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User Requirement Brief

NRC – Clinical Trial Material Facility (CTMF)

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Canada

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1.0 PROJECT OVERVIEW

1.1 Executive Summary

The National Research Council of Canada (hereafter, NRC) wishes to build a Clinical Trial Manufacturing Facility (CTMF) as a new annex at the NRC's Royalmount campus in Montreal.

The facility will be designed for production based on cell culture, purification, and bulk filling of biologics such as vaccines, viral vectors and/or monoclonal antibodies.

All production will use the same kind of unit operation:

- Cell Amplification
- Production
- Clarification using Depth Filtration
- Purification Chromatography
- Polishing Chromatography
- Ultrafiltration

Some unit operations will be specific to monoclonal antibodies due to the virus safety assessment: chemical inactivation and nanofiltration.

As a worst case, the design is based on typical production for monoclonal antibodies with a volume of a 500L bioreactor.

The facility will be designed to BSL2/CL2 requirements where required (in accordance with the Canadian Biosafety Standard, Second edition). The facility will be designed to accommodate one of two process options:

Option 1: One production line to BSL2/CL2 to accommodate both viral vectors and protein production, or

Option 2: Two production lines, one to accommodate viral vectors and one for protein production.

2.0 PROJECT DEFINITION

2.1 Project Objectives

A. Strategic Fit	1. Facility ready for clinical production by end of calendar year (December) 2022 2. Facility design allowing for future process technology implementation 3. Aligned with digital and automation strategies
B. Cost	1. Challenge and optimize project concept through value engineering and peer reviews. 2. ±15% estimate accuracy at the end of Basis of Design (BOD)

C. Performance

Available Weeks[1]	44 weeks/annum
Work Hours/Day	16 hours/day
Work Days/Week	7 days/week
Cell Culture Volumes	500L
Final Product Volumes[3]	12L- 20L
Number of Batches Year[3]	10
Number of Batches/Month	1 - 1.25/month

[1] Working Cell Bank (WCB) preparation included in overall production timeline.

[2] This production capacity excludes samples required for in process control, quality control, or other purposes.

[3] Production cadences based on a typical mAbs mass balance to be confirmed during Concept Design.

Assumptions:

- 2h for one preparation, then 5 preparations per shift
- 20 days of Subculture
- Preparation could be in parallel with production (dedicated team)
- No support operation during weekend
- Production 7 days/week
- Similar preparation schedule per week
- 15 days of mAb production

1. Optimized #FTE and running cost (benchmark)
2. Production success rate of ≥90%
3. Multi-product concept allowing change over ≤1 day
4. State-of-the-art facility, including maximum of flexibility for labs and production
5. Possibility to perform systems and equipment maintenance without interruption of the cGMP production and laboratories activities
6. Fill/Finish and secondary packaging are not in scope.

D. Compliance

Applicable Canadian Regulations

- Food and Drug Regulation, Division Part A, Part C (Divisions 1,2,4 and 5)
- Health Canada – Good Manufacturing Practices Guide for Drug Products, 2018, GUI-0001
- Annex 1 to the Good Manufacturing Practices Guide – Manufacture of Sterile drugs (GUI- 0119)
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Health Products and Food Branch Inspectorate, Guidance Document, Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines, Drugs Used In Clinical Trials, 2009, GUI-0036
- Guidelines for Temperature Control of Drug Products during Storage and Transportation, 2011, GUI-0069
- PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments,2016 (Referred by Health Canada GUI-0001)
- ICHQ5

3.0 DESIGN PHILOSOPHIES

The facility is designed for production based on cell culture, purification, and bulk filling of biologics such as vaccines, viral vectors, antibodies and other therapeutic proteins

Due to the nature of the facility and the ability to handle viruses, the facility will be designed to CL2 requirements where required.

3.1 Product Profile

3.1.1 Product Type

The primary purpose of the facility is to provide contract services to external clients. As such, it will not be designed to the requirements of a specific product. The CTMF shall be designed to be able to produce vaccines, viral vectors from animal cell systems and antibody based therapeutic proteins

The new facility will use different kinds of biological organisms, such as HEK-293 cells adapted for suspension growth to produce an adenovirus (Ad5-CoV) or CHO cells genetically modified to produce specific monoclonal antibodies.

3.1.2 Markets

The Canadian market (Heath Canada) is the primary target for products produced in the facility. Other standards (US, EU) should be incorporated in the design where feasible.

3.1.3 Material Characteristics

Representative material used in the facility are described below. According to the Health Canada ePATHogen-Risk Group Database the agents are classified as follows and the Centers for Disease Control and Prevention (CDC) Guidelines:

- HEK-293 Noninfected Cells
  - Classified as a Risk Group 1 (RG1). These organisms pose a moderate health hazard. CL1 containment is required for work with HEK-293 cell lines.

- Adenovirus in Suspension
  - Classified as a Risk Group 2 (RG2). These organisms pose a moderate health hazard. CL2 containment is required for work with Adenovirus type-5 vectors.

- CHO Genetically Modified Cells
  - Classification will depend on the gene modification. NRC chose the assumption to handle maximum Risk Group 2 (RG2). These organisms pose a moderate health hazard. CL2 containment is required for work GM CHO cells.

- The facility is not intended to produce non-biologic materials are use chemicals in bulk. Small volumes of IPA are likely to be used for cleaning and sampling, and a strategy to handle solvents within the warehouse and process areas will be required.
- Additional hazardous/toxic/corrosive materials are not intended for use in the facility.

3.2 Manufacturing Process

3.2.1 Upstream Processes (USP)

Cell Thawing

Cell lines, such as CHO or HEK 293 (depending on the process), shall be received from the GMP Master/Working Cell Bank, shipped to NRC and stored in a liquid nitrogen cryogenic tank. Frozen cells are thawed and then sub-cultured in shake flasks for several passages to maintain the cells in an exponential growth phase and to amplify the culture volume. Thawing and subculture will be performed in a dedicated Grade C, CL2 room using a biosafety cabinet. Cell culture will be conducted in incubators.

Note: The production schedule will be determined by the process running within the CTMF.

Virus Stock Preparation (in case of Viral Vector Production)

Viral stock received from an external facility shall be used to build up the production viral stock to be used for the infection of the culture in the production scale 500L Single Use Bioreactor. The virus stock preparation shall be performed in a dedicated Grade C, CL2 room. Cell line HEK-293 shall be cultured in the 50-liter bioreactor and then infected with the virus stock prepared in the Grade C, CL2 room. The viral stock produced in the 50-liter single use bioreactor shall be harvested in single-use bags and kept frozen at -80°C until needed for viral propagation in the 500L single use bioreactor.

Cell Culture

Sub-cultured cells shall be transferred from the Subculture Room to a single use seed bioreactor (50 L) for final expansion where they are cultivated at 37°C for a couple of days until the desired cell density is reached.

Cells shall be diluted with fresh medium up to the final volume and allowed to grow for additional days to reach the target cell density before being transferred to the 500L production scale single use bioreactor.

Dissolved oxygen shall be controlled during cell culture using sparging of clean oxygen. The pH value will be controlled using CO2 sparging and alkaline solution addition. The bioreactor itself is a closed system designed for cell culture in aseptic conditions. Connections between the bioreactor and medium bags/inoculum shall be performed aseptically by using a thermal tube welder and using sealable/weldable tubing designed for aseptic welding (or aseptic connector as Lynx® or Steamthru® technology).

Cell infection shall be performed in the Upstream Processing rooms (USP), dedicated Grade C, CL2 room.

Cell Infection (in case of Viral Vector Production)

Cells shall be grown in the 50L production bioreactor until the target cell density is reached, then diluted with fresh medium and infected with thawed viral stock. The volume of viral stock to use for infection shall depend on the titer of the viral stock and the cell density and culture volume of the bioreactor.

Cell culture is stopped approximately two days after infection with the viral stock. Cell infection will be performed in the Upstream Processing rooms (USP), dedicated Grade C, CL2 rooms.

Note: NRC will confirm the production schedule dependent upon the process to be carried out at the CTMF.

Biologics Production (in case of mAb production)

Cells shall grow in the production bioreactor until the target cell density is reached, then the cells are diluted with specific medium to change their metabolism. This action shall cause the cells to produce the target monoclonal antibody. During this phase of production, feeding additions should be controlled following in process control results such as glucose and lactate concentration in the media.

Biologics production is performed in the Upstream Processing rooms (USP), dedicated Grade C room (requirements for CL2 will be assessed based on the starting cell line)

Cell lysis and nucleic acid digestion (in case of Viral Vector production)

Two days after infection with the viral stock in the bioreactor, lysis of the cells is conducted by the addition of detergent-based lysis buffer into the bioreactor to release the Ad5-nCoV (viral vaccine candidate). Along with lysis buffer, benzonase (nuclease) will be added into the bioreactor to digest the released nucleic acids.

This step will be performed in the Upstream Processing rooms (USP), dedicated grade C room.

Clarification

The lysed cell culture shall be harvested from the bioreactor clarified using depth filtration to remove cell debris after cell lysis. The clarified broth is harvested into a tank that will be used to feed the clarified culture to the next process step, also taking place in a USP Grade C, CL2 room.

This step will be performed in the Upstream Processing room (USP), dedicated Grade C room.

3.2.2 Down Stream Process (DSP)

Chromatography

The purification process and operating conditions are designed to effectively reduce the residual host cell and residual host cell DNA content.

Depending on the process and the contamination risk assessment, the purification steps will be performed in the Downstream processing rooms, dedicated Grade C.

In case of viral vector, two chromatographic steps shall be performed in Downstream Processing Room #1: an anion exchange chromatography followed by a multimode chromatography (polishing). The eluate of the affinity chromatography is collected in a tank which will be moved to the second Downstream Processing Room.

In case of Monoclonal Antibodies production, one main purification step will be performed in the Downstream Processing No.1 as the affinity chromatography. The eluate will be transferred to a mixer for viral inactivation step (ref. below). The two next chromatography steps, such as Anion Exchange and Cation Exchange, will be part of the polishing steps. They will be performed in Downstream Processing No. 2.

Virus Inactivation and Removal (in case of mAb Production)

Protein products based on cell culture could represent a risk of viral contamination, especially if the production uses cell lines from human or animal origin. The CTMF will include the capacity for chemical inactivation and nanofiltration.

Inactivation will be based on acid addition in the mixer using calibrated peristaltic pump or floor scale. The pH will be maintained during a validated time to enable all potential viruses to be inactivated (be in contact with acidic solution). The product must be transferred to another mixer bag through depth filter to avoid any risk of non- inactivated product drop. Finally, the pH will be neutralized using basic solution. Osmolarity will be able to be adjusted to prepare the intermediate to be transferred to the polishing chromatography step.

After polishing, the product will be purified from inactivated virus using a nanofiltration skid. This skid includes peristaltic pump, pressor sensors, and depth filtration membranes.

UF/DF

Depending on the process, the final diafiltration shall take place either in Downstream Processing Rooms No. 1 or 2. This final step will be part of the final formulation step (boundary between clinical drug substance and clinical drug product). Indeed, the clinical drug substance formulation buffer will have the same composition as the final clinical drug product formulation buffer (excipients and stabilizer).

Drug Substance Formulation and Bulk Filling (in case of Viral Vector Production)

The UF/DF is followed by a concentration adjustment step to adjust the concentration of the clinical drug substance in the same processing room.

Each batch of clinical drug substance will be filtered through a 0.22 µm sterile filter and then stored temporarily in bulk bags until further processing and drug product formulation. The clinical drug substance will be stored in 2 and 8°C cold rooms. Samples of the clinical drug substance will be taken for quality control testing.

3.2.3 Supporting Processes

Warehouse

The CTMF shall include a Warehouse supporting various activities, such as raw material receiving, room temperature storage (racking), cold rooms, solvent storage, clinical bulk drug substance storage and shipping/receiving.

This storage area will be designed according to the following assumptions:

- 6 Weeks Storage of Raw Materials
- 6 Weeks Storage of Consumables

The CTMF warehouse will need to store various types of raw materials:

- Powders
- Media
- Concentrated Buffers
- Solvents
- Ready to Use Chromatography Columns
- Various Disposables, such as tubing, filter cartridges, connectors, bags etc.
- Gowning Items, as suits, gloves, shoe covers, etc.

Clinical bulk drug substance tanks will be transferred to the cold room storage (2-8°C) area in the warehouse to be quarantined before QC release.

Weighing & Dispensing

The CTMF facility shall include one weighing and one sampling room. These rooms will be classified as Grade C. Weighing of raw materials and sampling will be conducted within a LAF weighing booth.

Solution Preparation

The media and buffer preparation area shall be located in a Grade C clean room adjacent to the CL2 upstream and downstream suites. Additives, e.g., growth factors, will be purchased in bottles and vials and will need cold storage facilities local to the process

The solution preparation area will oversee the preparation of process solutions such as the media for seed culture and production culture. The buffers and solutions used for the purification of the products in the DSP rooms will also be prepared in the preparation room. Some of the solutions will be, however, bought ready-to-

use. To solubilize powders and mix liquids to obtain homogeneous solutions, mixing will be required. Sterilization of prepared solutions shall be required.

The area will require:

- Single Use Mixers (jacketed and non-jacketed)
- Weigh Scales (benchtop and floor standing)
- Transfer Pumps, Trays, Totes and Trolleys
- Tube Sealers and Welders

All the raw materials shall come from the warehouse, but some materials will be weighed and dispensed in a local Weighing Room located next to the Solution Preparation Room.

Prepared solutions will be transferred to the production suites using mobile tanks or bags (on cart) going through a wall pass-through.

Equipment Wash & Sterilization

The new CTMF facility will be equipped with a grade D component preparation room. for breakdown of non-Single Use components parts for cleaning. The area will contain one parts washer to support cleaning processes. There will be a local protection zone to minimize bioburden during final rinse and drying of items that are manually washed.

There will also be a clean equipment grade C preparation room to prepare components for sterilization. There will be a local protection hood at the outlet of the pass-thru parts washer prior to wrapping parts to minimize particulates. The area will also require some racks and staging areas. One pass-thru autoclave will be required; local protection will be required on the discharge of the autoclave to minimize bioburden during cooldown.

Finally, a grade C Sterile Equipment Staging Room will be required to stage sterilized equipment and components.

Prior to any parts arriving at the component preparation area, they will have been de- contaminated via decontamination autoclaves supporting all component and waste transfers out of CL2 areas.

3.2.4 Quality Control

The CTMF facility will include a basic quality control area for in-process quality control (IPQC) and microbiological environmental control (EC) laboratories.

This biochemical laboratory will support in-process control of the manufacturing processes.

Biological products will be tested according to the following representative analyses:

In-House Analysis	Method
Residual Host DNA	RT-PCR (Reverse Transcriptase Polymerase Chain Reaction)
Sterility	PCR, Microbiology Culture
Purity	HPLC (High-performance liquid chromatography)
Cell identity	Western Blot
Potency	Microscopy, Cell Culture

There will be the requirement for rapid analysis of in-process samples to make manufacturing process decisions. This is envisaged to take place within the manufacturing suites (in or at line monitoring)

All activities involving the open manipulation of biological material will be performed in a biosafety cabinet located inside the QC laboratory.

A separate microbiology laboratory will also be required. This laboratory will be available for microbial assays for environmental monitoring, bioburden testing, etc.

3.2.5 Containment and Segregation

The facility must meet the requirements for CL2 where required in accordance with the Canadian Biosafety Standards (2nd Edition). Air Handling Units (AHU) must be dedicated to CL2 areas if recirculated. In general, for crossing the containment boundary, entry airlocks should be bubbles, and exit airlocks should be sinks. Manufacture of viral vectors, mAbs or vaccines must be segregated by dedicated equipment, if possible (campaigned), and/or by time following appropriate changeover and cleaning validation.

3.2.6 Decontamination

All waste and re-usable components must be decontaminated out of all CL2 areas via dedicated decontamination pass through autoclaves.

Solid Waste

Two types of solid waste will be decontaminated within the new CTMF.

The first type of solid waste that will be generated by production operations will consist of single-use consumables, such as single-use bioreactor bags, tubing, and other single- use components. Once decontaminated, the waste will be transported to the warehouse for disposition.

The second type of solid waste concerns reusable glassware and components, which will be decontaminated and then moved to the component prep area before moving through the washing and sterilizing process prior to re-use.

Liquid Waste

All process waste and clean steam condensate generated during the processes will be collected by the biowaste inactivation system. Biowaste will be collected by dedicated drain networks and fed to a dedicated packaged biowaste inactivation system located on the lowest floor of the greenfield facility. Following inactivation, the waste will be sent to a waste neutralization system before discharge to the city.

3.3 Process Utilities

3.3.1 Water For Injection (WFI) Generation, Storage and Distribution

Due to the limited requirements for purified water (no requirement for PW), WFI will be utilized during the production processes and for cleaning. The generation system will be designed to provide water meeting compendial requirements as outlined by the EMA and US Pharmacopeia.

3.3.2 Clean Steam

Clean steam is required for sanitization of process vessels, transfer lines, sample ports, sterilizing grade autoclaves, and decontamination autoclaves. Clean steam will also be periodically used for sanitization of WFI storage vessel, pumps and distribution loop piping.

3.3.3 Compressed Air

The system will support two areas

- Instrument Air
- Clean Compressed Air (CCA)

3.3.4 Process Gases

Pharma Grade Oxygen

A bottle-fed oxygen distribution system shall be provided with cylinder changeover. Oxygen will be provided to both the IPQC and EC labs, plus all production suites. User stations will be located as close as possible to points of use.

Pharma Grade Carbon Dioxide

A bottle-fed Carbon Dioxide distribution system shall be provided with cylinder changeover. Carbon Dioxide will be provided to both the IPQC and EC labs plus all production suites. User stations will be located as close as possible to points of use.

Pharma Grade Nitrogen

A bottle-fed Nitrogen distribution system shall be provided with cylinder changeover. Nitrogen will be provided to both the IPQC and EC labs, plus all production suites. User stations will be located as close as possible to points of use.

3.4 Automation Philosophy

The automation strategy will be based on the most cost-effective solutions to meet the projects requirements while making sure the solutions can be implemented in a fast-track schedule.

A structured approach will be taken for the design and risk assessment of the automated systems specifications (Specifications, FDS, DDS, and traceability matrix).

The automation strategy will be based on several types of systems types of systems being used for the project:

- Specialized equipment will be specified and purchased with the automation designed and supplied by the equipment vendor. These types of systems will be provided with their own standard automation package, which will contain a local PLC and operator interfaces. Basic automation requirements will be prepared to make sure those systems are compatible with the minimal integration required at go live (including connection to the centralized historian, production reports and security management.). Typical equipment in this category - mixers, bioreactors, filtration systems (UF/DF), chromatography, bulk filling and process utilities systems (WFI, clean steam) etc.
- Some process systems will be manually operated.
- Process Data Historian shall be provided.
- Quality Management System shall be provided to support documentation requirements for the Quality Assurance group.

- Environmental Monitoring System (EMS) shall be provided to collect and record critical environmental conditions.
- Warehouse Management System (WMS) shall be provided to track materials and flow inventory as well as support production management.
- A centralized SCADA system shall be required to integrate the Process Control, Data Historian & Environmental Monitoring Systems.
- An IT/Automation Room will be required within the facility to enable integration to the existing campus IT systems. The scope of manufacturing IT requirements will be defined during the concept design phase.

3.5 GMP Area Classifications

When designing the facility, the following environmental requirements shall be adhered to:

3.5.1 Environmental Cleanliness Levels

Maximum number of particles permitted /m3						
EMEA					FDA	
	At rest		In operation			In operation
GR	≥.5µm	≥5µm	≥.5µm	≥5µm	Class	.5 µm
A	3,520	20	3,520	20	ISO 5	3,520
B	3,520	29	352,000	2,900	ISO 7	352,000
C	352,000	2,900	3,520,000	29,000	ISO 8	3,520,000
D	3,520,000	29,000	Not defined	Not defined	CNC	NA

3.5.2 Unclassified

Unclassified Spaces include all functions outside the manufacturing operations areas where personnel are not in contact with production. It contains support functions, including entrance lobbies, mud rooms, security, toilets, cafeteria/break rooms, all facility utility and process mechanical rooms, offices, conference rooms, general corridors, and storage rooms. Standard street clothing is permitted in these functional areas. Standard industry finishes and materials are permitted.

3.5.3 Controlled Non-Classified

Controlled Non-Classified Spaces include all functions that provide access directly to the manufacturing areas and spaces where no direct contact occurs between personnel and product, product processing equipment, or primary product containment components. It includes GMP support functions, dedicated inspection rooms, labs and controlled corridors. This classification requires personnel to wear dedicated plant shoes and dedicated manufacturing plant uniforms. Finishes that do not generate particulates are recommended.

3.5.4 Controlled Non-Classified/Grade D

This designation refers to areas that will be designed to achieve ISO Class 8 particulate levels at rest. These controlled areas are non-aseptic GMP zones where the environment will not come in direct contact with the drug product and/or intermediate materials. A risk assessment should be made regarding the handling of components and/or containers/closures in this area prior to final sterilization. Examples of these areas include support corridors linking locker rooms with production areas, material handling areas and component preparation rooms.

3.5.5 ISO 8/Grade C

ISO 8/Grade C spaces include all areas where components, product contact parts, and pre-filtered product are being prepared. These functions occur in media & buffer prep, cell expansion, cell culture, purification, and bulk filling. Environmental classifications associated with this zone include such designations as Grade C, ISO Class 8 in operation, ISO Class 8 in operation (ISO 7 at rest). Additional protective gowning is required within this function. All surfaces must be monolithic, designed with coved corners, and detailed for easy cleaning.

3.5.6 Local Protection/Grade A Air Supply

Local protection areas are maintained by providing HEPA-filtered supply air. These areas include weigh & dispense that is provided with HEPA-filtered air supplied through a laminar airflow (LAF) module overhead and on the discharge side of the parts washer and sterilizing autoclave.

3.5.7 ISO 5/Grade A

ISO 5/Grade A spaces include all functions where the aseptic process is exposed to the product. It includes the inside of an isolator where aseptic filling operations take place. This room classification is not required with the use of isolated filling lines since the isolator provides the necessary security from environmental contamination. Complete isolation of personnel from the aseptic manufacturing space is achieved through the use of a closed gloved barrier system such as VHP isolator technology.

3.6 Material Transfer & Gowning Philosophies to be Employed in the New Facility

3.6.1 Introduction

Standardized procedures must be adopted for all movements through all transition ports to protect the integrity of the adjacent functionally classified spaces. The following philosophies must be utilized when accessing transition ports.

3.6.2 Personnel Transfer

The personnel ports that transition between the two unclassified functions are typically locker rooms. These rooms are permitted to be bi-directional and should include cross- over benches for shoe changing, which becomes the transition between unclassified and Controlled Non-Classified (**Note**: Toilet rooms should not be a part of the locker room complex and shall be located in the unclassified portion of the building.)

Bidirectional flow options will be considered if required to meet budget and schedule restriction restrictions. The preference for personnel transitions between all other zones is to be unidirectional flow-through separate gowning and de-gowning rooms. These rooms require interlocked doors that prevent simultaneous openings between the two adjacent functional classifications. These rooms shall be designed to cascade air from the more to the less restricted adjacent zone, with the exception of the transition across a biological containment boundary where the entrance and exit airlocks may have a bubble/sink air flow respectively.

3.6.3 Material Transfer

Material airlocks shall be designed with interlocked doors that prevent simultaneous openings between the two adjacent functional classifications. The space shall be sized to safely stage material and material handling equipment free from all door swings. These rooms shall be designed to cascade air from the more to the less restricted adjacent zone, with the exception of the transition across a biological containment boundary where the entrance and exit airlocks may have a bubble/sink air flow respectively. Transition between the two unclassified functions can be bi-directional; all other material airlocks should be unidirectional where practical.

3.6.4 Gowning Philosophies

Unclassified to Controlled Non-Classified/Grade D

Employees shall retrieve clean uniforms (scrubs) from the clean plant uniform staging area and proceed to the men's or the women's locker rooms. They will then change from street clothes to their plant uniform, place their street clothes in the designated locker, remove their pharmaceutical shoes from their clean shoe locker, and proceed to the shoe change room. At the designated change bench, employees shall change into pharmaceutical shoes and place street shoes into their designated street shoe locker. Before leaving the shoe change room to the manufacturing suite, the employees shall don safety glasses and a clean hair net and beard cover, as applicable. Visitors shall enter the visitor locker room, don a lab coat and proceed to the shoe change room, obtain a pair of shoe covers, proceed to the shoe changeover bench, and don the shoe covers. Before leaving the shoe change room, the visitor shall don a clean hair net and beard cover as applicable.

Controlled Non-Classified/ Grade D to Unclassified

Employees leaving the manufacturing suite shall proceed to the shoe change room, pick up their street shoes from their designated locker, and proceed to the shoe change bench, change into their street shoes, proceed to their designated locker, remove and dispose of hair and beard covers in the provided receptacles, and place their pharmaceutical shoes into the designated locker. If planning to enter the unclassified corridor for any purpose, including proceeding to the toilet facilities, the employee shall change into street clothes. If returning to manufacturing the same day, the employee will hang the uniform in their designated locker; if leaving for the day, the employee shall drop the uniform in the soiled uniform area.

Controlled Non-Classified/Grade D to ISO 8/Grade C/Non-Aseptic Manufacturing

Upon entering the non-aseptic gowning room, all personnel shall obtain clean shoe covers and an over-gown (whites), don the whites, proceed to the shoe change over bench, and don the shoe covers. Personnel shall add hair and beard covers and clean hands with a sanitizing product. Personnel may then proceed through the interlocked doors to the ISO 8/Grade C/Non-Aseptic Suites.

ISO 8/Grade C/Non-Aseptic Manufacturing to Controlled Non-Classified/Grade D

Upon entering the non-aseptic de-gown room, all personnel shall remove their over-gown and shoe covers and dispose of them in the provided receptacle. When exiting Grade C Manufacturing Rooms that process agents of biological concern (CL2), two-stage gowning with a bubble/sink pressure design may be provided.

3.6.5 Material Transfer Philosophies

Unclassified to Controlled Non-Classified/Grade D

Material for the Non-Aseptic and Aseptic Manufacturing

Warehouse personnel shall obtain material from the racks, remove all cardboard from the material to be transferred, remove the cardboard to the waste collection room, and place the transfer material in a staging area to be transferred to the first floor and into the material staging airlock.

Grade D/Controlled Unclassified To Unclassified

Personnel will enter the material staging airlock, retrieve the material, return the unused manufacturing material to the warehouse racks, and remove the trash to the waste collection room.

Controlled Non-Classified (US FDA)/Grade D To ISO 8 (US FDA)/Grade C/Non-Aseptic Manufacturing

Personnel will place material into the non-aseptic manufacturing material airlock and leave, closing the interlocked door. Personnel from the non-aseptic manufacturing suite will then retrieve the material from the non-aseptic manufacturing material airlock utilizing material handling equipment dedicated to the non-aseptic manufacturing suite.

ISO 8/Grade C/Non-Aseptic Manufacturing To Controlled Non-Classified/Grade D

Non-aseptic suite personnel shall place all unused manufacturing material and trash in the non-aseptic manufacturing material airlock and close the interlocked door. Personnel will then retrieve the material from the airlock. Trash from a CL2 area will be transferred out via pass-thru decontamination autoclaves.

4.0 PROCESS BUILDING ASPECTS

4.1 Architectural Program

Either a single or multi-story design can be considered. Space restrictions exist at the proposed site and are likely to limit the potential for a single story. Maximum single floor footprint is estimated to be 18K sq ft. Overall building footprint is projected to not exceed 25-30K sq ft. Height restrictions are mandated by local ordinances.

The facility is expected to incorporate sustainable practices where appropriate to reduce carbon footprint without impacting facility performance.

A representative, but not proscriptive, program for illustration purposes is provided below.

4.1.1 Support (non-production) floor

- Mud Room/Lockers
- Change Rooms/Lockers
- Boiler and Chiller Plant Rooms (as part of the Concept Design review capacity available within main campus and location – can be removed if main campus capacity deemed adequate)
- Air Compressors and Generation (as part of the Concept Design review capacity available within main campus and location – can be removed if main campus capacity deemed adequate)
- Bio Kill System Plant Room
- Clean Utilities Plant Room (as part of the Concept Design review capacity within main campus and location – can be removed if main campus capacity deemed adequate)
- Waste Neutralization Room (as part of the Concept Design review capacity available within main campus and location – can be removed if main campus capacity deemed adequate.)
- IT/Automation Room
- Electrical Switchgear Room
- Warehouse

- Weigh and Dispense
- Sampling Area
- Cold Rooms (2-8°C)
- -80°C Freezer/s
- Waste Handling
- Shipping & Receiving
- Material & People Elevators (1)
- Maintenance Elevator (1)

4.1.2 Production Floor

- Change Rooms
- Material & Personnel Air Locks
- Material Handling & Staging
- Upstream Processing (USP)
- Downstream Processing (DSP)
- Bulk Filling
- Media & Buffer
- IPQC Laboratory plus Write-up Areas
- EC (Microbiology) Laboratory plus Write-up Areas
- Component (Dirty equipment) Preparation
- Clean Equipment Preparation
- Sterile Equipment Staging
- An interstitial floor will be incorporated above the first floor to enable access to equipment and maintenance to minimize intrusion into the clean spaces.

4.1.3 Utility Penthouse

- Primarily to support Air handling Units and Plant Equipment
- Cooling Towers (if required)

4.2 Civil & Structural

The Civil and Structural Engineering design shall be developed in a wholly integrated manner to suit the process equipment requirements and to provide an economical, flexible, and sustainable facility.

The scope of the civil and structural engineering works for the project comprises 5 main elements:

- Site-wide Civil Engineering Works (outside the building footprint), including roads, drainage, and services to accommodate the local constraints and conditions.
- Outline Structural Definition for the Buildings to accommodate the insurers' requirements, process, mechanical, utilities and associated equipment, as well as the personnel who will be working in the building.

- Outline Definition of the Below Ground Requirements based on site ground conditions to include earthworks, foundations, and drainage.
- Outline Definition of the Above Ground Requirements to include structural form, materials and arrangement, roofing, internal structural elements, including floors and walls and any specific production-related structural aspects, such as bunds, pits, cold rooms, and lifting beams.
- Review of Permit Requirements for the site chosen and the impact on cost and schedule.

During the project, the design will be reviewed to incorporate efficient and safe construction methods, being coordinated with other discipline engineering strategies within the overall construction sequence. A concurrent design-build strategy is required to meet project schedule.

4.3 HVAC and Building Services

4.3.1 Plant Utilities

The following systems shall be required. Scope details will be confirmed during the basis of design.

Plant Steam & Condensate

- Humidification steam to support the HVAC units (local steam-to-steam heat exchanger)
- Chilled Water
- HVAC Heat Recovery (Glycol Run around System)
- Process Cooling water
- Process Venting
- Domestic (potable water)
- Compressed Air
- Storm Water Drainage
- Sanitary Water Drainage and Venting
- Process Water Drainage (including biological waste) & Venting plus Waste Neutralization
- HVAC Units as required to support facility, including CL2 areas

4.3.2 Building Management System

The new CTMF facility shall be integrated into the existing Honeywell EBI campus Building Automation System. Definition of requirements shall be developed during the concept design.

4.4 Electrical

4.4.1 Electrical Service and Distribution

The new CTMF facility shall be supported as follows:

- Normal Distribution – New electrical feed is assumed to be required.

- Emergency Power & Distribution from Site Generators –a new emergency generator shall be required for the CTMF facility
- Uninterruptible Power Supply (UPS) & Distribution – A new central UPS shall be provided for the CTMF facility.
- All electrical outlets shall be designed for clean room applications where appropriate.
- Grounding rods shall be installed around the building and connected to the building steel. A ground bar shall be installed in electrical switchgear room and connected to the main ground bar. Equipment grounding shall be done through electrical bonding.
- A separate Instrument ground shall be provided in the electrical switchgear room to provide a dedicated grounding path for extra low voltage instrumentation.

4.4.2 Lighting

LED source lighting shall be used in all areas of the CTMF. In clean areas, recessed sealed clean room lighting shall be integrated into the ceiling by the clean room vendor. Emergency lighting shall be fed by a dedicated automatic transfer switch from the generator. Illumination by area:

Location	Average Illumination
Office Area	400 - 500 Lux
Mechanical Space	200 - 300 Lux
Clean Corridors, MAL, PAL	500 - 600 Lux
Clean Manufacturing Rooms	650 - 750 Lux
Warehouse	300 - 400 Lux
Emergency Lighting	To illuminate egress pathways

4.4.3 Hazardous Areas

The project scope does not see the requirement for any hazardous area classification; this shall be reviewed during the concept design.

4.4.4 Access and Interlock Control

Access controls will utilize and match existing campus security card access control manufacturer products and logistics. Access controls will be limited to card readers. Interlock controls will be via a new microprocessor-based controller with emergency override switches and push-to-exit buttons. Door locks and status will be furnished with the door hardware. All airlocks shall have interlocked doors with wave hand swipes. Access to the production suites, warehouse, and laboratories shall be controlled by card readers. Security cameras shall be installed exterior to the CTMF to monitor the building perimeter.

4.4.5 Telecommunications

The topology of the information communication technology (ICT) system shall be in accordance with the existing network architecture employed elsewhere on the campus and shall include interconnection with the networks of adjacent campus buildings (where appropriate). The ICT network shall provide the backbone for all voice and data communication within the building, including CCTV, PA and access control. The design shall include segregation of fiber-optic networks between sub-systems, where required or as part of network optimization. The design of this passive network shall be carried out in close consultation with the NRC team to ensure that it is fully in accordance with their specific requirements. Appropriate clean room fittings shall be used where needed.

4.4.6 Fire Alarm system

A fully addressable fire detection and alarm system shall be installed to protect the facility and its occupants. The system shall be designed to be capable of communicating with the existing campus' fire alarm system for both chemical and fire detection. The selection of fire alarm devices shall consider accessibility for maintenance and include measures to reduce the risk of false alarms which could impact operations. The fire alarm system shall be capable of communicating with third party systems, including access control, life safety, and fire suppression systems. Clean room fittings shall be employed were required.

4.5 Fire Protection

The fire protection system shall consist of the following elements:

- A wet-pipe sprinkler system to protect the CTMF facility
- Hose connections in the warehouse
- A double-interlock, pre-action system for the IT/automation room
- Portable fire extinguishers as per code

Guidelines:

The fire protection system shall be designed in accordance with applicable codes, regulations, and guidelines, including:

Quebec Construction Code - Chapter 1

- NFPA 13 – Installation of Sprinkler Systems
- NFPA 20 – Installation of Stationary Pumps for Fire Protection
- NFPA 30 – Flammable and Combustible Liquids Code
- NFPA 10 – Portable Fire Extinguishers

5.0 APPENDIX

Appendix 1 - Typical mAb Process

APPENDIX 1

Overall Process Flow- mAb