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DESIGN OF FILL AND FINISH FACILITY FOR ACTIVE PHARMACEUTICAL INGREDIENTS (API)

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Abstract

Fill and finish operations continue to be one of the most heavily outsourced activities in the biopharmaceutical manufacturing market today. There are a few aspects that need to be consider in outsource activities like logistic, storage condition, facility certification and audit as regulations and standards which the manufacturer should adhere. Risk would be greater and extra care should be taken when outsource from foreign fill and finish facility. Thus, the internal aseptic fill and finish facility with audit checklist will help to minimize the risk during logistic and storage and also minimize the cost for outsource fill and finish facility. The data collections are through survey and conceptual design with simulation as the execution part.

Keywords: Active pharmaceutical ingredients, Aseptic, Design, Facility.

1. Introduction

According to World Health Organization (WHO), Active Pharmaceutical Ingredients (API) is any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. The substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body [1]. There are two classifications of API which are inorganic substances or organic substances that isolated from materials of animal or human origin and synthetic or semi-synthetic or isolated from herbal sources or microorganisms.

Abbreviations

AHU	Air Handling Unit
API	Active Pharmaceutical Ingredients
cGMP	Current Good Manufacturing Product
EMA	European Medicines Agency
EPO	Erythropoietin
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HEPA	High Efficiency Particulate Air
ICH	International Conference on Harmonization
MAL	Material Airlock
MOH	Ministry of Health
NPCB	National Pharmaceutical Control Bureau
PAL	Personnel Airlock
PIC/S	Pharmaceutical Inspection Co-operation Scheme (PIC/S)
QA	Quality Assurance
QC	Quality Control
ROI	Return On Investment
SPAH	Satellite Process Assurance Hub (SPAH)
U SPAH	U Satellite Process Assurance Hub
WFI	Water for Injection
WHO	World Health Organization

For Malaysia, the regulatory pathway and mandatory control of API product is governed by the Ministry of Health (MOH) through the National Pharmaceutical Control Bureau (NPCB) division. The NPCB will reduce the risk of sourcing substandard or contaminated materials. Hence, secure a constant sourcing of active ingredient of appropriate quality which will safeguard the public. Generally for pharmaceutical manufacturing, the activities will be involved are research, development, manufacturing and finally marketing as shown in Fig. 1. In the manufacturing process, it will cover the inbound logistic, bulk active, bulk formulation, filling, packaging and outbound logistic. Based on the flow, it shows an aseptic filling of biologics drugs is one of the most crucial processes in biopharmaceutical manufacturing because it is a highly technique driven processes and have the potential safety impact to the compromised patient. Aseptic filling is an aseptic process that requires close coordination and complex interaction between personnel, sterilized product, fill and finish equipment or system, cleanroom environment and support facilities, as well as the sterilized filling components [2].

When outsource for external fill and finish facility, there are few aspect that need to be consider like logistic, storage condition, facility certification and audit as well as regulations and standards which the manufacturer should adhere. Risk would be greater and extra care should be taken when outsource from foreign fill and finish facility. Integrated bulk manufacturing and fill and finish plant offer huge advantages for the biopharmaceutical products because it deals with the finished product in its most valuable state where the risks of a contamination event or other failure area at their highest. Internal aseptic fill and finish facility will help to minimize risk during logistic and storage, minimize the cost for

outsource fill and finish facility and thus aid to shorten time for drug registration into market for commercialization.

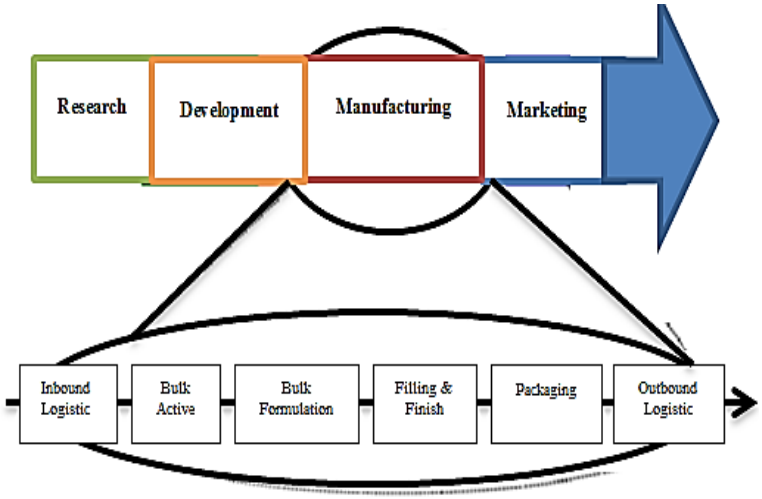


Fig. 1. Overall flow for biopharmaceutical manufacturing.

2. Methods

The data is collected and divided into two sections which are data collection through survey and conceptual design with simulation as the execution part. Both phases are detailed out in Table 1.

Table 1. Outline of project methods and expected outcomes.

Research Layout					
Survey			Execution		
1	2	3	4	5	6
Current plant auditing process and aspects to be inspect by auditor. -Provide checklist for plant audit	Feasibility study -Market and sales projection -Determine plant capacity	Develop flow sheet represent the overall process -Materials, operation conditions and parameters are specify	Perform simulation using SuperPro Designer for fill and finish operation	Process economics -Determine the capital cost estimation, operating cost estimation and profitability analysis	Propose project timeline for plant construction and commissioning

2.1. Survey

To conduct the survey, two data collections are required to establish audit checklist and determination of plant capacity.

To establish the audit checklist, a literature research about Malaysian guidelines for aseptic pharmaceutical facility is conducted by evaluating the premise requirements provided by the Ministry of Health (MOH) through the National Pharmaceutical Control Bureau (NPCB) division. Based on this, the current flow and highlight aspect is list out in a checklist format making the manufacturer easier to plan the intended facility layout thus meet the standard criteria. The audit checklist will also cover on overall good manufacturing practice according to Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme (PIC/S) and International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH). Both guidelines are similar as per European Medicines Agency (EMA) guidelines.

To determine the aseptic fill and finish facility, feasibility study will be conducted to evaluate the market and sales projection of the intended product. Data from the demand and supply of Erythropoietin (EPO) in Malaysia is study based on required injection needed per patient and vial volume. By calculation, estimation of potential quantity of vial production is decide whether with existing manufacturing plant capacity is tolerable or not. Through this, the equipment and machine needed for the dedicated process will be determined.

2.2. Execution

There are two parts to evaluate the execution section. First is to develop the flow sheet which represent the overall aseptic fill and finish process including the define materials, product and personnel flow to ensure no risk of cross contamination. Process for aseptic fill and finish will cover three different lines which are vial filling line, lyophilization or powder line and prefilled syringe line. Decision will make based on the guideline provided by PIC/S and the example of the established fill and finish facility plant. The conceptual layout design of the facility will also relate to the process flow sequence for dedicated line.

The conceptual design for aseptic fill and finish facility is define by knowing the capacity of the plant, process and equipment to layout in the process. After that, simulation will be conducted by using Super Pro Designer (Lite Ed.) software version 8.5, Build 3 by Intelligent Inc. By adding the process steps (unit procedure), the process batch modeling are executed.

Apart from that, cost analysis and economic evaluation will be obtain through Super Pro Designer where the operating cost estimation cover the raw materials, labor, utilities etc. Profitability Analysis will be performed by calculating the gross margin, return on investment and payback time of the proposed aseptic process based on the following formula.

$$\text{Gross Margin} = \frac{\text{Gross Profit}}{\text{Revenues}} \quad (1)$$

$$\text{Return on Investment (ROI)} = \frac{\text{Net profit}}{\text{Total investment}} \text{ x } 100\% \quad (2)$$

$$\text{Payback time (in years)} = \frac{\text{Total investment}}{\text{Net profit}} \quad (3)$$

The project timeline for construction and commissioning of the aseptic fill and finish also will be projected. Based on the Return On Investment (ROI) and payback time obtain, comparison between building an integrated fill in finish facility with the existing manufacturing facility or outsourcing for external fill and finish facility will be made. The decision will be based on the current EPO process for commercialization stage.

3. Results and Discussion

3.1. General requirement

Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme (PIC/S) and International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH) had set out a standard and guideline for premise and APIs which equivalent to EU Good Manufacturing Practice guide [3]. Before plant commissioning, the layout plan must be submitted to the Centre for Compliance and Licensing of NPCB for evaluation.

According to De Carlo et al. [4], the main key facility layout problems are transportation where the cost could be reduced by 10% to 30% annually with efficient facility planning. Effective facility layout also helps to decrease work in process and throughput times where it can simply facilitate the control of information and material flows. Meanwhile, Lamba [5] suggest that preferred layout for a pharmaceutical facilities are segregation between raw materials and final products involving different classes, perform closed operations where possible, ensure orderly flow direction, provide distinct staging areas if required between process steps, cleanable production suites and equipment with suitable environments for controlled areas for storage and process.

In term of external and internal environmental protection, environmental parameters such as temperature, humidity, cross-contamination control must be addressed in facilities dedicated to the manufacture and packaging of APIs [6]. The link between the premises' interior and exterior should be through airlocks which are Personnel Airlock (PAL) and Material Airlock (MAL) change rooms, pass boxes, pass through hatches, etc. These entry and exit doors, for materials and personnel, should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time [7]. Basically, the facility usually will consist of Current Good Manufacturing Product (cGMP) Manufacturing area, Utilities area, Quality Control (QC) laboratories, warehouse as well as administrative offices.

3.2. Design requirement

According to PIC/S Guideline as well as United States (US) Food and Drug Administration (FDA) and EMA Guideline, to maintain cleanliness, the manufacturing staff is required to enter the controlled environment of the process areas through a plant locker and wash up space. Personnel are required to change into appropriate garments. Then, they pass through an airlock to access controlled clean areas such as the preparation area and filing area.

To assure proper flow of equipment and materials, soiled equipment is removed from each suite through an air lock, and is staged in a soiled equipment area before cleaning. Cleaning is done in an equipment washing or glassware washing area, outside the staging area. After being washed, the equipment is stored in a designated clean storage area. Before use, the equipment is sterilized in the autoclave or a depyrogenation oven. After that, leaves the clean equipment area and goes into the production area through air locks.

Once released by QC, the raw materials from the warehouse will enter the production area through air locks into the dry storage area. Nonchemical materials may enter through personnel entrance. Materials are held in dry storage at ambient temperature, or in a cold box until needed in the weighing room. After various components are weighed, the buffers or diluents are prepared in the preparation area. The solutions are then filtered, sterilized, and transferred to next filling process. Solutions can be transferred by aseptic containers, but usually pressure are transferred through piping. Final formulation or finishing operations can be accomplished in many ways, from hand filing operations to semi-automated equipment. Final finishing operations are always conducted under aseptic conditions.

Because the area is clean, particulate-generating or dirty items (such as packaging) should be removed before materials are brought into the formulation or finishing areas. Cardboard boxes containing materials are brought to be filled are moved from the warehouse into the material staging area to be unpacked. All exterior cardboard materials are removed and the plastic-wrapped material is moved next to the washing or sterilization equipment. Shrink wrap and internal cardboard separators are removed at the in the feed tray of the washer or autoclave. Components such as fill heads or tubing that required in the filling suite, are cleaned and sterilized in a double-door autoclave. The second door opens into the cleanroom. Formulation tanks are outside the sterile filling room, in adjacent room. A single fill line passes from the bulk tank into the filling area, where a sterile connection is made with the filling equipment. A local sterile class 100 environment is maintained continuously above the filling and capping operation [3].

If lyophilization is required, filled vials are loaded and a vacuum is pulled within the chamber to remove all moisture from the product. The amount of time required for this operation depends on the amount of moisture to be removed. The materials are then capped and collected into tote bins, placed in cage, and transported to a cold storage box for holding until released by QC. Once released, they are moved into the packaging area for inspection, labelling and final package assembly.

A major design concern for the manufacturing areas is to assure optimal personnel flow patterns and material movement. This is important for efficient operations and for Good Manufacturing Practice (GMP) compliance. GMP requires that separate well-defined areas to be provided for different stages of the manufacturing process. GMPs also require the manufacturing area and each space contained therein, be designed to allow for the orderly arrangement of processing equipment to prevent product contamination or mix-up [8]. Figures 2 and 3 shows example of layout proposes by [6, 9].

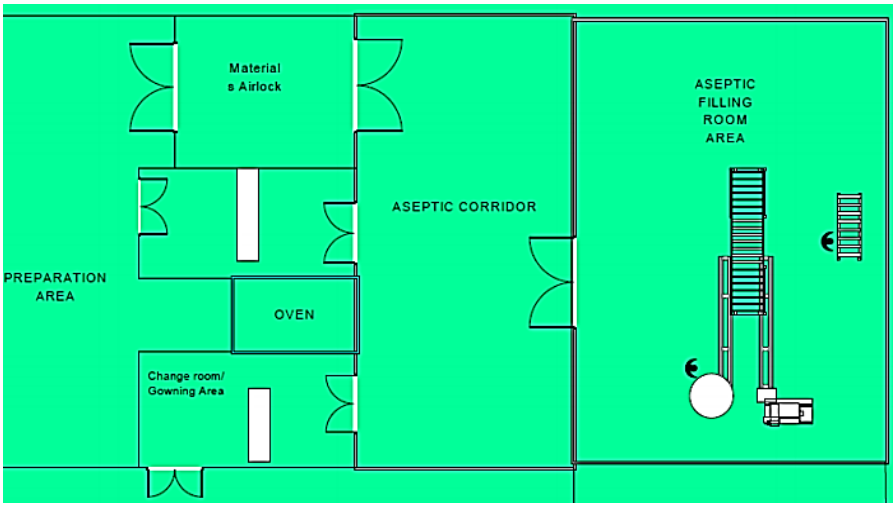


Fig. 2. Example of filling area layout [9].

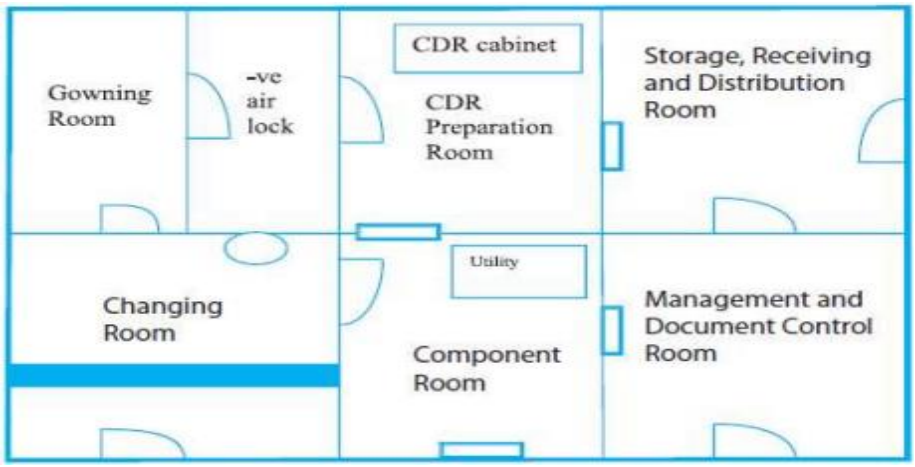


Fig. 3. Example layout plan for cytotoxic drug reconstitution preparation facilities [6].

3.3. Cleanroom classification

Cleanrooms are divided into different classes in standards. The equivalence of classes form different international standards is shown in Table 2. For the manufacturing sterile products, there is certain classification either grade A, B, C or D as per Table 3.

Based on the classifications of the room, there are limits outline by MOH which are particle count limit, microbial limit, temperature, humidity and air pressure differential limit to control the internal and external environmental in the cleanroom. Details of the specification are described in Tables 4, 5 and 6.

Table 2. Classification of clean areas [2].

WHO GMP	US 209E	FDA categories	ISO/TC (209) 14644	EU annex 1: 4 categories (A-D)
Grade A	M 3.5	Class 100	ISO 5	Grade A (Critical 100)
Grade B	M 3.5	Class 1 000	ISO 5	Grade B (Aseptic 100, non-unidirectional)
Grade C	M 5.5	Class 10 000	ISO 7	Grade C (Controlled 10 000)
Grade D	M 6.5	Class 100 000	ISO 8	Grade D (100 000)

Table 3. Terminally sterilized products [10].

Grade	Example of operation
A	Filling of product, e.g.: aseptic preparation and filling
C	Preparation of solutions e.g.: preparation of solution to be filtered
D	Preparation of solutions and components for subsequent filling, e.g.: handling of components after washing

Table 4. Particle count limit for cleanroom [6].

Grade	At Rest		In Operation	
	Maximum permitted number of particles/m^3 equal to or above			
	>0.5 µm	>0.5 µm	>0.5 µm	>0.5 µm
A	3,520	20	3,520	<5
B	3,520	20	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520	20	3,520	<5

Table 5. Recommended limits for microbial contamination in the operation state [6].

Grade	Recommended limits for microbial contamination			
	Air sample cfu/m^3	Settle plates (diam,90 mm) cfu/4 hours	Contactplates (diam,55 mm) cfu/plate	Glove print 5 fingers cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Table 6. Temperature, humidity and air pressure differential limit [6].

Room	Temperature (^{0}C)	RH (%)	Adjacent room	Differential Pressure (Pa)
Preparation	20 ± 2	55 ± 5	Gowning	+ (10-15)
Comp. Preparation	20 ± 2	55 ± 5	Changing	+ (10-15)
Gowning	20 ± 2	55 ± 5	Changing	+ (10-15)
Changing	20 ± 2	55 ± 5	Outside	+ (10-15)

According to Kitain [10], in order to reach the B, C, and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as High Efficiency Particulate Air (HEPA) for grades A, B, and C. For class D in operation, where the permitted particles number is not specifically define, just an appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, operating procedures should prescribe corrective action.

3.4. Filling process flow

Process flow must be separated from all other flows of people, raw materials, supplies and utilities. The greater the separation, the more likely the product purity and quality is maintained. The process and personnel flows within the production suite should allow for easy removal of rejected product without need to leave the suite or require other personnel to enter the suite simply to remove the rejected product. A separate passage, accessible form the suite should be considered.

A similar concept can be used for product passing from one production suite to another for next process. The use of product passage will allow production cleanliness in both suites to be maintained. Personnel can pass completed product to the passage, sample be evaluated and remove if rejected. Once the production is completed, product needs to be held in a quarantine area until QC evaluation and release.

The product flow should progress from the receiving of the materials through the production process, and finally shipping area. The path should be linear, continuous in one direction without backtracking to assure that contamination does not occur by mixing up released and rejected materials.

3.5. Personnel flow

Personnel flow is unlikely to parallel product flow. Product flow is located in the production area with prescribed path. Personnel flow occurs throughout the facility, with differing intensities and paths. People cross the boundaries of different areas, from production to administration, warehouse and lab. The most common paths of travel must be identified based upon the strongest adjacency and daily communication. The critical paths must be given top priority to minimize both travel time and interference with other operations. The number, frequency and distance personnel trips must be considered as the priorities are

established. As part of aseptic control, gowning rooms play a critical role in the facility layout since operator needs to wear dedicated cleanroom clothing which design to limit the rate of particle generation from the person. Usually two grades (levels) of changing rooms required: low for changing from normal clothing (street clothes) to factory (clean) clothing and high for changing from clean clothing to full coverage suit [9].

3.6. Product flow

The primary concern of a biotechnology is the integrity of the product start from the material delivery to final manufactured product shipment. Well defined flow paths enhance the ability to maintain the product integrity, reduces potential of contamination and mix-up of materials and products. Raw materials classified in several distinct categories quarantine, approved and rejected within the facility at the same time based on QC testing. The flow of raw materials and products through the facility should follow the production process. The flow should be arranged to eliminate backtracking and crossing paths, thus avoiding point of contamination. As quarantined as a rejected material without crossing the production material flow pattern.

Cunnigham [11] propose example design in Genentech's fill finish facility in Hillsboro, Oregon as per Fig. 4 where the design considering manufacturing process moves materials, equipment and personnel in a simple uni-directional flow, reducing the chance for cross-contamination. The product and materials entering through warehouse, moving 3 level manufacturing building and then stored in the distribution center prior to be distributed. Fill suites and inspection areas were positioned adjacent to each other with view windows to facilitate easy communication and monitoring the process.

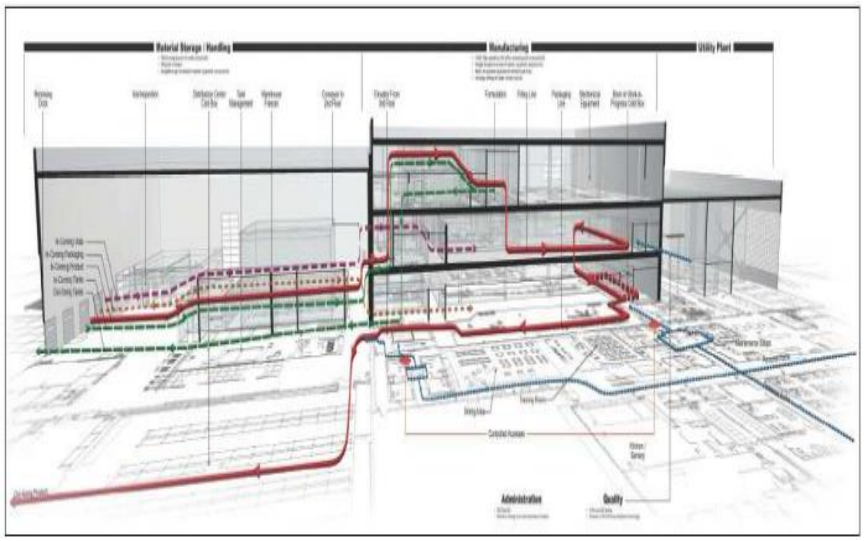


Fig. 4. Uni-directional flow of product and materials [11].

3.7. Material flow

As part of GMP requirements, raw materials must be kept separate from in-process materials and finished product to avoid mix up. Thus, raw materials should be received in an area separated from finished product shipping. Material flows considered the raw materials, finished goods, waste, product (in-process, intermediate and final) as well as equipment that either clean, dirty as well as containers [9] as illustrated in Fig. 5. The raw materials must be held separately until QC samples and verifies then. Once released for production, materials should be separated from rejected materials. The rejected materials must be kept separate from all other materials to eliminate the possibility of contamination of to release materials. Once raw materials are released for production, they are placed in the process circulation flow.

The layout of facility should consider the process flow, material flow and personnel flow to minimize risk of contamination or cross contamination have clear material and personnel flows (unidirectional whenever possible) with unambiguous definition of the GMP zones thus separate clean and dirty items [5]. As suggest by Manfredi [9], Fig. 6 shows the desired and less desired layout plan for a facility.

3.8. The combinations of all flow direction

Figure 7 shows the overall aseptic fill and finish process flow for three different lines of final product type to be manufacturer which are vial, lyophilization and pre-filled syringe. Each process step required different cleanroom classification for operation depends on the criticality and guideline requirement [10]. To assist on plant layout, the process step area is differentiate by color: gray for Grade A, red for Grade C and green for nonclassified.

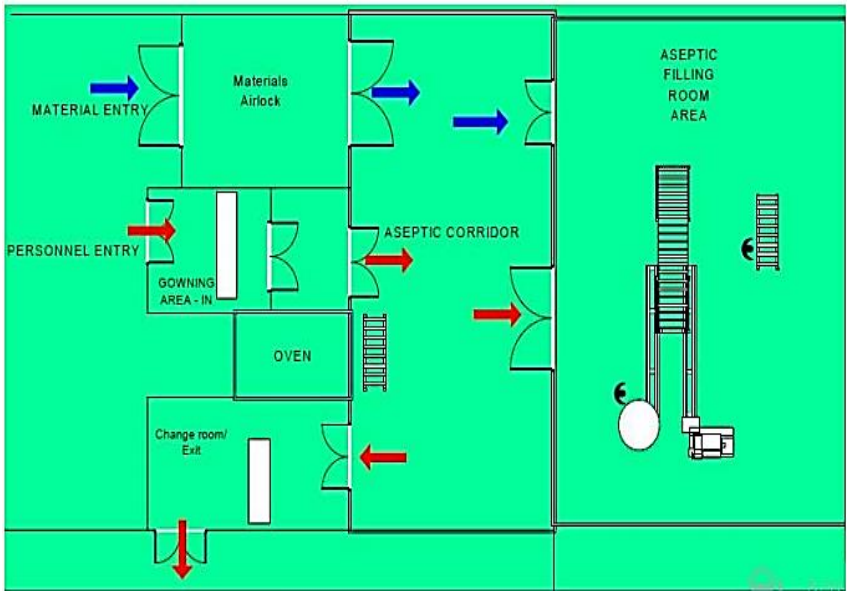
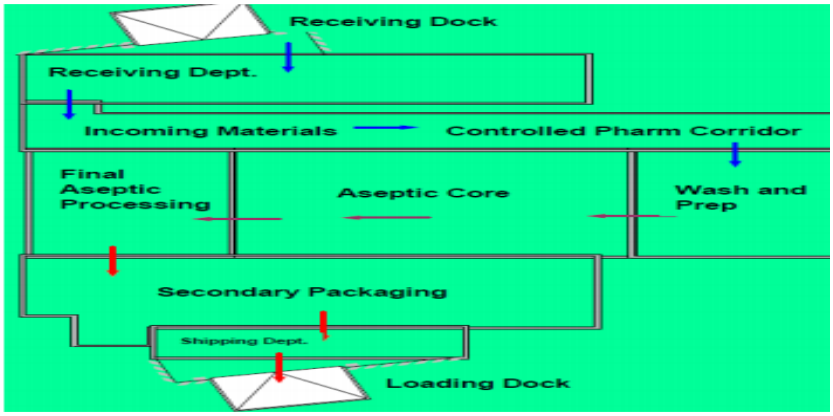


Fig. 5. Example of material and personnel flow [9].



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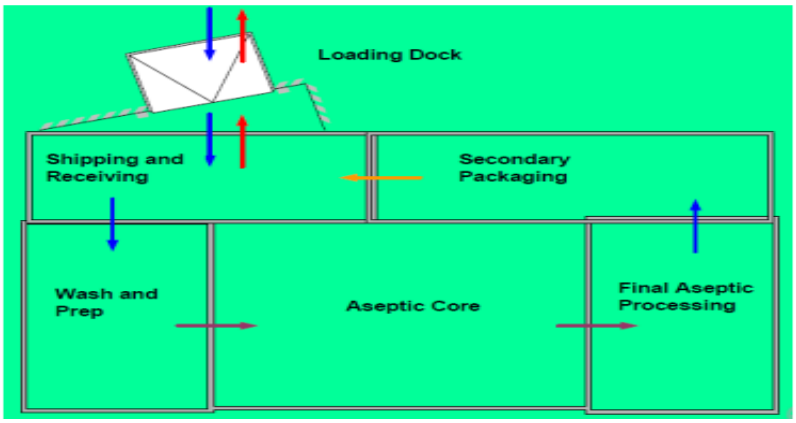


(b)

Fig. 6. Facility layout option after considering process, material and personnel flow: (a) Desirable layout (b) Less desirable layout.

The new aseptic fill and finish facility will be in two level modular plant comprises of receiving area, formulation buffer preparation area, fill and finish manufacturing area, distribution area, utilities area, QC laboratories as well as the administration office. The design follow Satellite Process Assurance Hub (SPAH) method by applying U shape layout where the manufacturing suites and inspection areas were positioned adjacent to each other with view windows to facilitate easy communication and monitoring of the process. This concept of control hub overlooking production suites apply in design is suggested by Brocklebank et al. [12] will help to ensure production process safety, compliance and quality.

Apart from that, the raw materials and finished goods loading areas location are separated to eliminate mix-ups. There will be an area for preparation of materials to be used in the manufacturing processes such as vial and stoppers, and these materials will be prepared in advance through cleaning and sterilization processes in a Grade C cleanroom.

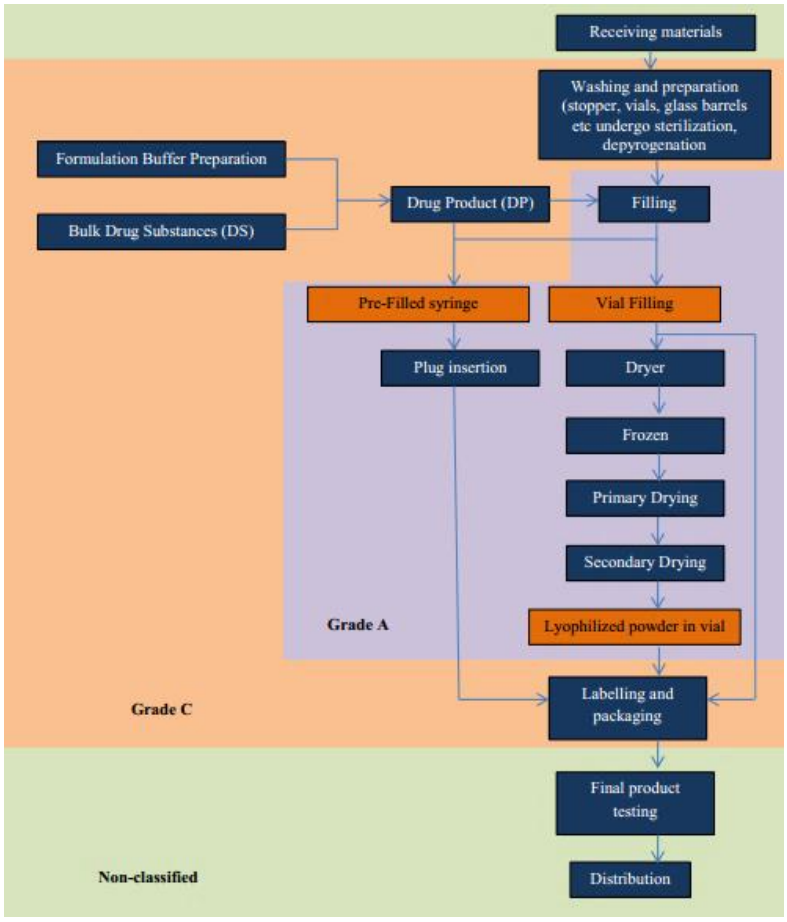


Fig. 7. Overall process flow.

Figures 8 and 9 detail out the proposed floor plan for both first and second floor. The first floor will consist the main operation area: receiving area, manufacturing area, distribution area and parts of administration office exclusively for Quality Assurance (QA) personnel. The receiving area in the first floor will be dedicated only for raw materials like stoppers, vials, syringe, and plungers excluding chemicals in a non-classified room. Meanwhile the manufacturing area will be divided into Grade C and Grade A based on process requirement as per Fig. 7. Once materials (stoppers, vials, syringe, plunger, etc.) are received, they will be sterilized and depyrogenated in a dedicated washing and preparation area, Grade C cleanroom. Then, operator will load the required materials at the dedicated filling line and the aseptic filling process will begin automatically in isolator (Grade A), where operator only controlled using HMI of the machine. Once the process completed, final drug in dedicated packaging will be store in the distribution area in a cold room (Grade C) at temperature range from 2 °C to 8 °C.

Meanwhile in the second floor, there will be another receiving area, final formulation buffer preparation area, QC laboratories, utilities area and administration offices to accommodate all administration matters with regards to the manufacturing processes and the products. The receiving area in the second

floor is dedicated only for chemicals storage where after loading from supplier, the materials will be transfer through lift to second floor. This will be easier for chemicals transfer during formulation buffer preparation. After bulk drug substance and buffer are mixing and filtered in the preparation room (Grade C), the final formulated API will be transfer through piping to manufacturing area in the first floor. Any in-process, release testing, stability testing and routine analytical testing will be conducted in the dedicated QC laboratories. Meanwhile the Air Handling Unit (AHU), black utilities, Water for Injection (WFI), pure steam, compressed air, nitrogen gas, etc. will be located at the utilities area (non-classified room) adjacent to QC laboratories.

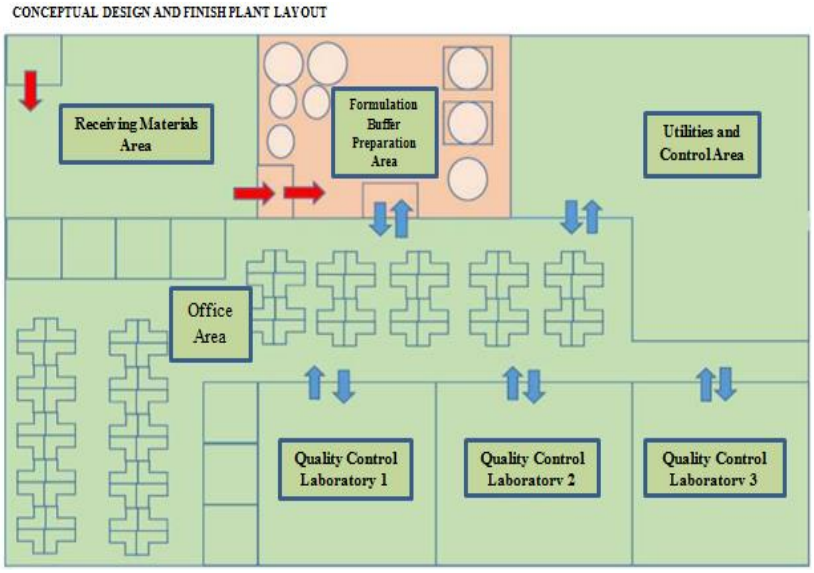


Fig. 8. Upper floor (Level 2) layout.

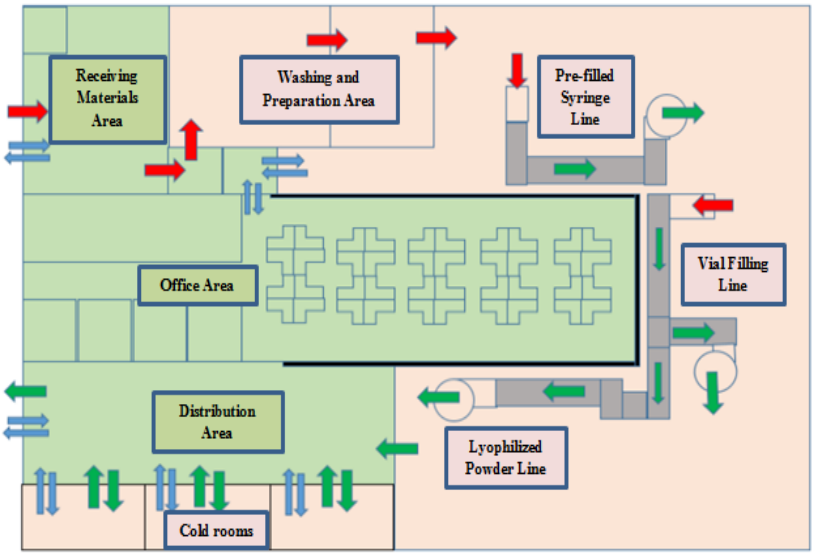
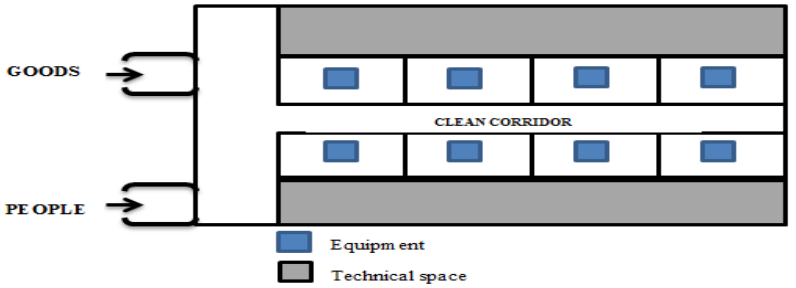


Fig. 9. Ground floor (Level 1) layout.

Based on the process sequence, materials, product and personnel flow are design to be in unidirectional flow as per suggestion to eliminate backtracking and crossing paths, thus avoiding point of contamination. Lamba [5] and Manfredi [9] suggested to differentiate receiving area and final product distribution area to avoid the cross contamination which had been implemented in this facility design. The flow direction for materials, personnel and product are detail out in Fig. 7 and 8 below using colour coding: green for product flow, blue for personnel flow and red for material flow.

3.9. Plant layout option

Brocklebank et al. [12], proposed a hub facility arrangement where the facility concept was developed by adopting an overall U flow of materials and process operations around a central spine designated as U Satellite Process Assurance Hub (U SPAH) as illustrated in Fig. 10 below. Material handling and production operations are 'wrapped' around the central spine which provides access for people. This concept adopt an overall unidirectional materials flow through the plant starting with raw materials in and final product out, maximize technical space adjacent to production rooms, avoidance of separate upper floor technical area above all of the facility footprint and close adjacency of the QC/QA laboratory to all operations. This concept also suggested by Lamba [5] as per layout plant of EISAI Pharmatechnology and Manufacturing at Vizag.



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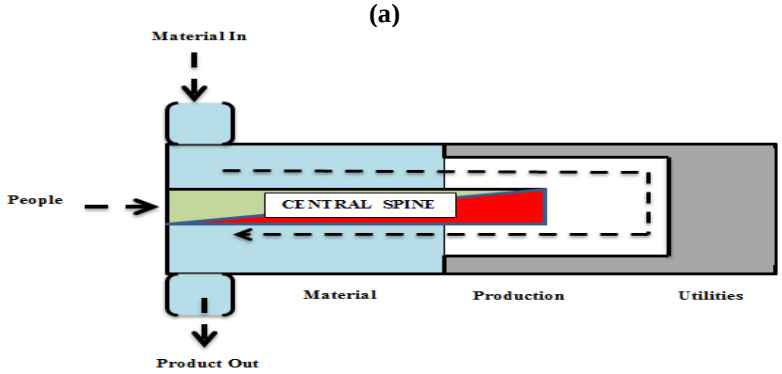

(b)

Fig. 10. Comparison between (a) typical production suite arrangement and (b) U SPAH concept.

Cunningham [11] suggest that a single building that housed all the facilities under one roof instead of multiple buildings scattered around the campus would reduce the travel and circulation time between different area of the building thus condensed the building's footprint to save construction dollars. However, facility at EISAI Pharmatechnology and Manufacturing build with QA/QC laboratories, drug product facility, administration and pilot plant scattered around the campus [5]. Table 7 indicate the different between conventional facility features and SPAH as suggested by [12].

Table 7. Comparison between conventional and U SPAH facility.

Features	SPAH	Conventional
Control hub overlooking production suites	Available for monitoring production process for safety, compliance and quality.	Not available
Plant layout direction	Unidirectional U-shaped layout of production suites according to process flow which more efficient and ergonomic operations.	Unidirectional, usually not in a compact U-shaped flow.
QC laboratory location	Close proximity to production suites thus speeds up QA time	Usually not in close proximity, scattered around campus
Raw materials and finished goods loading areas	Separated to eliminate mix-ups	Usually shared areas
Viewing gallery	Non-intrusive visitor viewing	Usually not available
Security hub	One cost effective security hub (concentration) at the entrance monitoring both material and people flow.	Material and people flow entrances and exit are not in close proximity to facilitate one security hub.
Technical corridor location	Wrap around production suites along perimeter of plant create non-intrusive maintenance of thru-the-wall process equipment	Usually not wrapped around

3.10. Audit checklist for aseptic fill and finish facility

Based on Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme (PIC/S) and International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH) guideline for premise, an audit checklist as Table 8 is shown as an outline to assist manufacturer in ensuring layout plant and facility comply with NPCB expectations. Thus this will help to reduce corrective action needed after audit and aid to shorten the time before obtaining manufacturing license.

Table 8. Audit inspection checklist.

Scope of audit	Compliance to PIC/S requirements	**Audit No.**		
Auditor/s		**Date Start/End**		
Auditee/s		**Inspection Type**	Annual	[ ]
Premise			Re-inspection	[ ]
Product Manufacture			Pre-licensing	[ ]

No.	Requirements	Reference	Observations
1.	**General**		
	Floor plant of facility, classification of production areas, flow patterns for personal, raw materials, product and waste for production area	PIC/S G. 3.1 -3.7; Part II 4.1;Annex 2, 5-18	
2.	**Personnel**		
	No. of staff, Organizational chart, Responsibilities, Qualifications, Experience, Hygiene concept, Medical Check-up/Monitoring Program	PIC/S G. 2.8; 2.9; 6.6 ICH Q7 3.1; 3.2	
3	**Training, awareness & competency**	PIC/S G. 2.6. viii; 2.8;2.9; 2.10; 2.20 ICH Q7 3.1	
	Identification of training needs, On job training, Training program, Standard Operating Procedures, Training Records, Evaluation of Training Effectiveness		
4.	**Process Equipment**		
	Calibration, Preventive Maintenance, Cleaning, Schedule, Equipment history, Log, Updated List, ID Registration, Usage Records, Product Change Over, Computer-controlled systems	ICH Q7 5.2	
5.	**Validation of Critical Equipment**		
	Qualification, Design Qualification, Installation Qualification, Operational Qualification, Process Qualification, Revalidation/Requalification, Specification, Acceptance Criteria, Process Validation, Cleaning Validation	PIC/S G. 2.6. vii; G. 3; 3.37 ICH Q7 12.1-12.7	
6.	**Process Control**	PIC/S Annex 2. 34-40; 41-44 Annex 18. 6; 7; 8; 12 ICH Q7	
	Area Line Clearance, Monitoring Data on conductivity, pH, Non-CIP Cleaning Validation, Cleaning Validation data, Swabbing, Total Organic Compound, Sterilization In Place Validation, Temperature, Sterilization method,		

	aseptic proof, media hold test	18.1; 18.3; 18.4
7	**Environment Control** Cleaning, Housekeeping, Method, Procedures, Equipment, Materials used, Cleaning Sanitizing Agent, Pest Control System, Monitoring and Schedule	PIC/S Part II 4.7 ICH Q7 4.7
8.	**Documentation and Records** Structure, Format, System, Controls Archive, Authorization, Numbering System, Distribution, Return, Revision, Equipment Cleaning and Usage, Batch Manufacturing Records, Back up files, Deviation, Corrective Action and Preventive Action, Change Control	PIC/S G. 4.1-4.11 ICH Q7 6.1- 6.3
9.	**Samples** Samples Handling, Labelling, Transfer, Distribution, Samples Tracking	PIC/S G. It. 6.4. PIC/S G. 64; 6.14 ICH Q7 7.3- 7.5
10.	**Packaging and Labelling Operation** Control, Mix-up prevention, labelling details	ICH Q7 9.1; 9.2; 9.4
11.	**Label Issuance and Control** Area access authorization, Procedures, Receipt, ID, Quarantine, sampling, testing, release, handling, Obsolete, Printing device control, Printed label specifications	ICH Q7 9.1; 9.3
12.	**Storage and Distribution** Separate storage, Authorization, Temperature and Relative Humidity control, Distribution procedure, Contractor/supplier	ICH Q7 7.4; 10.1-10.2

4. Fill and Finish by Using Superpro Software

The filling process to generate 5ml of final drug product with 5 g/L concentration is established. The base case process is vial (liquid) and pre-filled syringe line that yield an amount of 22,650,025 vials entities per year in 453 maximum batches carried out annually. Since the process of lyophilisation is needed to change the drug product from liquid in to lyophilized powder form, the process require additional equipment cost and had reduced the batch time and the annual rate to 82 batches with 4,100,005 vials entities per year only.

From the economic perspective, the investment cost of liquid filling in vial and pre-filled syringe are lower compare to powder lyophilized form filling. Consideration in order to determine the benefit on long term basis is based on Table 9 below that summarizes the overall comparison.

Based on Table 9, the payback time is only within one year of plant operation for liquid filling in vial and syringe with lower capital investment. Therefore, in constructing the new fill-finish facility, only liquid filling in vial and pre-filled syringe line will be completely build in. Meanwhile, the dedicated area adjacent to the two lines will be reserved for extension for powder lyophilized filling line.

Table 9. Comparison of economic evaluation for three simulation processes.

Parameters	Vial (Liquid)	Syringe (Liquid)	Vial (Powder)
Total Capital Investment (RM)	311,485,720	327,621,840	427,565,320
Operating Cost (RM/yr)	132,197,520	309,458,240	78,514,800
Revenues (RM/yr)	659,568,000	989,352,000	358,176,000
Cost Basis Annual Rate (Vial/yr)	22,650,025	22,650,025	4,100,005
Gross Margin, %	79.96	68.72	78.08
Return On Investment, %	106.53	129.22	44.29
Payback time (years)	0.94	0.77	2.26
NPV, at 7% interest (RM)	2,500,494,360	3,247,280,400	1,238,480,880

5. Conclusion

Fill and finish plant offer huge advantages for the biopharmaceutical products because:

- It deals with the finished product in its most valuable state where the risks of a contamination event or other failure area at their highest.
- Process for aseptic fill and finish will cover three different line which are vial filling line, lyophilization or powder line and prefilled syringe line. The decision will based on guideline provided by PIC/S and example fill and finish facility plant that already establish.
- This internal aseptic fill and finish facility would also add value to the existing facility and also will make profit because it can be outsource to other company.
- Due to the excess amount of vials produced per year, vials are able to market outside Malaysia specifically in ASEAN and OIC countries.

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