

Section 5:Specialized Facility Capabilities in General

5-1: Hydrogenation

There are three hydrogenation reactors, one located outside of the pilot plant and the other located outside of the main production plant, with specifications as follows:

- * Pilot Plant: 1136-L (300gal) stainless steel reactor; operating pressure and temperature are 100 psig max. and $-80\sim 150^{\circ}\text{C}$.
- * Production Plant: 1. 2600-L (700 gal) Hastelloy C22 reactor; operating pressure and temperature are 300 psig max. and $-15\sim 150^{\circ}\text{C}$.
2. 150-L Hastelloy C22 reactor; operating pressure and temperature are 100 psig max. and $-80\sim 150^{\circ}\text{C}$.

5-2:Cryogenic

There are five sets of cryogenic units which are located in the Process R&D Lab, Kilo Lab, Mini Plant, Small Manufacturing Unit (SMU), and Production Bay 2 with specifications as follows:

- * Process R&D Lab: 20-L Hastelloy C reactor, with operating temperature of down to minus 80°C .
- * Kilo Lab: 30-L Hastelloy C reactor, with operating temperature of down to minus 80°C .
- * Mini Plant: 80-L Hastelloy C276 reactor, with operating temperature of down to minus 80°C .
- * Small Manufacturing Unit: 1136-L (300gal) stainless steel reactor, with operating temperature of down to minus 80°C .
- * Pilot Plant: 1200 L (300 gal) stainless steel reactor, with operating temperature of down to minus 80°C .
- * Production Bay 1: 379-L (100gal) Hastelloyl reactor, with operating temperature of down to minus 80°C .
- * Production Bay 2: 3785-L (1000gal) stainless steel reactor, with operating temperature of down to minus 80°C .

ScinoPharm personnel have extensive experience in large-scale cryogenic operations. Additional units will be installed in other plant areas as needed.

5-3:Cytotoxics

Processing Capabilities

To process cytotoxics and high potency products and intermediates, the following contaminant technologies are designed into the processing facilities and equipment:

- * Drum charging isolation - standard design (with laminar flow hood partial station).
- * Drum charging isolation - for high containment operations.
- * Glovebox systems - alpha/ beta technology.
- * Glovebox systems - pneumatic seal technology.
- * Super sack charging unit and packaging system.
- * Slotted hood technology with charging funnels.

Listed below are the facilities used to prevent process cross-contamination and worker exposure, as well as their location, quantity and contaminant control levels.

5-4: Containment Facilities

No	Equipment	Contaminant Level ($\mu\text{g}/\text{m}^3$)	Location	Quantity
1	Partiallying Stations	100	Pilot Plant, SMU, Bay 1, Bay 2, Bay 3	5
2	Drum Tippers	25 -50	Bay 1, Bay 2, Bay 3	3
3	Ventilation Funnels	100	Pilot Plant, SMU, Bay 1, Bay 2, Bay 3	9
4	Packaging Systems (Small Units)	25 - 50	Pilot Plant, SMU	2
5	Packaging Systems (Large Units)	25 - 50	Bay 1, Bay 2, Bay 3	3
6	Weighing/Dispensing/ Charging Gloveboxes	1	Kilo Lab	2
7	Pressure Filter & Tray Dryer Gloveboxes	1	Kilo Lab	2
8	Mill Gloveboxes	1	Kilo Lab	1
9	Weighing/Dispensing/ Gloveboxes	1	Mini Plant	2
10	Transition Gloveboxes	1	Mini Plant	3
11	Pressure Filter & Tray Dryer Gloveboxes	1	Mini Plant	2
12	Packaging & Mill Gloveboxes	1	Mini Plant	2

To prevent cross contamination between the various processing areas and the R&D laboratories, a special design of the HVAC system is provided:

- * The airflow is designed to maintain a pressure differential between each operating area via a laminar flow curtain.
- * All make-up air streams pass through air filtration systems.
- * The average air change time is maintained at no more than 10 minutes.
- * A slight negative pressure is maintained in the processing areas.
- * Each process area will have its own and separate HVAC system, and are isolated from each other by check dampers on the exhaust side.
- * All exhaust systems vent through a wet scrubber or in the case of the Kilo Lab, through an activated carbon absorption system.

5-5: Purification Using Preparative Chromatography

7 sets of Dynamic Axial Compression (DAC) preparative chromatography with operating pressures ranging from 20 to 70 bars and volumes ranging from 22 to 500 L are installed to purify small molecule and peptide APIs that require high degree of product purity.

5-6: Ultra Pure Water System

Five sets of Ultra Pure Water systems are installed: four for the R&D Laboratories and one for the Kilo lab. Each system includes a pre-filter cartridge, a reverse osmosis membrane, mixed bed de-ionization and ultra-filtration membranes.

ZENON INC, a Canadian company, supplies this Ultra Pure Water system. It will produce high quality water with an Electrical Resistance $> 16 \text{ M}\Omega$, TOC $\leq 10 \text{ ppb}$, BIO bacteria $= < 1 \text{ cfu/ml}$. The system's output is 90 l/hr.

The three small-scale production units (mini, pilot, and SMU plants) are supplied with water that is equivalent in quality to USP Purified. This purified process water (PPW) system is a double-pass reverse osmosis (RO) system, including a multi-media filter unit, softeners, an activated carbon filter, RO membranes, and ultrafiltration membranes. Zenon Inc. supplies this PPW system as well. It generates approximately 5.5 US GPM. There are 10 use points throughout the distribution loop. The water is recirculated through the loop at 30 GPM, which helps prevent bacterial growth within the piping. The distribution loop is regularly sanitized with hot water at 90 degree C. Online TOC, conductivity, and temperature instruments constantly monitor the water quality. The entire system is controlled by PLC, providing remote monitoring as well as a significant degree of automated functions.

This Zenon PPW system produces high quality water with a conductivity $< 1.3 \text{ S/cm}$, TOC $< 10 \text{ ppb}$, and a total viable bacteria count $< 1 \text{ cfu/ml}$. With the Inline ultrafilters immediately downstream of the RO water storage tank, endotoxin level is well maintained below the USP WFI limit of 0.25 EU/ml.

The proposed system for the new large-scale production building will consist of a dedicated RO system as well. The generation rate will be approximately 6 US GPM. The water quality is similar to the existing system, except for the endotoxin level. Inline ultrafilters will not be included in this system, but if the need for endotoxin/pyrogen free water arises, 0.05-micron filters will be added downstream of the use point. Online instrumentation will be similar to the existing system as well, and as a minimum will include TOC and conductivity monitoring in the distribution loop. This loop will also be subjected to regular hot water sanitization.

5-7:High Temperature Operations

All reactors and crystallizers are equipped with fully automated and dedicated steam heating systems designed to reach 150^oC. Hot oil units on skids will be utilized for higher temperatures as processes warrant. Three sets of heat transfer fluid units using hot oil as heating media are installed in the Mini Plant, SMU and Production Bay2 with specifications as follows:

- * Mini Plant: 120-L G/L reactor, with operating temperatures of up to 200^oC.
- * Small Manufacturing Unit: 2893 L (750gal) G/L reactor, with operating temperatures of up to 200^oC.
- * Production Bay 2: 5678-L (1500gal) G/L steel reactor, with operating temperatures of up to 200^oC.

