Title: Designing a Good Manufacturing Practices (GMP) Certified Manufacturing Unit for Halal Products in Gambang

ABSTRACT

An industry is a most important aspect in order to increase the economic status. Industry can also define as a basic category of business activity. Therefore, it is a need for Gambang area to have one industry based on HALAL product due to development of population. This paper is written out to design a Good Manufacturing Practices (GMP) certified manufacturing unit for halal products in Gambang. For pharmaceutical manufacturing unit, there are some requirements for complimentary medicines. They are quality management, personnel, premises & equipment, documentation, production, quality control, contract manufacture & analysis, complaints & recall and self inspection. The GMP scheme contains requirements and conditions for the safety of the manufacturing unit besides ensure the quality of the product. A standard GMP manufacturing unit has many benefits. Firstly, the GMP manufacturing unit can supply medical needed in a very large quantity. Secondly, the standardize from GMP regulation will provide a quality product that will ensure the health of people. Third, there will be a lot of job to be fulfilled by people in order to reduce unemployment problems in Malaysia. This GMP manufacturing unit can be done by two methods. First is by doing research and second is by doing industrial visit to get real surrounding of an industry. This research is very suitable to be done in Malaysia based on demanding on pharmaceutical needed. In order to reduce our dependence on other

country for supplying the medical needed, we should have ours. Hence, a GMP manufacturing unit is the most suitable to accommodate out medical needed.

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CHAPTER ONE

INTRODUCTION

Title: Designing a Good Manufacturing Practices (GMP) Certified Manufacturing Unit for Halal Products in Gambang

1.1 Background of study

GMP stands for Good Manufacturing Practices and refers to the standards set by the United States Food and Drug Administration, FDA. Sometimes it also referred to as ‘cGMP’. The ‘c’ stands for ‘current’. GMP can be divided into four parts. They are Personnel, Premises, Equipment and Sanitation &Hygiene. This study of GMP manufacturing unit is started by investigation on pharmaceutical needed. Based on population in Gambang, Pahang, most of them are Muslim and need pharmaceutical products. That’s why this GMP manufacturing unit will be designed based on HALAL gel capsules.

Basically, GMP manufacturing unit is an overall regulation for all kind of industries. In this research, researcher only takes one part on manufacturing unit. Meanwhile, for HALAL products are the main production of the project.

1.2 Statement of Problems

'If you look at the human condition today, not everyone is well fed, has access to good medical care, or the physical basics that provide for a healthy and a happy life.'(Ralph Merkle). This situation shows that everyone in this world did not have enough medical care. This problem not just happens in Gambang Pahang. Actually, most developed country has to face the pharmaceutical crisis in order to ensure the wellness of the ecosystem. As one of living place among Universiti Malaysia Pahang students, this student and staff are facing this problem.

Based on the observation that researcher has made the pharmaceutical needed is most important to guarantee healthier life among students and staff. Furthermore, Universiti Malaysia Pahang only has one small clinic protect almost three thousand students and staff. Eventually, there are no places that can supply pharmaceutical needed in Gambang area. Since this happen, the problem might become worst. Hence, this paper is discussed about the designing of one manufacturing unit to produce HALAL products which follows GMP procedures in order to find an effective solution for this recent problem.

1.2.1 Research Objective

The objective of this research paper area follows:

1.3.1 To design a manufacturing unit of HALAL products in Gambang area which follow Good Manufacturing Practices (GMP) regulations.

1.3 Scope of Study

The scope of this study is to design a manufacturing unit that will produce pharmaceutical products. Basically, the method that will be used for designing a manufacturing unit will be divided into two parts. First is by doing research and literature review. Second task is by investigating the real manufacturing unit especially in Malaysia.

1.4 Expected Outcomes

This research is conducted in order to provide a HALAL pharmaceutical manufacturing unit in Gambang area. Besides that, this research will increase the economy development due to job opportunities for all citizens.

1.5 Significant of Proposed Study

A standard GMP manufacturing unit has many benefits. Firstly, the GMP manufacturing unit can supply medical needed in a very large quantity. Secondly, the standardize from GMP regulation will provide a quality product that will ensure the health of people. Third, there will be a lot of job to be fulfilled by people in order to reduce unemployment problems in Malaysia. Forth, GMP manufacturing unit will increase the stability of economic.

1.6 Conclusion

This research is very suitable to be done in Malaysia based on demanding on pharmaceutical needed. In order to reduce our dependence on other country for supplying the medical needed, we should have ours. Hence, a GMP manufacturing unit is the most suitable to accommodate out medical needed.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

GMP is an efficient and effective way of accomplishing a task based on repeatable proven procedures. For pharmaceutical manufacturing unit, there are some requirements for complimentary medicines. They are quality management, personnel, premises & equipment, documentation, production, quality control, contract manufacture & analysis, complaints & recall and self inspection. The GMP scheme contains requirements and conditions for the safety of the manufacturing unit besides ensure the quality of the product.

In the last decades, monoclonal antibodies (mAbs) have become increasingly important in terms of medical research, diagnosis, and therapy. They constitute more than 30% of total biopharmaceutical production (Rodrigues M. E et al., 2009). Georges Kohler and Cesar Milstein was the first people who produce the monoclonal antibodies in 1975. Most antibodies used in cancer diagnosis and therapy are derived from the IgG isotype. An IgG isotype antibody consists of two antigen-binding fragments (Fabs), which are connected via a flexible (the hinge) to a constant (Fc) region (Binyamin L, 2006). Now people can get another new technology in pharmaceutical field which is much better in curing the diseases.

Table 1 : Monoclonal Antibodies Approved for Clinical Application Until 2009, (Rodrigues M. E et al., 2009).

Product	Company	Clinical Indication	Approval
ORTHOCLONE	Ortho Biotech	Acute kidney transplant rejection	1986
OKT3®		Heart transplant rejection, liver transplantation	1993
REOPRO®	Centocor/Eli Lilly	Percutaneous transluminal coronary angioplasty	1994
PANOREX®	Centocor/GlaxoSmithKline	Colon cancers	1995
ZENAPAX®	F. Hoffmann-La Roche	Acute kidney transplant rejection	1997
MABTHERA®/ RITUXAN®	Biogen IDEC/Genzyme/F. Hoffmann-La Roche	Follicular CD20 positive non-Hodgkin's B-cell lymphoma (NHL), non-Hodgkin's B-cell lymphoma (NHL)	1997
		Rheumatoid arthritis (RA)	2006
SIMULECT®	Novartis	Renal transplant rejection	1998
SYNAGIS®	Abbott/MedImmune	Respiratory Syncytial virus Disease	1998
HERCEPTIN®	F. Hoffmann-La Roche/Genentech	Metastatic breast cancers overexpressing ERBB2	1998
REMICADE®	Centocor	Crohn's disease	1998
		Ankylosing spondylitis, psoriatic arthritis, ulcerative colitis	1999
		Rheumatoid arthritis (RA)	2001
MYLOTARG®	Wyeth	Acute myeloid leukemia	2000

CAMPATH® / MABCAMPATH®	Berlex / Genzyme / Millennium	B cell chronic lymphocytic leukemia	2001
HUMIRA® / TRUDEXA®	Abbott	Psoriatic and rheumatoid arthritis	2002
ZEVALIN®	Biogen IDEC / Schering AG	Non-Hodgkin's B-cell lymphoma	2002
RAPTIVA®	Genentech / Merck Serono International / Xoma	Psoriasis	2003
XOLAIR®	Genentech / Novartis / Tanox	Allergic asthma, severe persistent asthma	2003
BEXXAR®	GlaxoSmithKline / Corixa	Follicular CD20 positive non-Hodgkin's	2003
		B-cell lymphoma (NHL)	2004
AVASTIN®	Genentech	Metastatic colorectal cancers, metastatic non-small-cell lung cancers	2004
ERBITUX®	Merek & Co / ImClone	Metastatic colorectal cancers	2004
TYSABRI®	Biogen IDEC / Elan	Multiple sclerosis	2004
THERACIM®	YM BioSciences	Glioma cancers	2004
VECTIBIX™	Amgen	Colorectal cancers	2006
LUCENTIS®	Genentech / Novartis	Neovascular age-related macular degeneration	2006
SOLIRIS ™	Alexon	Paroxysmal nocturnal hemoglobinuria (PNH)	2007
CIMZIA ®	Celltech, UCB	Crohn's disease	2008

2.2 GOOD MANUFACTURING PRACTICES

GMP manufacturing unit was the only manufacturing unit that follow standardize of GMP regulations. Therefore, the production of medical need from this GMP manufacturing unit will be ensuring in their quality and safety. Good Manufacturing Practices are standard guidelines set out by the FDA to ensure drug development is carried out in safe and quality processes, to avoid contamination and ensure repeatability. Here, the medical supply will be less contaminated in order to people supplement.

According to Dias M.A.C *et al*. (2012), the implementation of GMP took place with the creation of a multidisciplinary team and it was carried out in four steps: diagnosis, report of the diagnosis and road map, corrective measures and follow-up of GMP implementation. The research in based on the implementation of good manufacturing practices in a small processing unity of mozzarella cheese in Brazil. GMP implementation was done in order to avoid or reduce the contamination of the products. General measures to be implemented by food industry accomplish with GMP as described by *Codex Alimentarius* include: hygiene in the primary production, hygiene design of equipment and facilities, control of operations, maintenance and sanitation practices, personal hygiene, transportation, product information and consumer awareness and training. The implementation of GMPs is a continuous process based on the management concepts of the PDCA cycle (plan, do, check and action).

According to Beaumont N. et al (2005) who had made a research on Best Practice in Australian Manufacturing sites has review that best practices can be divided into some components. They are continuous, simultaneous improvement in cost, quality and delivery, closer link with supplier and customer's effective use of technology for strategic advantage, flatter organizational structures, greater flexibility and preparedness to adopt structures and

processes to changed circumstances, human resource policies promoting continuous learning, teamwork, participation and flexibility and comparison of performance with similar firms. There are three aspects of Best Practices:

1. Operational Best Practices: Optimize operations on the factory floor. The objectives are usually tangible and include direct cost minimization, quality and on-time delivery.
2. Internal Best Practices: Optimizes the manufacturer's structure, staffing, systems and culture so that manufacturing strategy is optimally expressed. If, for example, customers services is emphasized, customers will be able to order through web pages, these orders will be made available to factory schedulers instantly, there will be sophisticated scheduling and order tracking systems: and flexible manufacturing systems.
3. External Best Practices: (a) Optimizes relations with external parties, especially customers and suppliers. (b) Obtains required resources (e.g. raw materials and labour) on the best possible terms and conditions. (c) Sells finished goods on the best possible terms and conditions.

Table 2: Component of manufacturing Best Practices (Beaumont N. 2005)

Element	Components
Manufacturing Strategy	Planning, manufacturing structure, factory operations.
Manufacturing Practice	Leadership, management of people, customer focus, quality of process and product, benchmarking, technology.
Manufacturing Outcomes	Cost, quality, flexibility. Timelines, innovation. Barriers, teams, competitiveness.
Business Performance	Sales, exports, employment, market share, cashflow.

According to Santana N.G, (2009) which have some research about good manufacturing practices in public school catering in Brazil. The aim for the investigation was to evaluate the food safety of the services used to prepare the free meals in Salvador, Brazil and to adopt good manufacturing practices (GMP) in order to assure a safe supply of food for students. It concludes that it is necessary to introduce GMP in these facilities in order to ensure safe meals for students. For adoption of good manufacturing practices, it was divided into four parts.

1. Educational training

Food safety, hygiene and good manufacturing practices (GMP) were introduced. Discussion about the major problems in the school meals preparation areas and suggestions for correction and improvement were prompted. Then, the food handler's behavior at the workplace was monitored for one week.

2. Cleaning and Sanitizing

These steps were monitored by visually inspecting for organic material after cleaning and sanitizing utensils.

3. Personal hygiene

Sanitation supplies including disposable gloves, disposable masks and antiseptic agents were obtained and introduced into the cafeteria.

4. Monitoring time and temperature

The time and temperature were monitored by inserting a thermometer into foods during all stages of the preparation and distribution. Measuring started as soon as the last food transformation was completed.

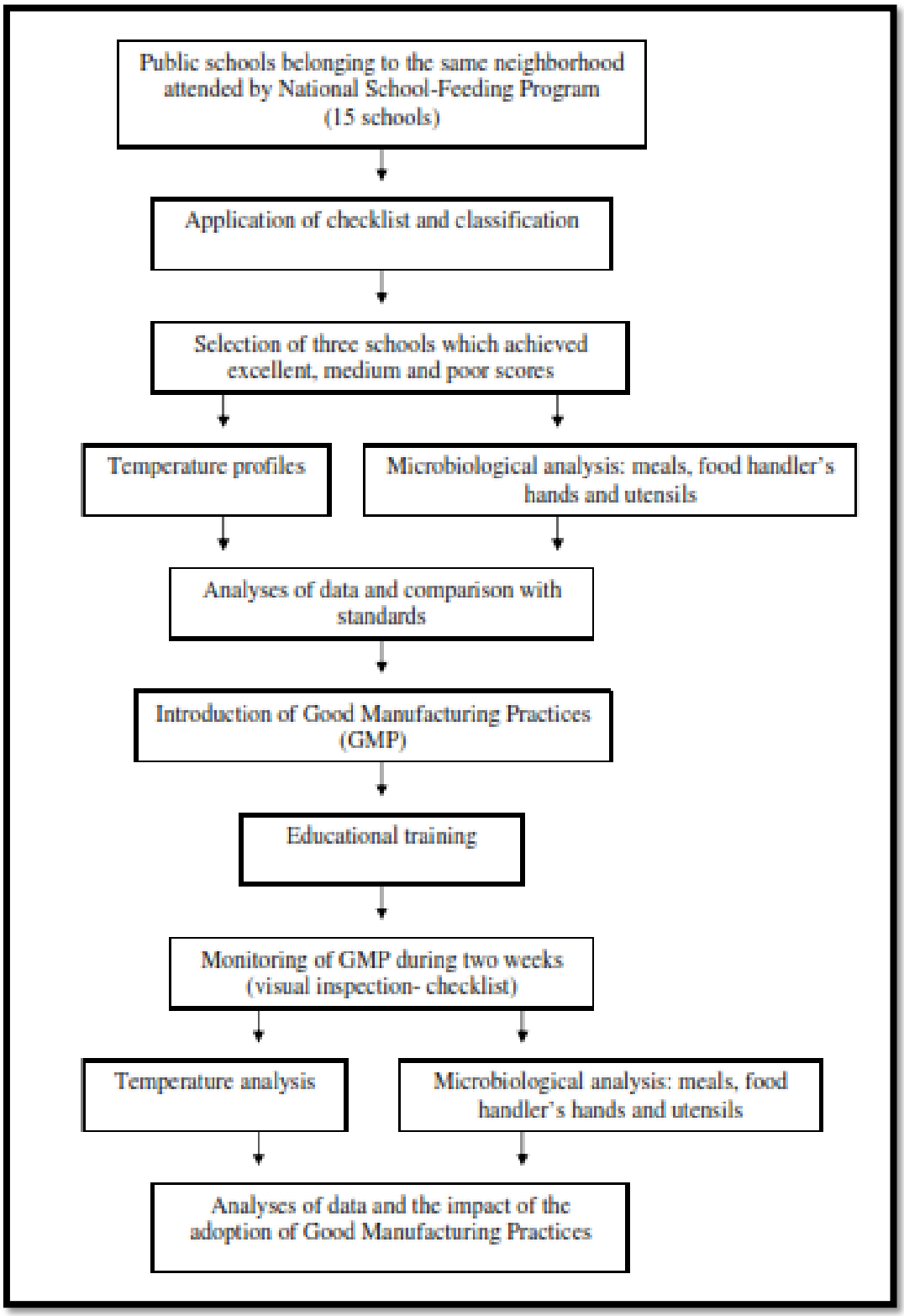


Figure 1: Flow Diagram used for GMP investigation. (Santana N.G, 2009)

Table 3 : The elements of a GMP system which apply to the manufacture of paper and board for food contact

Component of the GMP System	**Need**	**Comments**
General		
ISO 9001 or equivalent must be implemented	1	
Align quality policy to include aspects specific to food contact including aspects of internal audit.	1	
Management backing for GMP systems.	1	
Appoint a person to be responsible for GMP implementation and maintenance.	2	Applies generally to larger operations although it is always advisable to have a named individual with nominal responsibility.
New and existing personnel and contractors should be trained on GMP requirements and hygiene aspects specific to the food contact product.	1	Needs apply only to personnel working in areas where the food contact product could be affected. Informal briefings may suffice in circumstances where the risk is low.
Training records should be maintained for all personnel that have been trained.	1	Could be a full training course record or a tick in a box depending on the circumstances.
Perform a risk analysis and review once per year.	1	
Revise risk analysis.	3	Only needed when any major

		product or process change takes place
Specifications		
Review and implement changes in regulations, customer demands and other rules and procedures related to food contact materials. Communicate changes within the organization.	1	It is not necessary to perform the review of regulations within the organization. Instead, the knowledge could be acquired from elsewhere
The final product should be tested according to Bfr Recommendation 36 or the Industry Guideline or other relevant regulatory measures. The mill should have a documented procedure which defines which tests to carry out and the testing protocols to be used.	1	
The quality assurance system must contain guidelines for the determination of testing frequency for requirements contained in the regulatory measures.	2	
In cases where a decision has been taken to perform no tests on a particular requirement specified in the measures, documented reasoning must be prepared.	1	
Procedures for ensuring the accuracy of substance input using dosing equipment should be in place to ensure correct addition of chemicals with a compositional limit.	3	
Quality Control		
There must be a system in place to monitor and record the implementation and	1	

achievement of GMP. The system must also identify measures to correct any failure to achieve GMP and monitor the effectiveness of those measures. The system should cover also cases of non conformity with regulatory, internal and customer specifications.		
Document the food applications for which the end product can be used based on customer information or, in its absence, product knowledge. Document the effect which those applications might have on the selection of raw materials.	3	Ideally, the customer will provide details of end use but, if the customer is unable or unwilling to provide such information, then the customer must be told that he has responsibility for safe use of the product.
Raw Materials		
All raw materials and additives used in the production of the food contact material should be assessed to ensure accordance with current regulatory requirements.	1	Suppliers must provide documentation showing conformity with current regulations. In cases where suppliers introduce new raw materials or additives to their products, where new suppliers are used or the regulations change, a fresh declaration of conformity must be sought.
Keep records of all raw material deliveries so that conformity with regulatory requirements can be checked.	1	
Recipes of the end product, showing raw materials and additives used along the	2	Without this check, the operation will be unable to allocate

process, must be compiled and retained.		responsibility to a supplier in the case of defective raw material.
Suppliers of recovered paper must supply documented evidence of conformity with the Responsible Sourcing Guidelines and the requirement for that conformity should be included in the contractual arrangements with those recovered paper suppliers.	1	
The operation of paper mills using recovered paper must be adapted, if necessary, to conform to the Responsible Sourcing Guidelines.	1	
Personal Hygiene		
Personnel must wash their hands after using the toilet and any other activity that caused dirty hands.	3	
Clean working clothes and working shoes should be worn in the production and storage areas.	3	
It is not permitted to wear any loose items such as jewellery, watches, etc.	3	
Open wounds shall be covered with plasters having a deep, distinctive color. If any subsequent processing equipment has a metal detection system, the plasters should be metal detectable.	3	
Personal belongings must not be taken into the production and storage areas.	3	
Working clothes should be selected with the safety of both the employee and the product	3	

in mind. There should be rules in place for effecting the upkeep and repair of these clothes.		
Employees suffering from injuries and/or diseases likely to be transmitted to the food contact material must be excluded from the workplace.	3	
Eating, drinking, sweets, chewing gum and smoking are allowed in designed areas only.	3	
Rules shall be in place to ensure that visitors to the workplace wear appropriate clothing and remove jewellery and other loose items. Personnel accompanying visitors must have sufficient knowledge to pass on to them the special requirements needed when working close to a food contact product.	3	
Premises and Equipment		
All premises used by personnel working on food contact material, must be kept clean and tidy in accordance with a pre-determined schedule.	1	Applies only to the production areas.
Buildings, machinery, conveyors, transport devices, etc. must be cleaned regularly using a pre-determined schedule. Cleaning equipment and materials should be selected, used and stored in such a way that the food contact product is not adversely affected.	1	Applies only to the production areas.
Regular maintenance and inspection of facilities for hygiene purpose should form part of the quality management system.	2	Applies only to the production areas.

Engineering, maintenance and technical equipment together with any necessary temporary construction arrangements used for specific, short-term tasks close to the production facilities should be removed when the task is complete. Delays to this procedure must be referred to the person having responsibility for the GMP system.	1	Applies only to the production areas.
Lightning equipment, glass and plastic materials must be shatterproof.	1	Applies only in areas where the risk analysis has shown that debris from breakages could enter the food contact product.
All unnecessary glass and clear hard plastic should be removed from production and storage areas.	1	Applies only in areas where the risk analysis has shown that debris from breakages could enter the food contact product.
Hand knives used in production areas must be of an authorized type. Snap-off blades are specifically prohibited.	1	Applies only in areas where the risk analysis has shown that debris from blades could enter the food contact product.
In the event of the breakage of glass, plastics, knives, etc. in the area of the food contact product, a procedure must be implemented to ensure that the food contact product being produced at the time of the incident is free of such debris.	1	This will require liaison between affected departments in the paper mill and may require the affected product to be destroyed.
A documented pest control system must be in place. Execution of the system must be by specialist contractors or personnel trained in the necessary techniques. There	1	The system must ensure that pests cannot adversely affect the food contact product or its raw materials.

should be a recognized system for taking action where evidence of pests is noted.		
Wherever possible, doors and windows should be screened or closed to prevent pest ingress.	1	Does not apply to areas not used for production or product storage.
Documentation		
Arrangements must be implemented to produce documentation for external inspection.	1	Continuous production of documentation is not needed and reports could, for example, be produced in retrospect from computer records. Examples of the required information are: • Results of risk analysis • Changes in supply and suppliers • Raw material usage • Manufacturing and traceability documentation (mainly machine logs • Occurrences of deviation from specification and corrective measures (including changes required by new requirements from legislators). • Results of testing within quality control systems and all ISO 9001 (or equivalent)

		documentation.
Miscellaneous		
All vehicles used for transporting finished paper should be suitable for the purpose, well maintained and in a state of good hygiene. Ongoing contractual arrangements with transport companies shall include requirements for hygiene and cleaning. There should be a procedure in place for checking transport of finished products for cleanliness and water tightness.	2	
All external warehouses should be suitable for the purpose, have appropriate atmospheric conditions, be well maintained and in a clean state. Contractual arrangements with the supplier of warehousing facilities shall include requirements for hygiene and cleaning.	2	

Key to "Need" Column:

1 = fundamental part of GMP, must be implemented in all cases

2 = strongly advised

3 = needed only if called for by the risk assessment

2.3 MONOCLONAL ANTIBODIES (MABs)

Monoclonal antibodies (MAb's) are used in diagnostic tests as well as for therapeutic purposes. World demand for currently approved MAb's is on the order of a few kilograms per year. However, new therapeutic MAb's are under development that requires doses of several hundred milligrams to

a gram over the course of therapy (Seaver, 1997). The world demand for such products will exceed 100 kg per year. Current production choices for MAb's are limited to three well-established systems: ascites, stirred tank bioreactors (STR), and hollow-fiber bioreactors. Alternative technologies under development include transgenic animals and genetically altered plants (DeYoung, 1996). Currently, stirred tank bioreactors tend to be favored for production of MAb's in kilogram quantities. They are operated under batch, fed-batch, or perfusion mode.

Monoclonal antibodies (MABs) are widely used in pharmaceutical field as a main component for treatment of many kinds of diseases. Since the uses of MABs become larger day by day, countries are now competing to become MABs producer. Here are some examples on the uses of MABs:

1. Murine monoclonal antibodies (MoAb) potentially can be used in the radioimmunodetection and radioimmunotherapy of cancer (Chaudhuri T.R, 1994).

2. Antibodies are used in several diagnostic tests to detect small amounts of drugs, toxins or hormones, e.g. monoclonal antibodies to human chorionic gonadotropin (HCG) are used in pregnancy test kits (Biotech, 1989). Another diagnostic uses of antibodies is the diagnosis of AIDS by the ELISA test.

3. Antibodies are used in the radioimmunodetection and radioimmunotherapy of cancer, and some new methods can even target only the cell membranes of cancerous cells (Chaudhari et al, 1994). A new cancer drug based on monoclonal antibody technology is Ritoxin, approved by the FDA in November 1997 (Orrs, 1997).

4. Monoclonal antibodies can be used to treat viral diseases, traditionally considered "untreatable". In fact, there is some evidence to suggest that antibodies may lead to a cure for AIDS (P/S/L, 1997).

5. Monoclonal antibodies can be used to classify strains of a single pathogen, e.g. *Neisseria gonorrhoeae* can be typed using monoclonal antibodies (Wang et al, 1977).

6. Researchers use monoclonal antibodies to identify and to trace specific cells or molecules in an organism, e.g. developmental biologists at tyhe University of Oregon use monoclonal antibodies to find out which proteins are responsible for cell differentiation in the respiratory system (Fratella, 1998).

7. OKT3, an antibody to the T3 antigen of T cells, is used to alleviate the problem of organ rejection in patients who have had organ transplants (Transweb, 1996).

According to Kelly B, 2009. The field of bioprocess development for mAb production finds itself at a crossroads resulting from significant changes in multiple factors impinging on process design targets. The combination of excess production capacity and increasing cell culture titers enables simple strategies and platform processes to meet market demand for nearly all mAbs in the development pipeline, and enjoy sufficiently low production costs resulting in drug substance Cost of Goods, COGs not being a key process design driver. This could lead to a frameshift in process development strategies, and a slowing of the relentless march to develop processes with higher and higher titers. The new paradigm would suggest that if acceptable standards of productivity and COGs are met, then one should not make process design decisions based on perceptions of capacity limits, purification bottlenecks, or COGs pressures for anything but the most unusual situations (noting that clinical production drivers could be different).

In this case, the objectives of process development groups would shift from a focus on invention and innovation for new technologies to optimization and maturation of current production technology. The maturation phase should allow for continued refinement and improvements in manufacturing technology and COGs reductions, but will be more evolutionary than revolutionary. This may reflect a natural progression for process technologies driven by the introduction of new classes of products. In one theory of the link

between product and process innovation, process innovation lags behind product innovation, but eventually peaks and declines as the product class becomes a well-established market. The decreasing rate or need for process innovation could reflect maturing production technology, maximization of returns on the capital sunk into existing facilities, diminishing returns of new technology, and other factors.

This situation would allow companies to avoid risky process development designs that could have challenges in scale-up, technology transfer or reliance on a single raw material suppler. Novel production technology should be carefully evaluated and implemented only if it is clearly enabling and concrete drivers are identified. Novelty for novelty's sake is no reason to stray from an acceptable processing platform that enables portability among the many facilities that share a common design basis, and offers attractive economies of scale. A focus on controlling product quality and process consistency at all production scales and facilities would trump minor improvements in titer improvements or COGs reduction.

Development objectives should shift to a focus on understanding the process fundamentals of the current platform. There are many areas of research relevant to bioprocess technologies associated with antibody expression and purification that should continue to drive investment in areas of cell biology, biochemical engineering, protein chemistry and stability. Even today's state of certain critical quality attributes, such as stability and levels of mAb expression, minimization of sequence variants, etc. For production cultures, modeling and manipulation of cellular metabolism to control accumulation of waste products such as lactate, understanding recent observations of disulfide bond reduction in high-titer mAb processes, and refining scale-down process models would all be valuable areas of research. Considering purification processes, the complexities of cell harvest and depth filtration should be studied, measurement of product binding isotherms and binding kinetics would enable chromatographic modeling of product and impurity separations, virus retaining filter fouling behavior should be better understood, and characterization and control of both soluble and insoluble product aggregates offer fertile grounds for investigation. For all unit operations in the current platform, these investments in fundamental understanding will expand the knowledge space for the manufacturing

process, and enable the benefits of Quality by Design to be realized more quickly and broadly.

For companies with little or no installed commercial production capacity, commercialization strategies that would access the significant excess capacity currently available at CMOs and innovator companies by using conventional technologies could be wise approach. This avoids any capital investment at all, while still providing a path to unlimited demand and acceptable costs. The implications for clinical production processes are that they should be developed to take advantage of the eventual commercial processing benefits enabled by using current platform technology, driving similar process definition for Phase III and even Phase I processes, to avoid Issues of product comparability during the final process scale-up to large manufacturing facilities.

The mAb bioprocessing world is becoming flatter, meaning that access, understanding and implementation of the consensus technology should be assumed for those skilled in the art, and the majority of biopharmaceutical companies in all countries will have access to knowledge of common mAb drug substance production technology. While there may be financial incentive to foreign production in a tax-advantaged location, the low cost and high capacity enabled by use of existing facilities blunts the argument that this is driven by reduced labor costs, or that these foreign plants would benefit from new, more efficient production technologies. Note that a common process for global production would necessitate similar technologies in both domestic and foreign plants, further constraining the opportunities of using novel technologies to new plants built in foreign locations if they represent a very different processing philosophy.

Could our industry be at the cusp of defining a processing platform that has matured sufficiently to last several decades? Consider the plasma processing industry as an example of a current good manufacturing practice (cGMP) processing platform adopted by many manufacturers, which has stood largely unchanged since the 1960s. Few major changes were made to the basic manufacturing process until the introduction of chromatography in the 1980s and 1990s.

mAbs are becoming a unique class of therapeutic products. They are parenteral biologics with unlimited production capacity and low production costs, who's pricing will have no direct link to drug substance production. The pricing will instead reflect the innovator companies' clinical investment in addition to costs incurred from failed pipeline products. This represents an unusual combination of aspects of traditional recombinant protein therapeutics and small molecules, and our development and commercial production strategies will need to evolve in response to this shift.

These distinctive features of therapeutic mAbs produced by current platform processes should even be considered as key factors in drug discovery efforts, as non-mAb modalities or novel scaffolds may not all benefit from the advantages enjoyed by mAb production (e.g., much lower titers from Fc-fusions, or higher aggregate levels for non-native engineered proteins). The class of mAb products has many unique and valuable features derived from industrialized bioprocess technologies, which in themselves can become key factors in a unified and fully integrated drug development strategy.

2.4 TECHNOLOGICAL PROGRESSES IN MONOCLONAL ANTIBODY PRODUCTION SYSTEMS

According to (R.E Maria, 2009), monoclonal antibodies (mAbs) have become vitally important to modern medicine and are currently one of the major biopharmaceutical products in development. Moreover, great demand of mAbs in pharmaceutical needs has resulted in the need for the production of larger scale. These drastic changes have been promoting the use of mammalian cell culture as main ingredient in mAbs production. Production systems can be divided into two parts. They are systems for small-scale production and systems for large-scale production. Small-scale production systems usually have a simple design and a low level of instrumentation and control. In these systems, cells are usually grown adherently, because this is the normal/ physiological mode of growth of mammalian cells, and the process of adaptation to suspension can be time-consuming. System for small-scale can be divided into two types. First is adherent culture and second is suspension culture. Furthermore, systems for large-scale production, development of bioreactor have been introduced in order to fulfill the needs of mAbs in pharmaceutical field. For large-scale production, suspension cell-culture processes are usually the systems of choice.

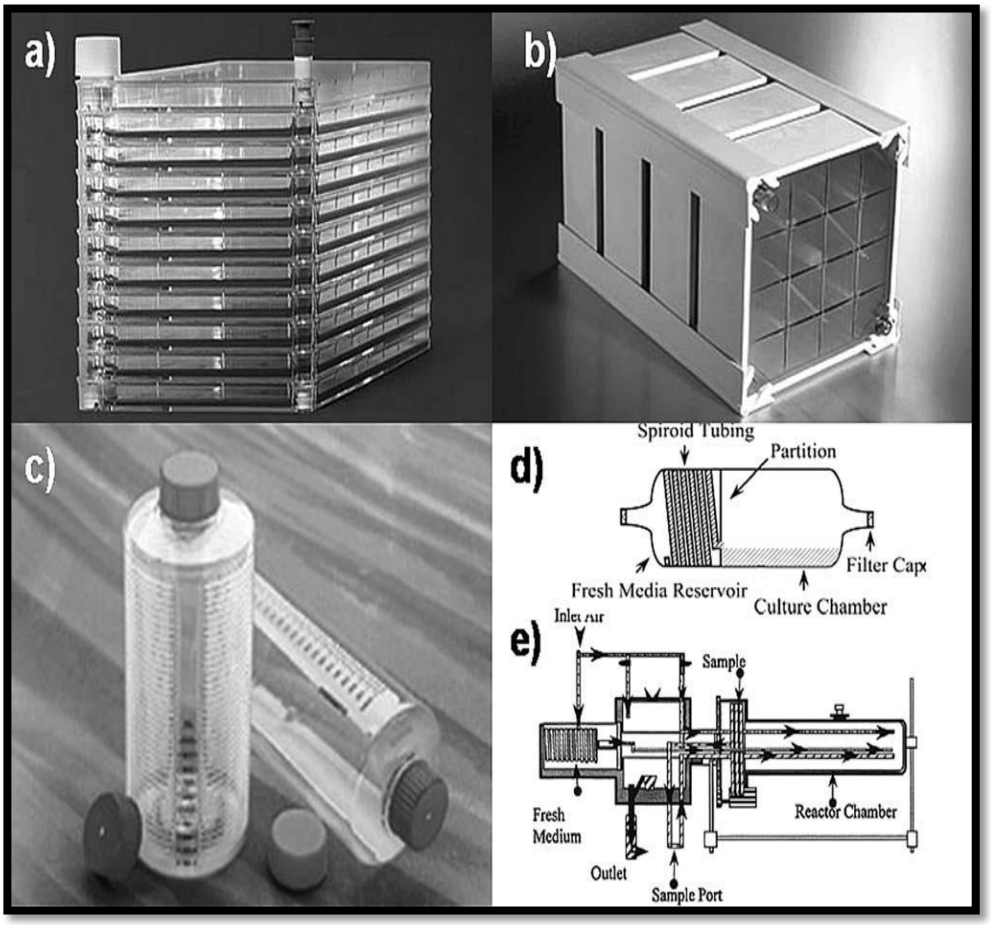


Figure 2: Systems for Adherent Culture in Small Scale, (a) Cell Factory, (b) Cell Cube, (c) Roller Bottle, (d) Spi-roll Bottle, and (e) CPRB, Continuous Perfusion Roller Bottle

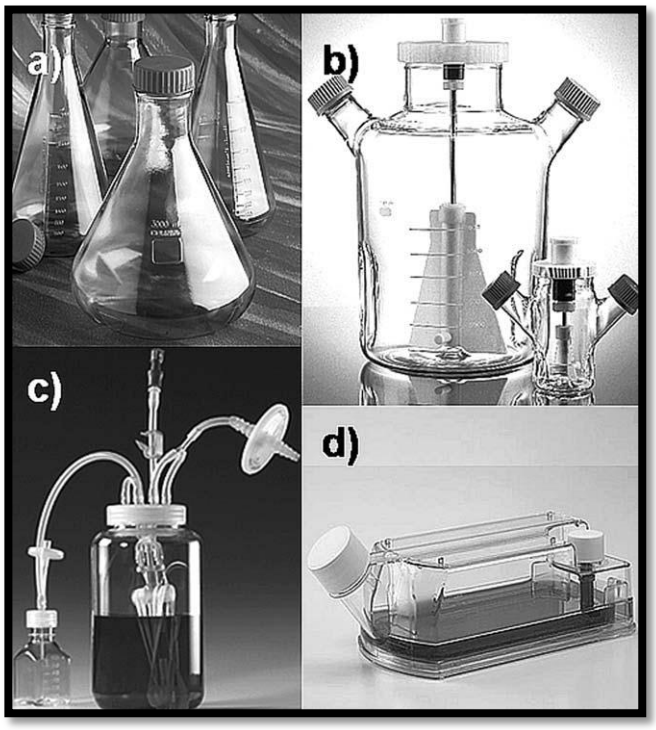


Figure 3: Systems for Suspension Culture in Small Scale, (a) Shake Flasks, (b) Spinner flasks, (c) Superspinner, and (d) CeLLine 1000

According to Binyamin L, 2009, Monoclonal antibodies have become widely used therapeutic agents for the treatment of cancer. Many are now being tested as components of adjuvant or first-line therapies to assess their efficacy in improving or prolonging survival. Selected unconjugated antibodies can exert clinically significant antitumor effects in many cancers. Antibody conjugates have been used to deliver toxic agents such as radioactive particles, chemotherapic drugs and catalytic toxins with increasing success in defined clinical settings. Advances in antibody engineering have permitted the systematic evaluation of structural manipulation on targeting and efficacy, and antibodies with novel specificities can now be isolated with increasing ease from naive and immunized phage display libraries. This accelerating progress, the rapid development and the convincing results using monoclonal antibodies clearly indicate that substantial gains can be expected in the next few years.

CHAPTER 3

METHODOLOGY

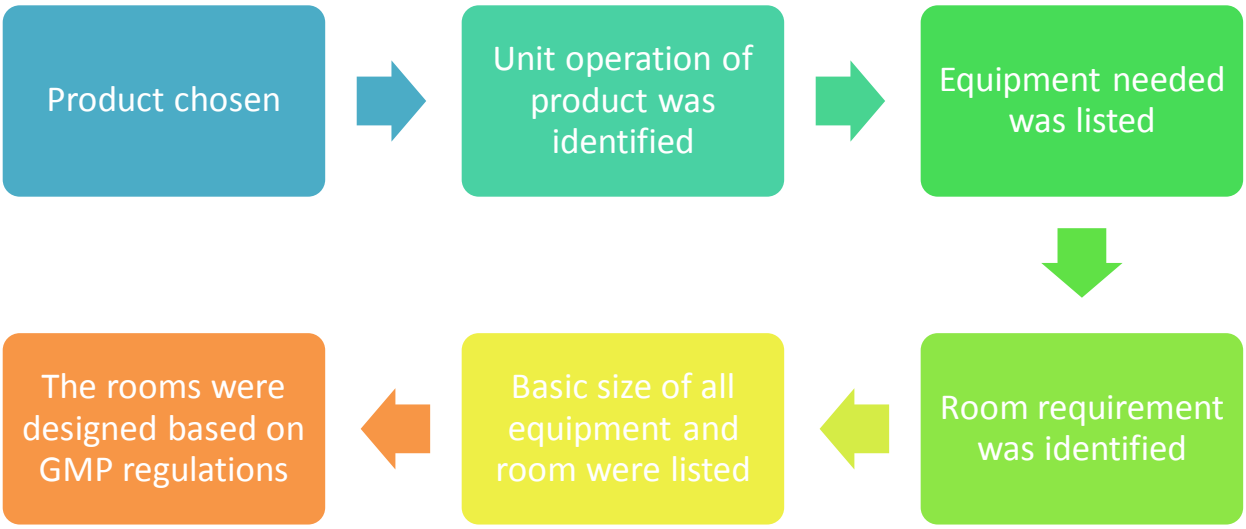
3.1 INTRODUCTION

In this section describes the methodology that will be used by the researcher to develop a GMP manufacturing unit in Gambang area.

3.2 DESIGN

This GMP manufacturing design will be done after doing some literature review on journals. The design shall be doing by using AutoCAD and it will be presented by small prototype. From that, we can see whether the design of GMP manufacturing unit will be accepted or not.

3.3 METHODOLOGY



3.3.1 JUSTIFICATION OF THE PRODUCT

From here, researcher will do some literature review on related journals. Moreover, researcher will know the theory of designing a GMP manufacturing unit. This theory can be applied on designing a perfect GMP manufacturing unit. At first, the researcher needs to consider the production unit for this manufacturing process. Then, from the production process, researcher can identify the equipment needed and room to be designed. Hence, researcher has chose production of Monoclonal antibody from mammalian cells as it manufacturing unit.

1. The manufacturing unit was chosen.

2. Unit operation of the process was identified.
3. All equipment based on production process was listed and room requirement was identified.
4. The rooms and all equipments were designed.

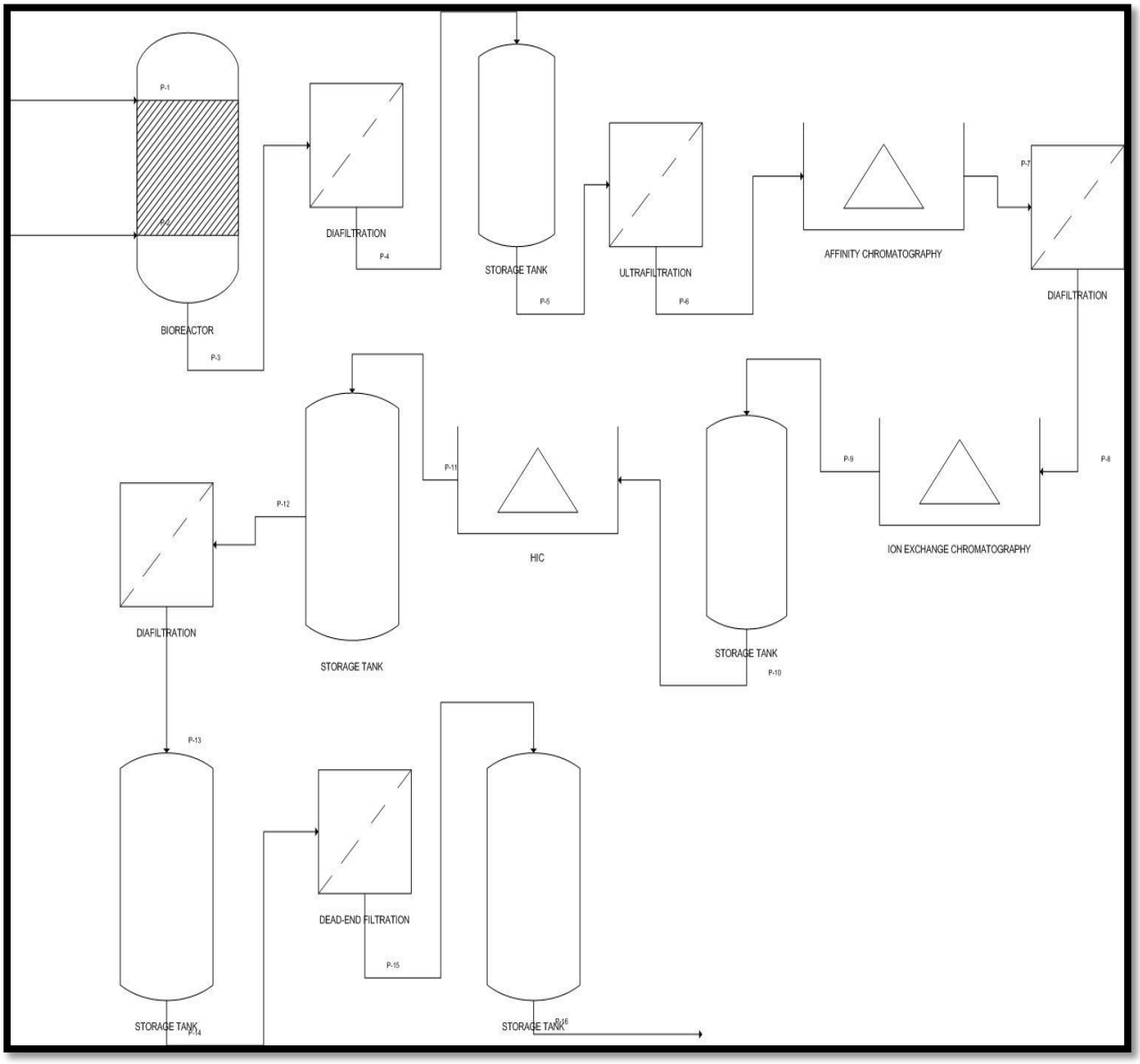


Figure 4: Unit Operation for Production of Monoclonal Antibodies

3.3.2 INDUSTRIAL VISIT

Second method is by doing some industrial visit. The visit will not done on company without GMP standards. Here, researcher will do some industrial visit on industries that follow Good Manufacturing Practices (GMP) regulations. Hence, researcher can go to the real GMP manufacturing unit to have a look on their real design.

Figure 5: Example of Manufacturing Unit That Follow GMP Regulation From BIOKEY, INC Which Responsible on a Drug Delivery and Specialty Pharmacy.

3.4 CONCLUSION

As a conclusion, this part is about literature review and industrial visit in order to design a Good Manufacturing Practices (GMP) Certified Manufacturing Unit for Halal Gel Capsules in Gambang

CHAPTER 4

RESULT AND DISCUSSION

4.1 INTRODUCTION

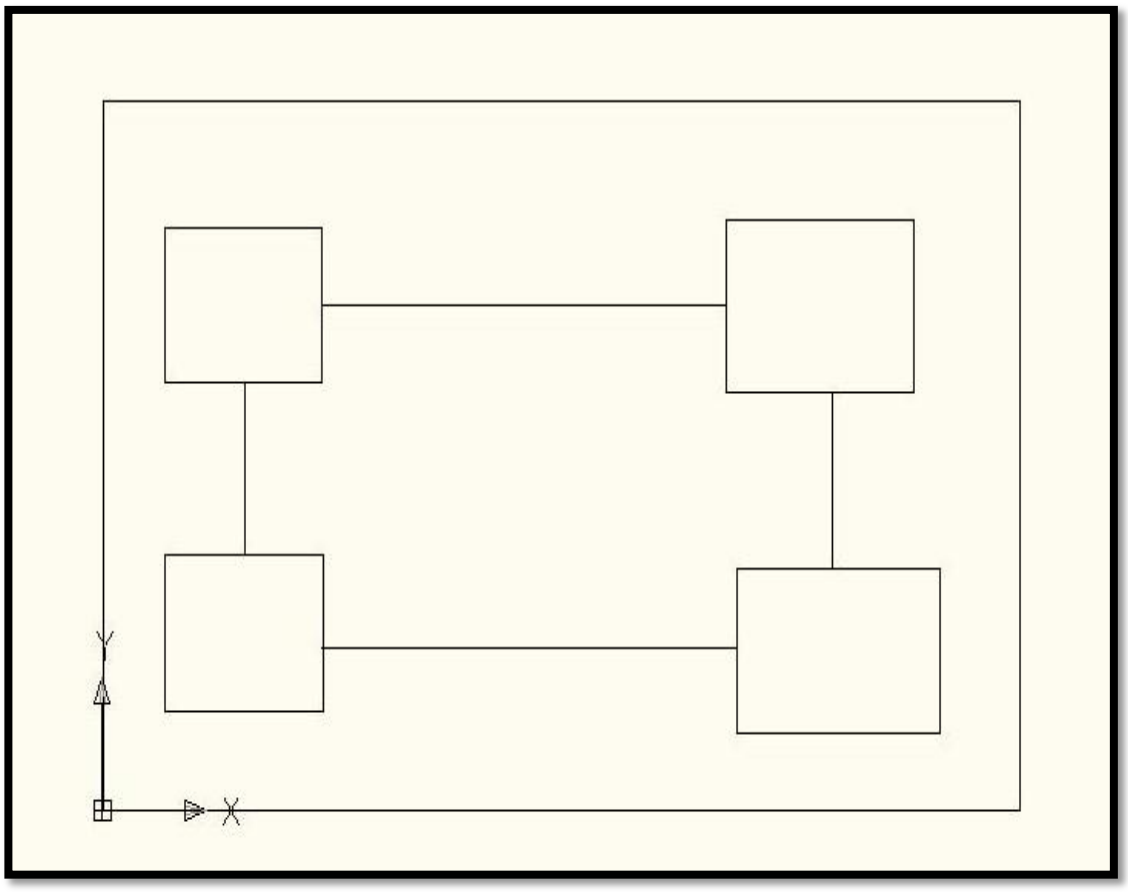


Figure 6: Basic Layout

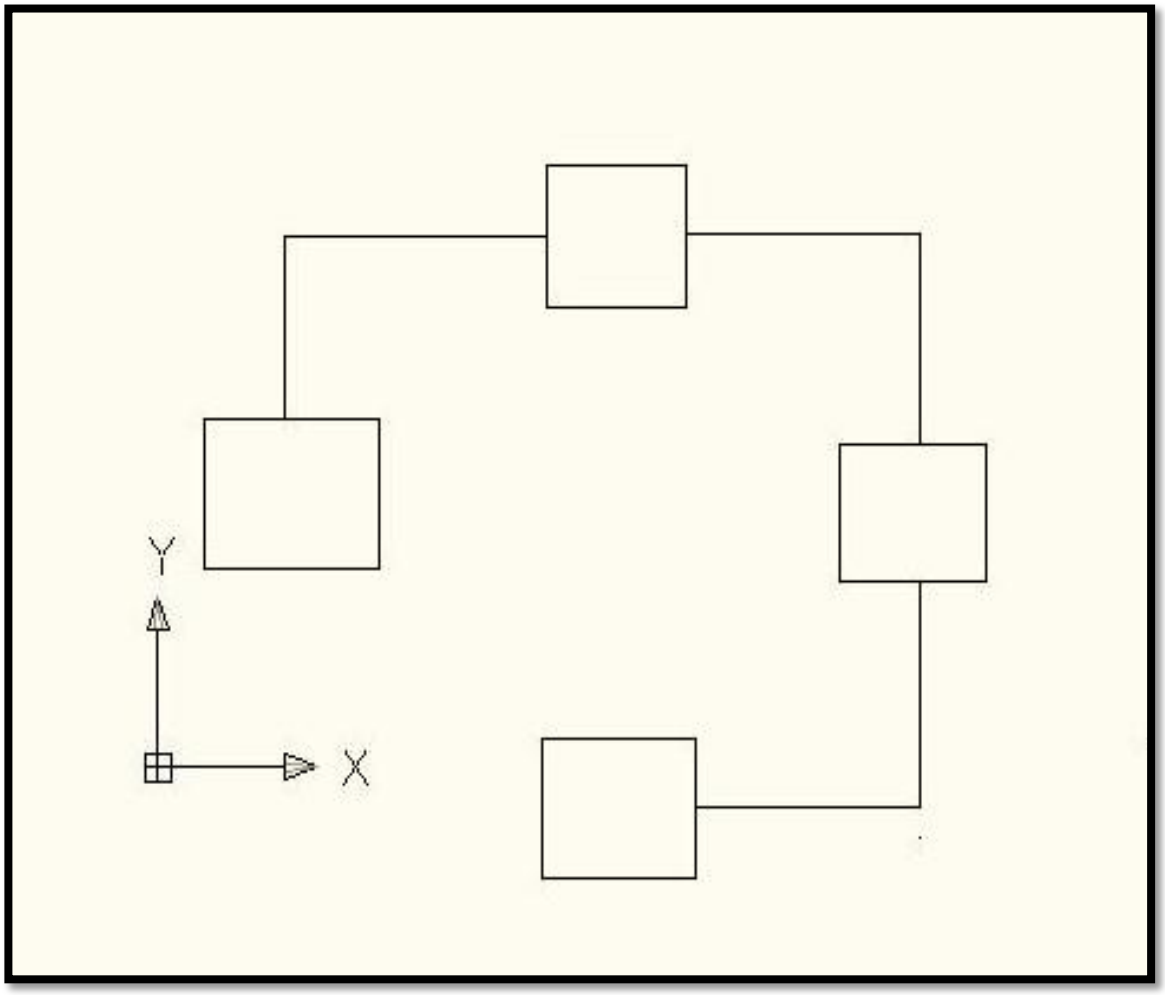


Figure 7: Basic Layout 2

This research is very suitable to be done in Malaysia based on demanding on pharmaceutical needed. In order to reduce our dependence on other country for supplying the medical needed, we should have ours. Hence, a GMP manufacturing unit is the most suitable to accommodate out medical needed.

4.1.1 EQUIPMENT

For the equipment needed in the process, they were divided into two main processes. They were production stage and purification stages. For the production stage or fermentation stage in the production of Mabs, the equipments needed were:

- Bioreactor.
- Diafiltration.
- Storage tank.

For the purification stage, they were:

- Ultrafiltration.
- Affinity chromatography.
- Diafiltration.
- Ion-exchange chromatography.
- Storage tank.
- Hydrophobic interaction chromatography.
- Dead end diafiltration.

Last but not least, the equipments were different based on their production process. Some process may need much equipment to give a better result in the final product.

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APPENDIX

Figure 8: Example of hard gel capsules

Figure 9: Example of soft gel capsules

Figure 10: Example of GMP room

Figure 11: Example of GMP room

Figure 12: Example of GMP room

Figure 13: Example of GMP room