 opens.
5.	Decontamination passed is displayed on the SCADA. Interlock requiring CIP cycle is set. Manual mode is now available.
6.	The cycle batch report is created. A unique chart recorder data file is created for this cycle run.

After the system is aerated, the cycle is complete.

3.2.6.10 Decontamination Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are listed in EF1114_AL (alarm list).

1. The following conditions cause the cycle to abort if steam has not been admitted:
   a. Failure of both the condenser pressure and chamber pressure probes.
   b. Failure of the chamber vacuum probe prior to decontamination
   c. Failure of potent process drain temperature probe
   d. Chamber main door closed failure or lock/unlock failure.
   e. Loading door closed failure.
   f. Loading door gasket failure.
   g. The user selects Abort at the SCADA.
   h. Upon return from power failure

   If steam has not been introduced into the freeze dryer, the decontamination cycle must be re-initiated by the operator. Once failure conditions have been resolved, the decontamination cycle will re-start at the step EVACUATE**.**

2. The following conditions cause the cycle to discharge steam through FV1128 and FV1129 until the chamber and condenser pressures are < 15.2 psia or for 60 minutes (in the event that the chamber pressure or condenser pressure probes fail during discharging), then abort:
   a. Failure of potent process drain temperature probe
   b. Failure of the condenser pressure or chamber pressure probes during decontamination
   c. Failure of the chamber pressure probe during discharge
   d. Failure of the chamber vacuum probe
   e. Chamber pressure or condenser pressure >= maximum safety pressure. This condition occurs when the pressure >= 40 psia. The condition clears when the pressure < 35 psia.
   f. The user selects Abort at the SCADA, if steam has been admitted and the chamber or condenser pressure is > 15.2 psia
   g. Upon return from power failure, if the chamber or condenser pressure is > 15.2 psia.
   h. During the Decontamination or defrost phases if the chamber or condenser pressure is > 15.2 psia and any of the following occur:
      i. Chamber main door closed failure or lock/unlock failure
      ii. Loading door closed failure
      iii. Loading door gasket failure

   If the decontamination phase has been started and the cycle was aborted, the decontamination cycle will be re-initiated by the operator. Once failure conditions have been resolved, the decontamination cycle will re-start at the step DECONTAMINATION**. No other operator intervention is required.**

3. A cycle failed message is annunciated if the cycle ends by aborting. Otherwise a cycle passed message is annunciated.

4. The following conditions cause the cycle to close FV1650, FV38, FV1128 and FV1129 and HOLD the cycle. *Defrost / Decontamination in hold mode* is annunciated:

a. Failure of FV1650, FV1651, FV38, FV1128 or FV1129.
b. Failure of TE203, TE204, TE205 and TE206 simultaneously.
c. Loss of the Drain Ready signal form the customer.

The system will continue once the signal causing the HOLD has cleared.

Decontamination Override function will clear the interlock requiring CIP and SIP cycles (bypassing Decontamination). Manual mode will be available. The Decontamination Override funciton is available on the alarms screen.
NOTE: Operation of this function requires a high-level security setting
NOTE: The customer is responsible for the safe decontamination of the drain lines and ancillary equipment that will be affected by discharging potentially active product down the drain.

3.2.7 Reserved

3.2.8 Reserved

3.2.9 Reserved

3.2.10 CIP Cycle (Recirculation) Integral Condenser below Chamber

The CIP cycle must follow a Decontamination cycle. Failure to do so will prohibit the operator from starting any automatic cycle other than CIP. Manual functions will be available.

The automatic CIP cycle is used to wash particulate matter and dried water soluble stains, which reside inside of the chamber and condenser, down the drain. The CIP system comprises a series of self-draining, fixed and rotary spray nozzles mounted on distribution manifolds positioned within the chamber and condenser.

The chamber and condenser are divided into 2 zones for cleaning.

Two potential free outputs are provided for: CIP cycle active (turns on at the start of a CIP cycle and remains on until final drain) and CIP fluid 1 request (turns on when fluid 1 is required by the freeze dryer during the cycle). One input from the customer's CIP system is provided to confirm that CIP water is being supplied.

A sanitary design sterilizable CIP re-circulation pump is included.

Water is collected within the condenser, which is used as a storage vessel. When sufficient water has been collected to prime the pump as identified by the total flow into the condenser, water is re-circulated first in the chamber through the CIP nozzles. If selected, re-circulation is preceded and followed by short programmed rinse phases to drain.

CIP Recipe Parameters
Bypass rinse cycles (yes/no)
Fluid 1 wash cycles
Cond rinse/wash time (sec)
Shelf ram cycles
Dry time (min)
Unld pushr rinse/wash time (sec)
CIP Engineering Parameters
Fill volume (liters)
CIP water low flow (LPM)

When activated, the CIP cycle operates as follows:

3.2.10.1 Lock Door

	Action
1.	The loading door gasket is pressurized per section 2.2.4.8 item c.i. If the chamber main door is not already locked, the liquid ring pump evacuates the chamber and condenser through FV9 condenser drain valve per section 2.2.10.4 item 3. The chamber main door is locked per 2.2.2 item 3. Then, the liquid ring pump shuts down according to the sequence described in section 2.2.10.4 item 5.

3.2.10.2 Aerate

	Action
1.	FV16 main drain valve remains closed. The chamber and condenser are aerated per section 2.2.14 item 3. Then FV16 opens.

3.2.10.3 Initial Chamber Rinse

	Action
1.	If CIP recipe parameter *Bypass rinse cycles* is set to yes, the cycle will proceed to section 3.2.10.7. If CIP recipe parameter *Bypass rinse cycles* is set to no, the main isolation valve opens to the CIP position per section 2.2.8. FV9 condenser drain valve, FV29 chamber inlet valve 1, FV1050 loading door drain valve, FV1128 chamber low pressure relief isolation valve, FV1129 condenser low pressure relief isolation valve open. FV19 supply isolation valve opens and the shelf ram bellows is rinsed to drain through FV29 chamber inlet valve 1 for a delay. Then zone 1 rinsing continues while the shelf ram is extended until the shelf ram pressure is reached (to lower the shelves completely for cleaning). Once the shelf ram is extended, rinsing stops. FV19 closes. FV29 closes**.** The shelf ram positions to the lowest shelf number unload position to allow unloading pusher movement.
2.	The main isolation valve remains in the CIP position. FV9 remains open. Once the shelf ram is in position, the unloading pusher extends to a position that allows the unloading pusher bellows to be cleaned. When the pusher is in this position, FV19 opens and the bellows is washed to drain through FV29 chamber inlet valve 1 for the duration specified by CIP Recipe Parameter *Unld pushr rinse/wash time*. Once the wash duration expires, FV19 closes. FV3, FV4, FV5, FV7, FV8 open and the unloading pusher retracts to the home position. The shelf ram retracts to the home position. Then the chamber continues to drain for 30 seconds. FV3, FV4, FV5, FV7, FV8, FV29**,** FV1050 close.

3.2.10.4 Reserved

3.2.10.5 Reserved

3.2.10.6 Initial Condenser Rinse

	Action
1.	FV1128 and FV1129 remain open. The main isolation valve moves to the open position per section 2.2.8. FV8, FV9 remain open. FV19 opens and condenser is rinsed to drain for the duration defined by CIP Recipe Parameter *Cond rinse/wash time.*
2.	FV19 closes. FV3, FV4, FV5, FV7, FV29 open and the condenser is drained for 30 seconds.

3.2.10.7 Recirculation

3.2.10.7.1 Fill / Wash Condenser

In this step, the condenser is filled to a level corresponding to the total volume of water that will be required to fill the CIP piping and provide enough water for operating the CIP re-circulation water pump.

	Action
1.	If *Bypass rinse cycles* is selected, the cycle will continue here from the aeration step. FV3, FV4, FV5, FV7, FV8, FV9 close. The main isolation valve is moved to the CIP position. FV19, FV29, FV1128 chamber low pressure relief isolation valve, FV1129 condenser low pressure relief isolation valve open if not already open.
2.	When CIP flow (totalized value) indicates that water has entered the drain lines, FV401 condenser recirculation valve and the FV67 CIP return valve open for a delay and then close .
3.	When CIP flow (totalized value) >= CIP Engineering Parameter *Fill volume*, FV29 and FV19 close.

3.2.10.7.2 Chamber Wash

	Action
1.	FV1128 and FV1129 remain open. The main isolation valve remains open to the CIP position per section 2.2.8. RCP1 CIP recirculation pump starts. FV67 and FV401 open and the CIP water is recirculated through FV29 chamber inlet valve 1. The shelf ram bellows is washed for a delay. Then the shelf ram is extended and retracted.
2.	Item 1 above is performed until the number of cycles equals Recipe Parameter *Shelf ram cycles.*
3.	The recirculation of CIP water continues through FV29 chamber inlet valve 1. The shelf ram positions to the highest shelf number unload position to allow unloading pusher movement. Once the shelf ram is in position, the unloading pusher extends to a position that allows the unloading pusher bellows to be cleaned. When the pusher is in this position, recirculated washing continues through FV29 chamber inlet valve 1 for the duration specified by Recipe Parameter *Unld pushr rinse/wash time*. FV29 closes. Once the duration expires, the unloading pusher retracts to the home position. Then the shelf ram retracts to the home position.

3.2.10.7.3 Condenser Wash

	Action
1.	The main isolation valve remains in the CIP position. FV67, FV401, FV1128, FV1129 remain open. RCP1 remains on. FV8 opens. The condenser is washed for the duration defined by CIP Recipe Parameter *Cond rinse/wash time.*

3.2.10.7.4 Reserved

3.2.10.7.5 Drain Chamber and Condenser

	Action
1.	RCP1 stops. The main isolation valve moves to the open position per section 2.2.8. FV67, FV401, FV1050, FV1128, FV1129 remain open. FV3, FV4, FV5, FV7, FV8, FV9, FV29, FV230, open so that the chamber, condenser, and all lines opened to the CIP water supply during this cycle are drained for 5 minutes. FV3, FV4, FV5, FV7, FV29, FV67, FV230 close
2.	The sequence described in sub-sections 3.2.10.7.1 - 3.2.10.7.5 above is repeated until the number of washes completed is equal to CIP Recipe Parameters *wash cycles.* If washing is not complete, FV9 closes. If CIP recipe parameter *Bypass rinse cycles* is set to yes, the cycle will proceed to section 3.2.10.8.

3.2.10.7.6 Final Chamber Rinse 1

	Action
1.	FV1128, FV1129 remain open. FV401 closes. The chamber is rinsed as described in section 3.2.10.3.

3.2.10.7.7 Reserved

3.2.10.7.8 Reserved

3.2.10.7.9 Final Condenser Rinse

	Action
1.	FV1128, FV1129 remain open. The condenser is rinsed as described in section 3.2.10.6.

3.2.10.8 Final Drain

	Action
1.	The main isolation valve, FV3, FV4, FV5, FV7, FV8, FV9, FV29, remain open. FV1128, FV1129 open or remain open if an initial rinse has been completed. FV67, FV230, FV401, FV1050 open and the chamber, condenser, and all lines opened to the CIP water supply during this cycle are drained for 5 minutes. The software interlock requiring CIP is cleared.

3.2.10.9 Dry System

	Action
1.	If this CIP Recipe Parameter *Dry time* is set to 0, then the CIP cycle ends with the chamber main door locked. The phases described in sections 3.2.10.10 and 3.2.10.11 do not execute and the main isolation valve closes per section 2.2.8, FV3, FV4, FV5, FV7, FV8, FV9, FV29, FV67, FV230, FV401, FV1050, FV1128, FV1129 close. CIP passed is displayed on the PC HMI. The loading door gasket is operated per section 2.2.4.8 item c.ii.
2.	If CIP Recipe Parameter *Dry time* is set to a value > 0, FV3, FV4, FV5, FV7, close. The main isolation valve, FV8, FV29, FV67, FV230, FV401, FV1050, FV1128, FV1129 remain open. The liquid ring pump evacuates the chamber and condenser through FV9 per section 2.2.10.4 item 3. When the PT105 chamber or PT203 condenser pressure is <= 3 psia, then drying continues for the duration defined by CIP Recipe Parameter *Dry time*.
3.	FV8, FV9, FV29, FV67, FV230, FV401, FV1050, FV1128, FV1129 close. FV16 remains closed. The loading door gasket is vented per section 2.2.4.8 item c.i.

3.2.10.10 Reserved

3.2.10.11 Aerate

	Action
1.	The liquid ring pump shuts down according to the sequence described in section 2.2.10.4 item 5.
2.	Main isolation valve bellows evacuation starts per section 2.2.10.5.2 item 3a. When PT307 MIV bellows vacuum < 999 micron or 5 minutes has elapsed, the main isolation valve is closed per section 2.2.8.
3.	When the main isolation valve is confirmed closed, the chamber and condenser are aerated per section 2.2.14 item 3.
4.	The main isolation valve bellows evacuation stops per section 2.2.10.5.2 item 3.b.
5.	FV16 opens.
6.	CIP passed is displayed on the PC HMI.
7.	The cycle batch report is created.

The cycle is complete.

3.2.10.12 CIP Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are listed in EF1114_AL (alarm list).

1. The following conditions cause the cycle to abort if water has not been admitted:
   a. The user selects Abort at the PC HMI.
   b. Failure of the CIP supply flow meter.
   c. Failure of either the condenser pressure or chamber pressure probes.
   d. Chamber main door closed failure or lock/unlock failure.
   e. Loading door or closed failure or gasket failure.
   f. Hydraulic stoppering position probe fail.

g. Upon return from a power failure.
h. Failure of the CIP supply flow meter.

2. If water has been admitted and the Dry System phase has not started yet, then the following conditions cause the cycle to retract the unloading pusher to the home position and home the shelf ram (if b and d inactive), drain as specified in section 3.2.10.8, then abort. If the main isolation valve fails to close before the shelf ram is homed, the cycle aborts without draining:

   a. Failure of the CIP supply flow meter.
   b. Shelf failed to reach position.
   c. Shelf ram movement over pressure. Note for this alarm, the operator must select Reset Hyd Sys before the abort sequence can start.
   d. Hydraulic stoppering position probe fail.
   e. Chamber main door closed failure or lock/unlock failure.
   f. Loading door or closed failure or gasket failure.
   g. The user selects Abort at the PC HMI.
   h. Upon return from a power failure.
   i. CIP supply isolation valve fails to open.
   j. Main isolation valve CIP position failure.
   k. Failure of the CIP supply flow meter.

3. During or after the Dry System phase, the following conditions cause the cycle to abort:
   a. Failure of both the condenser pressure and chamber pressure probes.
   b. The user selects Abort at the PC HMI.
   c. Upon return from a power failure.

4. The following conditions cause the cycle to pause until the condition is corrected:
   a. CIP water not available.
   b. A complete path to wash is not available due to valve failure or CIP Recirculation pump failure.
   c. A complete path to drain is not available due to valve failure.
   d. Unloading pusher failed to reach position. This condition will end the routine listed in item 2 above.

5. A cycle failed message is annunciated if the cycle ends by aborting as described above. Otherwise a cycle passed message is annunciated.

3.2.11 Reserved

3.2.12 Reserved

3.2.13 Reserved

3.2.14 Sterilization Cycle (SIP)

The SIP cycle must follow a CIP cycle. Failure to do so will prohibit the operator from starting any automatic cycle other than SIP.

In this cycle, sterilization is achieved by injecting clean saturated steam into the chamber, condenser, sterile filters, and all valves and piping that are exposed to the product. This also includes steaming through the CIP re-circulation pump and associated piping. The freeze dryer is sterilized until the drain temperatures achieve the required temperature and maintain that temperature for the required time. The sterilization temperature is measured at the drains because these locations typically are the coldest and the last to heat up. The sterilization process is automatically controlled. The freeze dryer will be held at the sterilization pressure setpoint which will achieve the desired temperature at the drains for the amount of time entered in the recipe. Once sterilization is complete, the steam will be safely discharged down the drain. During discharge, the steam is quenched with cool water to condense the steam as it passes from the freeze dryer drain to the customer drain.

The liquid ring pump is used to remove air and moisture from the system during the beginning of the sterilization process. The pump also is used after sterilization to dry the system.

SIP Recipe Parameters
Steriliz. exposure time (min)
Sterilization temperature (°C)
Sterilization pressure (psia)
SIP Engineering Parameters
Steam pressure offset (psia)
Number of purges
Purge pressure (psia)
Evacuation pressure (psia)
Post-purge discharge pressure (psia)
Post-purge discharge time (sec)
Maximum time below setpoint (sec)
Condenser cooling time (min)
Shelf cooling time (min)
Shelf cooling temp. setpoint (°C)
System drying time (min)
Sterility max time (hours)

PT203 condenser pressure will be used if PT105 chamber pressure probe fails except when verifying pressure to lock the chamber main door.

When activated, the SIP cycle operates as follows:

3.2.14.1 Evacuate and Lock Door

	Action
1.	The loading door gasket is pressurized per section 2.2.4.8 item b.i. The main isolation valve opens per section 2.2.8.
2.	Evacuation of the chamber including inlet/drain, condenser including inlet/drain, the CIP recirculation lines, the loading drain lines, and the sterile filter lines (up to FV4 air/N2 isolation valve): Liquid ring pump evacuation per section 2.2.10.4 item 3. After FV15 has been open for 5 seconds, the following valves open: FV3 chamber inlet valve, FV8 condenser inlet valve, FV9 condenser drain valve, FV21 sterile filter drain valve 1, FV29 chamber inlet valve 1, FV44 sterile filter drain valve 2, FV67 CIP return valve, FV230 CIP recirculation pump drain valve, FV401 condenser recirculation drain valve, FV1050 loading door drain valve, FV1128 chamber low pressure relief isolation valve, FV1129 condenser low pressure relief isolation valve open. Main isolation valve bellows evacuation per section 2.2.10.5.2 item 1.
3.	The main chamber door is locked per section 2.2.2 item 3 if not already locked.
4.	When the chamber main door is locked, evacuation continues until PT105 chamber pressure is <= SIP Engineering Parameter *Evacuation pressure*.
5.	FV15 closes and the liquid ring pump shuts down per section 2.2.10.4 item d.

3.2.14.2 Steam Purging

The purpose of evacuating and steam purging is to remove the air in the freeze dryer and replace it with steam. Steam purging occurs after each evacuation.

Up to 3 evacuation/steam purges can be selected as defined by SIP Engineering Parameter *Number of purges*. The final steam purge differs from the other steam purges as described below.

3.2.14.2.1 Steam Purge

	Action
1.	FV3, FV8, FV9, FV21, FV29, FV44, FV230, FV401, FV1050, FV1128 and FV1129 remain open. FV67, FV16 main drain valve, SV42 (if not closed already) close. FV38 steam supply valve opens and the system is purged with steam until PT105 chamber pressure is >= SIP Engineering Parameter *Steam Purge pressure (typically 15.2 psia*).
2.	If this is not the final purge, then the cycle advances to the Post-Purge Discharge phase.
3.	If this is the final purge, then the cycle advances to the Sterilizing phase.

3.2.14.2.2 Post-Purge Discharge

	Action
1.	FV16 opens, SV42 steam quench valve opens and the steam is discharged down the drain. Draining stops when PT105 chamber pressure <= SIP Engineering Parameter *Post-purge discharge* pressure (typically 14.6 psia) and the duration specified by SIP Engineering Parameter *Post-purge discharge time* (typically 30 seconds) is complete.
2.	FV16 closes.
3.	The cycle advances to the Evacuation phase.

3.2.14.2.3 Evacuation

	Action
1.	Evacuation proceeds as described in section 3.2.14.1.
2.	The cycle continues at Steam Purge.

3.2.14.3 Sterilizing

The actual sterilization of the freeze dryer occurs in this phase.

	Action
1.	FV3, FV8, FV9, FV21, FV29, SV42, FV44, FV67, FV230, FV401, FV1279, FV1050, FV1128 and FV1129 remain open. FV14 condenser drain steam trap bypass valve, FV1061 loading door steam trap bypass valve and FV1279 CIP recirc steam trap bypass valve close. FV16 opens.
2.	The freeze dryer is pressurized with steam. The steam pressure is controlled to Recipe Parameter *Sterilization pressure* using FV38 steam supply valve as the control output and PT105 chamber pressure as the process variable. FV38 opens when PT105 chamber pressure <= (Recipe Parameter *Sterilization pressure* - Engineering parameter *Steam pressure offset*) and closes when PT105 chamber pressure >= Recipe Parameter *Sterilization pressure*. If PT105 fails, PT203 is used.
3.	The F_0 calculation starts when all of the drain temperatures TE213 condenser drain temperature, TE215 sterile filter drain temperature 2, TE238 sterile filter drain temperature, TE297 recirculation pump drain temperature, TE298 loading door drain temperature are all >= 100 ºC. The F_0 value is calculated for reference only and is displayed in the batch report.
4.	The sterilization timer holds if any of the drain temperatures fall < Recipe / Engineering Parameter *Sterilization temperature.*
5.	If the sterilization timer is held longer than the time period defined by SIP Engineering Parameter *Maximum time below setpoint*, then the sterilization timer resets – it restarts according to the timer start conditions specified above.
6.	Sterilization continues until the sterilization timer expires (when it reaches Recipe Parameter *Steriliz. exposure time*.

The F_0 calculation determines the lethal effect of the sterilization portion of the SIP cycle by relating it to a hypothetical sterilization performed at the constant temperature of 121.1 °C. The accumulated lethality value is calculated periodically using a set interval according to the following equation:

$$F_0 = \Delta t \, \Sigma 10^{(T-121.1)/Z}$$

where:
Δt = the time interval (in minutes) between the measurement of T (typically 1/60 minute or 1 second)
T = the lowest value of all of the drain temperatures at time t
Z = the temperature coefficient, which is determined by the type of microorganism to be sterilized against (a value of 10 is used)

For example, a 15-minute sterilization at 111°C is equivalent, in terms of lethal effect, to 1.5 minutes at 121.1°C if Z = 10. This example is illustrated as follows:

$$F_0 = 15 * 10^{(111-121.1)/10} = 1.5 \text{ minutes}$$

3.2.14.4 Final Discharge

The cycle advances to this phase after completion of the Sterilizing phase.

	Action
1.	SV42, FV3, FV8, FV9, FV21, FV29, FV44, FV67, FV230, FV401, FV1050, FV1128 and FV1129 remain open. FV38, FV16 close.
2.	FV48 main drain bypass valve, FV14 condenser drain steam trap bypass valve, FV1061 loading door steam trap bypass valve, FV1279 CIP recirculation steam trap bypass valve open to allow the steam to discharge down the drain.

The smaller diameter main drain bypass valve is used to slow the exit of the steam during discharge allowing the steam quench to collapse the vapor and avoid steam discharge into the machine room.

	Action
3.	Steam is discharged down the drain until PT105 chamber pressure is <= 14.7 psia.
4.	FV3, SV42, FV48, FV401, FV1128 and FV1129 close.
5.	The software interlock requiring SIP is cleared.

3.2.14.5 Reserved

3.2.14.6 Dry System

	Action
1.	FV8, FV9, FV29, FV67, FV230, FV401, FV1050 remain open.

	Action
2.	The liquid ring pump evacuates the chamber and condenser. When the chamber pressure is <= SIP Engineering Parameter *Evacuation pressure*, FV3, FV21, FV44, open and drying continues for the duration defined by SIP Engineering Parameter *System drying time*. Main isolation valve bellows evacuation per section 2.2.10.5.2 item 1.
3.	FV9, FV21, FV44, FV1050 close. The liquid ring pump shuts down per section 2.2.10.4 item 5. The loading door gasket is vented per section 2.2.4.8 item b.i

3.2.14.7 Cool Condenser

	Action
1.	FV8, FV3, FV29 remain open. The condenser coils are cooled, as described in section 3.2.3. After at least one condenser coil temperature (TE203 / TE204 / TE205 / TE206) <= -40ºC, cooling continues for the time period defined by SIP Engineering Parameter *Condenser cooling time*.
2.	The chamber/condenser inlet valves, the sterile filter lines, and the steam/CIP isolation valve close.

3.2.14.8 Cool Shelves

	Action
1.	FV8, FV3, FV29 close. The shelves are cooled as described in section 3.2.2 to SIP Engineering Parameter *Shelf cooling temp. setpoint*. The shelf fluid heater is disabled.
2.	Once shelf fluid inlet temperature is <= SIP Engineering Parameter *Shelf cooling temp. setpoint*, the shelf fluid inlet temperature is controlled at this setpoint for the duration defined by SIP Engineering Parameter *Shelf cooling time*.
3.	The PLC automatically resets the internal thermostatic safety switch on the shelf fluid heater via a discrete output from this point on until the end of the cycle. The automatic reset is performed to preclude the user from having to locally reset the switch after every SIP cycle.

3.2.14.9 Reserved

3.2.14.10 Final Aerate

	Action
1.	Main isolation valve bellows evacuation starts per section 2.2.10.5.2 item 3a. When PT307 MIV bellows vacuum < 999 micron or 5 minutes has elapsed, the main isolation valve is closed per section 2.2.8.
2.	When the main isolation valve is confirmed closed, the chamber and condenser are aerated per section 2.2.14 item 3.
3.	The main isolation valve bellows evacuation stops per section 2.2.10.5.2 item 3.b.
4.	FV16 opens.
5.	SIP passed is displayed on the PC HMI. Chamber not sterile alarm is cleared. See section 6.1.2.9 for more information.
6.	The cycle batch report is created. A unique chart recorder data file is created for this cycle run.

The cycle is complete.

3.2.14.11 SIP Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are listed in EF1114_AL (alarm list).

1. The following conditions cause the cycle to abort and discharge steam until the chamber pressure or condenser pressure > 14.7 psia / 1.01 bara. At the time of failure, if both of these pressure probes have failed, then the steam is discharged for 15 minutes. Otherwise, the cycle just aborts.
   a. Failure of the chamber pressure probe when evacuating to lock the chamber main door.
   b. Failure of both the condenser pressure and chamber pressure probes.
   c. Failure of any drain probe
   d. Chamber main door closed failure or gasket failure.
   e. Loading door or closed failure or gasket failure.
   f. If at least one drain temperature does not reach the Recipe Parameter *Sterilization temperature* within 60 minutes.
   g. Once all drain temperatures reach the Recipe Parameter *Sterilization temperature* and the Sterilizing phase continues for an excessive amount of time (Recipe Parameter *Steriz. Exposure* time + 30 minutes) due to drains falling below temperature.
   h. Chamber pressure or condenser pressure >= maximum safety. This condition occurs when the pressure >= 40 psia. The condition clears when the pressure < 35 psia.
   i. The steam supply valve fails.
   j. The user selects Abort at the PC HMI.
   k. Upon return from a power failure.

2. A cycle failed message is annunciated if the cycle ends by aborting as described above. Otherwise a cycle passed message is annunciated.

3. A cycle failed message is annunciated if the cycle ends by aborting as described above. Otherwise a cycle passed message is annunciated.

3.2.15 Leak Test Cycle

This cycle tests if the system leak rate is within a pre-determined allowable rate. In this test the system is defined as the chamber, condenser, chamber/condenser inlet piping and filters.

Leak Test Recipe Parameters
Leak pressure (micron)
Leak test time (min)
Leak Test Engineering Parameters
Drying time (min)
Allow repeat test on fail (repeats)

When activated, the Leak Test cycle operates as follows:

3.2.15.1 Evacuate Chamber & Condenser

	Action
1.	The condenser is cooled as described in section 3.2.3 and the chamber and condenser are evacuated via the main isolation valve, FV2 main vacuum valve, and all components of the vacuum group as described in the leak test initial evacuation sequence of section 2.2.10.1 item 3. The loading door gasket is pressurized per section 2.2.4.8 item d.i.
2.	After the vacuum group is started, FV3 chamber inlet valve, FV4 Air/N2 isolation valve, FV7 sterile air supply valve, FV29 chamber inlet valve 1 open. FV8 condenser inlet valve opens after FV2 main vacuum valve is opened.
3.	When the chamber vacuum is <= 100 micron, then the cycle advances to the next phase.

3.2.15.2 Dry System

	Action
1.	Evacuation continues to dry the system of any residual moisture for the duration defined by Leak Test Engineering Parameter *Drying time*.

3.2.15.3 Test System

	Action
1.	FV2 closes.

Once FV2 main vacuum valve is closed, the system vacuum, as measured by the chamber vacuum, is recorded by the PLC and Recipe Parameter *Leak pressure* is added to the recorded chamber vacuum, resulting in the test pressure.

	Action
2.	If the system vacuum, as measured by the chamber vacuum, rises above the test pressure within the duration specified by Recipe Parameter *Leak test time*, then the test fails and the Leak test failed alarm is displayed on the PC HMI. At this point, FV2 main vacuum valve opens and the test is re-performed beginning with the Dry System phase. The test is automatically re-performed after failure for the number of times specified in Leak Test Engineering Parameter *Allow repeat test on fail* (typically 3 repeats). If the test fails after the number of allowed repeats has been reached, FV8 and FV29 close and the cycle advances to the next phase Aerate.
3.	If the system vacuum does not rise above the test pressure within the duration specified by Recipe Parameter *Leak test time*, then the test passes and the Leak test passed message is displayed on the PC HMI. FV8 and FV29 close, condenser cooling is disabled and the cycle advances to the next phase.
4.	The leak rate in micron per hour is determined.

3.2.15.4 Aerate

	Action
1.	Main isolation valve bellows evacuation per section 2.2.10.5.2 item 3a. When PT307 MIV bellows vacuum < 999 micron or 5 minutes has elapsed, the main isolation valve is closed per section 2.2.8.
2.	When the main isolation valve is confirmed closed, the chamber and condenser are aerated per section 2.2.14 item 3.
3.	The main isolation valve bellows evacuation stops per section 2.2.10.5.2 item 3.b.
4.	The cycle batch report is created.

The cycle is complete.

3.2.15.5 Leak Test Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are listed in EF1114_AL (alarm list).

1. The following conditions cause the cycle to abort:
   a. The user selects Abort at the PC HMI.
   b. Upon return from a power failure.
   c. The chamber vacuum probe fails prior to the Aerate phase.
   d. The chamber pressure probe and condenser pressure probe fail during the Aerate phase.
   e. The Evacuate Chamber & Condenser phase is active for 60 minutes.

2. A leak test passed / failed message is annunciated per section 3.2.15.3.

3.2.16 Shelf Ram Bellows Test Cycle

This cycle tests the integrity of the shelf ram bellows. The cycle consists of extending the shelf ram fully, evacuating the bellows to determine if the bellows can achieve the test setpoint within the test time, and then retracting the ram to the home position.

Shelf Ram Bellows Test Recipe Parameters
Test pressure (micron)
Pumpdown time (min)
Shelf Ram Bellows Test Engineering Parameters
N/A

When activated, the Shelf Ram Bellows Test cycle operates as follows:

3.2.16.1 Aerate Chamber

	Action
1.	The chamber is aerated per section 2.2.14 item 2.

3.2.16.2 Extend Shelf Ram

	Action
1.	The shelf ram fully extends until PT306 stoppering pressure >= 725 psig.

3.2.16.3 Test Bellows

	Action
1.	SV1406 rod gland drain back valve opens. Shelf ram bellows evacuation starts per section 2.2.10.5.1 item 2a. Once evacuation begins the Pumpdown timer is started. Once evacuation begins, if PT304 shelf ram bellows vacuum decreases <= Recipe Parameter *Test pressure* before the time period defined by Recipe Parameter *Pumpdown time* expires, then the test passes and the Shelf ram bellows test passed alarm is displayed on the PC HMI. The cycle advances to the Retract Shelf Ram and Vent Bellows phase. SV1406 closes.
2.	If the time period defined by Recipe Parameter *Pumpdown time* expires and PT304 shelf ram bellows vacuum is > Recipe Parameter *Test pressure,* then the Retest shelf ram bellows test phase message is displayed on the PC HMI and the cycle advances to the next phase.

3.2.16.4 Re-Test Bellows

	Action
1.	SV1406 closes and the pump down timer is reset. Bellows evacuation continues per section 2.2.10.5.1 item 2a.
2.	If PT304 shelf ram bellows vacuum decreases <= Recipe Parameter *Test pressure* before the time period defined by Recipe Parameter *Pumpdown time* expires, then the Shelf ram bellows test rod gland leak alarm is displayed on the PC HMI and the cycle advances to the next phase.
3.	If the time period defined by Recipe Parameter *Pumpdown time* expires and the shelf ram pressure is > Recipe Parameter *Test pressure,* then the Shelf ram bellows leak alarm is displayed on the PC HMI and the cycle advances to the next phase.

3.2.16.5 Retract Shelf Ram and Vent Bellows

	Action
1.	Bellows evacuation stops and the bellows vents per section 2.2.10.5.1 item 2b.
2.	The shelf ram retracts to the home position.

The cycle is complete.

3.2.16.6 Shelf Ram Bellows Test Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are listed in EF1114_AL (alarm list).

1. The following conditions cause the cycle to abort:
   a. The user selects Abort at the PC HMI.
   b. Upon return from a power failure.
   c. The shelf ram bellows vacuum probe fails during the Test Bellows or Re-Test Bellows phase completes.
   d. The chamber pressure probe fails during the Aerate Chamber phase.

2. The following conditions cause the cycle to pause until the condition is corrected:
   a. Shelf failed to reach position.
   b. Shelf ram movement over pressure.
   c. Hydraulic stoppering position probe fail.

3. A shelf ram bellows test passed / failed message is annunciated per section 3.2.16.3.

3.2.17 Main Isolation Valve Bellows Test Cycle

This cycle tests the integrity of the main isolation valve bellows. The cycle consists of evacuating the bellows to determine if the bellows can achieve the test setpoint within the test time.

Main Isolation Valve Bellows Test Recipe Parameters
Test pressure (micron)
Pumpdown time (min)
Main Isolation Valve Bellows Test Engineering Parameters
N/A

When activated, the Main Isolation Valve Bellows Test cycle operates as follows:

3.2.17.1 Aerate System

	Action
1.	The chamber and condenser are aerated per section 2.2.14 item 3.
2.	The main isolation valve is opened per section 2.2.8.

3.2.17.2 Test Bellows

	Action
1.	Main isolation valve bellows evacuation starts per section 2.2.10.5.2 item 2.a. Once evacuation begins, if PT307 main isolation valve bellows vacuum decreases <= Recipe Parameter *Test pressure* before the time period defined by Recipe Parameter *Pumpdown time* expires, then the test passes and the Main valve bellows test passed alarm is displayed on the PC HMI. If the time period expires before the test criterion is achieved, then the test fails and the Main valve bellows test failed alarm is displayed on the PC HMI.
2.	Once the test passes or fails, the cycle advances to the next phase.

3.2.17.3 Vent Bellows

	Action
1.	Bellows evacuation stops and the bellows vents per section 2.2.10.5.2 item 2.b.
2.	The main isolation valve is closed per section 2.2.8.

The cycle is complete.

3.2.17.4 Main Isolation Valve Bellows Test Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are listed in EF1114_AL (alarm list).

1. The following conditions cause the cycle to abort:
   a. The user selects Abort at the PC HMI.
   b. Upon return from a power failure.
   c. The main isolation valve bellows vacuum probe fails during the Test Bellows phase.
   d. The condenser pressure probe fails during the Aerate Condenser phase.
   e. The chamber pressure probe fails during the Aerate Condenser phase.

2. A main valve bellows test passed / failed message is annunciated per section 3.2.17.2.

3.2.18 Unloading Pusher Bellows Test Cycle

This cycle tests the integrity of the unloading pusher bellows. The cycle consists of extending the unloading pusher fully, evacuating the bellows to determine if the bellows can achieve the test setpoint within the test time, and then retracting the unloading pusher to the home position. The details regarding communication with the compact loader are specified in the loading / unloading system functional specification.

Unloading Pusher Bellows Test Recipe Parameters
Test pressure (microns)
Pumpdown time (min)
Unloading Pusher Bellows Test Engineering Parameters
N/A

The main chamber door must be locked to initiate an Unloading Pusher Bellows Test cycle.

When activated, the Unloading Pusher Bellows Test cycle operates as follows:

3.2.18.1 Aerate Chamber

	Action
1.	The chamber is aerated per section 2.2.14 item 2.

3.2.18.2 Extend Unloading Pusher

	Action
1.	The shelf ram moves to the highest number unload position to allow the unloading pusher to be extended onto a shelf.
2.	Once the shelf ram is in position, the unloading pusher extends to the bellows test position.

3.2.18.3 Test Bellows

	Action
1.	Unloading pusher bellows evacuation starts per section 2.2.10.5.3 item 2a. Once evacuation begins, if PT501 unloading pusher bellows vacuum decreases <= Recipe Parameter *Test pressure* before the time period defined by Recipe Parameter *Pumpdown time* expires, then the test passes and the Unloading pusher bellows test passed message is displayed on the PC HMI. If the time period expires before the test criterion is achieved, then the test fails and the Unloading pusher bellows test failed alarm is displayed on the PC HMI.
2.	Once the test passes or fails, the cycle advances to the next phase.

3.2.18.4 Retract Unloading Pusher and Vent Bellows

	Action
1.	Bellows evacuation stops and the bellows vents per section 2.2.10.5.3 item 2b.
2.	The unloading pusher retracts to the home position.

The cycle is complete.

3.2.18.5 Unloading Pusher Bellows Test Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are listed in EF1114_AL (alarm list).

1. The following conditions cause the cycle to abort:
   a. The chamber pressure probe fails during the Aerate Chamber phase.

2. The following conditions cause the cycle to retract the unloading pusher to the home position (if the loading / unloading system is ready) if it is extended, and then abort:
   a. The user selects Abort at the PC HMI.
   b. Upon return from a power failure.
   c. The unloading pusher bellows vacuum probe fails during the Test Bellows phase.

3. The following conditions cause the cycle to pause until the condition is corrected:
   a. Shelf failed to reach position.
   b. Shelf ram movement over pressure.
   c. Hydraulic stoppering position probe fail.

4. An unloading pusher bellows test passed / failed message is annunciated per section 3.2.18.3.

3.2.19 Reserved

3.2.20 Reserved

3.2.21 Reserved

3.2.22 Reserved

3.2.23 Reserved

3.2.24 Isolator VHP Hold Cycle

The automatic Isolator VHP Hold Cycle is used to put the freeze dryer into a ready state in order to allow for the VHP cycle to be performed on the isolator.

Isolator VHP Hold Recipe Parameters
N/A

When activated, the Isolator VHP Hold Cycle operates as follows:

3.2.24.1 Evacuation

	Action
1.	The main isolation valve opens as described in section 2.2.8. The loading slot door gasket operates as described in section 2.2.4.8 item 3.g.
2.	The liquid ring pump starts as described in section 2.2.10.4 item 3. Main isolation valve bellows evacuation starts per section 2.2.10.5.2 item 1. Evacuation continues until PT105 chamber pressure < 7 psia.

3.2.24.2 Isolator VHP

	Action
1.	Liquid ring pump evacuation continues. A “Lyo ready for Isolator VHP” signal is transferred to the isolator and will be displayed as a message on Lyo SCADA.
2.	The isolator will transmit an “Isolator VHP active” signal to the Lyo and maintain the signal throughout the duration of the VHP cycle. When the Isolator VHP cycle is complete, the “Isolator VHP active” signal will be removed. When the “Isolator Sterile” signal is received from the isolator, the cycle will advance.

3.2.24.3 Aerate

	Action
1.	The main isolation valve closes as described in section 2.2.8. The main isolation valve bellows evacuation stops per section 2.2.10.5.2 item 1. The chamber and condenser are aerated with clean air.

The cycle is complete.

3.2.24.4 Isolator VHP Hold Cycle Abnormal Shutdown and Critical Alarms

Alarms and messages related to or that directly affect the cycle are in EF1114_AL (alarm list).The following conditions cause the cycle to abort:

a. The user selects Abort at the SCADA.
b. Upon return from a power failure.
c. Chamber door closed failure.
d. Loading door gasket failure.
e. Failure of the chamber pressure probe.

3.2.25 Cycle Queue

Cycle Queue includes the following:

The freeze dryer can run all automatic cycles in sequence.

If this option is selected, the operator is allowed to build the cycle sequence (queue) containing all or part of the automatic cycles:

Freeze Drying
Defrost/Decontamination*
CIP*
SIP*
Leak Test
Shelf Ram Bellows Test
Main Valve Bellows Test
Unloading Pusher Bellows Test

*These cycles MUST be added to the cycle queue in this order if decontamination is required.

In order for the cycle queue to be started:

1. Each cycle in the queue must have a batch name
2. The first cycle in the queue must be in the Ready State
3. Each cycle in the queue must be in the idle state.
4. No cycle is active.

Once the queue advances to the next cycle, one attempt is made to start the cycle. If the cycle is interlocked, the cycle will be aborted.

If the active cycle is aborted, the cycle queue is cleared and the active cycle will bring the system to a safe state (as described in the Abnormal Shutdown and Critical Alarms section of each cycle).

If the *Clear Queue* button is selected while the queue is active, the current cycle continues to run. The remaining cycles in the queue are cleared and will not run.

Any alarm/warning that will abort a single cycle will automatically abort the cycle queue.

4 DATA

The components of the control system are described in sections 2.1 and 2.3. The control system is the only system on the freeze dryer for which the topic of data applies. The control system complies with 21 CFR Part 11.

4.1 PLC

The PLC stores System Engineering Parameters, Cycle Engineering Parameters, and Manual Controls setpoints.

4.2 PC HMI

The SCADA stores cycle recipes, historical trending files, batch reports, and audit trail files. Refer to section 5.1.1 for additional information.

4.2.1 Batch Reports

During the automatic Freeze Drying, Defrost, CIP, SIP, and Leak Test cycles, the batch reporting feature compiles data and cycle information into a report. Upon cycle completion, the report is automatically printed out and saved to an encrypted .PDF file.

1. Each batch report is generated at the end of the cycle and contains the following elements:
   a. Recipe Report
   b. Step End Report (Freeze Drying cycle only): Tabular snapshot of process-critical data for the end of each step of the freeze drying cycle
   c. Tabular Data Report: Tabular report of process-critical data from the start to the end of the cycle
   d. Graphical Data Report: Graphical report of process-critical data from the start to the end of the cycle
   e. Audit Trail Report: Report that includes all alarms, messages, and events annunciated during the cycle

4.3 Reserved

5 INTERFACES

5.1 User Interface

Two types of user interface are provided: HMI panel and PC HMI. For HMI panel specifications, see section 3.1.4.

5.1.1 PC HMI

The PC HMI consists of a SCADA PC. The SCADA PC runs on the Windows 7 Professional operating system. GE Proficy iFIX version 5.8 provides the SCADA environment.

1. The SCADA contains the following features and functionality:
   a. Tower PC with 19" LCD monitor, CD/DVD-RW and two Ethernet cards, and additional hard drive(s) for RAID
   b. 21CFR11-compliance, including the following:
      i. Storing the audit trail in an MS SQL database
      ii. Requiring an eSignature from the user for all actions that affect the integrity of the pharmaceutical product
   c. 7 security groups, listed here in order from lowest privilege level to highest: public, operator, supervisor, maintenance 1, maintenance 2, developer, and administrator
   d. Unit Graphic screen - P&ID-type representation of the freeze dryer that shows device I/O
   e. Recipe screens for each cycle
   f. Cycle Permissive screen
   g. Calibration screen
   h. Historical Trending screen - pre-configured and custom charts displaying historian data
   i. Manual Controls screen (provides pre-packaged functions such as shelf temperature control, condenser cooling, chamber pre-aeration/aeration, condenser aeration, chamber/condenser drain, etc.)
   j. Control Loops screen - pre-configured real-time chart for each control loop, PID functions
   k. Alarms screen – view / acknowledge alarms and messages and reset devices.
   l. Cycle and System Engineering Parameters screens
   m. Maintenance Screen (pump run time and time since last maintenance, filter run time, time since last oil change, calibration and preventative maintenance, maintenance alarm messages)
   n. Batch Report Screen - view / print / manage batch reports
   o. Shelf Positioning Screen – manage loading / unloading positions
   p. Macro screen - displays the step number / state for process macros
   q. Audit trail screen - view the audit trail from the MS SQL database
   r. Security screen - access to iFIX security, Windows security, Security Synchronizer

s. Secure Desktop application - provides an additional measure of security by limiting user access to the desktop
t. Metric units (°C, micron, psi) are supplied.

5.1.1.1 Manual Controls

To allow manual operation and testing of the freeze dryer, a Manual Controls screen is provided. The manual control functions are listed in section 3.1.3.2. Interlocks which enable/disable each function are managed by the PLC. These interlocks ensure safe operation of the freeze dryer in Manual Mode.

5.1.1.2 Alarms and Messages

Alarms and messages appear on the PC HMI Alarms screen. The user can acknowledge a single alarm/message or a page of alarms/messages using this screen. Once active, each alarm and message remains on the Alarms screen until it is both inactive and acknowledged.

Alarms and messages are categorized into four levels of priority with corresponding colors: info – cycle passed / step complete – Green background, low - cycle/maintenance messages – Yellow background, medium - non-process critical, technical (non-GMP) alarms – Orange background, and high – safety, process critical (GMP) alarms – Red background. The screen displays the following information for each alarm and message: acknowledgement status, date/time of last annunciation, alarm description, alarm tagname, and value (active or inactive).

In addition to the Alarms screen, the latest annunciated alarm is displayed at the top of each screen. The user can select this alarm to navigate to the Alarms screen.

Alarms and messages are contained in EF1114_AL.

5.1.1.3 Historical Trending

iFIX Historian is used to provide historical trending.

6 Non-Functional Attributes

This section explains the non-functional attributes of the system such as expandability, safety and protection devices, and failure of instruments and control devices.

6.1 Safety and Protection

The freeze dryer is equipped with devices and functionality intended to ensure the safety of personnel, protection of equipment and facilities, and reliability.

6.1.1 Power Failure

During a power failure:

1. The position of the main isolation valve remains unchanged. All other process-critical valves close to maintain the integrity of the plant and freeze dryer (e.g. the vacuum pump group inlet valves close to prevent leakage of air into the chamber/condenser via the vacuum pumps).
2. The PLC processor module contains a static RAM memory card which, in the event of a power failure, stores the PLC program and the current operating point of the freeze dryer.
3. The valves for the loading gasket to their last state. When the gasket is pressurized, this prevents water or steam from escaping the chamber through the door if power is lost during a CIP or SIP cycle, respectively. Note that if pressurized air is lost, the loading gasket may lose integrity over time.

On return from a power failure:

4. Control power fail alarm occurs.
5. All auto cycles are aborted except for the freeze drying cycle. The freeze drying cycle resumes at the point prior to the power failure.
6. PB29 control power reset must be selected to restore control power unless the freeze drying cycle was active at the time of failure. This manual reset prevents hazardous conditions due to unexpected restart. If the freeze drying cycle was active at the time of failure, control power reset is automatically performed by the control system.
7. Once control power is restored, abort sequences per abnormal shutdown and critical alarm section for each cycle will be performed.
8. If at any time PB8 control power emergency switch off was selected by the user, PB29 control power reset must be selected to restore control power regardless of active cycle / machine state.

6.1.2 Other Safety/Protection Features

This section details basic process control system safeguards that are used to reduce the risk or severity of their associated hazards.

Other software conditions prevent improper operation of the freeze dryer in Manual Mode and Device Mode.

6.1.2.1 Moving Parts and Entrapment

To protect against harm due to moving parts, the following software interlocks are included:

	Action
1.	The shelf ram must be home (i.e. the shelf ram must be fully-retracted) to allow the chamber main door to close. This interlock minimizes the risk of starting a cycle or pulling vacuum while a person is in the chamber or trapping a person in the chamber.
2.	The shelf ram must be home to allow an automatic cycle to start. This interlock minimizes the risk of starting a cycle or pulling vacuum while a person is in the chamber or trapping a person in the chamber.
3.	The shelf ram must be home (i.e. the shelf ram must be fully-retracted) to allow the main isolation valve to open.
4.	A stop button (refer to section 3.1.4), when pushed in, stops the movements of the shelf ram and loading door. To resume movement, first the button must be pulled out then a separate reset pushbutton on the panel must be selected.
5.	A control power stop button (refer to section 3.1.2), when pushed in, removes control power from all pumps, motors, valves, etc. To resume movement, first the button must be pulled out then a separate reset pushbutton must be selected.
6.	If the isolator guarding is breached or glove ports accessed, the loading movement stops. If the loading door is not closed, then the shelf ram movement also stops.
7.	To jog the shelf ram down in Manual Mode, the chamber main door must be closed. This condition prevents injuries by eliminating exposure to the pinch points that result as the shelf stack collapses.
8.	If the chamber main door on the maintenance room side of the freeze dryer is open, then the HMI panel on the loading side of the freeze dryer de-activates. This interlock prevents the situation where a person on the loading side can move the ram up while an open chamber door on the maintenance room allows entry into the chamber (and vice versa).
9.	If the chamber main door is not closed, then the loading door drive inverter will be inhibited.
10.	During all automatic cycles with the exception of the loading and unloading phases of the Freeze Drying cycle, the loading door drive inverter will be inhibited and the door brake applied.
11.	During automatic or manual mode when no cycles are active and no door manual homing/jogging functions are selected, the loading door drive inverter will be inhibited and the door brake applied.

6.1.2.2 Hot and Cold Surfaces / Gas / Liquids

To protect against harm due to surfaces, or the release of hot or cold gas or liquids, the following software interlocks are included:

	Action
1.	To prevent loss of steam containment from the main door due to incompletely engaged locking pins, the control system continues hydraulic pressure on the main door locking pins for a delay after the locked position is detected.

	Action
2.	To detect steam containment, the chamber pressure is displayed on the SCADA.
3.	To detect steam containment, the condenser pressure is displayed on the SCADA.
4.	To prevent explosive loss of steam containment, the control system confirms that the chamber main door and loading door is fully closed and sealed before and during pressurized steam admission to the chamber and condenser for steam sterilization.

The following conditions minimize the risk of misdirected flow of steam into the potentially occupied mechanical space:

	Action
1.	When pressurized steam is admitted to the chamber and condenser for steam sterilization, the air/N2 isolation valve must be closed.
2.	When pressurized steam is admitted to the condenser for steam defrost, the main isolation valve and the main vacuum valve must be closed.
3.	The sequence of valve opening and closing is controlled to direct steam through the chamber, condenser, and associated sterile piping, to the steam quenched drain.
4.	The main isolation valve must be closed in order to open the chamber main door.
5.	The main isolation valve must be closed in order to open the loading door.

6.1.2.3 Emissions of dust, gas, liquids

To protect against harm due to emissions of dust, gas, liquids, the following software interlocks are included:

1. To prevent releasing nitrogen into the mechanical room due to process piping or drain valve loss of containment, vacuum integrity testing should be performed after each steam cycle.

	Action
2.	To prevent flooding the clean room or mechanical room with nitrogen due to selection of nitrogen for aeration, only clean air is allowed for aeration.
3.	If FV7 sterile air supply valve limit switch indicates that it is not closed, FV6 N2 supply valve will be prevented from opening for risk of flooding the clean room with nitrogen.

6.1.2.4 Explosion / Pressure

To protect against harm due to explosion or high pressure, the following software interlocks are included:

	Action
1.	If, while aerating, either PT105 chamber pressure or PT203 condenser pressure >= 15 psia, then aeration stops to avoid over pressurizing the vessel(s).

	Action
2.	The chamber must be within acceptable high/low pressure limits to allow the chamber main door to open (PT105 chamber pressure must be <= 15.2 psia and >= System Engineering Parameter *Aeration setpoint* (typically 14.2 psia) and the chamber is not pressurized as indicated by the PSH11 chamber pressure switch).
3.	The chamber must be within acceptable high/low pressure limits to allow the loading door to open (PT105 chamber pressure must be <= 15.2 psia and >= System Engineering Parameter *Aeration setpoint* (typically 14.2 psia) and the chamber is not pressurized as indicated by the PSH11 chamber pressure switch).
4.	PT105 chamber pressure must be <= 3 psia in order to unlock the main chamber door.
5.	If the software upward over-travel limit is reached, then power is removed from the loading door drive inverter to prohibit the door from opening further.

6.1.2.5 Fire

To protect against fire, the following software interlocks are included:

	Action
1.	A circulation pump must be running in order for the shelf fluid heater to operate.
2.	Both thermostatic safety switches must be < setting in order for the shelf fluid heater to operate.
3.	Shelf fluid circuit temperature is displayed on the SCADA.

6.1.2.6 Controls

To protect against harm due to uncontrolled stop, start, emergency stop, or mode selection, the following software interlocks are included:

1. Power failure response according to section 6.1.1.
2. Refer to the servo drive system manual for a list of system fault codes that stop/inhibit movement of the loading door servo drive.
3. Cycles cannot be started unless all proper conditions are satisfied.

6.1.2.7 Equipment Protection

The following software interlocks are included to protect equipment and connected utilities from damage:

1. The chamber and condenser are always aerated before and during draining. Before the drain lines are allowed to open, however, the chamber (and/or condenser, as applicable) aerates to atmospheric pressure to prevent suckback through the drain lines. When the vessel pressure is >= System Engineering Parameter *Aeration setpoint* (typically 14.2 psia) for System Engineering

Parameter *Chamber/Condenser aeration time* (typically 60 sec), then the drain lines are allowed to open. Manual draining is always performed with air.

2. The vacuum pumps are protected as discussed in section 2.2.10.1.
3. The following devices have over temperature protection: vacuum pumps and heater.
4. If all applicable axes for the loading/unloading equipment (e.g. Unloading pusher) are not homed, then the PLC prohibits the loading door from closing.
5. If the software limit down is reached, then the loading door **is** prohibited from closing further.
6. If the software limit up is reached, then the loading door **is** prohibited from opening further.
7. When required, an evacuation routine pulls vacuum on the bellows within the chamber/condenser to protect the bellows against distortion.

6.1.2.8 Sterility Protection

The following software interlocks are included to process sterility:

1. When pulling vacuum with the liquid ring vacuum pump, the drain line valves are open/closed in a sequence that ensures flow in a direction from the chamber/condenser to the pump. This is discussed further in section 2.2.10.4.
2. For freeze dryers that have the chamber main door on the non-sterile side (e.g. the machine room), contamination is prevented by not allowing the loading door to open if the chamber main door is open.

6.1.2.9 Sterility Monitoring

The freeze dryer is considered sterile after the completion of a successful SIP cycle. If a Defrost cycle is not active then sterility will be breached when any of the following occur:

1. The chamber main door opened

2. Any of the following valves are opened:
   a. FV9 condenser drain valve
   b. FV19 CIP supply 1 isolation valve
   c. FV20 condenser steam defrost valve
   d. FV21 sterile filter drain valve 1
   e. FV44 sterile filter drain valve 2
   f. FV230 CIP recirculation pump drain valve
   g. FV1050 loading door drain valve

3. The time since the completion of the last successful SIP cycle is greater than SIP Engineering Parameter *Sterility max time.*

Any of the above events will generate a chamber not sterile alarm. This alarm will prevent a Freeze Drying Cycle from starting, inflate the loading door outer gasket per section 2.2.4.8 item 3.h. and

prevent opening of the loader door per section 2.2.4.9 item 2.b. This alarm remains active until an SIP cycle is run successfully.

The PC HMI Alarm screen contains 2 functions related to security monitoring. These functions require a high level of security access:

Enable/Disable Ster Mon - This selection terminates/activates Sterility Monitoring. When sterility monitoring is terminated, then breaches in sterility will not be monitored. Therefore the "chamber not sterile" alarm will not annunciate at the PC HMI if a breach occurs.

Override Sterility -This selection resets the "chamber not sterile" alarm as long as no sterility breach conditions exist. This alarm clears when the next breach occurs or when the next SIP is ran successfully.

6.1.3 Hardwired Conditions

The following devices have hardwired over current protection:

1. Circulation pumps
2. Vacuum pumps
3. Liquid ring pump
4. Hydraulic pump
5. CIP recirculation pump

The following devices have hardwired safety interlocks:

8. Steam supply valve
9. Loading door movement
10. Unlock chamber main door
11. Shelf movement
12. CIP supply isolation valve
13. Nitrogen supply valve
14. Heater

6.2 Instruments or Controls Failure

All the functions on the freeze dryer are controlled by the PLC. If this controller fails, it is not possible to run any manual or automatic functions on the freeze dryer.

Probe failures and the resulting actions are discussed throughout this document where applicable.