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**CENTER FOR GENETIC ENGINEERING & BIOTECHNOLOGY
HEPATITIS B RECOMBINANT VACCINE
PRODUCTION FACILITY**

GMP ASSESSMENT REPORT

September, 1995

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Section 1.0 Background

The main laboratories and manufacturing facilities for the production of the Hepatitis B recombinant vaccine are located within the Center for Genetic Engineering and Biotechnology complex (CIGB) in Havana, Cuba. This facility was built in 1986 to promote biotechnology development of leukocyte alpha interferon. The facility and its operations have experienced tremendous growth since it first opened and is currently a multi product manufacturing complex, producing over 160 commercial products from natural or recombinant origin.

The Hepatitis B recombinant vaccine manufacturing facility (HBMF) occupies approximately 500 square meters of space within the CIGB complex. The complex was originally designed to promote research and development of products. Because of its original goal of R & D, it was not designed to meet any specific regulatory requirements such as GMP's.

Section 2.0 Scope

The Hepatitis B recombinant vaccine manufacturing facility (HBMF) intends to operate in compliance with World Health Organization, Good Manufacturing Practices regulations for International Commerce. In attempt to meet market demand, it is intended that this facility be dedicated to the production of one single product. FermentaGen, Inc. was contacted by CIGB to evaluate the existing facility in terms of meeting GMP standards, which include facility design issues, cross contamination, segregation, functionality flows (product, raw materials, glassware, personnel, waste), containment, as well as mechanical and utility systems. The evaluation was based on information exchanged during meetings held in Havana, Cuba, Edmonton, Alberta, and Montreal, Quebec, Canada. Architectural plans, process schematics, video tapes, and round table discussions were used as the essence for this assessment. The results of the pre-assessment will be used as a basis for facility and system design modifications which will enable the facility to be validated to meet GMP's.

Section 3.0 Facility

3.1 Facility Design and Use

The HBMF is currently used for the manufacture of Hepatitis B recombinant vaccine for local market. Dedicated areas for the manufacture of the vaccine are located in various locations throughout the two story CIGB complex. These HBMF areas have been renovated over time to fulfill operations and production requirements. Six distinct HBMF dedicated areas exist within the complex which are:

- process testing labs,
- component prep and material storage,
- fermentation,
- cell harvest,
- semi purification,
- and purification.

With the exception of semi purification all the areas of the HBMF are located on the second floor of the CIGB complex. Each HBMF area has a dedicated HVAC system but exhaust/return air from each of the areas share common hallways for return air throughout the CIGB complex. The facility and the HVAC systems within operate twenty-four hours daily, throughout the year, employing personal for three shifts per day.

General Comments

- walls are constructed from cement blocks throughout the CIGB complex, which are hand trowelled with a gypsum mortar and then painted with a "brushed on" rubber based paint.
- ceilings are suspended T-bar which are hand trowelled with a gypsum mortar and then painted with a "brushed on" rubber based paint.
- light fixtures are flush fit into the ceiling.
- electrical conduit and wire-way ducts are mounted directly on the surface of the walls.
- floors are constructed of terrazzo tile.
- supply air is delivered to rooms via a dedicated zone air handling units, each with central hepa filtered supply air. No terminal HEPA diffusers are used on zone HVAC distribution systems.
- return air from various rooms/zones are directed to exhaust/return plenums via louvers or wall transfer grilles mounted over room doorways

3.2 Process Control Labs

This area consists of support labs 7.1/7.2 which are used for storage and testing of all working cell banks, and seed inoculum production for all the manufacturing operations in the CIGB complex. The rooms are constructed as per standard CIGB specifications. A bio-safety hood is utilized for "critical" operations.

RECOMMENDATIONS

1. The process control labs are multi product labs, in order to establish control of this area, as required by GMP's, only work with one product should be performed at a time with adequate validated change control procedures performed between products. Non-GMP work should not be performed in this lab, instead separate dedicated labs should be constructed solely for HBMF GMP processes.
2. All rooms mentioned above need to be completely upgraded to meet GMP's. In addition, access to these areas needs to be controlled since it is located within a multi-product manufacturing facility.
3. The flow of contaminated/dirty and clean glassware and equipment into these areas require separate entrances and exits to prevent cross contamination. This can be accomplished by the use of clean/dirty corridors and appropriate airlocks and pass-thru's. This will be discussed later in this report when reviewing the GMP options.

3.2 Raw Materials and Storage

Raw materials for the HBMF are first received at the CIGB central bulk warehouse located in the complex. To reduce costs, materials are purchased in large quantities and are dispensed to several manufactures within the CIGB complex, per their production requirements. A segregated area within the warehouse is setup for obtaining samples for CIGB quality control (QC) testing of incoming raw material shipments. Bulk raw materials are then placed in the warehouse and tagged quarantine. If Q.C. tests results are favourable then the material tags are change to "released". Rejected materials are removed from the warehouse upon notification from Q.C.

Ventilation and air conditioning (HVAC) for most of the warehouse is provided by using roof top ventilation fans which pull outside air from wall louvers (complete with bug screens) and exhaust air through the roof. Provisions for temperature sensitive materials exist, and are provided through the use of "walk in coolers" located adjacent to the sampling area.

When HBMF staff require raw materials for production operations, the required released materials are from the warehouse to the CIGB general shipping area. The materials are transported up to the second floor of the facility using These raw materials are treated as

released materials with no further testing or quarantine. Raw materials are removed from the storage area when needed and excess materials are not returned

RECOMMENDATIONS

- a A documentation system needs to be developed for the storage, receipt, quarantine, and release of raw materials specifically for the HBMF GMP operation. This should include the use of stickers and logbooks which track and clearly identify the contents and status of raw materials from receipt at the loading dock through use in manufacturing.
- b Dedicated space should be provided and identified with proper signage for the receipt of incoming raw materials used in GMP operations. The quarantine of materials in remote facility areas should be discouraged since this will necessarily increase the risk of chemical/bacterial contamination and mixups. It is recommended that facilities in the existing HBMF should be provided with dedicated properly designed areas for quarantine, testing, rejected components, released of goods, and in-process materials for the sole use in HB vaccine manufacturing.
- c Areas for storage of raw materials should use materials handling equipment that is smooth, impervious, cleanable (eg plastic, stainless steel, shelving, cabinets, pallets) and provide storage of materials off of the floor.
- d All storage areas for GMP materials should have environmental controls to maintain : nperature, pressure, and relative humidity (%R H) These parameters should be maintained monitored and recorded continuously
- e The GMP storage area for the HBMF should also be designed to accommodate obtaining material samples under controlled conditions (eg. a HEPA laminar flow hood).
- f A pest control program should be implemented in the facility

3.3 Component Preparation

Glassware, tanks, and materials needed in the HBMF are hand washed in the areas which they are used. Fermentation media components are weighed, and then transferred into clean containers or bottles, as per batch requirements. Upon completion of component preparation operations the tanks are then stored prior to being transported to the fermentation suite. Media is then pumped into a fermenter where it is steam sterilized. Also, other media is prepared in shake flasks and autoclave sterilized for use in inoculum preparation in the fermentation area

3.3 Component Preparation

RECOMMENDATIONS

1. Room finishes need to be completely upgraded to meet GMP's. In addition, access to these areas needs to be controlled since it is located within a multi-product manufacturing facility.
2. The flow of dirty and clean glassware and equipment into these areas require separate entrances and exits to prevent cross contamination. This can be accomplished by the use of clean/dirty corridors and appropriate airlocks and pass-thru's.
3. Room finishes need to be upgraded to allow areas to be easily cleaned and disinfected
4. Distinct areas are required for raw materials as stated in 3.2, as well as areas for dirty glassware, clean glassware, component prep, equipment storage, and batching mixing.
5. Glassware and container washing operations should be validated so that the cleaning process is consistent and reproducible.
6. Where water is used as a solvent for component preparation, USP purified water should be used.

3.4 Inoculation Preparation Room

Inoculum preparation is performed in the fermentation suite, cells from the working cell bank, are plated out on three petri dishes in a laminar flow hood in the fermentation area. The petri dishes are placed in an incubator in the fermentation area and after the incubation period is finished, the inoculum is transferred to five 50-ml erlenmeyer flasks, and transferred under laminar flow hood conditions. The flasks are again placed in a incubator before being transferred into 500ml erlenmeyer flasks again under similar conditions. The 500 ml flasks are placed in an incubator shaker, prior to inoculating a 50L fermenter.

RECOMMENDATIONS

1. The working cell bank is stored in a multi product lab, in order to establish control of this area, as required by GMP's, only work with one product should be performed at a time with adequate validated change control procedures performed between products. Non-GMP work should not be performed in this lab, instead a separate dedicated area should be provided for the storage of the working cell bank in the GMP HBMF.

3.4 Inoculation Preparation Room

2. The inoculation prep and seed suite should be physically separated with cleanliness levels of class 100,000 with critical operations being performed in a class 100 bio-hazard hood.
3. The rooms mentioned above should be designed to prevent personnel cross flows and minimize cross contamination. This can be accomplished by use of a separate clean/dirty corridor system complete with airlocks.
4. Room finishes need to be upgraded to allow areas to be easily cleaned and disinfected

3.5 Fermentation

The area dedicated to HBMF fermentation houses centrifuges, shakers, and 50L, 200L, and 2000L fermenters. The fermentation area is a metal fabricated building with exposed structural steel and metal panel walls. The floor is constructed of concrete with a open grated floor trench running down the center. There are no dikes around the fermenters to contain the complete contents of the vessel in the event of loss due to a rupture, leak, or operator error. If this does occur waste from the floor trenches is directed to the multi-product shared kill tank system

The fermentation area is served with a dedicated HVAC system consists of exposed over head supply and floor return ductwork. The room is maintained positive, with respect to surrounding areas, and its utilities are supplied from a mechanical room located directly under the area. Apart from fermentation equipment, a disk stack centrifuge is located in the room on a open mezzanine area. No special provisions exist for the containment and exhaust of aerosols generated by the centrifuges. Previous air monitoring tests have shown significantly high particulate levels during certification operations.

The process in the fermentation suite, starts with the seed inoculum being aseptically injected into a 50L fermenter in a laminar flow hood. Following growth of the inoculum, this culture is directed via pre-sterilized transfer piping to the 200L fermenter containing pre-sterilized media. Upon further growth, this culture is directed via pre-sterilized transfer piping to the 2,000L fermenter containing pre-sterilized media. Following fermentation, the broth is washed and concentrated in a disk stack centrifuge via sterile transfer lines.

A detailed equipment and specification review was not conducted but based on the material presented the fermentation equipment appears to be of adequate size, design, and quality to manufacture clinical grade material. However, it is strongly recommended that the locally generated fermenter controls and data acquisition systems be thoroughly documented in terms of their software and hardware.

3.5 Fermentation

RECOMMENDATIONS

1. The process and thus the equipment layout should be reviewed for its ability to provide consistency of operation with the prevention of mix ups.
2. The suite should be reviewed for compliance with BL1-LS containment guidelines.
 - "closed vessel" minimum HEPA (0.3u) exhaust, sterile (0.2u) in-line vessel additions, steam cross piping on all piping that intersects the vessel, use of double mechanical seals with sterile barrier fluid on all rotating shaft seals.
 - closed sampling and additions to minimize aerosols.
 - emergency plans in the event of a catastrophic release, loss of utilities, natural disasters,etc. based on a systems audit.
3. Aerosol generating equipment (centrifuges) should be relocated or replaced with new equipment designed for containment; or the HVAC system should be upgraded to properly capture particulate and exhaust emissions.
4. Flows should be addressed and the facility renovated to provide segregated areas for the inoculum prep., seed suite, and centrifugation areas complete with clean/return corridor system.
5. The plumbing should be revised to enable capping floor trenches.

3.7 Cell Harvest

For cell harvest operations tubular centrifuges and homogenizers are available. The area is supplied by a dedicated HVAC system, with a central HEPA supply, which maintains the room positive with respect to surrounding areas. The area is constructed using standard CIGB architectural methods and materials. Air locks are provided for equipment and personnel, and are used for both access and egress.

Concentrated washed cells are transferred to the area via sterilized tanks from the fermentation area, and the product is run through two homogenizers. Upon completion of the cell disruption process the product is transferred across the room to the next area where an acid precipitation step is performed prior to centrifugation. During centrifugation no provisions are made for the capture and exhaust of aerosols. Head room over the centrifuges are reduced by overhead electrical cable trays.

RECOMMENDATIONS:

1. The current equipment is not operating under GMP's, and if a primary barrier solution

were to be adopted (strongly recommend) it would require the replacement of the existing equipment with equipment designed for containment

2. Upgrades / modifications to the HVAC, architecture and product transfers are required
3. The current area is too small and does not provide adequate space for process operations. The operation should be either relocated or expanded to provide more space, along with provisions for adequate product, material, and personnel flows.
4. Cell disruption is an "live" process area and, should be segregated from "dead" areas or relocated to the fermentation area.
5. Room finishes need to be upgraded to allow areas to be easily cleaned and disinfected.

3.8 Semi Purification

The semi purification operations are conducted on the first floor of the CIGB complex. The area is quite large utilizing only ten out of the existing 13 rooms in the area. The architectural and mechanical features are constructed per CIGB standards. The area has additional mechanical systems such as fresh cooling system, chemical fume hoods, and soft wall HEPA supply hoods installed over key equipment.

Product is transferred via a hard piped transfer, and fed into three absorption reactors. Only closed, sterilized piping systems are utilized to transfer product between downstream process equipment. The desorption process is conducted with key equipment located under soft wall HEPA laminar flow hoods. Product is then transferred for hollow fibre concentration process. Operations of the semi purification area are supported by material prep lab, and all process equipment is either steam sterilized or chemically disinfected prior to use.

RECOMMENDATIONS

1. HVAC systems within all the semi-purification areas needs to be upgraded with provisions for HEPA filtration of supply air to all areas in this suite.
2. Room finishes need to be upgraded to allow the areas to be easily cleaned and disinfected
3. Plumbing systems and floor drainage must be upgraded, all floor drains need to be capped and sealed until needed and connected to a dedicated kill tank system. All process equipment needs to be diked in case of spills or leaks so that wastes can be pumped to proper waste systems

4. The Semi-purification areas are considered "critical areas"; the current architectural layout and should be redesigned to provide proper unidirectional flows
5. The Semi-purification occupies more space than is required for the manufacturing operations, and should be down sized to provide adequate manageable areas

3.9 Purification

Purification is performed in an area occupying approximately 200 square meters in size located on the second floor of the CIGB complex. It consists of three material preparation rooms, a glass wash/storage room, a walk in cooler, a equipment storage room, four purification rooms, and air locks for personnel, product, and waste. The area is constructed to standard CIGB specifications, with additional chemical fume hoods, and laminar flow hoods, for environmental controls.

Product is transported in a 10L container to a special room where chromatography processes are performed. Processed materials, are stored in 10L carboys in the walk in cooler, and held until a batch of product has been accumulated. The product is then transferred to a 50L ss vessel. The pooled product is then pumped through a transfer line into a 50L ss jacketed vessel, where it undergoes heat treatment. The final sterile in line filtration process is conducted under laminar flow conditions. The product is filled into 5L carboys within the laminar flow hood and transferred into a cooler.

RECOMMENDATIONS

1. HVAC systems within all of the purification areas needs to be upgraded to provide a cleaner environment with provisions for HEPA filtration of supply air to all areas in this suite (Class 10,000) with use of bio-safety hoods for open processes (Class 100)
2. Room finishes need to be upgraded to allow the areas to be easily cleaned & disinfected
3. Equipment storage area and walk in cooler are not necessary. A refrigerated cabinet could replace the walk-in cooler.
4. The architectural layout should be redesigned to provide proper unidirectional flows. The suite should have proper areas for dirty, wash, and clean glassware, along with a clearly defined component prep, and storage area. The affinity chromatography lab should remain separated, but the other purification areas could be combined.
5. Process steps should be minimized, the transfer step using the 50L holding tank should be eliminated. Instead a "pass through" should be provided to accommodate the transfer of 10L bottles to the next purification suite

3.9 Purification

RECOMMENDATIONS

6. Provisions for **pyrogen** free water are required for buffer prep and final rinses of equipment.
7. All product transfers should be performed sterilely in "closed" systems. Therefore all equipment that comes in contact with the product should be capable of being steam sterilized in place or chemically disinfected prior to use. Only closed, sterilized piping systems should be utilized to transfer product between downstream processing equipment.
8. Glasswash equipment should be installed, so that glasswash operations can be validated.
9. Autoclave must be validated to conform with GMP regulations.

3.10 Fill and Finish

Fill and finish operations are performed in another facility located outside the CIGB complex. Details on the specific fill and finish operations were not discussed and are not part of this assessment.

3.11 Utilities

Process steam is produced by a main central high pressure steam plant, and is distributed throughout the CIGB complex via a piping distribution system constructed of 304 stainless steel. 304 ss is used throughout the process steam system except in the boiler where carbon steel is used. This high pressure steam is used for all utilities and is the sole source of process steam apart from electric steam generators that are used in the autoclaves. The feed water for the process steam is from soft-water, and the return water condensate is treated prior to being re-introduced back into the boilers. Currently pure steam is not available, but plans exist for the installation of a new pure steam generator in the near future.

A RO membrane and recirculating loop system is used to manufacture RO/DI water and is distributed to user sites via a 316L stainless steel piping network. The system was not reviewed in detail, and the design should be reviewed in detail to ensure it conforms to GMP criteria. Water quality will need to be tested to ensure that it meets standards for USP Purified Water.

Process air consists of two (oil-less) piston compressors with oil-vapour filters which generate compressed air for the entire CIGB complex. The air is filtered for particulate through a five micron in line filter and distributed via carbon steel piping system throughout the complex. No provision exists for drying air, apart from this the system appears to be of adequate design for use in GMP manufacturing operations although the quality of the output will need to be tested to ensure that it meets appropriate standards (low hydrocarbons, moisture, and bio-burden).

Zone HVAC units are provided for each area in the HBMF. In the majority of the CIGB complex, air is supplied via ceiling diffusers and returned through room return air ducts. Return air louvers exist in some areas and are located above doorways. Air from the louvers is channelled down area hallways to the air handling system return air plenum.

Liquid waste handling systems for the HBMF process areas are common to the entire CIGB complex. The system consists of a drainage network of piping that is connected to a series of batch kill tanks.

3.11 Utilities

RECOMMENDATIONS

1. Dedicated GMP conforming HVAC systems will be required for all GMP manufacturing areas, including component prep., inoculum prep., fermentation, cell harvest, semi-purification, and purification. These systems should be insulated, double-walled units with proper pre-filtration of air (eg. 30%, 80-85%) capable of both cooling and heating. HEPA diffusers should be installed in all GMP manufacturing areas complete with low returns just above the floor level.

Aseptic processing areas of operation require separation and control depending on the nature of the operation. Exposure areas of particular importance to product quality are "critical" and "controlled" areas.

A critical area is one in which the sterilized dosage form, containers, and closures are exposed to the environment. Critical areas have a Class 100 level of cleanliness, and should be supplied at the point of use as HEPA filtered laminar flow air, having a velocity sufficient to sweep particulate matter away from the filling/closing area. Normally, a velocity of 90 fpm plus or minus 20% is adequate, and air should be of a high quality with an incidence of no more than 1 cfu per 10 cf.

A controlled area is where unsterilized product, in-process materials, and containers/closures are prepared. This includes areas where components are compounded, and where components, in-process materials, drug products and drug product contact surfaces of equipment, containers, and closures, after final rinse of such surfaces, are exposed to the plant environment. Controlled areas have a Class 100,000 level of cleanliness, and a microbial incidence of no more than 25cfu per 10cf.

2. A clean steam generator should be installed which is designed to produce high quality steam for GMP operations. The steam should be generated from treated water that is free of volatile additives such as amines and hydrazines. The steam and its condensate should have the chemical purity that is equivalent to the pharmacopeia grade waters where the condensate is equal to WFI. The clean steam system should be connected to wherever steam enters processing equipment and contamination of the product must be avoided. Plant sizing is important to ensure that consistent steam supplies are available. The piping should be constructed from 316l ss butt-welded and should be of high purity piping design in areas where the potential contact with product fluids exists. Clean steam systems can be shared with non-GMP operations but there needs to be an ongoing sampling and testing program to continuously evaluate the status of this system.
3. A water for injection system is needed in GMP aseptic process areas such as purification where water is used as a solvent for the preparation of parenteral solutions. WFI must fulfill the current requirements for United States Pharmacopeia (USP) purified water, meet endotoxin specification, contain no added substance, and be maintained at correct storage temperatures.
4. A shared RO unit can be used to produce USP purified water for both GMP and non-GMP operations; however, they can not share the same storage tank and distribution system. Therefore, a separate USP purified water storage tank and recirculating loop system will be needed for GMP operations.
5. Compressed air systems can be shared between GMP and non-GMP operations; however, special precautions need to be designed into the system to prevent any potential back-flow (e.g., check valves). Also, there must be an ongoing sampling and testing program to continuously evaluate the status of this system in terms of bio-burden, hydrocarbons and moisture. A air drying system should be installed to maintain moisture content in process air at a pressure dewpoint of -40 degrees C.
6. A dedicated waste collection and kill system is required to prevent cross contamination and back-flow of live organisms between other non-GMP operations.
7. Except for those noted above, all other building utilities can be shared between non-GMP and GMP operations such as chilled water, plant steam (dirty steam), electric power, and emergency power.

Section 4.0 Facility Overview

4.1 HBMF Facility Overview

Facilities design required for manufacturing GMP material must include the principles of proper component, and product, flows which proceed from the dirtiest to the cleanest steps without the two paths crossing. Additionally proper personnel flow must be incorporated into the design to provide flows which proceed from the cleanest areas to the dirtiest without the two paths crossing. In many cases this requires separate corridors for clean and dirty product and glassware to pass, as well as decontamination autoclaves within the production areas so that contaminated materials do not add to the facility or product bio-burden. The layout should be revised to provide for unidirectional flow in the facility, the layout should be designed with the provision of providing efficient material flow, efficient personnel traffic patterns, should utilize "pass thrus" and pipe transfers of raw materials and in-process materials, as well as adhere to NIH, GMP, guidelines and fire prevention codes. In addition regulatory requirements do not allow non-GMP activities to occur within the same space and environment as GMP manufacturing operations. Therefore, it is expected that major facility equipment, and utility upgrades will be needed to bring the GMP component to the HBMF up to these standards. In addition the GMP facility will need to be physically separated from other CIGB manufacturing areas. Areas such as control labs, materials receiving, quarantine, and storage, inoculation preparation, semi-purification, and purification will have to be relocated into one area. Fill and finish facilities can be performed offsite in a GMP facility without compromise. The GMP-HBMF should have its own separate entrances and exits, as well as personnel who are dedicated to the GMP-HB manufacturing operations.

4.2 GMP HBMF Facility Options

It is assumed that the production requirements of the HBMF have not outgrown the capacity of the plant to expand to meet these needs. Three options exist for the planning and design of a GMP-conforming HBMF and are as follows:

- Upgrade existing HBMF areas within the CIGB complex.
- Renovate the existing CIGB complex for GMP-HBMF.
- Construct a new facility for GMP-HBMF.

In order to effectively plan and screen alternatives a strategy must be adopted that takes in consideration the plants current requirements and operations. Currently the CIGB complex is fully utilized with "products waiting for areas". The current HBMF areas are fully utilized as well, and can not sustain product quota's if manufacturing activities were to be disrupted. Therefore revisions must be coordinated within the realm of manufacturing operations to be feasible. Design strategies should:

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- be flexible
- provide expansion potential
- provide ease of maintenance
- take into account construct ability
- take into account economics- initial cost, operating, and maintenance
- have the provision for timely construction / validation
- provide for the removal of equipment in the future
- provide necessary space for operation, cleaning, and maintenance of the equipment.

The need to physically separate the GMP facility from other manufacturing areas and the revisions required to provide adequate flows will have the greatest impact on options available. This requires either building a new facility or renovating the CIGB complex. Thus the option to upgrade existing HBMF areas located throughout the CIGB complex would not achieve a GMP conforming solution and can be ruled out.

Based on the fact that equipment, facilities, and utility systems are currently in place, a phased approach to renovate the existing CIGB complex may be feasible and would require an impact assessment and engineering review. One possible alternative that requires further investigation would involve relocating the Cell harvest and inoculum preparation areas into a renovated fermentation area, and relocating the raw materials receiving, storage, glasswash and support operations into the previous cell harvest area complete with GMP architectural finishes, utilities, clean and return corridors. The mechanical area below the fermentation area could be relocated/modified to enable moving the GMP semi-purification, purification, and shipping operations into the area. This would shorten product transfers and consolidate the manufacturing activities into one area separate from other CIGB manufacturing operations. If it is not feasible to use the mechanical area below fermentation, the existing semi-purification area can be renovated and will accommodate the entire semi-purification, purification and shipping operations complete with GMP architectural finishes, utilities, clean and return corridors. It can be stated again that renovation activities will have significant impact on the manufacturing operation and will limit the possibility of performing this work.

In order to establish a GMP-HBMF the current CIGB complex requires extensive utility, HVAC, electrical and architectural revisions. Thus the potential for constructing a new GMP facility may be feasible, combined with the fact that existing HBMF operations could continue without disruption makes it a viable option. Since it has already been stated that there are products waiting for facilities, relocating Hepatitis B vaccine production out of the CIGB complex would provide additional manufacturing opportunities. If production requirements have outgrown the capacity of the HBMF plant this would provide the opportunity to construct new facilities that would meet current and projected production through-put.

In order to effectively proceed on the viability of the two options a "basis for design" must be

established with all possible scenarios. This would require a brief manufacturing evaluation and assessment, process development, generation of a conceptual design and layout based on the client brief, preparation of a cost estimate, and finalization of conceptual design documentation.

4.3 Preliminary Facility - Construction Costs

Without first developing a Facility Conceptual Design Plan, it is difficult to provide any meaningful cost estimate for the GMP conforming HBMF. Additional information will be required before an accurate cost estimate can be developed, such as a final facility design layout, capital equipment requirements, and an engineering assessment as to what existing equipment and utility systems can be salvaged from the current facility. This project is estimated to take three additional months of with two full time personnel on site. However, a rough estimate can be provided based on cost per sq ft for constructing GMP facilities in North America for similar facilities. Therefore based on the above assumptions as well as the complexity of your facility, the cost per square foot could range between \$250-\$500 USD psf (WHO Certification). This estimate does not include the costs for demolition (local cost), or equipment and utility upgrades.

Concerning construction and validation time schedules, it is reasonable to expect that the construction of a new complex, may take 12-16 months to complete while an additional 6 months will be needed to complete facility and equipment validation work. Again, these are only rough estimates since needed information is lacking to develop more accurate estimates. Also, it has been our experience that construction times can be reduced if modular clean room systems are utilized, which is applicable to both options.

Section 5.0 Facility Design Features for Primary Containment of BL1/2-LS Operations and Clean Room Construction

5.1 Primary Containment BL1/2-LS

It is understood that the HBMF intends to operate their GMP manufacturing facility at BL1/2-LS containment level; therefore, primary process containment will be required when working with genetically engineered organisms. The typical process used for genetically engineered organisms includes certain key items of equipment. These include:

- Fermenters
- Centrifuges and micro filtration
- Cell disrupters

- Chromatography equipment

In general, the primary closed system physically contains the product. Important design features normally considered critical in process design of the primary closed system are:

- **SEALS:** for agitators/pumps/all rotating machinery- use double, liquid or dry mechanical seals. Dry seals are preferred since they are easier to maintain and offer less risk to product contamination. When working with live organisms, a sterile seal flush liquid should be connected to a waste/kill collection system.
- **PROCESS LINES:** all process lines should be free draining, no dead legs, where possible smooth radius bends, with minimum clamps. For BL-2 containment all clamps must have "O"-ring seals. All process lines including exhaust vent lines should be sterilized with saturated clean dry steam for at least 30 minutes at 20 psig minimum. Condensates should go to a kill tank or sanitary collection system.
- **VALVES:** only diaphragm valves should be used in product process lines.
- **INSTRUMENTS:** only instruments with ingold fittings or sanitary clamp connections should be used in product process systems
- **ENTRIES into VESSEL:** in general connections should be sanitary clamp type with "O"-ring seals.
- **AGITATORS:** top drive agitators are preferred to bottom drive systems due to potential of seal leakage. However, magnetic drives are best since they avoid the need for seals
- **SAMPLE PORTS:** sample ports should be designed to contain aerosols, and should be vented through 0.22 micron air filters or contained within bio-safety cabinets. Clean steam is recommended for sterilization
- **TANK VENTS:** all vessels containing live organisms should be vented to atmosphere through 0.22 micron filters (hydrophobic). Vent filters must be capable of steam sterilization. If filters need to be kept dry, then jacketed housings should be utilized
- **CONTAINMENT DIKES:** to handle large tank losses due to rupture, leakage or operator error, dikes must be installed and sized to handle the complete contents to the vessel. Liquid waste must be pumped to waste tank or straight to a batch kill tank.
- **BURSTING DISC/RELIEF VALVE:** these items need to be connected to the waste

kill tank system or directed into the containment dike. Use of relief valves at the vessel should be avoided if possible since they are prone to contamination with dirt and may leak. Use of a bursting disc at the vessel and a relief valve downstream of the bursting disc is a method commonly used to better control the system.

- **ROOM PRESSURES:** room containment is only required for BL-3, but it is recommended that rooms, where live microorganisms may be exposed, be under negative pressure with respect to surrounding rooms.

5.2 Clean Room Construction Design Features

- **CLEAN ROOM ARCHITECTURAL AND FURNITURE FINISHES:** must be non-porous, smooth crevice free (for the purpose of clean ability) The surfaces should be durable, non-chipping, non-flaking, and non-oxidizing, and should be impervious to process chemicals, water, disinfectants and cleaning agents.

- **CLEAN ROOM WALLS:** standard construction is gypsum board with primer, sealer, and epoxy paint; cinder block with primer, sealer, and epoxy paint, prefabricated panels either welded PVC, metal, plastic, or fibreglass.

- **CLEAN ROOM FLOORS:** standard construction is of epoxy resin and aggregated or PVC sheet vinyl cemented and welded with coved corners. The design should be sloped to sealed floor drains (no floor trenches) with coved floor base installed flush within the wall.

- **CLEAN ROOM CEILINGS:** can be either PVC, or epoxy painted panelling; Plaster with primer, sealer, and epoxy paint; or "T" bar ceilings, gasketed and sealed. In component preparation, and purification suites with "critical" processes occurring that can not be performed in a bio-safety hood (class 100 hepa) ceilings should be "total hepa" with tear drop florescent lighting.

- **CLEAN ROOM WINDOWS:** epoxy coated or stainless steel framed with 45 degree ledges installed into the walls with a minimum projection. In critical process areas window construction should be revised to ensure a flush wall in the critical area with sloped sills in adjacent areas of lessor classification.

- **CLEAN ROOM ELECTRICAL:** surface pipes, and wire ducts should be upgraded by installing concealed wiring and flush mounted electrical outlets with stainless or epoxy painted covers caulked to eliminate space between the utility and the wall. All lighting fixtures should be flush mounted caulked and sealed.