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QUALITY ASSURANCE, GOOD MANUFACTURING PRACTICES AND QUALITY CONTROL FOR VACCINE MANUFACTURE IN DEVELOPING COUNTRIES. A TRAINING WORKSHOP HELD IN BANDUNG, INDONESIA, 8-15 JULY 1996

NC/GLO/94/02D

GLOBAL

Report : Workshop Proceedings

Prepared in close collaboration with the International Vaccine Institute and Bio Farma (Bandung, Indonesia) for the Governments of Africa, Asia, Europe and Latin America
under UNDP-financed TSS-1 facility

The report was coordinated by the Chemical Industries Branch of Industrial Sectors and Environment Division based on the work of *Dr. Zoltan Csizer*, UNIDO, ISED/CHEM, *Dr. Gurinder Shahi*, International Vaccine Institute (IVI), International consultants: *Ms. Rosemina Merchant*, Bio-Ventures Alberta Inc., Edmonton, Alberta, Canada, *Mr. Nikola Cucakovich*, Bio-Med Technologies Consulting, King City, Ontario, Canada and *Mr. David Magrath*, Bucks, United Kingdom.

IN MEMORIAM

DAVID MAGRATH

UNIDO and the International Vaccine Institute (IVI) dedicate this publication to the memory of Dr. David Magrath. His contribution as a reviewer of the publication, on which he was working at the time of his death, was considerable. All of us who knew and worked with him are saddened by his untimely departure.

He was an inspiration to us all not only for his extensive technical expertise on biologicals, but also for his personal values. His dedication to the service of humanity, and his charming manner, affected everyone. He was a real gentleman.

His critical comments on this volume have contributed greatly to its value and usefulness. This is but one small part of the rich legacy of Dr. Magrath, covering all aspects of the provision of high quality vaccines, which will ensure that his contributions to our society continue long after his passing.

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ACKNOWLEDGEMENT

First of all, we would like to acknowledge the contribution of *Mr. Frank Hartvelt*, Deputy Director, Division for Global and Interregional Projects, United Nations Development Programme (UNDP), New York, USA who made this workshop possible to happen.

Special thanks go to *Drs. Darodjatun*, President-Director, Perum Bio Farma, Bandung, Indonesia and to *Dr. Seung-il Shin*, Chief Technical Advisor and Project Leader, International Vaccine Institute (IVI), the main co-sponsors of this event. Without their moral and professional support, we could not have achieved its objectives.

The contributions of *Ms. Erlinda P. Galvan*, UNIDO, Vienna who made all technical corrections and put this document together, and *Ms. Eunyoung Kim*, International Vaccine Institute (IVI), Seoul, Republic of Korea, whose secretarial assistance was most significant.

And finally, we would like to thank all the staff of Perum Bio Farma, Bandung, Indonesia, for an outstanding job in organizing and hosting the workshop, and for catering to the needs of all participants with such great hospitality.

Dr. Zoltan Csizer
Dr. Gurinder Shahi

PREAMBLE

The Advisory Panel Meeting for BIONUDI (the 8th Meeting of the Panel) was held in 1995 in Hungary in order to discuss vaccine production and supply for the major markets of the world, among them China, India and Indonesia. The meeting made the following observations [UNIDO/ISED.10 (SPEC), 1996]:

1. The Global vaccine industry is in a state of flux and uncertainty, due to:

   - Rapidly changing technology.
   - Globalization of the biologicals/vaccine industry leading to global competition, mergers, acquisitions and alliances resulting in global consolidation of the industry.
   - Profound changes in the transition economies particularly in the region of Central and Eastern Europe (CEE).
   - Greater efforts by traditional multilateral donor agencies to achieve greater efficiency and targeted assistance.

2. Changing vaccine markets (elimination of some diseases from the industrialized countries/greater and greater emphasis on QA/QC and a more stringent regulatory environment for biologicals/universal enforcement of Intellectual Property Rights (IPRs) (elimination of import barriers in most countries) will result in increased international competition in the vaccine industries. Small, inefficient, state-controlled vaccine producers that enjoyed protected, captive markets will no longer enjoy such a protective environment.

3. Sustainable "national vaccine self-sufficiency" no longer means national production. For most small countries, it would be more cost effective to import high-quality vaccines than to produce them.

4. How will the state-owned or subsidized vaccine producing organisations survive in the new market? Many of these institutions perform other socially and medically essential functions in addition to vaccine production.

5. UNIDO and other public institutions should assist these institutions in examining the available options and making the correct choices - sometimes including the closure of the operation.

6. While the current uncertainty clearly presents major risks, at the same time it represents a major opportunity to introduce rational and fundamental new thinking into the vaccine industry.

Based on the above, the Asian Group of the Meeting recommended that UNIDO should act as a catalytic agent in providing expert advice to the vaccine industry in emerging countries of Asia.

Furthermore, it was recommended that UNIDO in association with UNDP should form a close working partnership with the International Vaccine Institute (IVI) to develop and implement training programmes on technology transfer for the vaccine industry.

It is interesting to note that the participants of the Asian Group were *Dr. Su Wan Nian* of the National Vaccine and Serum Institute, Beijing, China, *Drs. Darodjatum* of Perum Bio Farma, Indonesia, *Dr. J.M. Mehta* of the Serum Institute of India and *Dr. Seung-il Shin* of the International Vaccine Institute, Korea.

With UNDP financing and the very active participation of IVI and Bio Farma, the follow-up was organised in Bandung, Indonesia as a Training Workshop on "QA/GMP/QC for Vaccine Manufacture in Developing Countries", from 8-15 July, 1996.

The present publication is the proceedings of this historic event, the first international training activity which has been organized jointly by IVI and UNIDO.

INTRODUCTION

by Dr. Gurinder S. Shahi
Coordinator for Operations Development
International Vaccine Institute (IVI), Seoul, Republic of Korea

Sustainability is seen as a key issue for developing country vaccine producers. Some experts believe that many developing country facilities will have to close operations in the coming years because they will not be able to access modern technologies or because their facilities will no longer be considered acceptable. A key to assuring sustainability is the extent to which the facilities can attain internationally recognized capabilities in terms of QA, GMP, QC, and access to modern technologies and know how for production of new and improved vaccines. Unless developing country producers can meet the exacting demands of modern biologicals production and quality control, they are unlikely to be sustainable as vaccine manufacturers.

The IVI/UNIDO/Bio Farma Training Workshop on QA/GMP/QC for Vaccine Manufacture in Developing Countries was, hence, aimed at helping developing country vaccine manufacturers gain the necessary competence and skills to help themselves develop effective action plans to become more sustainable. Such effort on the part of manufacturers would have many benefits, not least among which would be enabling them to become more attractive for mutually beneficial partnerships with leading vaccine producers. This would be a particularly effective means by which they might gain access to new technologies.

The workshop was held on the premises of Perum Bio Farma in Bandung, Indonesia, from July 8-15, 1996. Perum Bio Farma, Indonesia's national vaccine production institute, is recognized to be amongst the best managed and operated public sector vaccine producers in the world. It is a member institution of the Institute's Network Coordinating Group.

A total of 39 participants/observers from 13 countries were invited to participate in the workshop. Countries represented included: Brazil, China, Croatia, Hongkong, India, Indonesia, Iran, Korea, Malaysia, Mexico, South Africa, Thailand, and Vietnam. Faculty consisted of leading experts in production technology for biological products. Core Faculty for the Workshop included Ms. Rosemina Merchant and Mr. Nikola Cucakovich. They were supported by Dr. Zoltan Csizer (UNIDO), Dr. Benny Kaligis (Perum Bio Farma) and Dr. Sooyoung Stanford Lee (IVI). Dr. David Magrath, formerly Chief of Biologicals at the World Health Organization, served as Technical Advisor. The workshop was expertly hosted by the staff of Perum Bio Farma.

The Director-General of Indonesia's Food and Drug Administration, Dr. Anton Fric (who represented Dr. Uton Rafei, Regional Director of WHO's South East Asia Regional Organization), and Drs. Darodjatun (President-Director of Perum Bio Farma, and a member of the IVI Board of Trustees) attended the opening ceremony for the workshop.

Objectives and Rationale

The workshop was intended for senior management staff of vaccine production facilities with responsibility for QA/GMP/QC (it was aimed particularly at Quality Assurance

managers), and for senior managers of National Control Laboratories (NCLs). It sought to provide managers with an understanding of the key issues in current QA/GMP/QC, and was designed to equip them with the tools and skills to develop effective action plans towards upgrading and improving their institutional QA/GMP/QC standards and capabilities. Participants were advised on the need for their institutions to take full technical and financial responsibility for bringing about appropriate change that they themselves identified. The workshop incorporated write-ups, lectures, case studies, open discussions, group assignments, site visits and demonstrations. Faculty made itself available throughout the workshop for discussion and consultation.

Course Contents

The workshop focused on key issues in GMP for vaccine manufacture. Topics covered included:

- Philosophy and Principles of Good Manufacturing Practice
- Issues in The Design of Vaccine Production Facilities
- Validation Considerations for GMP
- Documentation Issues

The various topics were discussed in the context of developing a strategic approach to achieving GMP, the so-called GMP Action Plan (see Table 1).

Table 1: GMP Action Plan

The GMP Action Plan is a tool which managers could utilize to help provide a systematic framework for reviewing their institutional strengths and weaknesses, and developing an effective course of action. A generic plan might contain the following:

- **Executive Summary**
- **Introduction**
- **Statement of GMP Goals, Objectives and Targets**
- **Review of Existing Situation (analysis of strengths, weaknesses and opportunities)**

Facilities

- Description of existing facilities

Equipment

- Status

Staff

- Qualifications and Capabilities
- Access to Skills Enhancement and Training Opportunities
- Organization of staff - Roles and Responsibilities

Practices and Procedures

- Documentation
- Validation
- Operational Procedures

Other Related Matters

- Funding
- Access to Reference Standards
- Access to Technical and Regulatory Requirements
- Certification of Facility - National or International (WHO)

- **Recommended Strategy for Achieving CGMP Compliance**

Facilities

- Retrofit or new
- Multiproduct or dedicated
- Site for new facility

Equipment

- Upgrade
- Automation
- Containment
- Scale-up

Staff

- Qualifications and Capabilities
- Access to Skills Enhancement and Training Opportunities
- Organization of Staff - Roles and Responsibilities

Practices and Procedures

- Documentation
- Validation
- Reorganization of Operational Procedures

Other Related Matters

- Access to Funding
- Access to Reference Standards
- Access to Information
- Availability of Technical Support

- **Proposed Work Plan, time lines, use of consultants and/or engineering firms**

- **Funding Considerations**

Participants also considered issues in implementing effective GMP Action Plans, including, for example, the pros and cons of establishing GMP Task Forces made up of representatives from different areas of operation of their respective institutions, and the challenges which need to be overcome for successful action. It was emphasized that the development of an effective action plan would require a substantial investment in time and resources, and that it could easily take two years or more for effective implementation of all aspects of GMP - especially when such changes as facility renovation, updated equipment, and staff training and skills enhancement were called for. On the other hand, it would be possible to make substantial changes in documentation, approaches to validation, and in operational procedures almost immediately. Such action could potentially bring substantial benefit at minimal cost.

Write-Ups

Prior to attending the workshop, participants were asked to submit write-ups identifying strengths, weaknesses and opportunities which they saw in their respective institutions in relation to GMP. These write-ups enabled faculty to get a good sense of the concerns and circumstances faced by each participant and his/her institution (see Part I - Institutional Write-ups). This allowed some customization of the workshop in response to specific needs and concerns.

Facility Design Workshop

The facility design workshop provided an excellent opportunity for participants to think through key issues and concerns in facility design for GMP. Such issues included:

- facility layout;
- process, people and material flows;
- water system requirements;
- ventilation system requirements;
- facility maintenance considerations; and
- costing considerations.

After covering the fundamentals of facility design, participants were divided into 4 groups on the third day of the workshop, each of which was assigned to design a vaccine production facility for either 10 million or a 100 million doses of either oral poliomyelitis vaccine (OPV) or Diphtheria, Pertussis, Tetanus vaccine (DPT). They were advised to utilize the ideas and inputs discussed each subsequent day of the course in their planning consideration. On the final day of the workshop (Day 8), each group presented its design for representations on the facilities designed by each group were made (see Part III - Facility Design Workshop Reports).

Indonesia's Minister of Health, Dr. Sujudi, kindly officiated at the closing ceremony and presented certificates to each of the participants.

Follow up

The Institute intends to follow up the training course by working with those vaccine manufacturing facilities which request its assistance and advice in helping them in their efforts to improve GMP.

In addition, on the basis of feedback from participants, the Institute is looking into the feasibility of developing courses on such specific topics as validation issues, and bioprocess technology issues in vaccine production - for example, cell culture technology and fermentation technology.

Course Evaluation and Feedback

A Course Evaluation Questionnaire (see attached) was handed out at the end of the workshop to enable faculty and organizers to benefit from the feedback and suggestions of participants.

Feedback

Participants generally reported that they found the workshop extremely useful and seemed to find the facility design exercise particularly beneficial. One participant, for example, reported that she now saw her own facilities with new eyes, and realized many ways in which facilities, practices and procedures could be improved. Several participants also reported that they felt much more confident now in their ability to troubleshoot and rectify problem areas in their own facilities.

Participants filled out evaluation questionnaires at the end of the workshop. The mean score of their evaluations (on a scale of 0 to 10) are summarized below:

Organization/Planning	8.5
Support Facilities	8.7
Course Materials/Handouts	8.3
Subject Matter	8.4
Faculty	8.3
Overall Rating for Course	8.4

Approximately 4 weeks subsequent to the course, participants were asked if their institutions had either taken, or intended to take, any action as a consequence of their participation in the workshop. Most indicated that their institutions now had a better appreciation for what it would require to achieve internationally acceptable standards of GMP. Many also said that their institutions had agreed to implement several improvements in approach to documentation and validation, for example, in accordance with what was learnt at the workshop. Several institutions were also in the process of establishing GMP Task Forces and initiating the process of developing GMP Action Plans. It is to be anticipated that substantial improvements in operation and practice are likely to result from these efforts by the various institutions.

REVIEWER'S COMMENTARY ON WORKSHOP PROCEEDINGS

by Dr. Julie B. Milstien
Global Programme for Vaccine and Immunization
Vaccine Supply and Quality
World Health Organization (WHO), Geneva, Switzerland

This document describes a workshop on GMP held in Bandung, Indonesia in July 1996, and reflects the huge changes in the concept of vaccine quality control and quality assurance that have taken place in the past years. This change presents a major challenge to traditional producers of vaccines and their National Control Authorities to keep in step. This will require concerted local and international effort in terms of training, acquisition of technical expertise, investment of financial and human resources, and a reorientation of ideas. The workshop thus represents only one of the first in a long series of activities which must be undertaken in this area.

The workshop, although of short duration, was designed in such a way to maximize interaction among the participants and between the participants and the "faculty". It is fair to say that for the 8 day duration of the workshop, the participants were fully immersed in GMP. Furthermore, through this high level of interactive contacts, they developed bonds and relationships with counterparts in other countries which are already paying dividends in mutual support for implementing changes.

The workshop format emphasized the two pillars of GMP - Standard Operating Procedures and other documentation, and Validation. These provided practical exercises to emphasize the application of these principles.

Two parts of the document are particularly useful for WHO. The first is the description given by course participants of their own facilities and the problems they are facing. Even allowing for the natural tendency of the participants to put a positive spin on their descriptions of their own situations, this is important reference material to guide future planning. The second is the output of the working groups which were charged with designing production facilities for various products at various capacities. Although I suspect the costs for validation of these facilities were probably underestimated, this is the first time, to my knowledge, that participants in such an international workshop realistically looked at the true costs of vaccine production, and the implications of investment decisions on capacity and product line. In addition, the outputs will be useful references as to minimum equipment and facility costs, being in general much higher than historically quoted costs for similar facilities.

ADDRESS TO THE WORKSHOP

by Hon. Prof. Dr. Sujudi
Minister of Health of the Republic of Indonesia

Ladies and Gentlemen,

In June 1994, at the same place, I officially opened the CVI meeting on DTP-based Combination Vaccines for Asia with WHO as main sponsor.

I appreciated the meeting very much as it included the session on polio eradication, in which I had received valuable input.

Indonesia has been successfully performing a **National Immunization Week** during which time OPV was given to about 23 million children under 5 years since last year. This polio eradication campaign will be implemented until 1997. We expect to be able to reach the goal of **Polio Free Indonesia** by the year 2000. I am proud of Bio Farma for being so successful at playing an important role in supplying good quality vaccine to satisfy the needs.

The Government of Indonesia will continue to maintain its strong commitment to support the role and existence of Bio Farma as the sole vaccine producer in Indonesia which has made the country self-sufficient in vaccine supply. Bio Farma is now even ready to export the vaccines. I also strongly support Bio Farma programme of Research and Development in cooperation with several institutes in and outside the country.

Vaccine research and development is a long-term high risk investment and needs substantial funds which is commercially not attractive. This effort needs global cooperation to be able to produce a range of ideal vaccines to fight diseases of major public health importance. Such vaccines must be accessible to all who need them.

I believe, we all agree that any development programme should always be very carefully considered on the long-term benefit and risk for a particular country, mainly considered from strategic and economic point of view.

In the meeting of Ministers of Health of Non-Aligned and other Developing Countries convened in Geneva, in which Indonesia was the Chairman for the last 3 years until May 1996, we reviewed the progress of Technical Cooperation among Developing Countries (TCDC). It was stressed that while not an end in itself, technical cooperation between countries was regarded as an important tool for development in general and health development in particular.

In many developing countries TCDC has enhanced the capability of human resources to the point where their expertise can be made available to other countries as well. It is time for Bio Farma to take share in organizing the Third Country Training Programme in cooperation with donors.

Technical Cooperation among Developing Countries alone seems to be inadequate, the global effort and government commitment towards health development aiming at improving health status is very important.

As we come closer to the year 2000, it is saddening to note that foreign assistance devoted to health development in developing countries is decreasing.

In line with this situation, I would like to emphasize that we require strong partnership between United Nations Organizations and member states, between North and South, between South and South, between public and private sectors, including donors and international agencies. The partnership implies a social covenant, in a spirit of mutual responsibility, respect and sharing.

In this context, training/workshop today is extremely relevant and should be very useful to our TCDC programme on health development.

So I am very pleased to be able to visit you here on the final day of the Training / Workshop. I am really grateful that Bio Farma has had the honor of hosting this historic first meeting organized by the International Vaccine Institute, with participants from various vaccine production and regulatory agencies from 15 countries throughout the world.

I understand that this has been a highly intensive and stimulating workshop - where participants have had a chance to update themselves on the most important issues in current Good Manufacturing Practice of vaccine production.

You must, undoubtedly, have been extremely busy. Nevertheless, I hope you have been able to take some time off to enjoy the beautiful sights and rich culture of Indonesia.

We are grateful to IVI and UNIDO for organizing this very practical and much needed workshop in collaboration with Bio Farma, and to UNDP for providing funding support. We anticipate that this is only the first of many training and capacity building opportunities to be offered by IVI, in cooperation with UNIDO, UNDP and other partner institutions of the Children's Vaccine Initiative, especially WHO and UNICEF. We support this idea, and look forward to the Institute playing a major and leading role in promoting vaccine-related science and technology development. If the excitement and enthusiasm generated by this workshop is any indication of success, we can also expect close cooperation and collaboration between the Institute and centers of excellence in developing countries throughout the world.

I have been informed by the course faculty that you have all done extremely well and therefore you are all qualified to receive the certificate of participation in this workshop.

Congratulations, and I wish you success in your future work.

Thank you.

Minister of Health
Republic of Indonesia

Prof. Dr. Sujudi

ADDRESS TO THE WORKSHOP ON BEHALF OF THE PARTICIPANTS

by Dr. Ira Ray
Director
National Institute of Biologicals, India

Your Excellency, Prof. Dr. Sujudi, Minister of Health, Government of Indonesia, Drs.Darodjatum, President Director, BioFarma, faculty members.

It is indeed a great pleasure and privilege for me to convey the appreciation and greatfulness of all the participants of this workshop to the host country Indonesia, Organisers - Bio Farma, IVI, UNIDO and all staff members of BioFarma.

This is the first workshop on QA/GMP/QC organised by BioFarma/IVI/UNIDO and funded by UNDP. 34 participants from 13 countries participated in this 8-day workshop at this beautiful city of Bandung in the premises of BioFarma.

As you all know, biologicals and specially the vaccines are the most powerful tools to achieve the health goals of the developing countries. These vaccines have to be safe, effective and affordable and that is only possible if they are produced under strict GMP conditions with QA and QC.

This workshop brought together the manufacturers and National Control Authorities from all over the world to guide and assist them in their future planning and development. Various subjects such as GMP action plan, facility design, biosafety, validation, documentation and other issues were covered. The lively discussions gave a chance to compare the experiences of different countries and manufacturing units. As the faculty made themselves available round the clock, many of these discussions took place over lunch or dinner or beyond.

The added advantage of having the meetings on the BioFarma premises was the opportunity to visit one of the best vaccine manufacturers in the world and to interact with persons with vast experience and updated technical knowledge. We are greatful to BioFarma staff for their cooperation and patience.

Through this workshop, the basic requirements of GMP. and how to establish it has become clear to us. We would now go back to our own institutions and try to implement it. We know that it is not an easy task. Depending on the set up and availability modifications would be needed. And the faculty and IVI have confirmed that they would assist us whenever required. We should also interact with each other and solve problems on intra-country basis.

Although the course schedule was very heavy and we all wished that it was spread over a little more time we did get some time to look around Bandung and do some shopping. The organisers had looked into all our needs and made our stay extremely enjoyable and comfortable. In this friendly and informal environment a foundation has now been laid for further collaboration and association between institutions from different countries.

Participation in this workshop was a unique experience and I hope that all of us would be able to use it fruitfully. We would also remember the excellent time we had in this city of flowers.

I, on behalf of all the participants, take this opportunity to once again thank the Government of Indonesia, Bio Farma, the organisers, the faculty and staff of Bio Farma.

PART I

INSTITUTIONAL WRITE-UPS *

* **Note**: The Institutional Write-Ups included in Part I are listed in alphabetical order of country of origin.

PARTICIPANTS' INSTITUTIONAL WRITE-UPS:

1. China
2. Hong Kong
3. India
4. Indonesia
5. Iran
6. Korea
7. Malaysia
8. Mexico
9. South Africa
10. Thailand
11. Vietnam

QUESTIONNAIRE:

A. Background information of existing facilities/staff and plans for future developments in brief.

B. Institutional strength/weakness in GMPs/QA/QC.

C. Expectations from training course.

D. Specific issues.

1. CHINA

NATIONAL VACCINE & SERUM INSTITUTE

by Ms. Yuan Xiurong
Foreign Affairs Office
National Vaccine & Serum Institute (NVSI)
Beijing, P. R. China

A. Background

Most of NVSI's buildings were constructed in 1958. In the past several years, a few new vaccine product plants were built which can meet international GMP regulations. Take the Hepatitis B (recombinant) Vaccine plant for example, its production technology was introduced from Merck & Co. Inc. of the United States. Except some new plants, most of the buildings need to be improved.

The institute has a staff of 1500, 40% of which are technicians graduated from universities and colleges, and about 100 of them are senior researchers and senior engineers.

B. Institute's strengths on QA/GMP/QC

A good QC system has been established as well as a set of regulations through which the system can ensure high quality products.

The institute have obtained some practical experience in construction and validation of new plant through technical introduction and technical innovation.

Institute's weaknesses on QA/GMP/QC

The institute's QA system is not complete. The QA staff needs professional training.

In the training course, we hope to acquire more knowledge and experience of improving vaccine product facilities and validation, especially reconstruction of old buildings to better ones which can comply with GMP. We have several questions on how to renovate the old buildings, for example the storey height.

We would like to get written teaching materials and more materials of GMP standards and validation.

NATIONAL INSTITUTE FOR THE CONTROL OF PHARMACEUTICAL AND BIOLOGICAL

by Dr. Yong Xin Yu
Professor, First Viral Vaccine Division
National Institute for the Control of Pharmaceutical and Biological Products (NICPBP)
Beijing, P. R. China

A. Background

National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) is directly affiliated to the Ministry of Health of China. NICPBP possesses the obligations in the quality control of pharmaceutical and biological products of the whole country and functions as a drug quality control authority of China. NICPBP has a personnel of 744, among which 44 are senior research fellows, 66 are associate senior research fellows and 421 with doctor degree, master degree or bachelor degree. NICPBP is well equipped with various kinds of devices and equipment used for testing pharmaceutical and biological products including biotechnology products. NICPBP is designated by WHO as its Collaborative Center for Drug Quality Assurance and National Center for Viral Hepatitis Research. It is also designated by the Ministry of Health as National Center for Monitoring of Bacterial Susceptibility to Antibiotics, National Center for the Quality Control of Medical Laboratory Animals and the Key Laboratory for the Research of Quality Control and Standardization of Biotechnology Products.

NICPBP is not only the legally authorized agency for the nationwide quality control and quality management of pharmaceutical and biological products, but also a research center for quality control and standardization of pharmaceutical and biological products as well as for new testing techniques and methods. It also provides training and technical instructions for the professional testing personnel in the field of pharmaceutical and biological products.

The implementation of GMP was initiated in China in the 1980's. Since then multiple training courses have been organized by the Ministry of Health and supported by WHO by sending GMP experts and quality control specialists to give lectures or presentations in the courses. In 1988, Requirements for the Quality Control of Drug Production was issued by the Ministry of Health. Ever after GMP has been formally implemented in China in 1992, revised Requirements for the Quality Control of Drug Production was stipulated which was done in accordance with the GMP situation and experience accumulated over the past few years. Thus the new National GMP became comparable to the GMP standards of WHO and the developed countries of the world.

In addition to the fact that the history of GMP implementation in China is short, the existing facilities and equipment are obsolete in most pharmaceutical and biological manufacturers in China, it is necessary to carry out technical reform or upgrading the facility by renovation or reconstruction so as to gradually meet the GMP requirements. To realize the goal, big investment will be needed and the action plan worked out by China will be put into effect step by step.

The coming training course will provide us a good opportunity to update the knowledge of GMP by learning the progress and new requirements in foreign countries. Furthermore, the successful experiences in the GMP implementation in the developing countries will be especially helpful to us.

SCIENCE & TECHNOLOGY SERVICE CORP.

by Dr. Guo Xiu-Chan
Science & Technology Service Corp.
Chinese Academy of Preventive Medicine
Beijing, P. R. China

Brief Information:

Science & Technology Service Corporation belongs to Chinese Academy of Preventive Medicine. It is engaged mainly in research and manufacture of the recombinant hepatitis B vaccine which contains the purified surface antigenic protein of the virus. Using the genetic engineering techniques, we established a transgenic CHO cell line which secrets HBsAg in high level into the culture medium. On this base we have developed a large amount of cultivation of cell culture techniques in rolling battles and set up a HBsAg purification process by 3 steps of chromatography and 3 steps of membrane filtration. In order to develop our cell culture techniques and purification and assure the product quality, we need to know the latest news about vaccine, particularly on GMP, compute systems in vaccine manufacture and vaccine manufacturing facility design.

SHANGHAI INSTITUTE OF BIOLOGICAL PRODUCTS

by Mr. Miao Yin Chang
Director of Quality Control Department
Shanghai Institute of Biological Products (SIBP)
Ministry of Health, P. R. China

I. Brief introduction of SIBP

1. Production
   - Vaccine
   - Blood products
   - Antitoxin
   - Clinical diagnostic reagents

2. Area
   - Total: 340,000 m^2
   - Premises: 100,000 m^2

3. Facilities

Old facilities:
- for measle, DPT, etc.
- had been built before 1970

New facilities:

A. Human plasma fractionation
- completed in 1990
- technical reform project in China
- the largest scale
- the greatest investment
- the most sophisticated equipment
- the design and construction according to GMP of WHO
- the production area
  - closed system
  - artificial lighting
  - mechanical ventilation
  - clean room of different classes
  - advance installations
- Output
  - input of 300, 000 liter plasma/ year
  - 7500 kg albumin/ year
  - 1350 kg gammaglobulin/ year
  - 60 million IU Factor VIII concentrate/ year
  - several other products

B. CVP (Chinese Vaccine Project)
- building
- measles
- DPT
- the design and construction according to EV GMP

4. Staff

Total:	1700
Senior:	100
Intermediate:	350
Technicians:	500

II. SIBP complies with GMP at present

The head of SIBP is responsible for:

- the manufacturing operations in accordance with GMP of China;
- the manufacturing operations for EPI vaccines according to the marketing needs and quota;
- all products being consistently produced and controlled;
- the quality of all products to fit for their intended use.

1. Quality Assurance

There is quality assurance system in SIBP.

This system should ensure:
- production and control operations implemented with GMP and GLP;
- managers including the head of production, the head of quality control have clear responsibilities;
- correction starting and packaging materials are used;
- have necessary control for intermediate products;
- the control for final products according to written procedures;
- all products can not be sold and supplied before release;
- good arrangement for storage, distribution of all products;
- the samples of all products are kept throughout their shelf life;
- have a compliant and recall system;
- have a self-inspection to evaluate the effectiveness and applicability of Quality Assurance System.

2. GMP

SIBP complies with the basic requirements of Chinese GMP.

- all production and control operations have written procedures;
- all manufacturing processes are shown to be capable of consistently manufacturing;
- all products have met the requirements of China and fit for their intended used;

- critical steps of manufacturing processes and significant changes to the process are validated;
- have all necessary facilities;
- adequate qualified and trained personnel;
  - premises and space
  - suitable equipments and maintenance
  - approved procedures and instructions
  - suitable storage
- operators are trained every year and carry out procedures correctly;
- have correct records including;
  - all manufacturing records
  - all quality control records
  - distribution records
- have compliant and recall system
  - examine the sample of products
  - investigation on the causes of quality defects
  - take action to prevent reoccurrence

3. Quality Control

SIBP has a Quality Control Department, which is responsible for sampling, testing for all products, including raw materials, intermediate products and final products.

- the head of department is well qualified and trained
- the department is independent from others
- adequate facilities
- testing is carried out correctly according to written procedures
- test methods are approved by National Control Authorization
- sampling for all products according to written procedures is carried out correctly
- take part in the some measures for validations
  - environmental monitoring (particles and microbial)
  - quality of the water
  - autoclave
  - filling process
- to check the reagents, volumetric glassware, reference standards regularly

III. SIBP will be improved while GMP is carried out

1. The concept of GMP is required to be promoted especially by senior managers:
   - the effectiveness of production management needs improvement,
   - to establish QA office which is independent from QC and other departments,
   - the documentary system is required to be strengthened.

2. The practical effectiveness of training of GMP for all personnel will be improved, especially for continuous training. SIBP needs:
   - continuous training references especially for maintenance personnel;
   - qualified trainers;
   - some teaching tools, slide, videos, etc.

3. Some testing methods will be in line with international methods, especially for potency test.
   - the national standards do not correspond with international standards;
   - the methods approved by National Control Authority are different from the international methods;
   - not enough qualified personnel who engaged in these methods.

4. The contract manufacture and analysis is unsatisfactory in China
   - only testing by SIBP;
   - no investigation of GMP for contract manufacture;
   - no visit to the facilities of the contract manufacture.

IV. Special issues

1. How to prepare in order to assure that the new facilities (CVP) will be in compliance with EV GMP.

2. The concept of validation is not clear, especially for Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). How to carry out the validation at these three stages.

3. The acceptable limit of validation is not clear.
   - how many items need validation
   - how to do the validation of each item
   - what is the acceptable limit for each item

THE EXISTING STATUS OF QA/GMP/QC IN CHENGDU INSTITUTE OF BIOLOGICAL PRODUCTS

by Mr. Chen Xuekui
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Quality Control Department
Chengdu Institute of Biological Products, P. R. China

Chengdu Institute of Biological Products, situated in the south-western part of China, was set up in 1958, its main task is to produce the following vaccines for the expanded programme on immunization (EPI):

1. Measles Vaccine
2. BCG Vaccine
3. DTP Vaccine

It also produces Hepatitis B Vaccine prepared from plasma, Japanese Encephalitis Vaccine (live), Vi Polysaccharide Typhoid Vaccine, Meningococcal Polysaccharide Group A Vaccine, Rabies Vaccine, etc. It has made great contributions to the prevention and control of certain diseases since 1958.

Nowadays, most of the existing facilities in the institute are out-of-date. Our institute has begun to improve the old facilities or to construct some new facilities step by step. The BCG vaccine production facility and the Filling and Packaging facility are newly constructed and put in use. Another new building for vaccine production is under construction.

I think our institutional strengths related to QA/GMP/QC is that we begun to set up new facilities or improve some old facilities according to GMP requirements, to have our staff educated with these new concepts, and to use these new theories successfully to guide our work. Our institute has a staff of 1300, 49% of which are college and technical school graduates with practical experience and good theoretical knowledge. They have been working on vaccines for years. They are capable of working on technological process, quality control, research and development of new vaccines. Working with them is also a team of well-trained and skilled workers. They followed many strict regulations including the Requirements for Biological Products of China for many years even before the concepts of GMP are introduced into our institute. An enterprise's life lies in its quality. In 1980s a comprehensive quality control and GMP were practiced. We have now developed an effective system of quality control. Pursuing the policy of "quality first", the quality control committee, headed by the Director of our institute, strictly carries out quality veto in the economic responsibility system. Our institute possesses advanced control means and testing facilities and a quality control network, the institute, workshop, and group at three levels, are in charge of the whole process of making and implementing quality standards, testing, control and auditing. Furthermore, we have a prospective market for our biological products, and our products enjoy a good reputation of high quality.

The institutional weakness in relation to QA/GMP/QC is that most of our facilities are out-of-date, and meanwhile we do not have enough funds for construction, and lack such

persons who know quite well about QA/GMP/QC and can give instruction to the construction of GMP facilities.

I hope to get a better understanding on the requirements of QA/GMP/QC through the participation on the training course, and then manage to become an expert in this field who will be capable of guiding the design and construction of facilities according to GMP, meanwhile to accelerate the implementation of GMP in production, quality control and scientific research, thus benefits our institute.

I wonder if the organizers could show us an example of facility design, to teach us in details what should be always considered during the design, what kind of special constructive materials are usually used, in which part of a facility. How about QA/GMP/QC in other countries?

LANZHOU INSTITUTE OF BIOLOGICAL PRODUCTS

by Mr. Xinliang Shen
Lanzhou Institute of Biological Products
Lanzhou, Gansu, P.R.China

A. Outline of our existing facilities, staff and plans for future development

(a) Institute

Lanzhou Institute of Biological Products, MOPH, a state establishment subordinated to the China National Biological Products Cooperation, is one of the six national institutes in China. It covers a total area of 430,000 m^2, of which over 100,000 m^2 is occupied by buildings. The institute consists of 14 production and 5 research departments and several other administration divisions. Currently, its employees are about 1,700. It is responsible for the scientific research and preparation of biological products used for the prevention, treatment and diagnosis of various infectious diseases and other diseases. Over 130 million of doses of various products are distributed annually to the markets of nearly all over the country.

(b) Laboratory

The 4th research department is one of the 5 research departments in our institute, 11 staffs work in the department. Among them, 10 persons are researchers, including two vice professors, one senior engineer, four engineers and three researchers on practice. It is equipped with the following laboratories : molecular biological, monoclone antibody, protein purification and electricity microscope. We focus our work on researching hepatitis E virus. We hope to develop HEV vaccine in the future.

B. Institutional strengths in relation to QA/GMP/QC

(a) Staff and training

There are certain members of staff with various levels, including administrators, professionals and producers in the fields of production and quality control in our institute.

Since 1980's GMT management have developed a series of teaching and training for our staff. In 1987-1989, our senior staff, both management and production, had taken part twice in the GMT training workshops organized by MOPH and UNICEF at Lanzhou and Beijing Institute of Biological Products and attended the training workshop for standardization of Biological products and its quality control by WHO in 1991. GMP training courses in turn is taken annually by all staff at each level, in order to obtain the concept of GMP to conduct their work under the requirements.

(b) GMP hardware

To meet GMP requirements, a rabies vaccine workshop has been built; a filling and packing workshop in recent years and is running out already; animal facility and quality control building as well as China Vaccine project are under constructions and will be put into operation in 1996-1997.

(3) GMP software

Since the "Management Standards for Pharmaceutical Production" was issued by the authority in 1982, it is followed by the GMP plan and its detailed protocols by the institute. Action has been taken to standardized the primary production workshops with the Total Quality Control.

Institutional weaknesses in relation QA/GMP/QC

The institute was established in 1934. It is an old enterprise equipped with many workshops and equipment which do not meet the GMP standards, are faced to be reformed and rebuilt. A large amount of financial fund has to be expended and has to be solved one by one. It is the weakness in the quality management system and its regulations. And we hope to develop GMP training repeatedly in our institute.

C. Hope to benefit from this training course

(a) To connect to the international vaccine production and quality control of GMP management module.

(b) The modern workshops and equipment for the current vaccine production.

D. Specific issues

QA/GMP/QC requirements to the production of recombination DNA vaccine, its building design, production process design and quality control.

2. HONG KONG*

HONG KONG INSTITUTE OF BIOTECHNOLOGY LIMITED

by Dr. Simon C. W. Kwong
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Hong Kong Institute of Biotechnology Limited (HKIB), Hong Kong

Background

The Bioprocessing Unit was set up by funding supports from the Hong Kong Government Industrial Support Fund (ISF) and the Hong Kong Jockey Club Trust Fund (HKJC) in 1994. It is located on the ground and mezzanine floor areas of HKIB building, with a total area of approximately 12,000 square feet. The Bioprocessing Unit is a pilot scale R&D and manufacturing facility for multi-purpose bioprocesses. It is set up to provide R&D services and support for product commercialization to local companies. The Bioprocessing Unit facility renovation started in November 1995 and completed in May 1996. It is scheduled that the Unit will be fully operational by April 1997. Since the current facility of the Bioprocessing Unit is not designed to manufacture clinical grade materials, HKIB is further upgrading the facility to GMP standards in the next two years.

In October 1995, the United States National Institute of Health (NIH) has awarded HKIB a Material Transfer Agreement in which the NIH agreed to supply HKIB the know-how of manufacturing an antimalarial vaccine. In December 1995, HKIB was selected by the World Health Organization as the site to manufacture the vaccine licensed from NIH.

With the help from the ISF, HKJC, NIH, and WHO, the Unit has expanded its scope to cover many different areas including Good Manufacturing Practice (GMP) technical support services, quality control test services, gene cloning support services, etc. In addition, the Bioprocessing Unit will be upgraded to WHO's GMP Standards and a Quality Control Unit will be set up and will be fully functional by 1998.

I. Introduction

The Bioprocessing Unit is a pilot scale R&D and manufacturing facility for multi-purpose bioprocesses. In addition, the Unit will expand and upgrade part of its facility to WHO's GMP standards by 1998. The primary functions of the Bioprocessing Unit are:

- To provide process development capability to evaluate and improve production conditions, and to develop low-cost production strategies for a potential product with commercial value.

* Note: Hong Kong Special Administrative Region, the Government of the People's Republic of China resumed the exercise of sovereignty over Hong Kong effectively from July 1, 1997. During the time of the workshop (July 1996), Hong Kong was a British crown colony.

- To allow the pilot manufacturing of a diverse range of products of bacteria and human origins.

- To provide downstream product recovery and purification services from pilot manufacturing or from other sources.

- To provide pre-production and GMP manufacturing of microbial products.

- To provide quality control tests for biotechnology products.

The design of the facility was based on the Biological Laboratory Safety Level 2 Large Scale (BL2-LS) guidelines set by National Institute of Health, USA. The facility are being upgraded to WHO's GMP standards. In order to support these various functions, the facility was designed to allow great flexibility to reflect the anticipated growth of the Bioprocessing Unit. The Unit includes many different laboratories with different functions. The major laboratories and service facilities are listed as follows:

Process Development

- Microbial Process Development Laboratory
- Cell Culture Process Development Laboratory
- An Environmental Controlled Incubation Room

Pilot Manufacturing Plant

- Pilot Fermentation Suite
- Protein Purification Suite
- Medium preparation room
- General equipment room
- Environmental controlled room (cold and warm rooms)
- General utility and service rooms (purified water, plant steam, compressed air, vacuum, etc.)
- Decontamination room
- General wash room
- Storage and warehouse

GMP Manufacturing Plant

- GMP Fermentation Suite (Class 100,000)
- Protein Purification Suite with walk-in cold room (Class 10,000)
- Medium preparation room
- General equipment room
- Environmental controlled rooms (cold and warm rooms)
- GMP utility and service rooms (WFI, clean steam, CIP system, sterile compressed air system, etc.)
- Decontamination room

- General wash room
- Clean Storage and warehouse

Quality Control Unit

- Analytical Laboratory
- Microbiological Laboratory
- General Quality Control Laboratory

II. Process Development

Any product with commercial value will need to be evaluated in both technological and economical aspects before moving to the stage of manufacturing and marketing. The set-up of the cell culture and microbia process development laboratories is the first step for product commercialization. The objectives of the process development laboratories are first to exploit different production methods for specific product with commercial value, and to optimize the production conditions before going to pilot production. In other words, the operation of the process development laboratories is to evaluate and improve the technical production process of a product with commercial value to reduce the production cost and increase its profit margin.

The Bioprocessing Unit can offer our clients the following process development services:

- A Medium Formulation
- Method Development (Culture, Purification, etc.)
- Production and Process Optimization
- Small Scale Manufacturing (2 to 20L Scale)

Facility

A Microbial Process Development Laboratory
A Cell Culture Process Development Laboratory
An Environmental Controlled Incubation Room

Processes

Bacterial (*Brevi bacterium flavum, corynebacterium glutamicum, Halobacterium halobium, Hyphomicrobium methylovorum, Methylobacterium sp., Escherichia coli etc.*), Yeast, rDNA, Mammalian Cells (murine hybridomas, CHO cells, BHK cells, human hepatoma cells, murine sarcoma cells, human chondrocytes, chicken embryo fibroblasts, etc.), Insect Cells [(*Spodoptera frugiperda* (Sf-9 and Sf-21) and *Trichoplusiani* (Hi-Five cells, and MG-1)], Plant Cells, etc.

Products

Recombinant Proteins, Speciality Chemicals (amino acids, isotopic chemicals), Agricultural Proteins, Clinical/diagnostic-grade monoclonal antibodies, Food and Health Products, etc.

Major Equipment

Autoclave
Biosafety Cabinets
Freezers and Refrigerators
Lyophilizer
Shakers
Incubators (CO_2)
Small Fermentors (2 to 20L)
Bioreactors (2L)
Microscopes
Bench Top Microcentrifuges
Ultra-Centrifuge
Refrigerated Centrifuge
MF/UF system with cassettes and hollow fibre filters (laboratory scale)
HPLC
Gradient liquid chromatography system
Spectrophotometers

III. Gene Cloning and Protein Expression

Gene cloning and expression are the key steps in genetic recombinant technology. The technical aspect of gene cloning and expression has been thoroughly elucidated and the experimental approaches have become routine and standard. Therefore the Bioprocessing Unit has set up Gene cloning and Protein Expression Services along with the Process Development services to serve Hong Kong companies by generating the bioengineered cells to provide the companies with cost-effective manufacturing processes as well as new tools for them to expand their product pipelines. The Bioprocessing Unit is offering the following Gene Cloning and Protein Expression Services:

Complete gene cloning service from a given idea and organism process to industrial production

- Gene library
- Part of amino acid sequence of the relative gene
- Gene cloning on a vector, DNA sequence and its coding amino acid sequence
- Modified gene and its information
- Strain of host cell carrying the modified gene and suitable for industrial production
- Medium formula for fermentation
- Protocol for fermentation
- Protocol for end-product purification

cDNA library (based on lambda or plasmid vector) construction

- cDNA library and library information

Genomic library (based on cosmic, lambda replacement or lambda insertion vector) construction

- Genomic library and library information

Gene screening and DNA sequencing with commercial gene library and given probing information

- Gene cloning on a vector
- DNA sequence and its coding amino acid sequence
- Screening information

DNA sequencing

- Gene cloning on a vector;
- DNA sequence and it's coding amino acid sequence

Gene modification from a given gene

- Modified gene and its information
- Strain of host cell carrying the modified gene and suitable for industrial production

Facility

- A Molecular Biology Laboratory
- A Radio-chemical Laboratory
- A Dark Room

Products

Human Genomic Libraries

IV. Pilot Manufacturing Plant (Available in April 1997)

The Pilot Manufacturing Plant is the heart of the Bioprocessing Unit. It is equipped with a 350L pilot scale fermentor and some recovery equipment including micro-filtration and ultra-filtration units and procession tanks. One of the objectives of the Pilot Manufacturing

Plant is to provide pilot manufacturing of the product being developed in the process development laboratories for the purpose of optimization. Another use of the Pilot Manufacturing Plant is to provide contract manufacturing for companies in Hong Kong and from overseas. In addition, pilot-scale purification capabilities are being set up and the plant will also be equipped with micro/ultra filtration equipment, chromatography columns, and some basic analytical equipment. It is scheduled that the Pilot Manufacturing Plant will be fully commissioned and functional by April 1997. The Bioprocessing Unit is offering our client limited services in the following areas:

- Scale-Up Process Optimization
- Pilot Manufacturing (20 to 350L Scale)
- Bulk Product Purification

Facility

Pilot Fermentation Suite
Protein Purification Suite
Medium preparation room
General equipment room
Environmental controlled room (cold and warm rooms)
General utility and service rooms (purified Water, plant steam, compressed air, vacuum, etc.)
Decontamination room
General wash room
Storage and warehouse

Processes

Bacterial and Yeast Fermentations

Products

Recombinant Proteins, Specialty Chemicals (amino acids, isotopic chemicals), Agricultural Proteins, Food and Health Products, etc.

Major Equipment

Autoclaves
Biosafety Cabinets
Chemical Fume Hoods
Freezers
Refrigerators
Pilot Fermentor (20L Seed, 350L Fermentor)
Processing Tanks
Medium Filtration

Centrifuge
Homogenizer (2L/min, 250-2000psi)
MF/UF Dual System (Pilot-scale)
Preparative LC
Computers
Ice Makers

V. GMP Manufacturing Plant (Available in June 1998)

In order to manufacture Phase I and II clinical materials, it is important to have a manufacturing site in compliance with GMP guidelines. Therefore, the Pilot Manufacturing Plant is being upgraded to meet the WHO's GMP requirements and will be completed in 1998. The Pilot Manufacturing Plant is being set up with an initial product target of a yeast-based anti-malaria vaccine based on a technology transfer from the Malaria Vaccine Section (MVS) at the National Institute of Health (NIH) of the U.S. Government and in collaboration with the World Health Organization (WHO). The manufacturing of the malaria vaccine will be under the guidance of MVS and WHO.

By the year 1998, the Pilot Manufacturing Plant will possess the crucial elements in GMP manufacturing, including a GMP Manufacturing Plant and scale-up expertise and know-how in GMP processing and validation.

Facility

GMP Fermentation Suite (Class 100,000)
Protein Purification Suite with walk-in cold room (Class 10,000)
Medium preparation room
General equipment room
Environmental controlled rooms (cold and warm rooms)
GMP utility and service rooms (WFI, clean steam, CIP system, sterile compressed air system, etc.)
Decontamination room
General wash room
Clean Storage and warehouse

Processes

Bacterial and Yeast Fermentations

Products

Clinical-grade supplies for Phase I and Phase II clinical trials

VI. Quality Control Unit (Available in June 1998)

As the Pilot Manufacturing Plant is being upgraded to WHO's GMP standards in the next three years, a Quality Control Unit will also be set up to perform in-house quality control and quality assurance tests and validation procedures according to the GMP standards. The Quality Control Unit (QC) will include three quality control laboratories, i.e. an Analytical Laboratory, a Microbiological Laboratory, a Biological Laboratory and a Quality Assurance Office (QA).

The Quality Control Unit will be housed with basic analytical equipment which will be sufficient to perform basic analyses and tests (i.e., tests for product identity, purity, stability, and safety). The Quality Control Unit will focus on the microbiological and biological tests which HKIB already has in-house expertise and some basic equipment to perform these tests. The initial focus of the quality control tests will be based on the technology transfer of the malaria vaccine. The Quality Control Unit will develop tests by collaborating with MVS and the Biotechnology Unit of NIH for product identity, purity, stability, and safety for biopharmaceutical products.

Facility

Analytical Laboratory
Microbiological Laboratory
General Quality Control Laboratory

QA/GMP/QC OF VACCINES IN HONG KONG

by Dr. Lim Wei-ling
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Introduction

In Hong Kong, various immunizations for infants and children have been introduced since 1950s. At present, immunizations of children against nine diseases are recommended. They include hepatitis B, mumps and rubella in addition to the six EPI targeted diseases, namely, diphtheria, pertussis, tetanus, measles, poliomyelitis and tuberculosis.

All vaccines imported into Hong Kong have to obtain license from the Department of Health. Currently, except for oral poliovirus vaccines, all other vaccines used in the immunization programme are imported in ready-to-use form straight from the registered manufacturer. Oral poliovirus vaccine is imported in concentrated form of monovalent type 1, 2 and 3. They are diluted to make up the type 1 and trivalent vaccines by the Institute of Immunology, Department of Health, and then supplied to public hospitals, maternity homes, health clinics as well as clinics and hospitals run by private practitioners. Immunization of newborns with type 1 poliovirus vaccine in addition to trivalent vaccines later at 2-6 months were introduced in 1966 following a large outbreak of paralytic disease due to type 1 poliovirus. In terms of sero-conversion and antibody titre, it was confirmed by serological studies that children who had type 1 vaccine at birth in addition to trivalent vaccines compared more favorably with those who had only trivalent vaccine.

The Institute of Immunology in Hong Kong used to manufacture plague, smallpox, typhoid, cholera and rabies vaccines for use in Hong Kong until the early 1980s. At present, apart from diluting and bottling poliovirus vaccine, it also dilutes and bottles tuberculin. Quality control of products is performed for every batch prepared. Quality control testing of other live virus vaccines is also undertaken as and when required.

Facilities and staff

The three story building with a floor area of around 1,000 m^2 with adjacent animal houses started operation in 1973. The vaccine production area was under positive pressure ventilated with clean air filtered through HEPA filter. Walk-in cold and warm rooms are available. All equipment including laminar flow cabinets, microbiological safety cabinets, refrigerated centrifuge, freezers and steam autoclaves are maintained regularly by trained staff.

Staff consisted of 3 well qualified medical technologists, 4 laboratory attendants and 3 workmen. One of the medical technologists had attachment training for 3 month on quality control of vaccines at the National Institute for Biological Standards and Control, Potters Bar, U.K. in 1992. Documentation of procedures are available for use by staff.

Vaccine production

The Institute distributes 600,000 doses of type 1 and trivalent oral poliovirus vaccine annually. The existing arrangement for polio vaccines is working satisfactorily and less wastage is observed by self preparation from bulk vaccine. With the eradication of poliomyelitis in sight, the Advisory Committee on Immunization in Hong Kong has resolved to continue the practice of immunizing newborns with oral type 1 poliovirus for the next few years.

Assessment of antibody response

At present, the Institute undertakes regularly to measure antibody responses to various vaccines, including measles, mumps, rubella, polio, hepatitis B, tetanus and diphtheria. This aspect of activity may be expanded as more and more vaccines are used/recommended in the immunization programme.

Vaccine Control Laboratory

Quality control of oral poliovirus vaccine prior to distribution is currently undertaken routinely in the Institute. However, it is also necessary to monitor continuously the quality of vaccine being used at the most peripheral point of the territory. As testing of other imported live cirrus vaccines is often requested, establishing technical competence on this would be essential.

As a control laboratory, it is also necessary to give scientific advice on the suitability of vaccine registration and procurement, thorough knowledge on all stage of manufacture of various vaccines and ability to examine critically all procedures would be imperative.

Development of molecular technique is yet another aspect we need to explore. Ability to characterize virus strains, whether vaccine or wild strains, would facilitate post marketing surveillance.

3. INDIA

NATIONAL INSTITUTE OF BIOLOGICALS MINISTRY OF HEALTH & FAMILY WELFARE

by Dr. (Mrs.) Ira Ray
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Ministry of Health & Family Welfare, India

A. BACKGROUND

The National Institute of Biologicals has been established by the Ministry of Health & Family Welfare in joint collaboration with the USAID and OECF (Japan) to fulfill the need for a high standard of quality of biological products like vaccines, blood and blood products, reagents and immunodiagnostic kits used in the country. It was registered as a society under the Societies Registration Act, 1860 in January 1992. It has the status of an autonomous body.

The NIB has the following mandate and functions:

Mandate:

(i) To develop a lay down standards for quality control testing procedures for biologicals and immunobiological products.

(ii) To develop linkages with other National/International Institute and keep abreast of world-wide scientific research and technology developments in quality control of biologicals and immunobiologicals with a view to advising on the suitability of their adoption.

(iii) To provide training facilities in quality control for personnel of related institutions including manufacturing units.

(iv) To assess from time to time availability of qualified manpower to meet the needs of quality control and manufacture of biologicals so as to advise the Government on appropriate measures and the scope of upgrading existing testing facilities in the country.

Functions:

The following functions are assigned to the Institute:

(i) The Institute will undertake systematic examination of the quality of biological and immunobiological products, with a view to enable the release of indigenous and imported products after certification, according to the procedures prescribed under the Drugs and Cosmetics Act, 1940.

(ii) The Institute will establish national reference standards and serve as a repository and a national bank for reference standards and reagents for biologicals and immunobiologicals.

(iii) The Institute will develop suitable network/linkages with related institutions set up by the Central or State Government or within Universities so as to effectively disseminate knowledge, develop manpower and act as a resource backup for long term development of reference standards and quality.

(iv) The institute will, in consultation with the Indian Pharmacopoeia Committee, develop and establish pharmacopoeial specifications appropriate for biological products for use in India.

(v) The Institute may function as an accredited testing and reference laboratory for quality control of biological products available in the future and it may evaluate and advise on the emerging technologies in these fields in terms of their specificity, sensitivity and replicability.

(vi) The Institute will provide training to scientific and technical personnel in the procedures for development of standardization and quality control methods of immunobiologicals.

(vii) The Institute will develop technical guidelines/manuals on standards to be used by manufacturers and also for training scientific technical manpower for standardization and quality control.

(viii) The Institute will monitor ongoing research, establish linkages and exchange personnel with different institutions in India and abroad for the furtherance of its mandate.

(ix) The Institute will act as National External Quality Control Laboratory for microbiology laboratories at users level and set up a network of such laboratories on a regional basis at least up to District level.

Though the primary objective of NIB is quality control, the institution will conduct research to maintain its level of expertise in the development of new manufacturing and testing process. Keeping in view the multi-dimensional activities, NIB has been envisaged as a Referral Laboratory for testing of all biological products for the country and for the South East Asia Region.

Present status of testing of biologicals

Production of vaccine, sera and blood products on India requires license from the Central Licensing Authority (CLA) set up in the Central Drugs Control Organization. The manufacturing units are required to produce up to six batches of vaccines, in the smallest lot that can be manufactured using the technology proposed and get the sample tested for each batch in a national reference laboratory. License for production is issued only if each batch passes tests. License is issued for a period of two years and renewed from time to time. Manufacturers premises are also inspected by Drug Controller General (India) prior

to the issuance/renewal of license. Vaccines, etc. can be produced only from seed lots obtained from approved sources.

The manufacturing firms have internal quality control machinery for testing sera, vaccine etc. produced by them for potency, safety, toxicity, sterility, etc. as per pharmacopoeial requirements. Under the National Immunization Programme (NIP) (re-named as National Child Survival & Safe Motherhood Programme) Polio Vaccine, DPT, DT, TT and Measles require to be compulsorily tested at quality control research laboratory, CRI, Kasauli before release. BCG vaccines used in the programme have so far been tested by producers i.e. BCG laboratory, Guindy. All the other vaccines can be sold by the producers on the basis of clearance from their in-house quality control unit.

Imported biologicals are required to be tested at Quality Control Reference Laboratory before they are released by customs. For all human blood products test for HIV antibodies is compulsory. HIV test kits required for use in National Programme on AIDS are imported through WHO, Geneva which makes its own evaluation. Local evaluation made by designated Indian agencies is also furnished to WHO.

Future Role of NIB

The NIB is being set up as an apex body for quality control of biologicals. This will cover quality control and assurance at manufacturers and users end. Eventually the Central Licensing Authority may appoint NIB as the Advisory Body for all matters relating to licensing and Quality Control of Biologicals. It will also be declared as the National Reference Laboratory under Drugs & Cosmetics Rules. The manufacturers may then be required to provide trial batches of biologicals to NIB and get the samples tested for each batch before issuance of license for bulk production. The Drug rules may also eventually provide for pre-release testing of biologicals by NIB.

NIB as an expert body may be required by the Central Licensing Authority to carry out the following functions:

(i) Examine the proposed technology and determine the suitability in the context of the conditions provided by the applicant.

(ii) Inspect the building, plant and machinery and other facilities offered by the applicant.

(iii) Validate the manufacturing technology and quality control procedures.

(iv) Examine the qualifications and experience of the key personnel engaged in production and quality control.

(v) Test the final product.

(vi) Report on items (i) to (v) to CLA along with the recommendations.

The NIB may also be required to conduct a technical audit of all licensed manufacturing units/blood banks.

The NIB will standardize quality control methodologies and set up Standard Operation Procedure and National Reference Standards.

Project Details

The establishment of the Institute will be funded by the Government of India with a soft loan assistance from the Government of Japan through OECF (Overseas Economic Cooperation Fund) and grant assistance from US Government through the USAID. The project estimate, as approved by the Government of India, is as follows:

(i) Government of India	Rs.	24.25 Crores
(ii) Government of Japan (OECF)	Rs.	37.17 Crores
(iii) Government of USA (USAID)	Rs.	8.32 Crores
	Rs.	69.74 Crores

(This figure may require revision consequent on escalation in cost and revision of exchange rates).

The funds allotted by different agencies will be utilized for the purpose mentioned below:

(i) Government of India	:	Purchase of land, land development, designing and construction through A&E firm (HSCC) maintenance including staff cost.
(ii) US Government (USAID)	:	Procurement of movable scientific equipment including computer, training of technical staff and technical assistance for Building design (Laboratory and Animal House).
(iii) Government of Japan (OECF)	:	Construction cost, cost of fixed equipment, furnishings and vehicles.

Hospital Services Consultancy Corporation (India) Limited, Government of India Enterprise, under the Ministry of Health & Family Welfare has been appointed as A&E Consultants for the project.

The Permanent Facility of National Institute of Biologicals is being built on a plot of land measuring 18.28 acres (74,000 m^2) in NOIDA, UP. Construction work for Administrative Block, Hostel, Guest House and Cafeteria is in progress and the structures are nearing completion. These buildings are scheduled to be completed by March, 1997.

Designing of the Laboratory and Animal House Blocks of the NIB which are highly prestigious and sophisticated is being done by the A&E Consultants appointed by NIH Washington who have also incorporated the views of eminent scientists of various institutions in India, Japan and USA. Designs are in final stages of completion and, when completed, the work will be awarded and construction work will be taken up. The

laboratory and Animal House will be ready for commissioning by 1999. The laboratories has been designed on modular basis to provide flexibility. Provision has also been kept for further expansion of the laboratory building.

The laboratory Block/Animal House will have the following functional groups:

(1) Bacteriology, Parasitology and Mycology
- Tuberculosis
- Leprosy
- Pertussis
- Cholera
- Salmonella
- Shigella
- Malaria
- Schistosomiasis
- Leishmaniasis
- Mycoplasina
- Toxin/Antitoxin
- Bacterial Polysaccharides

(2) Virology
- Poliomyelitis
- Hepatitis
- Japanese Encephalitis
- Acquired Immunodeficiency Syndrome
- Measles
- Rubella
- Mumps
- Influenza
- Yellow Fever
- Rabies

(3) Blood Products and Blood Grouping
- Human Hyper-Immune Globulins
- Blood Typing Sera
- Plasma Derivatives
- HLA Antigens

(4) Immuno-diagnostic kits
- HIV kits
- Hepatitis B kits

(5) Supporting Activities
- Cell Culture
- Reference Standard
- Media Preparation
- Sterility Testing
- Recombination DNA
- Analytical/Organic Chemistry

Bioassay: Pyrogen, safety, potency and toxicity

ANIMAL FACILITY

Small Animal Production, Monkey Quarantine/Testing Animal Pathology

Interim facility

Pending completion of the permanent facility at NOIDA, it was proposed to start the scientific programme. For this purpose, accommodation was hired at Jhandewalan Extension, New Delhi. This has been renovated and put to use for locating the administrative infrastructure and laboratory and ancillary functions. Most of the equipment required for commencing work on blood grouping, testing of HIV/Hepatitis B Virus (HBV) Test kits has been received and is being installed to store the samples and sera which are being collected by the scientists from various institutions in the country. All action has been taken to provide the supporting facilities like additional power supply, generators, special air-conditioning, etc.

Scientists required for Interim Facility have already been recruited and are being trained in various institutions in the country to provide them an exposure in general and specific areas. A detailed programme for training these personnel was taken up recently (January, 1996) by a team of Public Health Laboratory Chiefs from USA which was in India for this purpose. Two of the scientists have already been trained in CBER, FDA Washington, USA and would soon be put under validation.

Laboratory QA/QC - Clinical Microbiology

National Institute of Biologicals has an important role to play in ensuring the quality of testing by clinical microbiological laboratories in the country. At present, due to lack of mandatory standards, infrastructure and external quality control laboratory facilities, the consumers are unable to get safe and reliable clinical microbiological testing facilities.

NIB has taken steps to address this problem by organizing workshops/seminars for different client groups such as at district hospitals, medical college, research institutions, etc. It has brought out a Manual of Standard Operating Procedures for Microbiological laboratories which is undergoing pre-testing.

Following exposure of laboratory scientists, as the consumer of biological products in clinical microbiological laboratories, it has been appreciated at the national level that NIB should take a lead role in establishing a network of laboratory diagnostic services for developing uniform standard of laboratory procedures, methodologies followed and interpretation of laboratory results to support clinical services. NIB has identified some medical institutions of excellence in different regions to act as lead centers in that region in the first phase. These Lead centers under the guidance of NIB, would collaborate with other important health and medical care institutions in the region for establishing external and internal quality control system. These collaboration centers would be supported by the lead centers and will be identified as the regional centers.

In the second phase of the programme these regional centers would further establish a network of quality control system with other health care facilities up to the district level.

With the comprehensive network, the diagnostic services will be substantially improved for better patient care management.

With the up gradation of secondary level hospitals in many of the States this would be the most important activity. The need for and importance of quality control system could also be visualized in the light of the dependence on the laboratory findings in various National Control Programmes like TB, Leprosy, Malaria and other communicable diseases. It is only through such a programme that we can expect to have a uniform standard and methodology in the clinical laboratory services for better health and patient care management at all levels in the country.

As this is a very vital programme, the proposal has been placed before the World Bank who have agreed to support the programme in principle.

B. Institutional strength of NIB in relation to QA/GMP/QC

NIB is a national-level super speciality institution functioning in close collaboration with the Ministry of Health and Family Welfare and Central Drugs Control Organization. The heads of these organizations, which formulate national policies on public health and overseas their implementation are on the Governing Body and other policy-making bodies of NIB. This ensures that priorities of NIB are in complete harmony with national health policy.

The Laboratory and Animal House of NIB is being designed by National Institute of Health, USA in line with world-renowned biological laboratories like Center for Biologics Evaluation (CBER), USA. In this task, NIB had the benefit for advice of renowned microbiologists of USA, UK and Japan. A team of eminent Indian scientists from National level microbiology laboratories in India provided valuable inputs regarding design, laboratory layout and equipment. The laboratory design, therefore, has taken into account the environmental and climatic conditions in the country. This would also ensure that the laboratories are of International standard and could be serviced and maintained properly.

Functionally the laboratories will cover the entire spectrum of National priorities in QC/QA of biologicals and immunobiologicals. They will be equipped with the latest and sophisticated scientific equipment.

NIB has prepared a strategic Science Programme with the assistance of Training Consultation and Management Resources (TCMR) and William Joiner Foundation, USA. Detailed time-lines have been worked out for identified priority areas. NIB is in the process of setting up a Technical Assistance Team with microbiology experts drawn from institutions like US Public Health Laboratories, CBER, NIBSC, UK, Pasteur Institute Paris, WHO, etc. to standardize testing procedures, provide scientists international training experience, validate test results, etc.

Located as it is in Delhi which has number of super-speciality institutions, big hospitals and blood banks, NIB has access to laboratories for collection of samples of blood, sera etc. It has already collected adequate samples for preparing reference panels.

NIB has developed close working relationship with National level laboratories situated all over India. The scientists and technical staff of NIB have been trained in such laboratories in the areas of Quality Control testing methodologies, testing of blood grouping, reagents, HIV/HBV test kits, vaccines etc. were held in different parts of the country which made recommendations for drafting Standard Operating Procedures.

NIB is assured of financial support from the Government of India which will meet its operational cost in full. The project cost is shared by the Government of India, the Government of Japan and the Government of USA.

NIB has formulated a scheme for Regional Quality Control of Biologicals through a network of Centers of Excellence. It will act a s a National External Quality Control Laboratory for them. This will help in spreading quality consciousness among microbiology in the Government of India. World Bank has agreed in principle to fund this project. Thus, NIB's strength is that it can ensure that the basic role of quality control of biologicals is made effective by their proper application at user's end. It will also provide the user's angle to manufacturers.

Institutional Weaknesses in Relation to QA/QC/GMP

The NIB project is still in the process of implementation. The full-fledged permanent facility with Animal House will be commissioned only by about 1999. In the meantime, NIB needs facilities for developing standards, reference materials, training of staff, etc. A small hired premises is being used for this purpose. In view of limited space, constraints of infrastructure, etc. NIB is not in a position to grow to its fullest potential immediately.

The laboratory that is being established at permanent facility is first of its kind in India. There will be a need for close interaction with CBER, USA, NIBSC, UK, etc. to ensure that methodologies and procedure followed by NIB is according to International standards. A mechanism for continuous consultation by exchange of visits by eminent scientists, exchange of views by E-mail, etc. is essential.

The regulatory mechanism for biologicals needs to be streamlined in order to enable NIB to function as National Quality Control Reference Laboratory (NQCRL) for biologicals. The power of licensing authority to prescribe pre-release testing of biologicals in NQCRL has to be made clear. Manufacturers of biologicals should be required by law to forward test and manufacturing protocols for each batch of biologicals to the NQCRL along with specified quantity of samples.

After NIB is fully operational, manufacturers should be required to use reference materials available with NQCRL for testing of sera and vaccine by them.

The Drug Rules governing biologicals and India Pharmacopoeia need review to remove some anomalies.

On the consumer's side, it is difficult to implement the programme because of the vastness and diversity of the country, lack of regulatory mechanism, lack of uniform standards and due to laboratories being under state control.

C. How do you hope to benefit (both personally and institutionally) by your participation in the training course?

The Institute is in the process of being established. The design of Laboratory and Animal House has been finalized and construction work will be taken on hand. The broad items of Science Programme have also been identified. Since the project is being implemented and I am the Director, any input relating to Science Programme, laboratory design, etc. gained by me during the course of training can be incorporated in the project. It will help us to review our programmes and find out whether we have missed anything vital in the area of QC/QA.

The course will also help me in exchanging notes with eminent participants from other countries who may have undergone similar experience in establishing national-level laboratories and profiting by their experience of problem-solving in the areas of project management and developing science programme.

NIB has formulated a scheme for regional quality control of biologicals at users end. This envisages the setting up of a National External Quality Control Laboratory in NIB, about 12 Centers of Excellence (to be known as lead centers) in different parts of the country and selected regional centers affiliated to the latter. The experience of other countries in setting up similar network as well as valuable suggestions from participants will help NIB in effective implementation of the scheme.

A lot of technological changes have taken place in the sphere of manufacture of vaccines such as use of recombinant DNA, dispensing with animal testing, development of multiple vaccines, etc. New vaccines are being developed and existing vaccines are being refined. The techniques of disease control are undergoing changes. In this state of flux, the methodology of QC/QA needs to be constantly reviewed. Participation in the training programme will help me in keeping abreast of new developments and fine-tuning procedures and methodology in line with changing scenario.

Discussion and interactions with participants from several vaccine manufacturing units/national control laboratories will lead to cross-fertilization of ideas. It will also help me to have access to an informal network of eminent microbiologists participation in the programme, which will be of use to NIB in its formative stages.

D. Any specific issue or concern of NIB the faculty may consider or address

NIB has been set up recently and the strategic plan for science programme is being formulated, keeping in view its mandate. The advice of the learned faculty regarding the areas which we should emphasize will be valuable and NIB would like them to consider this issue.

CENTRAL RESEARCH INSTITUTE, KASAULI (HP) INDIA

by Dr. J. Sokhey
Director, Central Research Institute (CIR)
Kasauli, Dist. Solan, Himachal Pradesh, India

A. Background

Central Research Institute (CIR) under the Ministry of Health and Family Welfare, Directorate General of Health Services, Government of India was established in 1905 for the manufacture of Antirabies Vaccine. Soon after its establishment the Institute for the first time in the country introduced two important biological products (a) Serum for the treatment of snake bites and (b) Vaccine for the prevention of typhoid fever.

With the passage of time several bacterial/viral vaccine and sera were added to the list of products manufactured by the Institute. This is the only Institute of the Government of India. The total staff strength at the Institute is 800+.

Existing Facilities at CRI Kasauli are:

I. Production Units for Bacterial/Viral Vaccine and Antisera
II. Quality Control Division
III. Labeling, Packing and Supply Department
IV. Surveillance of Influenza and JE
V. National Salmonella and E. Coli Center
VI. National Collection of Type Culture
VII. Supportive Services:
- Administration
- Treatment Center for dog/snake bite cases
- Clinical Laboratory
- Animal House
- Stables
- Library
- Workshop
- Stores

VIII. Central Drugs Laboratory

B. Institutional Strength in Relation to QA/GMP/QC

- Reputation, Cooperation and Goodwill
- Reliability and creditability of products
- High Standards of Quality Control and Quality Assurance

Institutional Weakness in Relation to QA/GMP/QC

- Lack of CGMP and CGLPs
- Absence of Latest Technologies for Vaccine Production
- Machinery/Equipment, old and worn out
- Shortage of Laboratory animals

C. Opportunities

- Increasing requirements of Government/Public for Immunobiologicals
- Availability of new technologies
- Liberalization of procurement of equipments

D. Specific Issues or Concerns the Faculty to consider

- Entry of multinationals and indigenous private Vaccine manufacturers
- Obsolete technologies
- Financial resource crunch

SERUM INSTITUTE OF INDIA LTD.

by Dr. S.D. Ravetkar
Director, Projects and Materials
Serum Institute of India Ltd., Hadapsar, Pune, India

A. Background information providing a brief outline of the existing facilities and Staff and plans for future development

The existing facilities are designed in accordance with WHO guidelines for various bacterial and viral vaccines manufacture. The facilities are also approved by UNICEF and WHO. Future developments include the manufacture of combination vaccine like DPT-HB vaccine for which facilities are under design stage. Future expansion also include manufacture of Tissue Culture Rabies vaccine.

The existing staffs are technically and highly qualified microbiologists, biochemists, pharmacologists, pharmacists, biotechnologists, medical doctors and engineers from various facilities. The company also hires outside experts from various disciplines as consultants. The company also conducts technical audit by appointing technocrats in particular areas.

There are no weaknesses of QA/QC in the institutes besides upgrading is carried out constantly.

B. Institutional weaknesses in relation to QA/GMP/QC

The company has a separate QA and QC which works independently. QA department independently controls on line process, validation and calibration process. QC is responsible for testing of raw material to finish products. The GMP is as per WHO norms. Internal and external GMP audit is also conducted. The QA/QC people are trained in various laboratories abroad. The company is also participating in various collaborative studies with other laboratories.

C. Hope to benefit (both personally and institutionally) from the participation in the training course

I am involved in facility designing and working on techno-commercial aspect of project management. I have designed facilities for viral vaccine as well as Bacterial vaccine manufacture from greenfield stage up to commissioning. As the course involves discussion on piping, utilities, water for injection, validation, I can learn as well as contribute to the workshop. Being the head of some of the Vaccine Production areas and Materials and Projects, the session on computer system in Vaccine manufacture and on purchase functions will also be helpful for me. As I am working in vaccine production and validation, this course will give a good opportunity to widen my horizon on both these vital aspects of vaccinology.

D. The curriculum should include the following topics

a) Internationally accepted GMP requirements as per WHO, US FDA, MCA and EU.

b) Discussions on total aspects of Project management on designing vaccine manufacture facilities in general and DNA recombination vaccine in particular. This should involve bulk vaccine manufacture as well as filling areas right from green field stage till commissioning. It may me a good idea to take hypothetical case of designing vaccine manufacturing facility of say 20,000 sq.ft. for bulk vaccine till finished product in containers like vials and ampoules. This could involve discussion on design lay-out, HVAC, utilities, m/c, etc. There are lots of debated points on designing utilities e.g. Whether one should have utility floor above manufacturing facility or not. Starting with green field course can end up with ready validated facility.

c) There should be a session on automatic inspection and final vialed vaccine by telescopic camera vs manual inspection with human eye.

d) Clean Area Designing vs Barrier Isolation Technology for vaccine filling.

e) Discussion of live case studies on each above aspects will make the course sessions more interesting and fruitful.

f) If the course involves discussions on how to select building material, plant and machinery like Multi-column Distilled Water Plant or Thermo-compression, high speed filling lines tunnel, etc. will help participants a lot.

PASTEUR INSTITUTE OF INDIA

by Dr. Y. Udaya Bhaskara Rao
Deputy Director, Pasteur Institute of India
Coonoor 643 103 Nilgiris, Tamilnadu, India

A. Background

The Institute is situated on a grassy knoll in the upper reaches of Coonoor town amidst beautiful surroundings with tush greenery, manicured lawn and colorful flower gardens. It has a glorious tradition of single minded dedication to alleviating the suffering of humanity by its contribution to the research and development of vaccines. Among its noteworthy contributions may be mentioned the research work on rabies, influenza adeno viruses, the introduction of a BPL inactivated sheep brain tissue rabies vaccine for the first time in the country, the production and release of more than 3 million doses of indigenously produced oral polio vaccine, the contribution of substantial quantities of DPT group of vaccines to the National Immunization Programmes of the Government of India, and more recently, the development of a Vero cell based rabies vaccine for use in canines and humans by a totally indigenous technology as part of its R&D effort.

Started as the Pasteur Institute of Southern India in the year 1907, the Institute took a new birth as the Pasteur Institute of India (registered as a society under the societies Act, 1860), and stared functioning as an autonomous body under the Ministry of Health and Family Welfare, Government of India since 1976. The affairs of the Institute are managed by the Governing Body of Institute comprising of the Secretary to the Government of India, Ministry of Health and Family Welfare, as the Chairman and the Director of the Institute as the Member Secretary. The Institute follows all Central Government Service rules and its own Bye-laws for all administrative purposes. It has a strength of 310 staff members on its rolls. The Institute manages all its activities with its own financial resources and income generated bu way of sale of vaccines, charges and fees collected for training and technical assistance to other Institutes, clinical and diagnostic service offered, and the interest on the investments of its funds. In addition, the Government of India offers financial assistance to specific Plan projects from time to time.

Presently the Institute is engaged in the production of DPT group of vaccines, two types of antirabies vaccines namely the sheep brain-BPL inactivated and the vero cell based vaccines. The Institute runs a clinical laboratory, a rabies diagnostic laboratory and a treatment center. It also offers training programmes to personnel from other institutes and to students from different universities pursuing Medicine, Pharmacy, Biochemistry, Biotechnology and related subjects.

Staff

The Institute has 310 staff members.

- Ph. D. in Microbiology	01
- Postgraduates	23
- Graduates	30
- Technicians	30

Vaccine Production

Vaccine	1993-94	1994-95	1995-96	1996-97
		(In Million doses)		
DPT	12.96	16.68	12.00	20.00*
DT	8.50	8.40	12.14	18.00*
TT	10.55	12.39	15.00	15.00*
Rabies (BPL Sheepbrain)	5.30	5.28	4.00	6.00*
Rabies (Vero Cell Canines)	0.02	0.01	0.01	0.02*
Rabies (Vero Cell Human)	-	-	Exp	0.05*

* *Production target for the current year*

Plans for future development

a. Develop and produce an indigenous vaccine for Hepatitis B.
b. Development or acellular pertussis vaccines.
c. Increase in the production level of DPT vaccine from the present level of 24 million doses/annum to 40 million doses per annum.
d. Increase the production level of Tissue Culture (Vero) rabies vaccine.

B. Strengths in relation to QA/GMP/QC:

a. A glorious tradition in the field of vaccinology since 1907.

b. A good infrastructure to take up any challenge with dedicated staff. New buildings for quality control with all specifications to meet CGMP will be ready for occupation in six months time. A new animal house is getting ready with controlled air changes in six months time.

c. Assistance from international agencies like World Bank to strengthen the quality control and Quality Assurance and Research and Development departments.

d. Autonomy in day to day activities.

e. A low price line for the vaccines produced without compromising the quality and safety of the vaccine.

f. Standard Operating Procedures (SOPs) have been revised twice and needs a little up gradation.

Weaknesses in relation to QA/GMP/QC

a. The National Central Laboratory or Authority (NCL or NCA) is located in a remote corner of North India and it doesn't have any regional laboratories to serve more effectively. We are attempting to get a regional NCA to be set up in our Institute as soon as our new building is ready.

b. Strengthening of Quality Assurance Department is required.

C. Benefits from participation in training courses

The knowledge and practical experience gained during the workshop will enable us to improve the quality of vaccines produced in this Institute.

B.C.G. VACCINE LABORATORY

by Dr. M. Jayasheela
Director, BCG Vaccine Laboratory
Ministry of Health and Family Welfare, Madras, India

A. Background

BCGL, Madras is a vaccine manufacturing institution under Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.

It has the following functions:

(a) To produce freeze dried BCG vaccine in ampoules of twenty doses each.

(b) To act as National Control Laboratory for both indigenously produced BCG vaccine as well as imported BCG vaccine.

(c) To stock both the indigenous and imported vaccines and supply the same to different States as per allocation.

1. Existing facilities

(a) Utilities:

Sufficient online and stand by power
Sufficient water/ steam
Central air conditioning/ handling units
Guinea pig breeding facility/ incinerator
Walk-in cold rooms/ incubator rooms
Telephone/ fax/ computers

(b) Manufacturing:

Sterile rooms/ laminar flows/ air shower
Ampoules washing (semi automatic)/ Sterilizing hot cases
Ampoule filling (semi automatic)
Freeze drying (manual loading/ unloading)
Vacuum sealing of ampoules
Media preparation / culture/ harvesting/ diluting
Physical checking/ labeling/ packing/ transport

(c) Quality control:
Sterile rooms/ laminar flows
Sterility/ viability/ stability testing
Optical density/ oxygen uptake/ CFU estimation
In-vivo testing using guinea pigs
Moisture estimation

2. Staff

BCGL Madras has a total of 180 staff. It is headed by a medical graduate with post graduation in microbiology and experienced in manufacture of biologicals. Manufacturing unit is headed by a medical person who has been working as manufacture in charge for the last 8 years. Quality control is headed by a veterinarian with long experience in the field. Supporting staff include:

(i) Engineer, in-charge of maintenance
(ii) Administrative officer and
(iii) Stores officer.

Amongst laboratory staff, three are science post graduates and 13 are graduates in science.

3. Plans for future developments

At present, BCGL is supplying about 30 million doses of BCG to national programme of immunization. This is insufficient as actual need is about 51 millions. Hence, a plan has been drawn up to increase the production capacity so that entire need can be met indigenously. Different inspecting teams have found the existing laboratory wanting in space and in GMPs. So, the government has decided to put up an entirely new facility capable of producing about 60 million doses of BCG in an environment of international standards. At the same time technology will also be changed to produce BCG in vials using latest equipment.

As of now, same laboratory (BCGL, Madras) is engaged both in manufacture as well as NCL for BCG. This is not acceptable. Hence the functions of NCL are expected to be shifted to another laboratory.

This Laboratory is making only BCG vaccine but not it's diluent. When new plant is ready it is expected to take up diluent manufacture also.

B. Institutional strength/weaknesses in GMPs/QA/QC:

GMPs

	Strength (S) Weakness (W)
PERSONNEL	
Whether headed by a person who is trained in the techniques used in manufacturing biologicals.	S
Whether personnel who work in aseptic areas are selected with care-whether they can be relied upon to observe appropriate codes of practice- whether they practice high standards of personnel hygiene, etc.	W
Whether only minimum number of persons required are present in aseptic areas	S

Whether persons engaged in production process are separate from persons taking care of animals	S
Whether names/qualifications of those responsible for approving protocols are registered with NCL/DCI	S
Whether personnel are trained in GMPs and GLPs	W
Whether all persons are vaccinated	W
Whether all personnel are periodically evaluated for presence of tuberculosis	S
PREMISES/EQUIPMENT	
Whether building is suitably designed for manufacture of a biological	W
Whether interior surfaces are satisfactory	W
Are sinks excluded from aseptic areas	S
Whether there is sufficient space for all operations	W
Whether lighting ventilation satisfactory	S
Whether air conditioning air handling, filtering systems satisfactory	W
Whether seed lots are stored separately	S
Whether are there any chances of product mix up	S
Whether suitable effluent treatment plant is used	W
ANIMAL CARE	
Is there a separate suitable building	S
Special clothing/changing facilities/showers	W
PRODUCTION	
Whether SOPs are available for all processes	S
Specifications and testing of raw materials	W
Whether sterilization in situ of media practiced	W
Validation of sterilization procedures	S

LABELING	
Are the labeling methodology practiced is satisfactory	S
Whether information given on labels are approved by NCL	S
Whether label shows all required information	W
Whether a satisfactory leaflet is enclosed	S
PROTOCOLS	
Whether protocols are properly maintained	S
Whether they make it possible to trace all steps of manufacture/ QC	S
Are they approved by NCL	?
QA / QC	
Whether detailed instruction are available for each test	S
Whether adequate identification/segregation of samples done to avoid mixup	S
Environment monitoring	W
Equipment validation	W
Procedures for release reject raw materials	S
Procedures for release/reject packaging, materials	W
Procedures for release/reject a lot of product	S
Evaluation procedures for adequacy of storing conditions of products at various stages	W
Evaluation procedures for quality and stability of finished product	S
Evaluation of expiry dates relative to specific storage conditions	W
Testing of returned product	W
Location of the QC laboratory	W
Facilities in the QC Laboratory	S
In process quality controls	S

Whether certificates issued by the manufacturer of raw materials are insisted upon and scrutinized	W
Whether samples of intermediate products retained	W
Whether samples of final product is retained for sufficient period to allow repeat testing	S
Post marketing monitoring	W
Separate NCL/NCA available for BCG	W

C. Expectations from training course

What is the situation of GMPs/QA/QC in other laboratories? What are their Strong/Weak points? How they have gone/going about desired changes in the fields. How much success they have attained.

Advise from Experts in these fields how our laboratory can bring about desired changes in these fields.

D. Specific Issues

Our laboratory has plans to put up an entirely new plant to manufacture BCG. This plant should meet International Standards of GMP so that if we wish to export Vaccine at a later date it should be possible. Hence we wish to acquaint ourselves with the parameters - which have to be implemented at the time of construction of building/installation of equipment - so that new plant will not suffer from faults inherent to bad planning with reference to GMPs.

E. ORGANOGRAM OF THE BCG VACCINE LABORATORY

DIRECTOR		
IN-CHARGE PRODUCTION	-	Washing
	-	Media Preparation / Sterilization
	-	Culture harvest
		Filling/Freeze drying/Sealing
IN-CHARGE QC	-	Quality Control
	-	Animal House
	-	Labeling/Packing/despatch
ENGINEER	-	Utilities
ADMINISTRATIVE OFFICER	-	Administration
	-	Accounts
	-	Watch/Ward
STORES OFFICER	-	Stores

4. INDONESIA

PERUM BIO FARMA'S CURRENT GMP/QA/QC

by Drs. Yenni Siti Chaerani
Perum Bio Farma, Bandung, Indonesia

A. Background

Indonesia is one of the 107 countries in the world that requires the pharmaceutical products on the market to be made under GMP. This has been profaned by endorsing the deadline for implementing GMP in pharmaceutical industries as announced by the Ministry of Health (April 1, 1994).

Bio Farma as a state owned institute under the auspices of the Ministry of Health and also known as the sole vaccine producer in Indonesia is responsible for the production of vaccines needed for Expanded Programmed of Immunization (EPI).

Taking into account the government's urge for the immediate implementation of GMP, Bio Farma's staff has committed itself to unite in enforcing this by comprehending the WHO's GMP guideline and translating this into practical standard and operating procedures.

In order to attain the highest level of quality, several efforts have been made to ensure real assurance of quality which requires immense care and responsibilities of manufacturing and full control throughout the entire manufacturing process from raw material to final product by following the national requirements.

In addition to GMP, Quality Control (QC) is entirely the responsibility of the manufacturer. Hence, QC must be optimized to provide total security for ultimate performance of the product which include guarantee of quality, safety and efficacy.

It is very important to develop our technical know how on production and quality control by continuous training, transfer of technology and know how in the form of training programme, practical exchange, lecture, workshops, etc. which are related to QA/GMP/QC.

Current situation of GMP implementation in Bio Farma

1. Building and production facility

Currently, Bio Farma possesses manufacturing facilities of heterogeneous quality as a result of numerous international cooperations. The polio and measles production and control facilities, for instance, has been considered to be the best in Asia with regards to GMP standards. However there are still many facilities in which GMP standard has yet to be optimized. Implementation of GMP is based on priority bringing not too drastic a change in the existing building. This is obvious where resources is a constraint.

During the last 5 years several improvements on the existing facility have been done gradually by renovation or installation up-to-date equipment and application of software.

At present Bio Farma has separate production facilities for each product such as Tetanus production, Diphtheria, Pertussis, BCG, Polio and measles which are dispersed.

In general, the lay out of building, equipment and others depend on specific features of the product connected in a logical manner, corresponding to the sequence of operation and requisite level of cleanliness and air classification.

2. Quality Control facility

Quality control can be defined as part of GMP which is not only concerned with sampling, specification and testing but also with the organization of documentation and release procedure which have been found satisfactory.

The Quality Control department in Bio Farma has functioned separately from production department be it building, staff and facility.

QC laboratory is completely independent conducting several control activities such as physiological, biochemical and immunological tests including various immunoassays especially in the control of identity, potency, safety, sterility of which each tests has it own specific, sensitivity, and accuracy of analysis.

In addition to biological control, every batch is subjected to a strict control by using reference preparations which are internationally accepted and all the tests are done by highly qualified staff.

The control system implemented is assessed and evaluated periodically so as to cope with recent information, with this there is a strong built-up confidence where judgement is concerned.

The implementation of SOPs and working sheets as guidance has led the staff to be more aware of what they are doing and thus disciplined. All this has led to an understanding of the importance of good documentation as the fundamental aspect in GMP.

Clearly written document will prevent error from spoken communication and will act as an easy way to find or trace back the history of a production batch.

Recording of production and control is documented in three parts, then summarized in one summary protocol of production and control file. This is latest presented directly to the directors production and quality control. This summary protocol then sent to the National Control Authority.

3. Staff/ Personnel

400 of 530 Bio Farma's employees comprises of university graduate from different discipline, analysts and attendants involved on production and control activity.

Although Bio Farma have adequate number of personnel of all levels having skills and capability, however knowledge on GMP has still to be upgraded at all levels.

It is realized that quality of the product is closely associated with quality of man power behind it. Therefore it is ultimately essential for the staff to increase the knowledge and their capabilities in every aspect.

Adequate training of the technical personnel is programmed regularly in order to upgrade their capabilities and experience. This training has been conducted by experienced senior personnel qualified in their respective jobs or by guest lecturers with the hope that the knowledge and experience will be utilized effectively.

B. Strength/Weaknesses

Strength

The fundamentals of GMP have been smoothly implemented by commitment, strong back up, support and participation of our top management.

Successful technical cooperation among other institutions either locally or abroad and their implementation of GMP to adapt our new facilities has given us special meaning in improving our technical know how, experience and an opportunity to develop in our conventional facility and other vaccine production in a similar way.

Weaknesses

There are still many facilities in which GMP standard has yet to be optimized. According to the recent condition considering the limitation of funds and resources has been made it difficult to built new facilities.

C. Benefit of the courses

The opportunity to participate in this course is of great benefit as it will provide more information and know how and sharing a lot of experience in QA/QC/GMP among the participants. It is hoped that better reasoning and understanding as to the philosophy will be acquired throughout the course. This course will serve as an excellent opportunity to exchange information among the participants.

D. Future

In the future this institute will continue to exert its full effort in the exchange of information with other countries for the advancement of control system, setting up Quality Assurance system and efforts have been drawn to develop our facility especially with regards to infrastructure.

REPORT ON QA/GMP/QC FOR VACCINE PRODUCTION

by Drs. Suhaeri Suramihardja
Perum Bio Farma, Bandung, Indonesia

A. Background

The Workshop on QA/GMP/QC organized by IVI/UNIDO/Bio Farma will be held at Bandung, Indonesia from 8-15 July 1996.

This brief report, which inform the present situation relating QA/GMP/QC, is in accordance with the request from the coordinator of the workshop.

The short information presented here covers the topics such as, existing facilities, staff, institutional strengths and weaknesses in relation to QA/GMP/QC, the expected benefit and specific issue for the faculty to be considered.

Existing facilities and staff

All vaccines for EPI in Indonesia is produced in Bio Farma, Bandung, Indonesia.

Bacterial vaccines are produced in relatively old buildings, most of these buildings have been renovated to fulfil GMP requirement. At present, the production of all bacterial vaccines are carried out in clean room areas with different classes. The cultivation of bacteria are performed in fermentors. There are 10 fermentors of 90 liters, 1 fermentor of 250 liters, 2 fermentors of 500 liters and 2 fermentors of 1000 liters.

Viral vaccines production is conducted in a newly built facilities which has fully met GMP regulation.

Quality control department is totally separated from production department.

There are about 550 employees in Bio Farma of which about 12% are university graduated. Most of the employees have long experience in their work and they have been trained domestically or abroad.

For future development, Bio Farma always try to prepare and produce other new vaccines or new biological products.

B. Institutional strength relating to QA/GMP/QC

In implementing QA/GMP/QC regulation, Bio Farma has the following points as the institutional strength:

1. The GMP team in Bio Farma has been established since 1992.

2. Bio Farma has a good cooperation with the experts from well known vaccine manufacturers abroad. This cooperation enables us to study the implementation of QA/GMP/QC in their institution.

3. Most of Bio Farma staff have been trained abroad and the experts from other countries visit Bio Farma to supervise and to provide guidance how to work according to GMP regulation.

4. At present, there is a facility in viral vaccine production department that has fully met GMP regulation. This facility is used as our reference in implementing GMP in other departments.

5. The commitment and support of Bio Farma top manager to continuously improve GMP implementation in every department in Bio Farma.

6. Most of the building facilities for production and quality control have been renovated and improved to fulfil GMP rules.

Institutional weaknesses relating to QA/GMP/QC

Implementation of QA/GMP/QC in Bio Farma is considered to have the following points as the weaknesses:

1. The availability of budget for implementing GMP is limited.

2. There are still some employees who have not yet understood GMP properly.

3. The quality of some part of the building, the equipment and the support system still needs improvement.

C. Expected benefit from the Workshop

The workshop on QA/GMP/QC is very important for everyone who works in the field of vaccine production. Personally, by participating in the workshop, it is expected to absorb important, latest knowledge and information relating to QA, GMP and QC. This important knowledge and information will be put into routine practice in the institution where the participants works.

The participant will also teach or inform other employees in his institution. Lastly, the knowledge and information obtained from the workshop will be spread through out all employees working in the participant's institution. This kind of knowledge transfer in an institution will result in a good progress of QA/GMP/QC implementation in that institution.

D. The specific issues to be considered by the Faculty

The tentative agenda of the workshop covers all important points of QA/GMP/QC. Nevertheless, it is tried to put forward to the faculty to consider the matters such as personnel training, self inspection, sanitation of premises and equipment, wasted material treatment, production process validation and maintenance of the equipment used for production.

NATIONAL QUALITY CONTROL LABORATORY OF DRUG AND FOOD (NQCL DF)

by Ms. Sri Endreswari
National Quality Control Laboratory
Directorate General for Food & Drug Control
Ministry of Health, Indonesia

A. Background

National Quality Control Laboratory of Drug and Food (NQCL DF) is a center for the Government Quality Control of Pharmaceutical (including vaccine), food commodities and medical devices.

Since 1986, I was been appointed as WHO Collaborating Center for Essential Drugs; while since 1993 as WHO Collaborating Center for Essential Drugs and Vaccines.

Facilities

Physical space of the center is + 8000 m^2, consisted of several laboratories:

- Laboratory of Drug Quality testing
- Laboratory of Cosmetic of Medical devices quality testing
- Laboratory of Traditional Drug Quality testing
- Laboratory of Food and Beverages Quality testing
- Laboratory of Narcotic and Hazardous Substances
- Laboratory of Microbiology (including Bioclean for sterility testing of vaccine and other commodities)
- Laboratory of Vaccine quality testing equipped with bioclean room for potency test of polio, measles, BCG and maintain cell cultures
- Laboratory of Toxicology
  - Performing the abnormal toxicity test for drugs including vaccine; acute and sub-chronic toxicity; mutagenicity test; teratogenicity test, etc.
- Laboratory of Pharmacology
  - Performing pharmacodynamic testing; Pyrogen test; Bioassays, etc.
- Laboratory of Reference Standard Substance
- Laboratory of Biopharmacy
- Laboratory of Breeding animal

Facilities with barrier sister animal room (for breeding and holding) and food fabrications. The species of animals are mice, rats, Guinea pig and rabbits (SPF of origin) used for quality testing of vaccine, drugs and other commodities

Staff of NQCL DF

Area of expertise	Post Graduate	Professional	Supporting
Chemical analyses	4	41	38
Microbiological analysis	1	13	7
Biopharmacy	-	3	1
Vaccine Quality Control	-	14	6
Toxicology	-	5	4
Pharmacology	1	6	1
Animal care	-	7	12
Administrative affairs	1	5	31
Total	7	94	100

Activities regarding the vaccine quality control

1. We have done routinely the quality testing of EPI vaccine and rabies, vaccine, following the WHO requirement and methods.

2. The routine activities:

   - Testing and certification of EPI and rabies vaccine
   - Testing of vaccine in the case of cold chain break
   - Establishing some working reference standard for EPI vaccine in cooperation with Bio Farma
   - Establishing the stability testing for finished product

3. Proficiency testing for potency test of polio and measles vaccine (by WHO).

Plan for Future development

1. Performing the quality testing for other vaccine mostly marketed in Indonesia.

2. Developing the National Reference Standard of EPI vaccine

B. Institutional strengths/weaknesses in relation to QA/GMP/QC

The strengths:

- The staffs of vaccine laboratory had been trained in the laboratory which is recommended by WHO.
- The methods, facilities for vaccine quality testing follow the WHO requirement.
- NQCL DF has been appointed to be the WHO collaborating center for drugs and vaccine since 1993.

The weaknesses:

- Stability testing;
- Establishing the National Reference Standard;
- Lack of information concerning to the vaccine Quality control (i.e. information from WHO, etc.);
- We hope that the training course could give the following benefit:
  to improve our knowledge in the field of quality control of vaccine and our institute well functioning to ensure the vaccines complies with an agreed upon set of standard.

C. Expectations from training course

We wish the training could contain:

1. National Control mechanisms (Licensing system, postmarketing surveillance, inspection, clinical data for vaccine assessment, etc.).
2. Validation of quality testing of vaccine.
3. Validation of calibration for reference standard of vaccine, etc.

5. IRAN

RAZI VACCINE & SERUM RESEARCH INSTITUTE

by Dr. Ali A. Mohammadi
President, RAZI Vaccine & Serum Research Institute
Tehran, Islamic Republic of Iran

Razi Vaccine and Serum Research Institute with more than 71 years of experience in the research and production of a great variety of human as well as the veterinary vaccines, sera and diagnostic kits is among the oldest and most reportable establishments of its kind in the world.

The Institute with more than 1,200 employees, including 120 members of the board of scientists, is using very updated equipments including fermentors and HPLC and enjoys very close cooperation with the international organizations such as WHO, FAO, OIE and some big relevant Institutes such as Merieux of France, Pirbright of England and Friedrich Ebert of Germany.

Razi Institute is the best Institute in the world to develop and produce anti-Leishmania as well as the oral form of anti Diphtheria-Tetanus vaccine.

It is also necessary to mention that Razi Institute is the first Institute in Asia and the third world and among a handful Institute in the world capable of producing SPF laboratory animals.

Further development of Biotechnology Department and production of recombinant vaccines along with the rapid expansion of educational activities in the fields of holding M.S. and Ph. D. courses and training courses are among the first priorities at the Razi Institute for the future.

6. REPUBLIC OF KOREA

CHEIL FOODS & CHEMICALS INC., KOREA

by Dr. Wan Gyu Choi
Quality Control Manager
Cheil Foods & Chemicals Inc., Republic of Korea

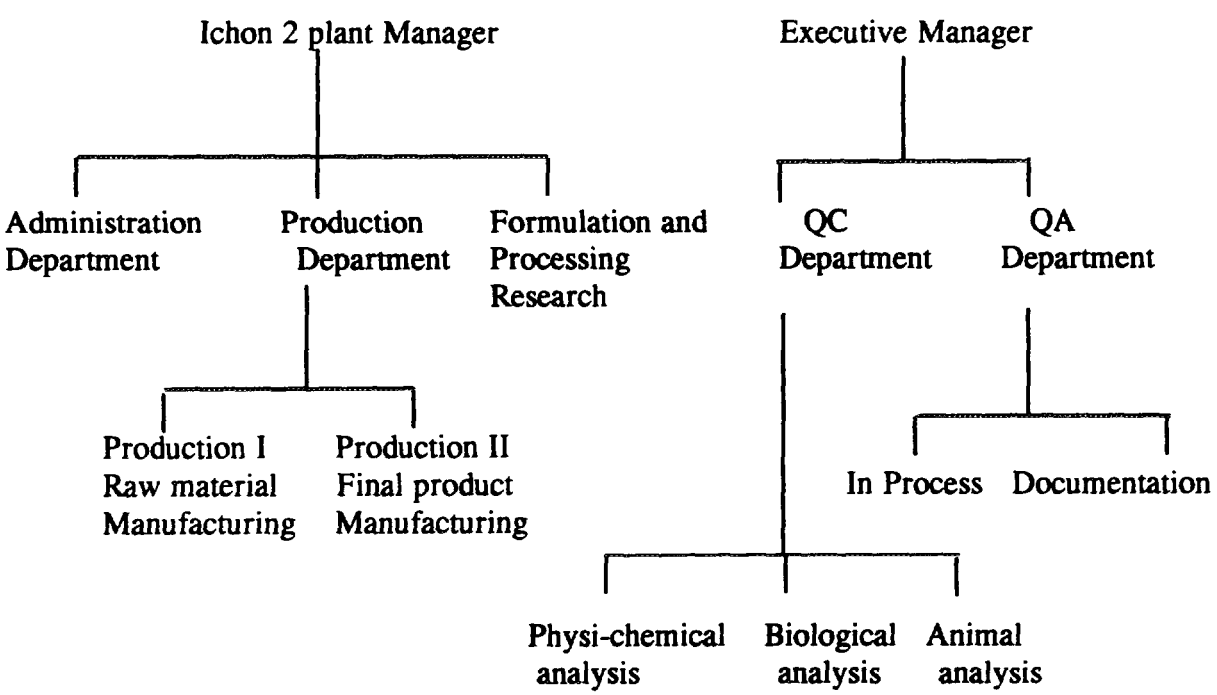
A. Background information providing a brief outline of your existing facilities and staff, and plans for future institutional development, if any

Cheil Foods and Chemicals Inc., the largest foods processing and chemicals company in Korea, produces and supplies industrial products.

As a part of eight divisions in Cheil, pharmaceutical division consists of two plants (Final product plant, Bulk pharmaceuticals plant).

Our final product plant, Ichon 2 plant has produced and is suppling ethical products centered around vaccines and other medicines.

Ichon 2 plant was organized in 4 departments as below.



B. Our strengths in relation to QA/GMP/QC

Assignment of clear differences in responsibilities between production and QC/QA.

Hire the best people that we can find, train them, and give them the authority to do their jobs. People work hard and creatively to meet the challenge, so they grow sufficiently education persons to perform tasks.

Our weakness in relation to QA/GMP/QC

Validation, especially process validation, is not proceed effectively because personnel capacity and mind to perform the necessary validation is very short. If we were starting a new facility and process, we don't draw up a master plan exactly to get the work done well and as soon as possible.

C. How to benefit from participation in this course

In this training course, I want to learn how to perform validation exactly and documentate all files of QA systematically. In addition, I will try to know Quality approaches of cGMP, European GMP and other's GMP.

7. MALAYSIA

NATIONAL PHARMACEUTICAL CONTROL BUREAU

by Wan Othman bin Wan Ismail
Pharmacist (GMP auditor)
National Pharmaceutical Control Bureau (NPCB)
Ministry of Health, Malaysia

A. Background information of the institution
(existing facilities and staff and plan for future development)

The National Pharmaceutical Control Bureau (NPCB) was established by the Ministry of Health, Malaysia with the objective that it functions as a government department responsible for ensuring pharmaceutical products marketed in Malaysia are effective, of high quality and safe. It is also responsible to ensure that traditional medicines and cosmetic products distributed to the public are safe and of quality. In short, NPCB is a regulatory agency for the pharmaceutical, traditional medicine and cosmetic industries in Malaysia.

The regulating system introduced for the pharmaceutical, traditional medicine and cosmetic industries by NPCB is enshrined in the Control of Drugs and Cosmetics Regulation, 1984. It involves the requirement of registration of the drugs and cosmetics in the market and licensing of local manufactures, importers and wholesalers by Malaysian Drug Control Authority (DCA). Manufactures are compelled to meet the requirement of Good Manufacturing Practices (GMP) as recommended by WHO, while importers and wholesalers are to meet the requirement of Good Storage Practices (GSP). Only pharmaceutical, traditional medicines and cosmetic products which are registered can be marketed/distributed/supplied and only licensed manufacturers, importers and wholesalers are allowed to manufacture/trade registered pharmaceuticals, traditional medicines and cosmetic products.

The registration of pharmaceuticals (scheduled poison and non-poison), traditional medicines and the licensing of manufacturers, importers and wholesalers was successfully implemented. The registration for cosmetic products, medical devices and veterinary products will be implemented later.

At the international level, NPCB has been made the center for training government officers from drug regulatory agencies from ASEAN countries, Bangladesh, Pakistan, Sri Lanka, Hong Kong, Cambodia, Nepal and Tonga. As an outstanding pharmaceutical regulatory agency in the ASEAN region, NPCB was appointed by WHO as the Collaboration Center for Regulatory Control of Pharmaceuticals in this region.

B. The institutional strengths and weaknesses in relation to GMP

As a regulatory agency for the pharmaceutical, traditional medicine and cosmetic industries in Malaysia and training center for other regulatory agencies, NPCB was equipped with the modern and high technology facilities and qualified staff. Up to now NPCB has 180 staff and 35% are pharmacists. All the staff especially the pharmacists and pharmacy assistants are well trained and experienced in order to give the best services to the clients. The role of NPCB for protection of consumers has been carried out with full commitment and responsibility.

For the future development, the pharmacists need more exposure especially in the manufacturing of specific pharmaceutical products such as vaccine, biotechnology and blood products, thus this course will be very beneficial for the pharmacists and the institution.

C. The benefits from the participation in the training course.

Since the vaccine manufacturing is a new field in pharmaceutical industry in Malaysia, the participation in this training workshop will give a lot of benefits to the participant and institution involved. All the subjects/topics to be covered in the workshop will provide not only the knowledge and exposure on the vaccine manufacturing facility design but also all aspects of GMP involved, such as clean room facilities, documentation system, validation plan, water quality and other areas related to the pharmaceutical industries. So the participation in this course absolutely will benefit the participant with high knowledge and exposure of GMP in vaccine other drugs manufacturing and this directly will help the institution in determining the GMP compliance of the pharmaceutical industry in Malaysia.

8. MEXICO

GERENCIA GENERAL DE BIOLOGICOS Y REACTIVOS

by Dr. Jorge Fernando Gomez Herrera
Secretaria de Salud
Subsecretaria de Regulacion y Fomento Sanitario
Gerencia General de Biologicos y Reactivos, Mexico

A. Background

We are an official Institution of the Secretary of Health from Mexico. We have four different facilities in Mexico City.

1. Central office

We have in this area:
- General Direction
- Quality Assurance Direction
- Financial Direction
- Purchases Direction

2. National Institute of Hygiene

We produce in this area: Bacterial vaccines DPT, TT, BCG, Td, Sera and Biological Reagents.

3. National Institute of Virology

We produce in this area: Viral vaccines Poliomyelitis, Measles, Rabies for human and dogs.

4. Central Laboratory of Reagents

We produce in this area: Reagents for tests of clinical laboratories.

For this year we will produce approximately

80 millions/doses of vaccines
175,000 vials of different sera
10,000 vials of biological reagents
38,000 liters of reagents for tests of clinical laboratories

We have 725 persons in total for the four facilities.

We are the only country that produces all the vaccines of Expanded Programme on Immunization in Latin America.

I am at present the Quality Assurance Director and have the following activities documentation, audits, validation and training and my experience in this position is 5 years. Before I was in the production of bacterial vaccines, sera and biological reagents for 20 years.

B. Institutional strengths

The most important strength are the people that are working with us. They have a long experience in Production, QC and QA of 20 or more years and also we have a very good young people.

Other are the organization and the development of permanent programmes for the total quality.

Institutional weaknesses

We have old facilities in some laboratories and we need more money to purchase new equipment and build new facilities.

Now we have a special budget for equipment and facilities for the National Institute of Hygiene and it is also necessary to have a similar special programme for the National Institute of Virology.

Additionally, we need more personnel in order to increase the activities in Production, QC and QA.

C. Benefits

As a participant to the course, I will be benefited because I will know the advances in QA/GMP/QC and compare the systems of other countries' programme development and establish relations and communication with people from other countries.

The Institutionally benefit is that the new information to be gained from the course will help us to improve the programme of total quality.

9. SOUTH AFRICA

SOUTH AFRICAN VACCINE PRODUCERS (PTY) LTD.

by Dr. Jean Morgan
South African Vaccine Products (PTY) Ltd.
Sandringham, South Africa

A. Background

South African Vaccine Producers (SAVP) is a private company formed in 1995. 100 % of the shares are owned by the South African Institute of Medical Research, a parastatal organization.

The company comprises 3 manufacturing sites:

1. SAVP- Johannesburg where Diphtheria, Tetanus and Pertussis are manufactured and compounded into their various dosage forms. Anti-sera (snake, spider and scorpion) are also produced.

2. Oral Polio facility at a site adjacent to SAVP. Although partly constructed, work on this facility has been halted while a decision is made regarding a Joint Venture Partner.

3. State Vaccine Institute in Cape Town produces Rabies Vaccine and BCG (percutaneous). The facility and staff of the State Vaccine Institute have as yet not been transferred to the company SAVP from the government. This will only be done when a decision regarding privatization and a Joint Venture partner have been decided on.

At present only the site in Johannesburg belongs to SAVP, however as Quality Executive I visit Cape Town once a month for approximately one week and am involved in all Quality decisions.

I. Existing facilities and staff

SAVP

Staff :

Total number of employees	105
Management	7
Maintenance	4
Tetanus	4
Diphtheria	3
Pertussis	4
Filling and packing	12
Research and Development/Anti-sera	5

Fermenter Development	2
Stables	12
Animal Unit	15
Quality Assurance /Control	10
Administration	10
Grounds, security, hostels, stores	17

Facilities (Appendix 1 : Refer site plan)

State Vaccine Institute

Staff :

Total number of employees	34
Rabies production	3
BCG production	7
Diluent production	2
Quality control/assurance	7
Administration	8
Packaging, labeling, storage, despatch	7

Facilities (refer site plan)

II. Plans for institutional development

Future plans for SAVP are to develop and start producing Diphtheria, Tetanus and Pertussis in fermenters rather than the current bottle production. Once this has been done we hope to expand our production. However, all future plans are very much dependent on privatization and the choice of a joint venture partner.

State Vaccine Institute

The Rabies facility has recently been refurbished and is currently being validated prior to full-scale production.

The BCG facility has been closed down and is currently being rebuilt to comply to GMP standards.

No further development is being planned at this stage.

Oral Polio

Dependent on the Joint Venture partner this facility could be completed as a Polio facility, a production facility for another vaccine, or as a bulk filling and packaging facility.

B. QA/GMP/QC strengths

SAVP

An internal audit system programme has been successfully initiated as has a supplier's auditing programme. This allows us to identify major areas for concern.

Experienced and careful staff in all areas, in spite of adverse conditions contamination is minimal.

State Vaccine Institute

A person was employed to upgrade the GMP at SVI. Most procedures are in place and most of the staff have received basic GMP training. This training has lapsed since the person responsible for GMP training left and needs to be reinstated and reinforced.

Batch Documentation although cumbersome, is well organized as procedures.

QA Manager is experienced in Vaccine Production and has learnt a great deal from the pharmacist previously employed.

Design of new facilities allows for good flow and well controlled production

QA/GMP/QC weaknesses

SAVP

Batch documentation is sketchy, deviations are not always recorded or followed up. This means that problems with anally.

Lack of experience in calibration and validation.

Numerous critical procedures have yet to be documented.

Tetanus production: The product flow is extremely bad allowing for crossing of toxin and toxoid. Toxin and toxoid are stored in the same incubator. This is currently being addressed to ensure the best possible flow with the minimum of expenditure. General access to the Tetanus area from Research and Development is also being addressed.

Outdated filling equipment for filling and capping. The machines create particles and bad capping is resulting in high rejects due to smashing. Parts are no longer available for the machines.

Strong resistance to change - This is how things have always been done and we haven't killed anyone yet.

State Vaccine Institute

Poor back-up and after sales service for equipment resulting in lengthy delays and equipment functioning erratically.

C. How I hope to benefit from the participation in the course

Firstly, I hope to gain some insight into how other companies view GMP in the vaccine industry. I have had a number of situations where GMP is not acceptable to me, coming from the pharmaceutical industry. However, I have been told that it is always done this way in the Vaccine industry. I have been fortunate in being able to verify some of these statements when we have been audited by International Companies however I would like to expand my knowledge on this.

I would also like to be able to make contact with other people so that in the future when a specific problem occurs, either one of my colleagues or I can contact someone who may have had the same problem to avoid re-inventing the wheel. By the same token I am always willing to share any information I have that others may need.

SAVP is at present only now setting up a validation programme, any ideas on improvements would be welcome.

D. Specific issues or concerns

1. Validation of Fermenter process production.

2. Cleaning validation of fermenters and cleaning validation generally.

3. Storage of in-house reference standards. Should these be lyophilized - if so, then this process should also be validated? Is there a source which supplies reference standards in larger quantities than WHO.

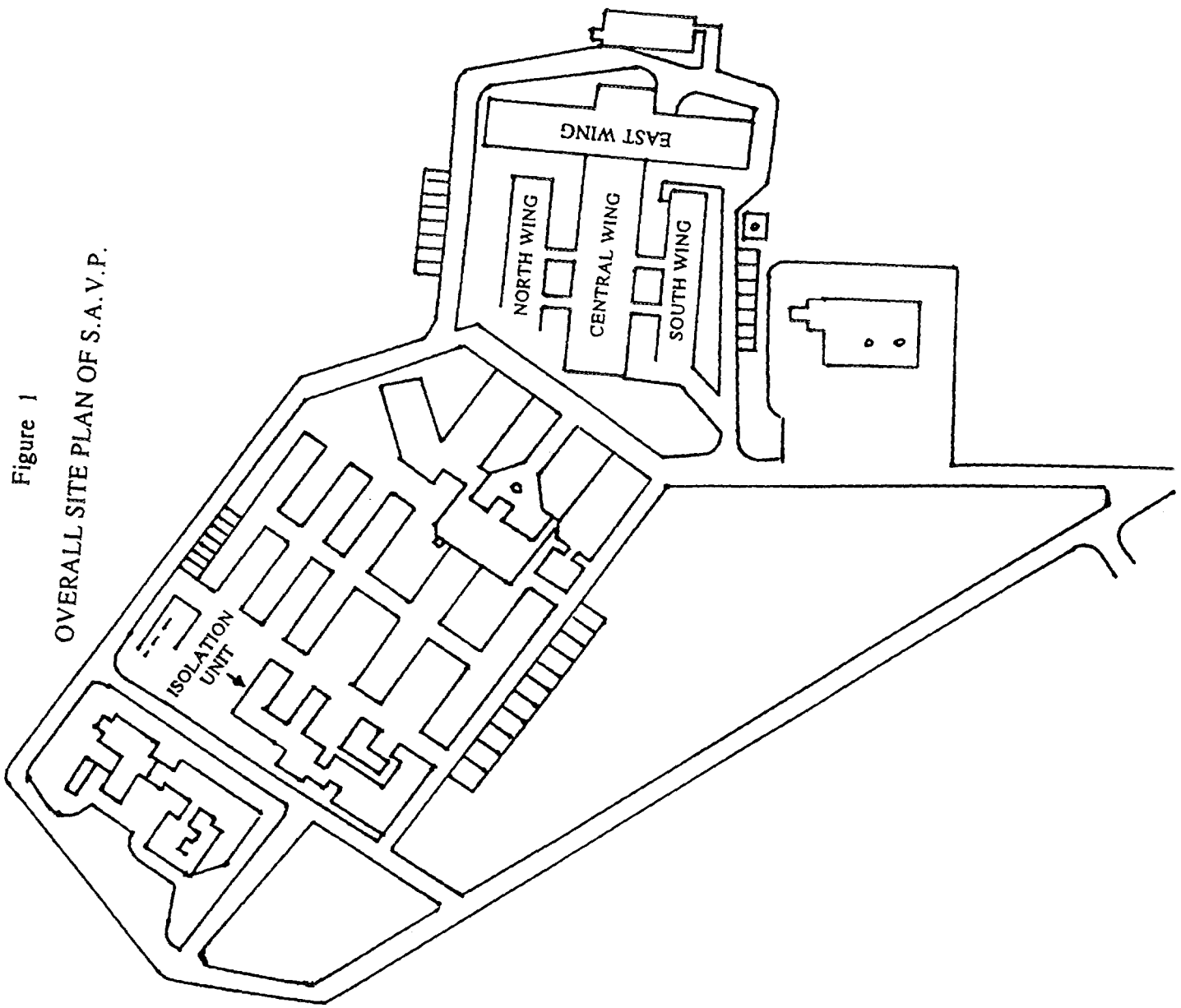
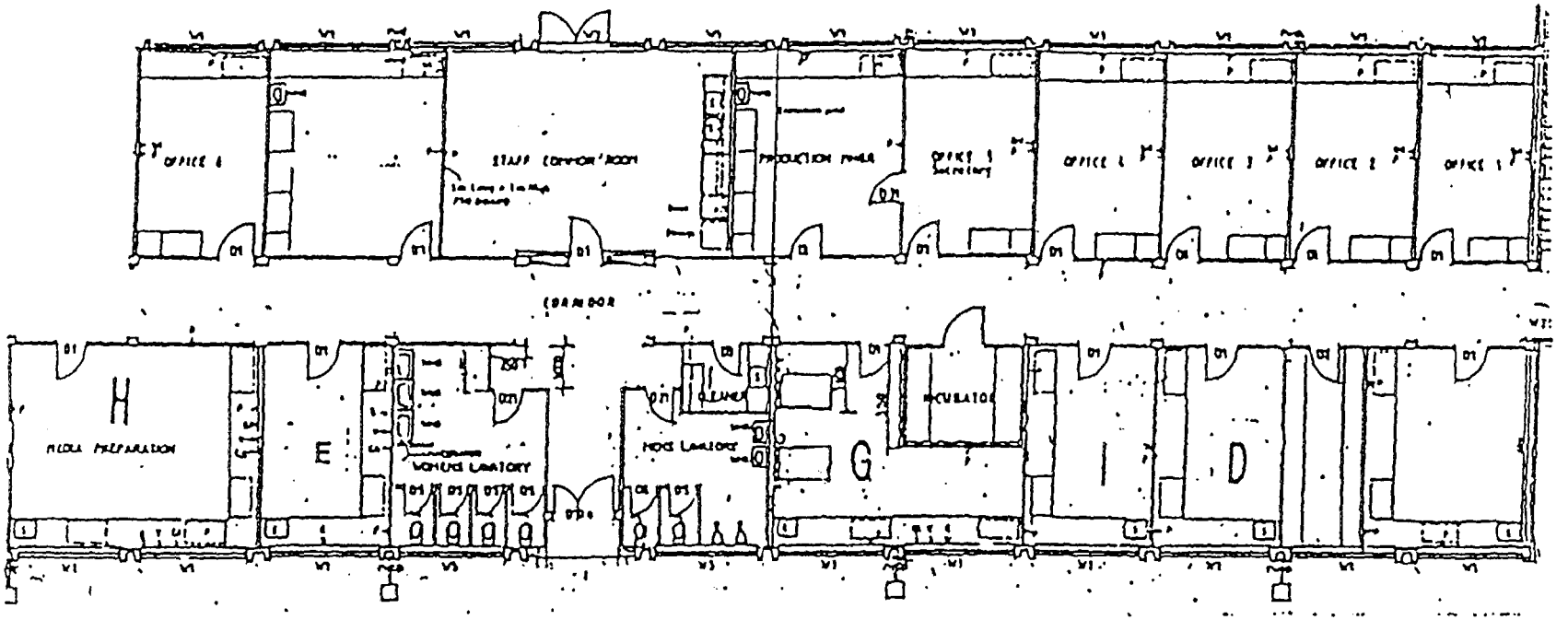


Figure 1

OVERALL SITE PLAN OF S.A.V.P.

Figure 2

DIPHTHERIA AND PERTUSSIS PRODUCTION IN THE NORTH WING
LOWER FLOOR

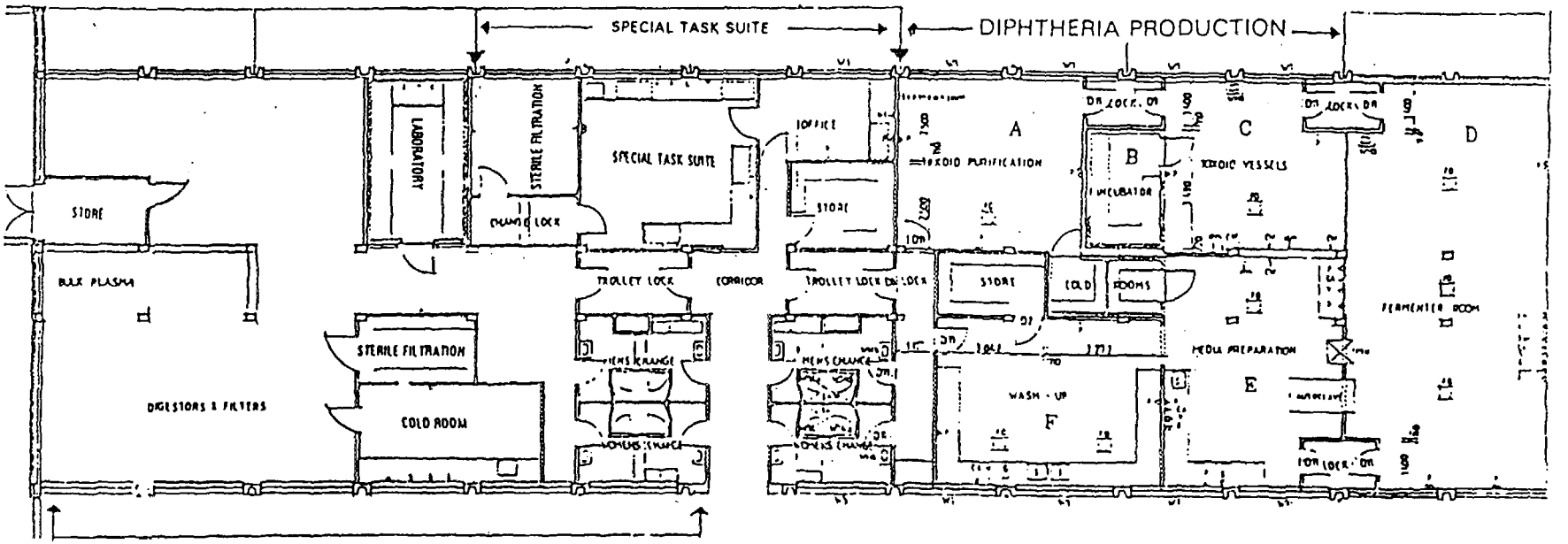


KEY:

[D]	Inoculation of the Diphtheria cultures and sterile filtration of growth medium.
[E]	Diphtheria Toxin Production and Harvest Procedures in room D are carried out in a class 100 laminar air flow booth. Room E is provided with a HEPA (99.997%) air supply and exhaust filters.
[G]	Seeding, centrifugation and production of the Pertussis culture.
[H]	Pertussis media production
[I]	Pertussis harvesting and combining process.

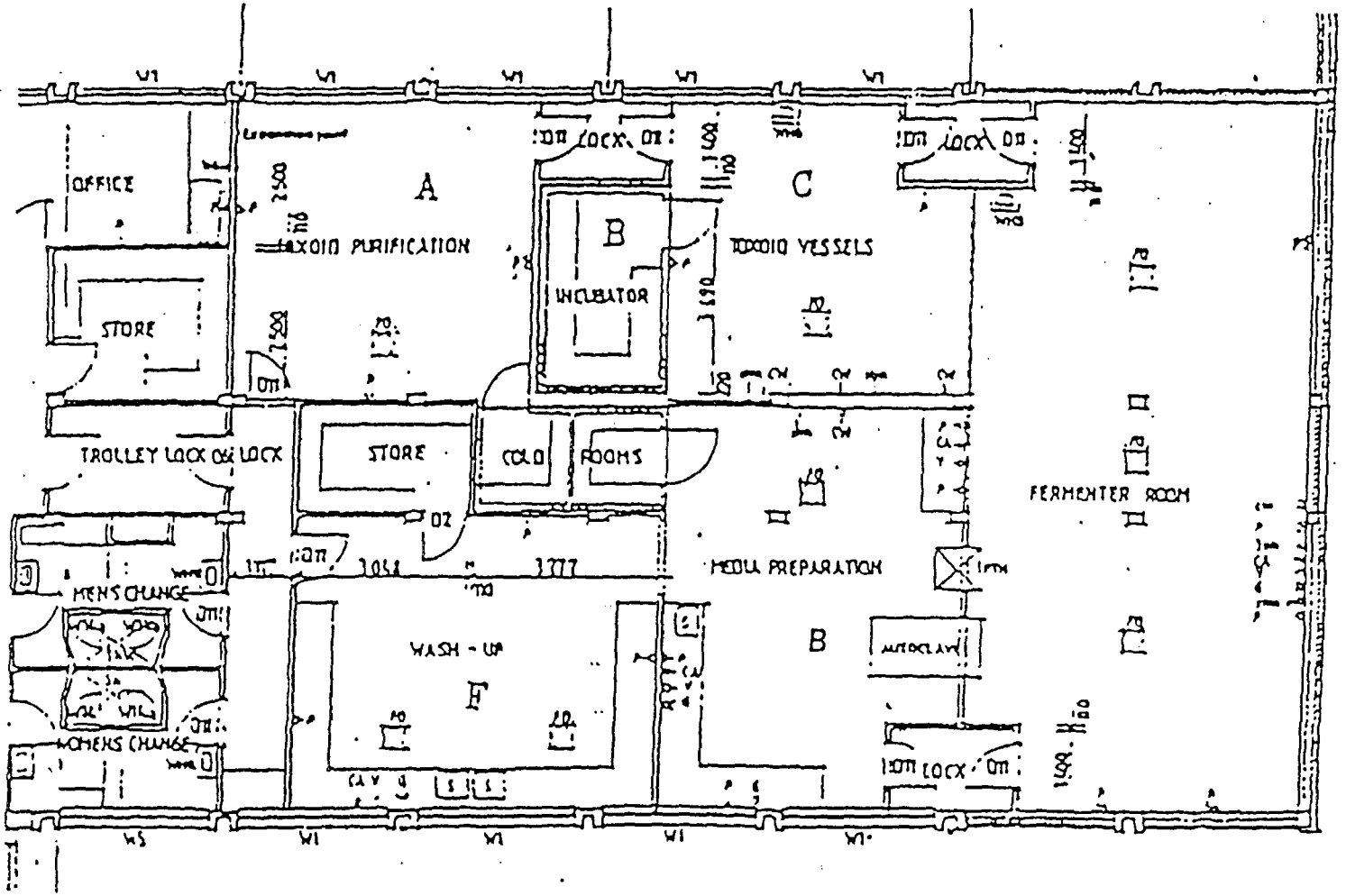
Figure 3

NORTH WING - UPPER FLOOR



ANTISERUM PRODUCTION

Figure 4



KEY:

[A] Purification process.

[B] Media production for diphtheria.

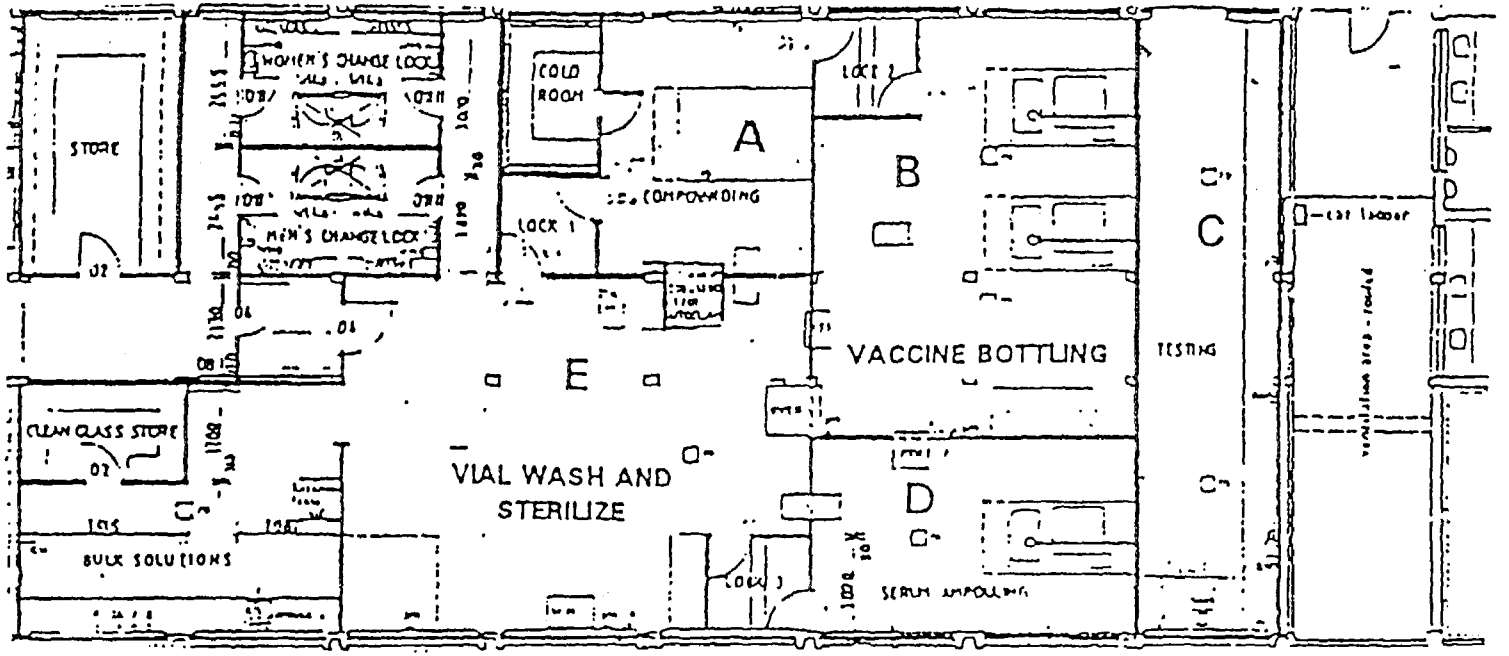
[C] Toxoiding process.

All above areas are air conditioned and supplied with filtered air (class 100,000).

After completion of the above processes, the purified product constitutes the primary production lot of Diphtheria toxoid.

Figure 5

COMPOUNDING AND FILLING PROCESSES - CENTRAL WING



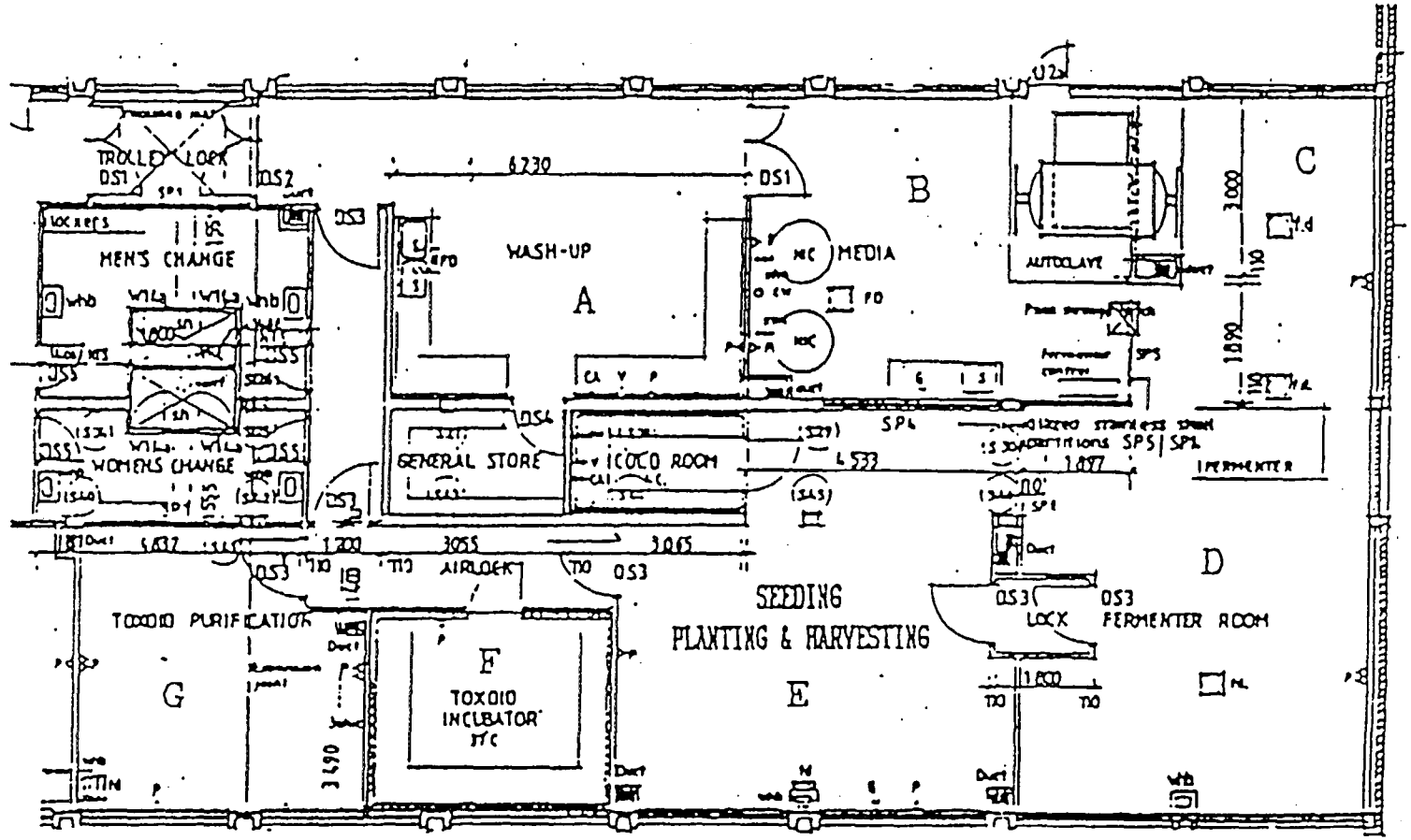
KEY

(A)	Compounding area (class 10,000).
(B&D)	Filling and sealing area (class 10,000).
(C)	*Testing area (c) class* (300,000).
(E)	Vial and ampoule washing and sterilising (class 100,000) area.

All compounding and filling procedures are done in curtained laminar flow booths, supplied with air of class 100 or better over the working areas. All small equipment is pre-sterilised by autoclaving. These premises are used for the compounding and filling of all injectable products for human use produced by South African Vaccine Producers (Pty) Ltd., but only a single product is processed at any one time in a filling or compounding room.

Figure 6

TETANUS TOXOID PRODUCTION AREAS



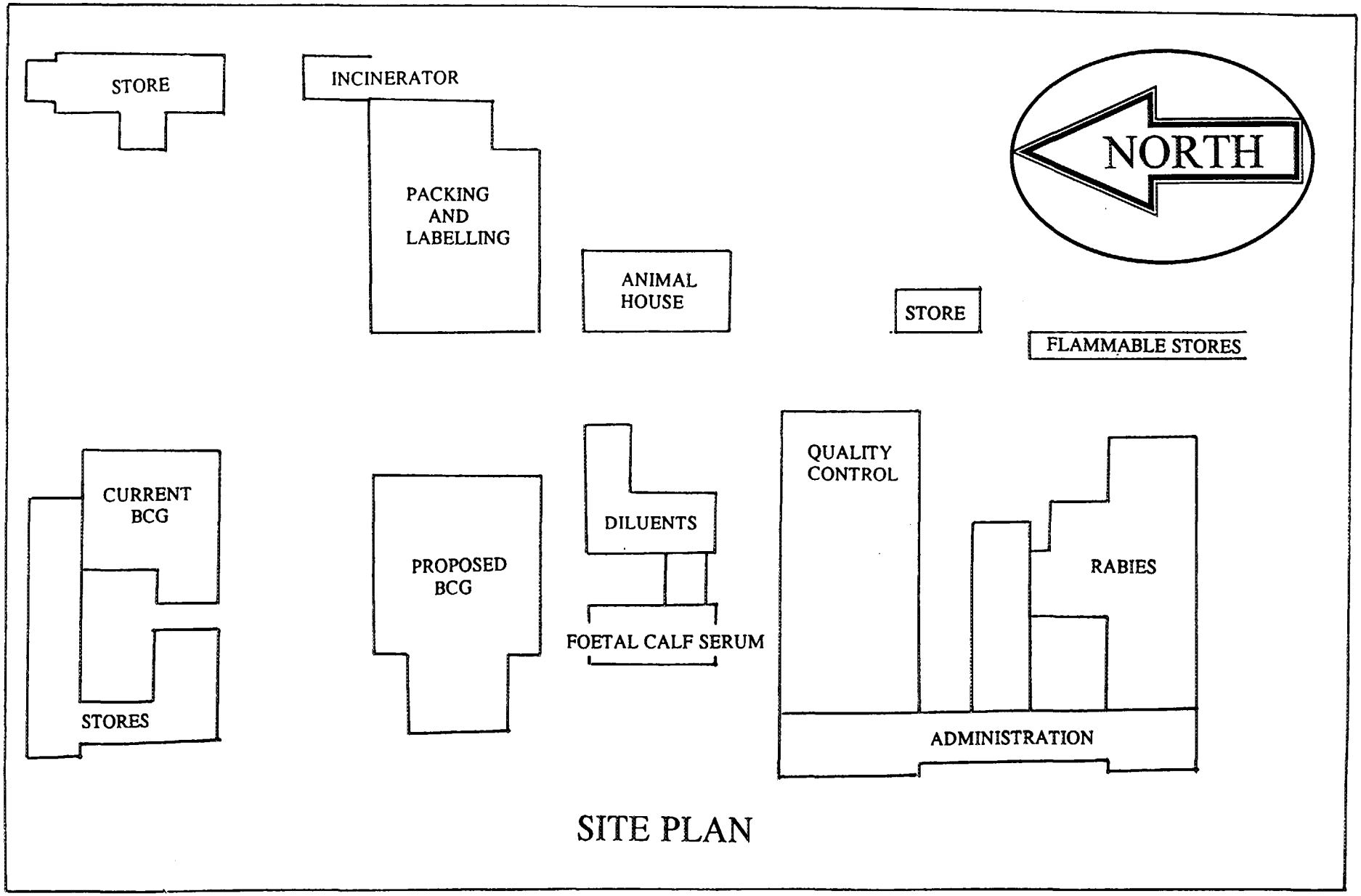
KEY

[A]	Preparation of culture flasks.	[B]	Media preparation.
[E]	Seeding of production culture.	[E]	Harvesting of toxin.
[F]	Toxoiding process.	[G]	Purification process.

All above areas are class 100,000. After completion of the above processes, the purified product constitutes the primary production lot of tetanus toxoid.

Figure 7

THE SITE MAP OF STATE VACCINE INSTITUTE



SITE PLAN

10. THAILAND

THE GOVERNMENT PHARMACEUTICAL ORGANIZATION (GPO) OF THAILAND

by Mrs. Suchada Subhachaturus
Director, Biological Quality Assurance Division
The Government Pharmaceutical Organization (GPO) of Thailand

Institutional Profile : Background

The Government Pharmaceutical Organization (GPO) of Thailand, a state enterprise, is a major supplier of pharmaceutical products including vaccines to the Ministry of Public Health. The organization currently supplies most of the vaccines required by the National Expanded Programme on Immunization. The GPO began producing vaccine in 1946 at which time its organization status was that of the Pharmaceutical Plant under the Pharmaceutical Division of the Medical Science Department. The first product of this type was smallpox vaccine. Over ensuring years, other vaccine, toxoids, and sera came into production, and at present, the GPO produces 15 biological products.

GPO's Bio-product department has 6 divisions with 154 staff. The division of Biological Quality Assurance is one division of the Department of Biological Product, which has been responsible for inspecting and controlling of vaccine and serum.

Biological Quality Assurance Division

1. Role of QA and Responsibilities

At present we are conducting the establishment of QA System for the Production of Biological products. The activity we have performed are as follows:

- Validation and calibration of equipments
- Validation of sterilization process, autoclave, air filtration system
- Training (GMP)

2. Role of QC and Responsibilities

- Keep samples
- Keep records, documentation
- Set up product specification
- Monitor product stability studies
- Check the validity of expiry dates
- Deal with claims of return product
- Contact with international organization (WHO)

- Control of
    - starting materials (raw materials)
    - intermediate products
    - finished products (final bulk and final product)
    - filling materials (vials, syringes, stoppers)
    - packaging items

3. Facilities

4 laboratories in QC consists of

- Physio-chemical laboratory
- Biochemical, Radio immunological laboratory
- Bacteriological laboratory
- Virological laboratory
- Control on Animal Laboratory
- Other Facilities in QC (Washing-Sterilization units, Technical Administrative unit for typing, release of batches and protocol certificates)

QC facilities is crowded and very old and must be urgently upgraded to satisfy the minimum GMP requirements.

Staff in Biological Quality Assurance Division

Scientists	10	persons
Administrative Officers	3	persons
Technicians	3	persons
Laboratory workers	6	persons
Total	**22**	**persons**

Plans for future development

- Establishment of laboratory quality assurance system on quality control testing following the requirements of ISO/IEC Guide 25 : to assure the quality control testing of vaccines.
- Establishment a GMP task force to provide guidance to production and QC staff in the preparation and application of SOP's and compliance with GMP.
- Development and promotion of staffs.
- Arranging locally academic seminar.
- Overseas individual training on QC test of various vaccines.
- Overseas group study tour on GMP inspection of biological products manufacturing quality assurance system in biological products testing laboratory.

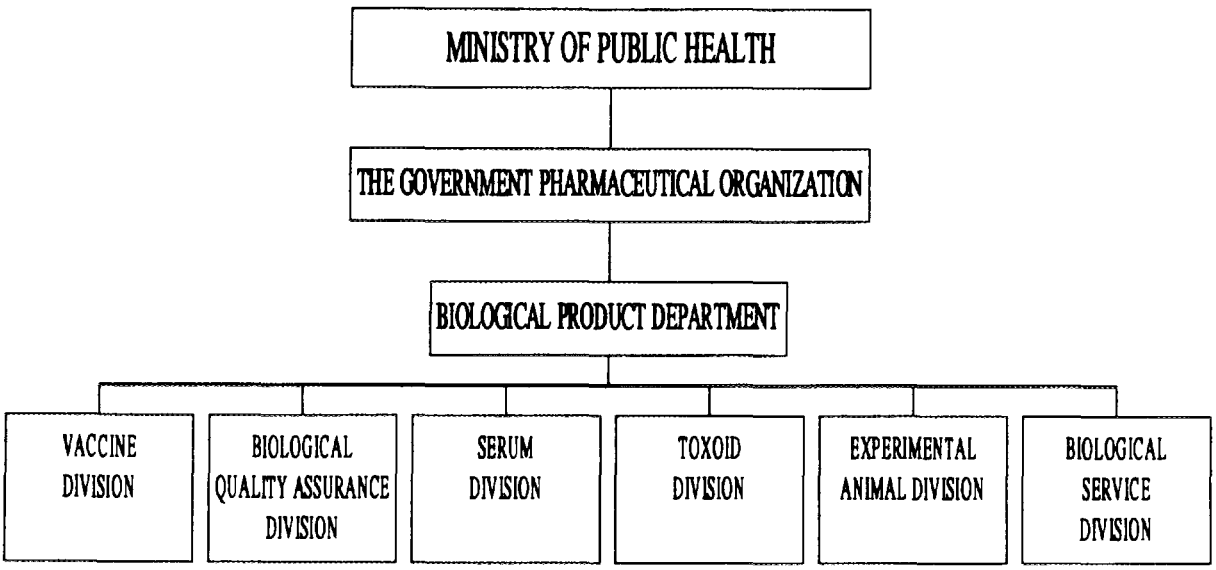
Benefit from my participation

- Be able to apply the knowledge gained and improve our system.
- Improve the facilities in the manufacture area in order to achieve ISO 9000.
- Provide the knowledge and experience gained to other staffs.
- Cooperate with staffs from other countries in the future.

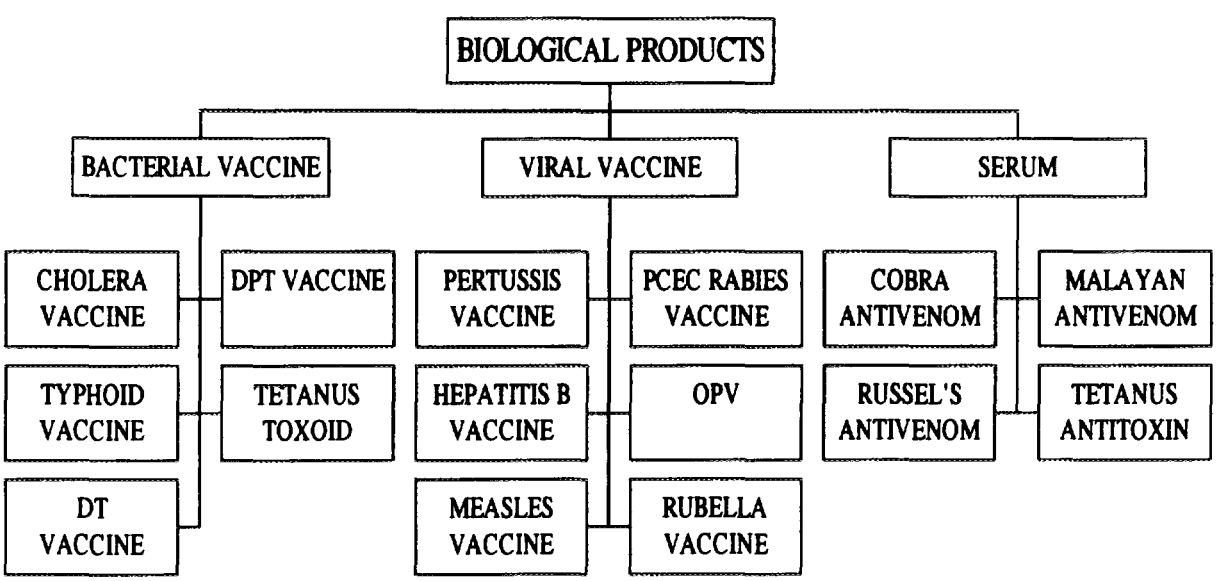
The present production capacity is inadequate and mainly hampered by the limitation of space and quality assurance system under the production installation. The organization is currently importing bulk vaccine to supplement locally-produced vaccines in order to match the increasing needs for EPI. A new production plant is needed to improve the capacity, yield, as well as the quality of the vaccines. Facing with technical problems concerning consistency in the yield of production and the need for improved quality assurance, GPO needs support from IVI, to assist in identifying and solving the problems and in providing guidance for improvement.

The GPO conducts a Feasibility study on construction of a new Vaccine Production Plant complying with US FDA Standards, which would consider the following methods of financing the project by seeking budgetary support from the government, securing loans or issuing state enterprise bonds, entering into a turn-key contact, entering into a joint venture.

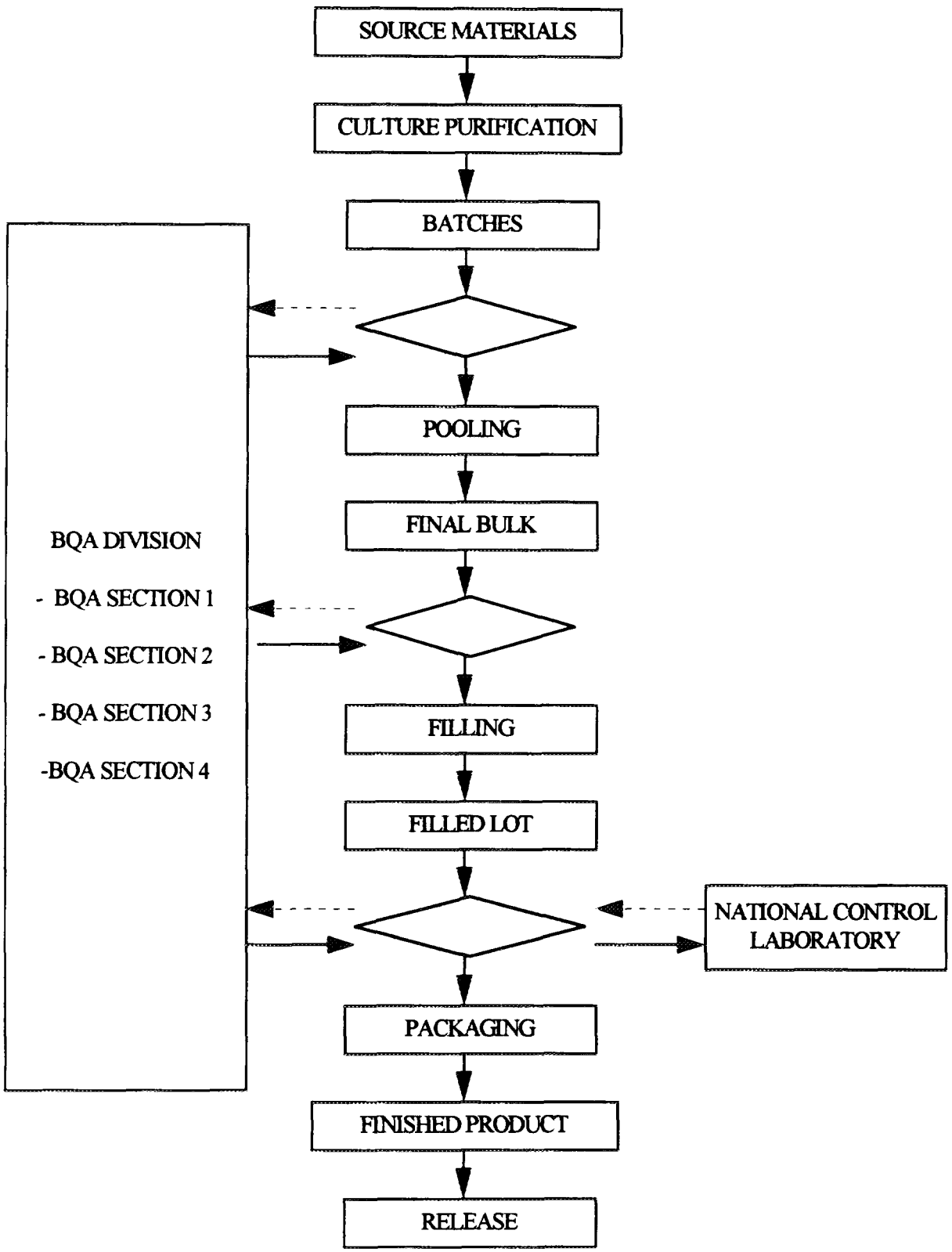
ORGANIZATIONAL CHART



FLOW CHART
BIOLOGICAL QUALITY ASSURANCE DIVISION



MANUFACTURING



QA/GMP/QC OF VACCINES IN THAILAND

by Teeranart Jivapaisarnpong
Chief, Biological Standardization Section
Division of Biological Products, Department of Medical Sciences
Ministry of Public Health, Thailand

The Division of Biological Products of the Department of Medical Science acts as the "National Control Laboratory for Biological Products". The main responsibilities are: performing the quality control of biological products used in Thailand both locally produced and imported, preparing the national references and standards as well as research on vaccine development and application.

There are 40 staff working in the division including 22 scientists, 4 technicians, 7 administrative officers and 7 workers.

At present the division is developing the quality assurance system for quality control of vaccines used in EPI as well as strengthening our facilities in quality control of biological products.

Our Institutional strength is: we have very good laboratories and equipment; but the weakness is: most of our staff (about 90%) are new comers and they have very few skills and experiences in QC, GMP and QA of biological products, so in our next five year plan (1997-2001) we are going to focus on development and promotion of our staff.

As I am the Quality Control Coordinator who is responsible for performing and coordination on QA system development in the division, the knowledge I will gain from this training course will be very useful for me and my institute. Moreover, it is a good opportunity to meet and discuss with the people who works in the same area and I wish to have the future cooperation with them on QA/QC.

The specific issues which I really want to be considered is the establishment of the network for interlab calibration between the institutes that perform the QC of biological products.

11. VIETNAM

NATIONAL CENTER FOR QUALITY CONTROL OF BIOLOGICAL PRODUCTS

by Miss Mai Nguyet Thu Hong
National Center for Quality Control of Biological Products
Hanoi, Vietnam

A. Background information providing a brief outline of our existing facilities and Staff and plans for future development, if any:

The Pasteur Institute of Ho Chi Minh city produces two kinds of vaccines: the BCG and the Rabies vaccine. The BCG vaccine was provided to the EPI. At present, the BCG vaccine has been produced in the freeze-drying form (surface culture), and the Rabies vaccine has been produced in the liquid form. We desire to improve the technique of culture (disperse of culture) in the BCG vaccine in order to have a high viable counts of the BCG vaccine. This gives a good immunization of the BCG vaccine. In the Rabies vaccine, we hope to produce a freeze-dried of vaccine. This is useful in the transportation and the storage of the vaccine.

B. Our institutional strengths in relation to QA/GMP/QC:

- All of the persons who produce and control the BCG and the Rabies vaccines have been trained in the Pasteur Institute of Paris-France.
- The Chief of Quality Control in the vaccine laboratory has been trained in the Pasteur Institute of Paris, in the National Institute of Health of Tokyo-Japan and in the National Quality Control Laboratory for Food and Drugs-Jakarta-Indonesia.
- The National Center for Quality Control of Biological Products provides the requirements for the Quality control of the vaccine laboratory and regularly inspects our production and control activities.
- Every year, WHO experts visits and survey our production and control laboratory system.

Our institutional weakness in relation to QA/GMP/QC:

The only BCG laboratory has been supported by the Pasteur Institute of Paris. The other laboratories have been equipped by ourselves. Therefore, the conditions for work are not as good as the requirements of WHO. We attach to realize the QA/GMP/QC in the

production and control but not yet completely as we have desired. We think that there are many things to be done such as:

- The department of animal should be improved in order to have a good animal as criteria.

- The old machines should be replaced.

- Give the training course on QA/GMP/QC to all of the persons who work in the Production and control laboratory.

C. Benefit from your participation in the training course

I hope to improve my knowledge on QA/GMP/QC in this course and help everyone realize the QA/GMP/QC in order to produce good vaccines.

PART II

TRAINING WORKSHOP HANDOUT*

* **Note**: Part II is not a comprehensive description of the QA/GMP/QC for vaccine manufacture but only a workshop handout which guided the discussion and facilitated the understanding of the issues. Therefore, it should be regarded as an illustration for the above-mentioned topic.

IVI/UNIDO/BIO FARMA TRAINING WORKSHOP ON QA/GMP/QC FOR VACCINE MANUFACTURE IN DEVELOPING COUNTRIES

BANDUNG, INDONESIA
8-15 JULY 1996

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SECTION I

1. INTRODUCTION TO CURRENT GOOD MANUFACTURING PRACTICE (CGMP)[1]

CGMP is a term used by most countries to describe industry specific expectations designed to assure appropriate, consistent and rigorous product quality.

1.1 RATIONALE FOR CGMP

The rationale for CGMP is related to the **danger potential.** In the event of product failure or in the use of a defective product, there is a great danger to inflict serious injury or death.

The quality of a drug cannot be determined by the patient because he or she is not able to determine whether or not a drug product or a vaccine has failed specifications and is defective. Examples of product failure or defective products are exemplified below:

1938 - Sulphanilamide, the elixir of death

The "miracle drug" came into use. It was marketed as a pediatric elixir. It was a raspberry flavoured solution in a liquid industrial solvent, diethylene glycol. Generally an elixir is designated as an alcohol-based product, but this particular formulation was of diethylene glycol. Upon ingestion, ethylene glycol was metabolized to oxalic acid.

203 gallons of this elixir were produced in 1938; it led to
- 358 poisonings
- 107 deaths
- 251 sick but survived

At that time there was no legal authority to remove this drug from the market but this incident was instrumental in the passage of the Food, Drug and Cosmetic Act of 1938 and FDA (US Food and Drug Administration) was born. Although it can be argued that this problem arose due to toxicology issues and not directly related to GMP deficiencies it still is a cumulative effect. If there was full GMP there would be safety testing to ensure prevention of such coincident.

Regulation: ***Safety had to be tested before releasing drugs into the market.***

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[1] For introducing CGMP, the North American perspective has been used.

1955 - Polio Vaccine (Cutter Labs, USA) (Lambert, E.C., Medical Mistakes, Indiana University Press, 1978)

51 Children paralysed
10 Deaths

Several possible reasons:

- Inconsistent viral inactivation process.
- Quick scale-up of production without proper validation of inactivation steps.
- Active live virus production process which used a heat inactivation step. For a virus, scale-up of heat inactivation steps may not have been sufficient.

Regulation: ***Batch by Batch testing and release programme.***

Result: ***Safety evaluation of drugs and biologicals by FDA as well as factory inspections.***

1962- Thalidomide

Thalidomide was commonly prescribed for insomnia and nausea in pregnant women in Europe; as a result thousands of babies were born without arms or legs.

Possible Reasons:

One enantiomer caused sedation which was the desired effect, while the other enantiomer caused devastating birth defects known as Phocomelia.

Solution:
To remove the undesired enantiomer by a validated purification process assured by Assay Validation. Again, GMP deficiency by not having adequate QA and QC programmes which could have answered assay validation. This led to guidelines on the development of New Stereoisomeric Drugs (1992) US FDA.

Regulation:

- ***Drugs must be shown to be effective and safe before release.***
- ***Drugs are defined as "adulterated" when produced in a facility not in compliance with CGMPs (i.e. production must occur using a validated process).***

1970 - Contaminated Caps of Large Volume Parenterals (Lambert, E.C., Modern Medical Mistakes Indiana University Press 1978)

In the 1970's, patients in several hospitals in the USA developed bacteraemia: 40 died and 378 infected but survived.

Cause:

A Pharmaceutical company selling the intravenous (IV) solutions in one kind of packaging (shellac lined lid), changed to another type of packaging (plastic lined) on all IV bottles. All reported cases of bacteraemia were associated with the new plastic lined lids.

40% of plastic lined lids contaminated
0% of shellac lined lids contaminated

Result: ***All incoming materials should be thoroughly tested by QC before release for production.***

1982 - Tylenol Poisoning

7 people die of taking Cyanide-laced tylenol (acetaminophen) capsules. A 12-year-old girl complained of a scratchy throat to her parents who gave her tylenol (extra strength). Three hours later, she died. Within days, 6 more people died. Although this example is not of a deficiency while the drug is in production, it illustrates that GMPs have to stretch all the way from R&D laboratories to production and to marketing. That there is safety built in all the way to the point where the product is expired.

Regulation: ***All medications must have the tamper resistant packaging.***

1987 - Tryptophan

Showa Denko of Japan, a bulk chemical manufacturer of amino acid L-tryptophan. L-tryptophan is an unregulated genetically engineered nutritional supplement sold in health food stores as a "natural sleeping pill."

30 deaths from Eosinophila-myalgia syndrome (EMS). It is estimated that these victims ingested less than 200 mg of L-tryptophan per day! It is speculated that unexpected process contaminant/impurity present at less than 0.0089% was due to incomplete cleaning between batches of product i.e residue from one safe product mixed with the residue of another safe product with deadly consequences.

Unfortunately, the current situation in the Pharmaceutical and Vaccine Industry is such that it is not possible to provide unequivocal assurance of Quality. Incidences described above have led to tighter regulation and increased awareness to what can go wrong. However, there are some draw backs even with tighter regulations.

For example:

a) Presumptive Testing

Tests performed on incoming raw materials, in-process samples and finished products are presumptive because they test for the components which are *PRESUMED* to be there.

These tests cannot be performed for unforseen contaminants. For example, contaminants which are introduced as a result of inadequate precautionary measures in the manufacture of different products in physically adjoining areas, and/or contaminants which are incorporated into the formulation as a result of inadequate environmental controls. Therefore, despite testing, contaminants can enter and become part of finished vaccines and because of this potential, it is important to test many different physicochemical aspects during lot release in an effort to show up contaminants.

b) Samples Testing

In lieu of 100% testing for a desired attribute in a vaccine, an evaluation of the lot is made by performing the test for the attribute on a small number of items (sample) which is ostensibly felt to represent the lot. Samples do not always represent the lots from which they are taken. Every sampling plan is subject to two types of risk factors, the Alpha factor and the Beta factor.

The Alpha factor states that there is a finite probability that samples from good lots will fail to pass the quality attribute test(s). Good lots will therefore be rejected. The Beta factor states that a finite probability exists that samples from a bad lot will pass the tests applied to them. In this case, bad lots of products will be accepted. The manufacturer's have developed acceptance/rejection sampling plans which reflect that firm's definition of quality for purchased or manufactured items. The sampling plans take into consideration four factors:

- Acceptable Quality Level (AQL) is the minimum quality level a lot must possess before it may be accepted.
- Risk is the probability that a firm's good lot will be rejected by the sampling plan even when the number of defects present in the lot is less that the AQL.
- Unacceptable Quality Level (UQL) is the minimum quality that a firm is willing to accept. This may be thought of as the maximum number of defectives in a lot which the sampling plan will accept.
- The risk is the probability that a lot which contains more than the UQL of defects is going to be accepted by the consumer's sampling plan.

Ideally, the sampling plan should have an AQL that is equal to the UQL.

c) Weight Balance Check

In the case where a bulk vaccine is purchased from a supplier, formulated and vialed at the firm the weight balance check is often used during formulation. A common current practice is to verify the addition of all components required in the formulation of a vaccine by determining the weight of the completed batch. The operative assumption is that if a component in a formulation had been inadequately overlooked, the "underweight" or "short" weight of the batch would disclose the error. In an analogous manner "overweight" would suggest the addition of more materials. Meeting the target weight of a formulation, however, **does not** guarantee that the formulation is as it should be, that is, that the formulation contains all and only the components of the formulation. It is however, felt that by using as many precautionary measures as possible it may be possible to reduce the chances of catastrophic situations.

1.2 CONCEPT OF CGMP

The objectives of CGMP are to be able to **consistently** manufacture vaccines of high quality and to be able to **detect** defects whenever they are found. The quality of a vaccine, like the quality of any other manufactured item, is determined by the degree to which the product conforms to specification. The concept of GMP presented here is based on eight key areas in vaccine manufacture. Specification is therefore a very important criterion to be considered as early as possible in vaccine development as it will provide a goal to work forward. Specifications must be developed in conjunction with production, QA and QC must be based on sound scientific rationale.

a. Component Attributes

- raw materials
- components
- closures
- labels/labelling system

b. Product Attributes

The development of an appropriate set of product attributes should, as a minimum, consist of specifications for the final two or three stabilities approved formulation candidates which are samples for the final market requirements. Product attributes must be made with stability in mind. Many vaccines show excellent attributes when firstly prepared however, after a few months the story can be different.

c. Process Specification

Validation and documentation during GMP production are required. Production of contamination free and defect free vaccines **consistently** and **reproducibly** is the goal.

d. Process Validation

The complete process for manufacturing the vaccine is first accurately defined. Each critical step is identified then each critical step is validated. In context of vaccines, validation means:

To attain and document sufficient evidence to give reasonable assurance, given the current state of art of manufacturing, that the process under consideration will do what it is expected to do. Validation can be defined as a process of verification which consists of 4 phases:

- qualification
- challenge
- monitor
- requalification

Validation is one of the most important ways in which one can show consistent product quality.

e. Documentation

The most critical documents include:

MPR (Master Production Record)

The MPR is a document which embodies the 4 quality elements of manufacturing (personnel, materials, equipment/facilities and methodology) are required for accurate and precise preparation of a specific vaccine.

SOPs - Standard Operating Procedures

Certain procedure in the manufacturing plants which are not related to the production of a specific batch of a vaccine is made reproducible through constant adherence to SOPs.

f. Manufacturing Strategy

The single most important unit in the manufacturing organization that should be credited for accomplishing the objectives of CGMP is the Production unit. Obviously if Production does not function responsibly, no amount of validation or technical support will help.

The strategy for responsible manufacturing is based on leadership and training. Manufacturing personnel can only be effective if they are provided with adequate equipment, facilities, appropriate material and methodology. **BUT, the key element is personnel.** Production people must recognize that they are responsible not only for the quantitative aspects of manufacturing such as production rate, scheduling, etc. but also for the **compliance of the product to specification.**

Subsequent to the approval of the MPR, Production must understand that the MPR is now the tool by which Production is protected from making a "bad vaccine." Therefore Production should scrutinize and challenge heavily any MPR that is presented for approval. Once Production has approved the MPR it is obliged to follow it completely. Only when it is totally followed, can specifications be met. In this context, operating compliance of personnel is the single most important contribution toward producing a defect free vaccine.

g. QA Strategy

The strategy for assuring that every unit of vaccine manufactured is identical to every other unit of the same product, irrespective of whether the units belong to the same lot or to different lots. This is based on **screening all incoming shipments** and **testing all completed lots before releasing** them for distribution.

The screening of all incoming materials starts with the preparation of adequate specifications and provision of qualified vendors. The act of purchasing is restricted by specifications retained for each material and purchase is restricted to approved vendors only. All incoming shipments are quarantined and inspected before being transferred to a Released Material area. Lots in-process are sampled at critical stages of production and tested to determine if the manufacturing process is progressing as expected. Completed lots are testing before releasing the lot for distribution.

h. Post Marketing Surveillance Strategy

Three principal attributes comprise this event:

- sampling and testing of retained samples*
- sampling and testing of field samples
- investigation of complaints

* *testing for full compliance to specification at their expiration dates.*

1.3 PHILOSOPHY OF CGMP

a. GMP - Definition

GMP is defined in the United States as "the minimum necessary level of operation and administration of methods, facilities and controls to assure that the product meets the requirements of safety, identity, strength, quality and purity which the product is represented to possess." This definition is also strongly influenced by Industry Standards set by individual companies. UK defined it as "the guide which describes the special precautions and checks that must be taken at all steps of manufacture upon which the quality of medical products depends."

Is GMP necessary or is it merely desirable?

Is GMP a purely bureaucratic prerequisite or is it to be treated in a fundamental professional ethical matter?

Earlier on we described certain customary practices in the vaccine industry, such as end product testing, in-process testing and raw materials testing. Each of these practices carries a significant risk of failure, and they are clearly inadequate to guarantee the provision of defect-free vaccine. To date, the singular known solution to avoid manufacturing and distributing defective vaccines is the adoption of full CGMP; specifically process validation to establish accuracy and documentation to assure precision and reproducibility.

b. GMP - Cost

With respect to the issue of cost, typically in organizations where CGMP is implemented fully, it is common to have 20% of the overall staff dedicated to QA and QC activities. This can be prohibitively expensive. In addition to extra staff costs, the higher quality of components and closures, gowning supplies, maintenance of clean rooms, monitoring, etc. can add a significant cost to capital and operations.

How much will GMP cost, who will pay for it?

- Relationship between GMP and profitability
- Is there an optimum cost of GMP/profitability ratio?
- Who can afford it? How does it impact the cost of the vaccine and consequently its availability to the population?

These are issues which need to be assessed by individual countries, their National Control Authorities and the companies producing the vaccines. It will not be discussed further as it is outside the scope of this manual.

c. GMP - Scope

What is the scope of GMP? Where does it start and where does it end?

- at the production stage?
- at the fill and finish stage?
- only for sterile material?

In the case of vaccine production, CGMP starts right at the beginning of the process, ie. at the Cell Bank stage and all the way to the Final Release of the product for distribution and also while the vaccine is on the market. Another aspect of the GMP dealing with scope is in the level of the economy and the environment in which the practice is in use.

It is very important to note that there is **only 1 GMP**, but the GMP will be regarded as a continuously evolving process which has to incorporate all R&D results, process and test improvement, new product development, results of clinical trials and changes in regulations which have relevance to the safety, quality or efficiency of the vaccines. Consequently, to achieve the quality objective reliably, there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporated GMP and thus Quality Control (QC) which is subject to certain amendments from time to time. Due to the above continuously evolving nature of GMP, its actual level of implementation may vary from country to country, region to region.

d. GMP - Implementation

How can it be implemented? The implementation of GMP starts with a strong unequivocal declaration by the organization. For example:

GMP compliance is a condition of employment.

The organization must employ leadership personnel in manufacturing who are credible and who are respected by their peers and by the organization. These leaders must be knowledgeable about the product. They must understand that their responsibilities encompass both the customary quantitative aspects of materials management, manufacturing schedules, rates and profitability and the qualitative aspects of the products including the consistent compliance to purity, strength and stability specifications.

The management must provide a respected quality organization, a group with the knowledge and the authority to discharge their corporate responsibilities without obvious or subtle conflict. This group must be equipped to plan, execute and audit strategies for QA, preventing defective components from filtering into the plant, utilizing highly developed discovery systems for defectives formed during manufacturing operations, skilfully screening of all lots before introduction into the marketplace, and thoroughly scanning the product's performance while the product is in the field.

2. BASIC ELEMENTS OF A QUALITY ASSURANCE PROGRAMME

The function of Quality Assurance (QA) is to design a programme with the objective of ensuring that medicinal products are of the quality required for their intended use. QA therefore incorporates GMP, Good Laboratory Practice (GLP) and thus QC.

2.1 QUALITY

Establish the quality. Determine the attributes of the raw material, and how will it impact the process or performance of a product. Then determine what could go wrong that could significantly impact the safety, uniformity, reliability and performance of final product, finally, go on to choose quality parameters and test methods that are scientifically rigorous.

Always set limits for the attributes; for example, express as:

NMT (no more than) and
NLT (no less than)

Specifications must be set such that they are wide enough so that you don't routinely trigger deviation but tight enough to have respect. It is quite common for companies to want to set tight specifications. However, this routinely triggers deviation which presents a scenario that the company is not capable of meeting its own specifications. It is obvious that the quality system has failed. On the other hand, setting specifications which are too wide will prove that the organization is not able to produce a consistent product.

2.2 MONITOR QUALITY

Monitor quality so that you assure that the standards you have set are routinely met. This is the heart of Quality Assurance. This means setting up a comprehensive system to ensure that you routinely meet the quality parameters you have established.

For Example:

If the item is a raw material with written specifications, it is appropriate to perform a documented inspection of the item when it is received at the facility, i.e. to monitor its established quality routinely.

2.3 CONTROL CHANGE

Change is inevitable; however, uncontrolled change is dangerous. This is because there is always the potential that product improvement (which is in fact a product change) may have an adverse impact on the safety or effectiveness of the final product. Regulatory agencies do not expect a manufacturer to stop change, only to control change.

2.4 DOCUMENT IT

- Document the quality standards you have established (2.1).
- Document the monitoring programmes and the monitoring data that you collect (2.2).
- Document any changes that occur (2. 3).
- Documentation is the **CURRENCY** of a vaccine manufacturer; without it, it cannot market the product it has made.

MOST WIDELY USED GMP REGULATIONS ARE:

United States

Code of Federal Regulations, Title 21 (21 CFR)
Parts 210 and 211 - Current Good Manufacturing Practices for finished pharmaceuticals

World Health Organisation

WHO Expert Committee on Specifications for Pharmaceutical Preparation, 32nd Report, WHO Technical Report series No. 823, 1992, Annex 1 - Good Manufacturing Practices for Pharmaceuticals. 34th Report, WHO Technical Report Series No. 863, 1996, Annex 6 - Good Manufacturing Practices : Guidelines on the validation of manufacturing processes.

WHO Expert Committee on Biological Standardization, 42nd Report, WHO Technical Report Series No. 822, 1992, Annex 1 - Good Manufacturing Practices for biological products and Annex 2 - Guidelines for national authorities on quality assurance for biological products.

European Community

The Rules of Governing Medicinal Products in the European Community, Volume IV, Good manufacturing practices for medicinal products. Commission of the European Communities, 1992.

United Kingdom

Rules and Guidance for Pharmaceutical Manufacturers, 1993, London, HMSO.

2.5 QUALITY SYSTEMS

Due to global harmonization practices, the emphasis from Quality Assurance and Quality Control is shifting to Quality Systems. Thus, instead of a department within an organization being in charge of assuring and controlling quality, quality is now the responsibility of the entire organization.

What does a quality system do?

- Assures that the work will be performed in accordance with the quality requirements and documented consistently and reproducibly. The statement is the heart of GMP and validation.

- Assures the accountability and traceability of information.

- Assures access to integration of that information in a manner that supports consistent decision making.

- Minimizes redundancy of information which can lead to operational and decision making inconsistencies.

- Assures flexibility so that organization can respond to change effectively and efficiently.

Examples of Quality Systems:

ISO 9000	Series International Standard Organization
GMPs	Good Manufacturing Practices
TQM	Total Quality Management

Differences between North American GMPs and ISO 9000

ISO	GMP
General	Industry Specific
Voluntary	Law
Market Driven	Regulatory Driven

Similarities

- Basic systems of Quality Assurance
- Both set specifications.
- Both evolving.

GMP is evolving:

- Current North American GMPs are production oriented.
- New proposed GMPs will be design, purchasing, production and service oriented.

SECTION II

1. FACILITY DESIGN FOR CGMP COMPLIANCE

1.1 REGULATORY ASPECTS OF PHARMACEUTICAL FACILITY DESIGN

What do the Regulations say about Facility Design?

Some illustrative examples are described below:

Plant Lockers

- Personnel engaged in the manufacture, processing, packaging or holding of a vaccine will wear clean clothing, appropriate for the duties they perform. Protective apparel, such as head, face, hand and arm covering will be worn as necessary to protect the vaccine from contamination.

- Every personnel entering the manufacturing areas should wear protective garments appropriate to the operations being carried out.

- Outdoor clothing should not be brought into the changing rooms associated with clean and aseptic areas and personnel entering these changing rooms should already be clad in standard factory garments. Changing and washing should follow a clearly displayed written procedure.

These statements clearly discuss the need to proper design of the gowning room.

Design and Construction Features

- The building must be of suitable size, construction and location to facilitate cleaning, maintenance and proper operations.

- Do not build on a flood plain or where interruption of power is frequent.

Adequate Space

Adequate space for the placement of equipment and material must be allocated to prevent mix-ups. The flow of components is to be such so as to prevent potential contamination. *Thus, one must design for unidirectional flow.*

Defined Work Areas

Operations need to be performed within special defined areas of adequate size, to prevent contamination or mix-ups. There should be dedicated space for:

- receipts identification, storage and withholding
- rejected components
- release components
- in-process materials
- manufacturing and processing operations
- packaging and labelling
- quarantine of drug products, storage of released drug products
- control of laboratory operations
- aseptic processing

Thus one must spatially separate functions and yet allow design integration so that the process flow is smooth and unidirectional.

Lighting

- Adequate lighting is to be provided

Heating Ventilation Air Conditioning (HVAC)

- Adequate ventilation should be provided.

- Equipment for control of air pressure, microorganisms, dust, humidity and temperature is to be used when the operations require.

- Air filtration systems are to be used when appropriate. If air is recirculated, control of dust must be accomplished. When air is contaminated by the process, adequate exhaust must be provided.

Washing and Toilet

- Adequate washing facilities are to be provided
- No toilet facility will be opened into a manufacturing area
- Germicidal hand washing

Sanitation

- Building used in the manufacture of vaccines is to be maintained in a clean and sanitary

condition. Buildings are to be free of infestation of vermin and trash. Organic waste is to be held and disposed of in a timely and a sanitary manner.

- The use of bug zappers, sealed penetrations, screens are to be encouraged where appropriate. Written procedures are required identifying responsible parties and methods utilized in the cleaning of buildings and facilities. Cleaning schedules are required.

Insect Control Programme

- Written procedures are required when using rodenticide, fungicides and fumigating agents. All of these materials must be registered and used in accordance with Federal or equivalent (country) regulations.

Plumbing

- Potable water meeting Environmental Protection Agency (EPA) or equivalent, one to be provided under continuous pressure.

Drains

- Drains are to be adequately sized and provided with an air break or other mechanical device to prevent back siphonage, when connected directly to a sewer.

Sewage and Refuse

- Sewage, trash and other refuse are to be disposed of properly (safe and sanitary method). For example: flow out of an operating area, vials must be crushed and labels removed or destroyed from the products which cannot be salvaged.

Spore Forming Organisms:

- Facilities for vaccines produced by using spore forming micro-organisms, eg. tetanus toxoid vaccine by clostridium tetani shall be separated from other manufacturing facilities.

- These facilities shall have dedicated equipment and personnel as well as their own separated utilities to prevent spores that might become airborne, to contaminate other areas of manufacture and filling and packaging departments.

- All facilities (building, equipment, utilities, personnel) shall be validated.

Live Vaccine Processing

- Space used for processing live vaccines will not be used for any other purpose during the processing period for that vaccine and such space will be decontaminated prior to initiating processing.

- Live vaccine processing areas will be isolated from and independent of any space used for any other purpose by either a separate building, a separate wing of a building or in quarters at the blind end of a corridor and will include adequate space and equipment for all processing steps up to filling of final containers.

2. FACILITY DESIGN

Facilities intended for the manufacture of vaccines require special attention to design, construction techniques and qualification or validation strategies. This is because quality cannot be completely tested in the final product and therefore it must be built into the process used to create the vaccine. Additionally, the majority of facilities today are also built to accommodate or permit multi-use (contain areas used for manufacturing two or more products, either concurrently or on a campaign basis). Thus, measures to prevent cross contamination of products and demonstration of sufficient control over all manufacturing operations to minimize potential for mix-ups must be supported by the multi-use facility. This is particularly important for those steps in the manufacturing process where the product may potentially or is "open" to the environment.

2.1 GENERAL CONSIDERATIONS FOR FACILITY DESIGN

- Design of the facility should include selection of building materials that are non-porous and resistant to frequent exposure to a variety of disinfectants and cleaning agents. This means floors, walls, and ceilings should be designed to ensure adequate cleaning and maintenance.

- Piping/equipment which is difficult to clean should not be exposed. It should be enclosed to prevent build up of dust, etc.

- Facility design should provide for movement of equipment, raw materials, product, waste and personnel through the facility whilst minimizing the interaction between staff and process streams from different process trains or stages.

- Adequate space must be provided for each operator and storage of supplies and equipment sufficient for the campaign approximately 20 m^2 are required per operator as a minimum. Clean and controlled rooms should not be used as a warehouse. Minimization of supplies, equipment and people will lead to a much cleaner controllable environment which in turns reduces the chances of contamination.

- Use of separate air handling systems are required to establish isolated manufacturing areas. Fermentation, where line operations are carried out, must have a separate air handling system. Purification is usually performed in Class 10,000 environment. Final filtration and filling are performed under Class 100 air within a single building.

- Air pressure differential between manufacturing areas and the use of anterooms and airlocks are instrumental to prevent airborne cross-contamination of products, raw materials and organisms between areas and should be implemented where possible.

- As the purity of the product or process increases, a higher quality of room finish and air quality is required.

- Facilities designed for work with pathogenic agents should address design issues for both containments of the pathogen, as well as prevention of cross-contamination.

2.2 CONTAINMENT CONSIDERATIONS IN FACILITY DESIGN

The main purpose of containment is to reduce exposure of laboratory personnel, other persons, the environment and processing stages (product) to potentially hazardous or pathogenic agents.

Mechanisms and design considerations to achieve containment are attained through both primary (protection of personnel and immediate product environment) and secondary (protection of environment external to laboratory or process) means. Secondary containment is achieved through a combination of facility design and operational practices (i.e. specialized air handling system and access control).

The following are key design considerations for biological containment level 2 (BL2) facilities which are required for the manufacture of almost all vaccines available in the worldwide market:

Room Air Supply

- Air supply must be independent from adjoining facilities for different manufacturing operations.

- Air supply HEPA filters equipped with magnetic gauges to monitor pressure drop of the HEPA.

- Directional inward, non-recirculated airflow for live, pathogenic manufacturing (i.e. fermentation) must be implemented.

- It must be interlocked with exhaust ventilation to prevent pressurization.

- It must be equipped with audible alarms to detect pressurization failure.

- Duct work must be sealed, reasonably airtight and independent from other ducting in facilities. Ductwork must be accessible from an outside containment laboratory in case of repairs.

- It must be equipped with manual damper to permit sealing for decontamination procedures.

Exhaust Ventilation

- Exhaust air is dispersed away from occupied areas or air intakes, preferably in vertical fashion.

- Exhaust from room should be directly connected to outside via dedicated exhaust system. If exhaust is ducted to common exhaust ducts shared with other rooms of different hazard levels then the exhaust air from the room must be filtered (HEPA) before entering common ducts. This practice is not recommended due to problems which can occur during system failure or when fumigation of a certain area is required.

- Exhaust ventilation may be required to be HEPA filtered, not recycled, and connected to audible alarm depending on local regulations.

- Exhaust ventilation can be equipped with manual damper to permit sealing for decontamination if necessary.

- Exhaust from the laboratory must meet a minimum of at least ten room volumes per hour.

- Recirculation of HEPA filtered air maybe permitted if it is not coming from a live area.

- Air exhaust system should be designed to be isolated to permit decontamination, to avoid back flow of organisms in the event of a fan failure.

HEPA Filters

- HEPA filters should be of a design to allow it to be tested and installed in-situ and decontaminated in-situ.

- HEPA filters to have minimum particle removal efficiency of 99.97 % for particles of $\geq$0.3 micron.

- HEPA filters are to be installed as close as possible to the source of hazards in order to minimize length of contaminated ductwork.

- HEPA filters are to be installed in housing with leak proof junctions between filter frames and ducting.

Directional Air Flow

- An air flow indicator (magnetic gauge for example) is required to ensure that exhaust/supply systems are functioning properly.
- Air pressure in the laboratory should be maintained at a lower pressure than less contaminated area.
- Airlock must be at a lower pressure than that of outside or uncontrolled areas.
- A monitoring log of the pressure differential should be maintained.
- Individual supply and exhaust systems having interlocked controls and malfunction alarms to maintain pressure differential ie. automatic dampers present so that in the event of a power failure, air flow cannot reverse.

Room Finish

- A laboratory has to be designed so that it can be cleaned easily. Walls, ceilings and floors should be smooth, easily cleanable, impermeable to liquids and resistant to chemicals and disinfectants normally used. Exposed pipes and ducting should stand clear of walls for ease of cleaning.
- Bench tops must be impervious to water and resistant to disinfectants, acids, alkalis, organic solvents and heat.
- Wash sinks should be provided in laboratories near an exit.
- Foot or elbow operated wash hand basin should be provided at an exit.
- Doors must be self closing and have vision panels.
- Windows must be closed and sealed.
- All light fixtures, pipes, conduits must be sealed to preserve biological separation between contaminated and clean zones.
- Perforations in walls and ceilings should be kept at an absolute minimum.
- All corners and junctions of surfaces should be water tight and readily accessible for cleaning.
- Laboratory furnishings should be kept to a minimum to allow directed air movement to sweep facility.

- Any service ducts that traverse the facility must be continuous and sealed where they penetrate the room (entry and exit).

Utilities

- Central vacuum lines should be isolated to protect cross-contamination (HEPA; check valves, etc.).
- All liquid and gas services should be protected by devices that prevent backflow.
- Traps must be kept filled with fluid that is suitably disinfected routinely.
- When unavoidable, exposed piping and ducting should stand clear of walls for recontamination.
- Open drains should be closed when not in use.

2.3. EQUIPMENT DESIGN

General

- Designed to limit or prevent contact between operator and infectious agent.
- Constructed of materials that are impermeable to liquids and corrosion resistant.
- Designed, constructed and installed to facilitate maintenance, accessibility for cleaning and ease of decontamination and certification testing.
- Written emergency procedure to be in place in the event of mechanical failure.

Biological Safety Cabinets

- Procedures or processes that have a high potential for creating hazardous aerosols must be conducted in biological safety cabinets that are HEPA exhausted.
- Cabinet Class I and II are permitted.
- Biologically safety cabinets must be certified at installation and at least annually, preferably biannually thereafter.
- Maintenance on the biological cabinets can only be performed following decontamination.

- Exhaust from Class III cabinet must be HEPA exhausted directly to outside, no recirculation is allowed.

- Room supply air systems, equipped with dampers to prevent backflow if biological safety cabinets, are connected to exhaust ductwork.

- If biological safety cabinets are connected to exhaust ductwork, connections are made by thimble units where appropriate and room exhaust ducts are equipped with manual dampers to permit sealing for decontamination.

- Biological safety cabinets must be located away from doors and windows that can be opened, from room supply air and from heavy traffic laboratory areas.

- A minimum of 30 cm clearance is recommended, where possible, behind each side of the cabinet to permit cleaning and testing and a minimum unobstructed clearance of 40 cm at the exhaust filter discharge to permit testing.

- HEPA filters in biological safety cabinets must be monitored by magnetic gauges at all times.

Ultracentrifuges

- Install HEPA filters between centrifuge and vacuum pump. Loading and unloading of the head or buckets should be performed in a biological safety cabinet.

- Use safety centrifuge buckets, safety cups or sealed heads.

Homogenizers, tissue grinders, sonicators

- Operate and open equipment in biological safety cabinets.

- Purchase homogenizers which have special design features to prevent leakage from rotor bearing at bottom of bowl and rubber o-ring/ gasket seal in the lid.

Culture stirrers, shakers and agitators

- Operate in containment equipment.

- Use of heavy duty, screw capped culture flasks with filter protected outlets is recommended.

Freeze-drying apparatus

- Unit must be sealed throughout using o-ring connectors.
- Use air filters (HEPA or equivalent) to protect vacuum line and oil pumps.
- Use satisfactory method of decontamination (such as low pressure steam) following each production run.

Fermenters and similar containment vessels

- Exhaust must pass through HEPA filter and/or incinerator.
- Rotating seals in fermenter must be designed to prevent leakage or be fully enclosed.
- Fermenter vessel warrant double o-ring design seals at all flange joints.
- Instrument connections on containment equipment may need to be designed to avoid dead legs and the need for routine removal for calibration.
- Vents must be sterilized and must be sanitized.
- Where possible, monitors, recorders, printers and similar monitoring equipment should be located away from containment area.
- Surface area of equipment should be sanitized and all ancillary equipment in contact with the product should be sterilizable.

2.4 VACCINE PRODUCTION FACILITY DESIGN PROJECT MANAGEMENT

There are four main stages in a project:

- Feasibility Study - Economic, Technical and Regulatory
- Process Engineering - Personnel flow and Process Utilities
- Project Review and Layout Considerations
- Construction and Validation

A. FEASIBILITY STUDY: What is the purpose?

Economic Feasibility

The main objective of a feasibility study is to provide an Order of Magnitude (OOM) cost estimate for the facility. All projects must be constrained with strict financial limits based on the Return On Investments (ROI). An expenditure ceiling must be applied on the operating costs of the plant.

Technical Feasibility

With respect to technical feasibility, the criteria to consider are:

- Can it operate satisfactorily in terms of producing a consistent product within defined specifications and produce the required quantities and range of products required?
- Can it be operated reliably during its expected life cycle and within defined operating conditions?

Regulatory Feasibility

What regulation will the plant or new facility have to operate under?

What is the economic output? Can we afford the regulatory constraints imposed by the country in which the product needs to be sold?

Regulations depend on a global market. For example if you want to sell your product in Europe, regulation of European Union must be followed.

Feasibility study is a very useful exercise because it allows rapid rescoping of project if the "wish list" exceeds budget.

At the end of the feasibility study, one has the basis for schematic/conceptual design.

B. PROCESS ENGINEERING

Process Constraints

Make a list of constraints or special process needs which will affect the design or choice of location. Typical examples include:

- What hazardous materials will be used (toxic, flammable, explosive)?
- Are there effluent problems (airborne, drainage, special disposal)?

- What equipment will be required (unusual services for example vibration free)?

Macro Process Review

A macro process review entails a review of the project on a macro scale and starts with Process Flow Diagram (PFD). A Process Flow Diagram is prepared by considering the following:

Manufacturing Process

- What type of process, continuous or batch?
- What type of equipment - existing or special that requires development?
- What is the output per item of equipment?
- What is the space required based on equipment size and product flow configuration?
- What are the service demands?
- What are the regulatory constraints?
- Ancillary plant and service requirements

Ancillary Plant and Services

- What type and size of ancillary plant are needed to support the process and provide the necessary services and utilities?
- What are the required specifications?
- HVAC, quality of air class?
- Water - city, treated, purified, Water for Injection (WFI)
- Steam - house or process, clean
- Compressed air - grades
- Electricity
- Vacuum/special gases
- Effluent treatment
- Inert gases

Support Areas and Storage Needs

- What type of support areas are necessary to facilitate viable operations of the process and to provide for the needs of the personnel?
- Product material and testing facilities.
- Engineering and maintenance areas.
- Locker and change room.
- Offices.
- Cafeteria and personnel needs.
- Goods receiving area.
- Warehousing.

Future Operating Costs

- Labour
- Materials
- Services

C. PROCESS REVIEW AND LAYOUT CONSIDERATIONS

The financial aspects of the project must be reassessed at this stage before detailed design is undertaken, or any commitments are made. Regular review of this kind should be undertaken at reasonable intervals throughout the execution phase.

The detailed design of the plant will now have taken into account the following aspects:

Process Routes

Well-defined process flow diagrams which include all existing products and any that may be in the Research and Development pipeline.

Equipment Layout

Layout of equipment and ancillary plant areas must be developed as soon as details of the individual items of equipment are known. Dimensions of areas must permit equipment to operate and to be maintained and space must be adequate for persons performing those functions.

Space

Use of floor and volume within the building *must* be efficient, as construction costs are high. Finally, the impact of layout on the service design must be considered as unnecessary lengths of ducting, piping, and cable route all add to the cost and duration of the construction work.

Personnel Flow

- What are the personnel requirements for this operation?
- Reducing the number of head counts to minimal. This is a major consideration in terms of contamination in clean rooms.
- Layout of equipment to facilitate personnel movement.
- Changing facilities for personnel.
- Number of offices for personnel needs. Offices for document storage.

Material Flow

Material Flow needs to be identified with reasonable accuracy at an early stage as the viability of equipment location and layout will depend on this information.

- raw materials
- receiving/quarantine
- released materials
- manufacturing-fermentation, primary recovery, downstream processing, formulation, final filtration, filling
- in-process samples and materials' storage
- in-process bulks and partly processed material storage
- products awaiting packaging
- packaging
- finished goods
- quarantine
- released area

At this stage, the project team will have a list of space requirements and sketches of individual needs for each of these areas. This completes the macro process review.

Layout Analysis

This next step after the macro process review is to prepare an initial plant or process layout.

Layout analysis includes the following:

- personnel flow
- material flow
- product flow
- biowaste flow
- other overheads

Layout Evaluation

Primary

- efficient material flow
- efficient personnel flow pattern
- compliance with containment guidelines eg. live vaccine, pathogenic organisms
- compliance with local and country building codes
- compliance with CGMPs

Secondary

- flexibility
- expansion potential
- ease of maintenance
- construct ability
- economy of cost and operating costs

Tertiary

- Where will the operators stand when the unit is started?
- Is there enough space?
- Is there enough space for maintenance and trouble shooting?
- Is there enough space for opening lids, use of cranes?
- Will the whole unit ever be removed in the future? If yes, can this event be achieved?

Layout Planning

A full understanding of the operations with respect to the process area, flow of personnel and material through the facility is imperative in order to design an acceptable layout. Definition of the operation must come from the user groups in the form of written description or logic diagrams. This is a detailed description of operation from one step to the next.

Spatial requirements and relationships should be identified with input from users. In this context, equipment sizes, services and clearance must be established. In addition to space for equipment itself, adequate space should be provided for carts, control panels, sinks, laboratory benches, vacuum system, in-house balances, and walls for concealing piping or low return duct work or service corridors for access to controls, valves and piping.

Once the sizing of primary and support spaces for the facility and process areas have been established, room classifications should be defined. From this information, flow diagrams are developed to establish the organization of the facility, suite or rooms.

The next step is to develop a layout. The layout is a translation of previously developed flow diagrams, incorporating requirements of the operation as well as integrating the anticipated mechanical systems required to service the space or spaces. Full integration of the architectural and engineering designs must take place from initial development of these layouts in order to ensure that mechanical systems will fit, operate efficiently, are easily maintained and cost effective.

In vaccine production facilities, engineering systems are present throughout the premises; above the ceiling, below the ceiling, running horizontally, vertically, exposed and concealed. It cannot be over emphasized that the space provided by the architect must also be a well-engineered space. Thus when layouts are being developed, actual wall thickness rather than single line delineation must be shown so the actual area is considered.

A good process layout should consider the following criteria as a minimum:

- Flow patterns must be logical and simple.
- Route lengths to be kept to a minimum.
- Material routes and locations should be such that segregation between work in-progress, sterile and non sterile product, quarantine and release materials is adequate.
- Personnel and materials should be kept apart.
- Utilities should be directly routed from plant rooms to process areas and should be grouped together whenever possible by use of utility panels.
- The space allocated to each area of the process should be in line with the previously defined needs, with agreed allowances for growth.
- Clean areas should be kept to a minimum volume in view of the high unit costs of such areas.

The layout should facilitate future expansion of the process - avoid critical processes installed against the outside walls or sandwiched between other critical processes.

Process flow considerations

The basic criterion from which any plant is designed is based on an understanding of the process, the equipment, material and people flow through the facility.

There are 3 documents which need to be produced at an early stage of the development of the facility. These are:

- Process Flow Diagrams (PFD)
- Engineer Design Criteria
- Plant Operations and Safety

Process Flow Diagrams (PFD) are developed from direct knowledge of the project. The intent is to define the process philosophy and process design criteria to best meet the immediate and future requirements of the product. The main purpose of any drawing, is to communicate information in a simple and explicit way using unscaled drawings which describe the process. Sufficient detail must be presented on the PFD to give any experienced process engineer an adequate understanding of the process concepts, operating conditions and equipment sizes and to permit a critical review of the process design with minimum reference to other documents.

Each PFD has a separate set of tables which show the quantitative and qualitative data for any process system. These include heat and material balances. This is the minimum information required for sizing the lines and development of P & ID's from the PFD. P & ID's (Piping and Instrumentation Diagrams) also have their own function and should show instrument control which is necessary for the operation of the process. The type of service, flow rates, temperatures, pressure and material balance information is important. Separate diagrams are preferred for each utility system such as clean steam, purified water, compressed air, HVAC, specialized gases, etc. The diagrams should show all items of equipment connected to the systems in continuous use and show consumption levels, capacity levels and specifications for the requirements of air and air flow volume. In addition, the route of disposal for the effluents must be shown.

Following the completion of P & ID's and PFD's the project is reassessed at this stage, before detailed design is undertaken, or any commitments are made. Regular review of this kind should be undertaken at reasonable intervals throughout the execution phase.

D. CONSTRUCTION DETAILS

Schedule of Finishes

Clean room data sheets (see the example of a room data sheet) have to be prepared. These would specify, by the classification of area, acceptable types of finishes and design details. New materials should be evaluated with care before major installations are undertaken. The architect must work with the user groups and facility planners to identify the finishes most suitable to operational needs and budgetary requirements.

Floor

Regulations require that *surfaces are impervious to cleaning agents and water, durable, cleanable, non shedding and non dripping*. They must be caulked such that no dust collecting ridges are exposed. This is most critical of all finishes and is most often, incorrectly selected. Choices range from flat floors to those laid to gradient for drainage. If floors are sloped to drain, they must be sealed to facilitate cleaning.

Typical finishes are:

- Epoxy paints finish over concrete - medium cost range (moderately priced but not long lasting). Usually in GMP areas and related support spaces.

- Welded PVC - excellent chemical resistance but costly. If heavy traffic is anticipated, it is not a good choice as it damages easily and requires maintenance. Very common in GMP aseptic spaces, because it is compatible with adjacent wall finishes for a fully monolithic environment.

- Self levels (epoxy, polyurethane).

- Epoxy terrazzo - most expensive but longest lasting in comparison to the first three. Inclusion of granite chips for best chemical resistance. Good in high traffic areas.

Walls

- Walls must be air tight (sealed) and smooth with no recess or grooves. Surfaces should be resistant to cleaning agents.

- Epoxy coating - low cost, durable and impact resistant. Best in high traffic areas. Because of the hardness of the material, cracking potential is greater than with PVC and not as desirable in aseptic areas.

- Polyester coating - similar to epoxy and similarly priced.

- Seamless PVC - sprayed-on-coating for use in GMP areas. Very good resistance to chemicals and water and flexibility to avoid cracking. Quality of installation is critical. If it is not installed expertly, it can create headaches. Not recommended in high impact areas.

- Welded PVC - the same as seamless PVC but thicker. Most durable but most expensive. It is a material of choice in aseptic areas more.

- Prefabricated wall panels (see clean room section for more details).

Ceilings

- Smooth, acid and cleaning agent resistant surface.

- Class 100,000 - non shedding tiles with hand drawn clips are sufficient. Simple ceilings over structural concrete, painted or vinyl-covered gypsum plaster or modular is adequate for this classification.

- Class 10,000 requires a cleaner epoxy painted finish.

- Class 100 environments. Filters and lighting fixtures usually occupy the entire ceiling grid work.

The quality of ceiling material must reflect pressurization within the room. A stronger ceiling will be required for rooms which are highly pressurized. Stainless steel ceilings are becoming more popular (advantages include: smooth, cleanable, water and chemical resistant). If this type is to be installed, care must be taken not to have chrome plating of outlets. This is because of the chemicals used in washing down. Such chemicals cause flaking of the chrome plating.

In case of walls, ceilings and floor, it cannot be emphasized too strongly that "monolithic" surfaces and finishes are maintained. Most attention must be paid to penetrations (such as doors, windows, pass thru's, piping, service outlets, air terminals, panels, lighting, etc.) and intersections which include surface intersections (such as floor to wall and joints between dissimilar materials).

Windows and Doors

Windows and frames should be either metal or constructed with materials that are smooth and impervious to corrosion. Windows are required for monitoring purposes and communication. Doors may not be wooden. Window frames and ledges must be constructed to minimize horizontal effects which can cause bacteria to grow.

Using the Process Flow Diagram, the layout in terms of people, material, product and biowaste flow is designed.

Following this, the space required is determined and the number of rooms required and the requirements of each room determined by using a room data sheet.

Example of a Room Data Sheet

Project _____ Room number _____
Room name _____ Area _____

Specifications and locations of required services

Electricity
Voltage and number of outlets _____
Temperature _____
Horse power _____
Phase _____
Resistance _____

Air-conditioning
Humidity _____
Special exhausts _____
Dust collection _____
Filtered supply _____

Gas
Type _____
Pressure _____
Quantity _____

Water supply
Hot _____
Cold _____
Distilled _____
Deionised _____
Floor drains _____

Steam
Pressure _____
Quantity _____

Air
Pressure _____
Quantity _____
Oil free _____

Ceiling Height
Special _____
Other _____

Equipment and Specifications: _____

Room #: _____ Title _____

Design Requirements

A. Design class: 300,000 _____ 100,000 _____
10,000 _____ 1,000 _____ 100 _____

1) Temperature _____
2) Humidity _____
3) Air Changes _____
4) Filtration _____
Terminal _____ In-Line _____
5) Return
High _____ Low _____
6) Air Pressure _____
7) Recirculate _____ Exhaust _____

B. Ceiling Height _____
C. Number of people _____
D. Gowning requirements _____
E. Fumigation required _____

Finishes

A. Wall: Material _____ Finish _____
B. Ceiling: Material _____ Finish _____
C. Cove wall _____ Cove ceiling _____
D. Base: _____
E. Floor: _____

Services

A. Air _____ Use _____
B. Nitrogen _____ Use _____
C. Vacuum _____ Use _____
D. Gas _____ Use _____
E. Central dust collection _____ Use _____
F. Central Vacuum system _____ Use _____

G. Water (types) _____
1) USP _____
2) Domestic _____
3) Distilled _____

Liquid Nitrogen _____

Room data sheet is an integral part of the facility design and is an invaluable source of information for Architects and Process Engineers. Once this information is complete, then only can one decides whether all the required number of rooms fit into the existing building retrofit or should a new building be constructed. If a new building is desired then site selection becomes an important consideration.

Site Selection

The decision to look for a new location is based on a number of facts concerning the existing facilities. The existing site may be unsuitable for a variety of reasons such as:

- The production requirements have outgrown the capacity of the plant to expand and meet these needs.
- A completely new range of products will be manufactured.
- The site is outdated by the development of modern manufacturing systems and CGMP requirements.

Having arrived at the point where refurbishment of existing facility site is not possible, then, the company has to draw up a list of points that must be considered for the selection of a new site.

This means that a greenfield site has been agreed. Thus, what steps are needed to be undertaken in selecting this new site? The most fundamental is the development of a business plan which will define the objectives of the management team in the new location and the goals of the Production Staff [Management by Objectives (MBOs)]. It is essential to fully develop this plan at the start as many of the existing departments within the company will have differing priorities and interpretation of the requirements. Each group will provide a list of their needs. The resulting final project goal is the culmination of all these decisions and should be used by management to arrive at a final decision. Remember, events can take over some of the best decisions, so there has to be a built-in framework of flexibility.

Having arrived at the decision that a grass roots (greenfield) site is the only way forward, what factors must be considered in its selection? Most new projects of this nature commence from the viewpoint of a completely restrained budget, and the next question is, what will it cost? Only when this cost is addressed then the objectives count to more realistic levels.

Site Survey Checklist

I. Location

A. Provide complete address
B. Cost

II. Zoning Restrictions

Get complete copies and a competent opinion on exceptions that might be granted.

III. Building codes

Get complete copies and a competent opinion on exceptions that might be granted.

IV. Water Supply

		Requirement	Availability
A.	City and Municipal authorities should be consulted	_____ m3 _____ PSIG _____ °C _____ cent 5/m3	_____ m3 _____ PSIG _____ °C _____ cent 5/m3
B.	What has been the experience in the area	_____ m3 _____ PSIG _____ °C	_____ m3 _____ PSIG _____ °C
C.	Tower, Pond or River	_____ m3 _____ PSIG _____ oC	_____ m3 _____ PSIG _____ oC

V. Telephone Service

Describe current or future status.

VI. Power

		Requirement	Availability
A.	Volts	_____	_____
B.	Cycles	_____	_____
C.	Phase	_____	_____
D.	KVA- 15 Minute demand	_____	_____
E.	Reliability; would standby generators be needed	_____	_____
F.	Cost	_____ mils/kW	_____ mils/kW

VII. Gas		Requirement	Availability
A.	Natural or manufactured	_____	_____
B.	Heating value	_____ BTU/m3	_____ BTU/m3
C.	Volume	_____ m3	_____ m3
D.	Cost	_____ $/m3	_____ $/m3

VIII. Sewage		Requirement	Availability
A.	Flow	_____ GPD	_____ GPD
B.	Type	_____	_____
C.	B.O.D.	_____ ppm	_____ ppm

D. What are the Municipal authorities regulations toward water and air pollution?

IX. Building Site

A. Topography of land _____
B. Fill or cut required _____ m3
C. Drainage, a contour map should be provided _____
D. Geological character of land (Rocky, Loam Sand) _____
E. Bearing value of soil _____
F. Piling experience, Type, depth _____
G. Depth water table, High and low _____
H. Name, address, phone number, etc., of agent representing Owner:
I. Name, address, phone number, etc., of Owner of record

X. Transportation

A. Roads Available

1. Type of construction
2. Locations with respect to site

XI. Climatic Conditions

A. Summer wet bulb temp., max. _____ °C
B. Summer dry bulb temp., max _____ °C
C. Winter dry bulb temp., min _____ °C

D. Altitude _____ m
E. Prevailing Wind _____ km/h

XII. Neighbourhood

A. Neighbour to the North
B. Neighbour to the East
C. Neighbour to the South
D. Neighbour to the West
E. Type of buildings and industry in the area
F. Specify nearest important towns and distance from the site

XIII. Transportation Facilities

A. Bus service frequency
B. Is transportation available for night shift workers
C. Taxi service from the nearest town
D. Do employees drive own cars to work

XIV. Eating Facilities

A. Are restaurants or cafeterias near by?
B. What are the eating habits? Are hot lunches expected.

XV. Fire Equipment

A. Is there a municipal fire department?
B. How well equipped is it?
C. What service could our plant expect?
D. Distance from plant

XVI. Labour Supply

A. Availability of unskilled labour/Availability of skilled labour
B. General education level in neighbourhood
C. Can good supervisors be obtained/What is the experience with trade unions in the area?

XVII. Fuel Oil

A. Availability
B. Cost
C. Heating value

Building Project Checklist

I. Project Description: _____

_____

II. Managerial Justification Data:

1) Sales and profits - last five years _____
2) Projected sales and products - next five years _____
3) Why project is necessary ? _____

_____

_____

III. Design Requirements Data:

1) Last year's unit sales by product (may not be necessary if its a new product)

_____

2) New products scheduled for introduction. Indicate presentations and volumes of each _____
3) Present equipment list. Show products for which each piece is used and percentage of time in use _____
4) Established space requirements for new facility _____
5) List service requirements _____
6) Sterile area requirements _____
7) Heating, Ventilating, and Air conditioning _____
8) Process or equipment requiring special ceiling heights, platform construction and/or two floor (gravity feed) systems _____
9) Electric power requirements - present and future _____
10) Warehouse requirements - present and future _____
11) Sanitary facilities - number of toilets, showers, lockers required _____
12) Personnel requirements
    a. List present personnel by job title
    b. List estimated additions (for five year period)
    c. Social services required
        1. Cafeteria and lunch room
        2. Kitchen
        3. Nursery
        4. First-aid rooms, doctor's office, nurse
        5. Unique facilities specified by local social laws
    d. Is a laundry required ? _____
13) Control Laboratory Requirements
14) Office Requirements
15) Maintenance Department Requirements
16) Communication Systems Required
17) Sprinkler Systems Required

IV. Site Survey Data

1) Size
2) Cost
3) Topographical Survey
4) Zoning and Pertinent Governmental regulations concerning plot
5) Availability of right type of labour force - very important
6) Access roads
7) Water availability and quality
8) Sewage systems
9) Storm drainage system
10) Power line
11) Building code for Area

SUMMARIZING:

What are the most important inputs in vaccine manufacture design?

- site master plan
- architectural programme
- process requirements
- building code analysis
- site requirements or restrictions
- employee amenities
- aesthetics or public image

How Does One Approach This?

- understand the process, i.e. steps involved and adjacencies
- interview the users
- develop schematic layouts
- evaluate layout with regulatory people
- refine the layout

Layout Development

- process flow diagrams
- operational flow diagrams
- manufacturing philosophy

E. HEATING VENTILATION AIR CONDITIONING DESIGN - HVAC SYSTEM

Definition of System

An HVAC system is required to maintain room temperature, humidity, pressurization and air filtration or air cleanliness for controlled and critical environments. A controlled environment is classified as Class 100,000 or 10,000. A critical environment is Class 100. The degree of control or specification required depends on different degrees of environmental control required for the processing stage or criticalness of the operation (with respect to sterility assurance). Thus, fermentation to produce a vaccine can be performed in a Class 100,000 environment whereas final filtration or filling of vaccine must be performed in a Class 100 environment. Controlled areas are categorized usually into room classifications, (i.e. 100,000, 10,000, 1,000 or 100). Each clean room or specification will provide the design of HVAC in order to achieve that need.

System Description

HVAC systems serving a building typically consist of one or more air handling units (AHU) with various supply and exhaust ducting systems. Typically, outside air is filtered through a series of prefiltration efficiency filters. The air is then pre-heated and then reheated with steam heated coils and cooled with chilled water or sometimes glycol chilled coils. Additional humidification is achieved usually with pure steam. Dehumidification may be achieved through various technologies. Typical RH values in most pharmaceutical companies range between 40-50% RH. Values lower than 40% create problems with electronics while values higher than 60% promotes mould growth. In tropical countries, it can be very expensive to maintain RH at 40-50%. In such cases, RH of 55% may be more practicable provided mould control is possible. The supply air is then HEPA filtered before being discharged into the controlled room. HEPA's maybe located remote central or terminal (at entry into the room), depending on cleanliness requirements. It is not advisable to use central HEPA's for classifications 100,000 or lower. Central HEPA's are much less expensive, but quality of air may not be as clean as would be the case with terminal HEPA's. However, validation cost is greater with terminal HEPA's when compared to central HEPA's as each filter has to be certified. Exhaust air is then returned through a return duct and may be 100% exhausted by a fan or a certain percentage returned to the supply system. Percentage returned varies with the design aspects but typically ranges from 10-30%. The exhaust may or may not require HEPA filtration. It is recommended that air leaving BL2 level of containment be HEPA filtered on the exhaust.

Key Design and fabrication requirements for HVAC systems

- Design of the system should be such that it sweeps or purges the rooms and removes any particulate generated. This means that HEPA filtered air is brought into an area through individual diffusers located in the ceiling and exhausted through return air ducts generally located near the floor through the periphery of a room and must not be blocked by equipment.

- Prefilters should be rated at 85-95% ASHRAE prior to HEPA filters. HEPA filters should be rated at 99.97% to 0.3 micron removal efficiency and installed in non-shedding stainless steel frames.

- Duct work should be minimized running downstream of HEPA filter to eliminate shedding and possible duct leakage.

- Filter placement should be such that they can be serviced without contaminating the room (remote service).

- Grill diffusers for supply to room should be directionally louvered to allow flexibility of air flow, depending on room design, equipment location, etc. They should be designed to allow adequate cleaning and sanitizing.

- Return air grills or louvres should be located low and uniformly distributed along the base of the room to minimize effect of turbulence. They should be designed to allow adequate cleaning and sanitizing.

- All duct work downstream of HEPA filters should be stainless steel and pressure tested. Length of any flexible duct work should be as short a distance as possible.

- Access space to ducts and filters should be provided outside the clean room for maintenance.

Installation Qualification (IQ)

Confirm compliance to the general acceptance criteria as follows:

- System installed according to approved drawing.
- Equipment and instrumentation is identified to vendor, model, capacity, material and other important criteria.
- Critical instrumentation must be calibrated.

Confirm the following:

- HVAC duct work and associated utility piping have been cleaned of construction debris and documented.
- Ducts have been leak tested.
- All valves/dampers and interlocks operate.
- All HEPA filters have been certified.
- All pressure, temperature and humidity monitoring devices should be certified.

Operation Qualification (OQ)

- Compile and review air distribution and balancing reports to verify the following;
  - room volumes
  - air changes
  - grille velocities
  - room pressure relationships
  - air flow directions

- Monitor the defined areas during OQ to ensure temperature, humidity and room pressure meet specification.

- Containment evaluation in the event of a HVAC failure needs to be assessed. How quickly do interlocks between supply and exhaust fans react?

- Start-up operates as designed.

Performance Qualification (PQ)

- This phase of validation should demonstrate how the HVAC System works in harmony with the facility design to provide the appropriate controlled environment or clean room specification/class.

- Performance qualification is preformed on 3 separate days while the facility is "at rest" or is in the static state.

- Following completion of this validation, typically the exercise is completed during "dynamic" or at use conditions. This however, now brings many other factors into play outside of HVAC performance including cleaning procedure, gowning procedures and equipment functioning.

HVAC Requirements

Air supplied to controlled and/or critical environments must meet the following requirements;

CLASS 100: Particle count not to exceed 100 particles per cubic foot air of particle size 0.5 micron and larger.

CLASS 10,000: Particle count not to exceed a total of 10,000 particles per cubic foot of air of particle size 0.5 micron and larger and 65 particles per cubic foot of air of particle size 5.0 micron and larger.

CLASS 100,000: Particle count not to exceed a total of 100,000 particles per cubic foot of air of particle size 0.5 micron and larger and 700 particles per cubic foot of air of particle size 5.0 micron and larger.

In addition to particle count, there must be a pressure differential to control the environment.

- Pressure differential of at least 0.05" of water between adjacent areas of differing classifications.
- A measurable pressure differential present between 2 controlled areas of same classification.
- A pressure differential always present.
- Temperature range of 17 - 21 °C.
- Relative humidity generally of 40 - 55%.

Control Plan

- Once the system is validated, a routine environmental monitoring programme should be implemented that includes routine testing and preventive maintenance. Area should be monitored each day of use.

- Filters should be integrity tested at least annually.

- Pre filters should be changed as required.

- Spare parts programme should be identified.

- A change control programme implemented.

The success of HVAC design depends on paying attention to detail such as:

- design of doors and windows
- service penetrations
- special fittings
- corners and joints
- ventilation duct

All of the above are sources of leakages. This is especially important when containment is a major issue which is likely in vaccine production.

The most fundamental qualities required of an HVAC System are:

- Quality of air is determined by the number of air changes per hour. This establishes the correct quantity of air necessary to displace from the environment, pressurize the space and control the temperature and humidity.

Air changes per hour	Class
> 120	100
> 40	10,000
> 20	100,000

- Quantity of air

  The quantity of air is affected by the location, quality and standard of maintenance of filters in a given space. Selection of air classification is dependent upon process burden. In general,

AHU panel filters	are used in a unclassified environment
AHU bag filters	are used in a class 300,000
HEPA filters	are used in a class 10,000

- Flow pattern of air

  Symmetrical supply and exhaust configuration has to be optimal, especially as classification decreases (lower than Class 100,000) low level exhausts become much more important.

Other Considerations

- Avoid too many levels of pressurization which can lead to high leakage rates and make it virtually impossible to validate.

- Any controls or sensors mounted in the controlled area should be mounted flush; whenever possible, reduce the number of controls and sensors in the controlled areas and locate remotely to facilitate monitoring .

- Provide ports of DOP challenge to HEPA filters.

- Specify factory prescanned 99.97% HEPA filters and scan again after installation.

- Sealants must be bacteriostatic and not support biological growth e.g. GE silicone, Dow Corning RTV 732 are quite acceptable.

- Avoid/eliminate sound traps.

- Always move from cleanest to dirty.

3. CLEAN ROOM

3.1 DEFINITION OF A CLEAN ROOM

A clean room is defined as a specially constructed environment wherein precise control is maintained over temperature, humidity, pressurization, degree of air filtration, number of air changes, direction of air flow, noise, vibration, and electrostatic potential and type and count of microbial contamination. It is constructed, maintained and used in such a way as to reduce the

introduction, generation and retention of contaminants (viable and non-viable) within the area.

Primary Considerations in Clean Room Design and Construction

When considering clean room design and construction the major criteria which need to be evaluated include:

- Room size and layout:
  This is of paramount importance and is the first item for decision. Following the size and layout the second most important decision is the level of cleanliness. ie. the classification required.

- Gown-up and entry areas:
  Major considerations here are size and relative pressure differentials.

- Procedures for operations:
  Consider if the operation is dust generating or if there is going to be shift work. Number of people per shift will impact particle count, heat load, humidity and eventually the overall cleanliness and hence design to maintain the level of cleanliness.

- Utility penetrations:
  Penetrations must be sealed tight to minimize leakage rates.

- Spill containment:
  Use of dikes, kill tanks to contain spills

- Door, windows, pass-throughs:
  Areas where leakages can occur and must be minimized.

- Interior surface:
  Monolithic and cleanable.

- Temperature, humidity, pressurization:
  Temperature and RH must be evaluated carefully to minimize mould growth and maintain comfort levels for staff. Pressurization needs to be decided in order to control cleanliness and containment. For example, if the clean room is used for fermentation, pressurization needs to be negative with respect to adjacent rooms. On the other hand, if it is a clean room for filtering then it needs to be positive with respect to adjacent rooms.

- Air flow and direction

- Future expansion or relocation

3.2 MAIN CRITERIA FOR CLEAN ROOM DESIGN FOR VACCINE MANUFACTURE

- effectiveness
- functional/reliability
- cost efficiency

3.3 BASIS FOR CLEAN ROOM DESIGN

- Cleanliness

  Room air cleanliness is affected by:
  - amount of contamination released in the room
  - quality of air supplied to the room, for example, VLPA or HEPA filters
  - quality and method of supply of room air, ie. central or terminal HEPA's
  - amount of ingress of contamination from adjacent areas

  How does one design for cleanliness?
  - HVAC
  - number of air changes per hour
  - temperature control
  - humidity control
  - terminal filtration
  - high supply low return - positive pressurization

- Containment

  How does one design for containment?
  - negative pressurization
  - entrance and exit air locks
  - filtration
  - glove box technology

- Prevention of cross contamination

  How can cross contamination prevented?
  - no air recirculation between areas
  - HEPA filters in room exhaust registers
  - positive pressurization
  - locate Air Handling Unit intake upstream of building exhaust

3.4 CLEAN ROOM AIR FLOW CHARACTERISTICS

Three most common types of air flow encountered in clean rooms are:

- Random air flow : In this design the HEPA filters are located randomly throughout the room to provide clean air. This design results in zones of cleanliness in the room. Random air flow rooms are usually greater than Class 1000 and most common in Class 10,000 and 100,000 situations.

- Laminar flow, horizontal : Horizontal laminar flow of air from HEPA filters provide an even, continuous, unidirectional flow of air from one wall in the room, the air washes the entire room, with the greatest cleanliness at the work stations closest to the wall of filters. However, as one moves away from the wall the level of "dirtiness" theoretically increases. This type is not common in pharmaceutical industries. It is however, useful in conditions of Class 10,000 and 100,000 environments where head space is a problem for the ductwork and wall HEPA's is the only practical solution.

- Laminar flow, vertical : Vertical laminar air flow from HEPA filters provide an even continuous unidirectional flow of clean air from the ceiling toward the floor (air usually returns through low level exhaust vents).

3.5 CRITICAL VERSUS CONTROLLED AREAS

Critical Areas

A critical area is defined as that area in which sterilized dosage forms, containers and closures are exposed to the environment. In these areas there is no further filtration or additional terminal sterilization and therefore has the greatest potential impact on product sterility assurance. This typically would apply to an area immediately surrounding the filling operations (Class 100 Turbulent is the background environment for the critical manufacturing process). This is typically encountered in the fill and finish area. Class 100 conditions must prevail for critical areas when measured twelve inches from the work site and upstream of air flow. Air must be laminar flow, with at least greater than 120 air changes/hour and the velocity of air is at 90 feet/min $\pm$ 20%. Microbial count must be less than 1 cfu/ft^3 with the pressure differential at least of 0.05 inches of water to adjacent less clean areas. Containment areas should not share air handling units with non contained areas.

Controlled Areas

Controlled areas are those areas where non sterile products or components are handled. Controlled areas are required to meet Class 100,000 conditions or better which translates to about 20-40 air changes/hour, having less that 25 cfu/ft^3 of microbial contamination and a room pressurization of 0.05 inches of water relative to adjacent areas. Typical areas which are Class 100,000 include cold rooms, warm rooms, gowning, fermentation, buffer preparation, media preparation, inoculum preparation, weighing, etc. In cases where Class 100,000 prevails and level of activity is low and the potential for dust generation is minimal it is conceivable that 20 air changes per hour may be adequate. In other cases where the room has heavy usage to maintain Class 100,000 one would require much greater number of changes. Thus, the number of changes per classification is a rule of thumb and does not categorically constitute a classification.

Class 10,000 is typically used in purification suite and where bulk solutions are prepared prior to final, sterile filtration, rooms where components or equipment are washed and assembled prior

to steam sterilization or depyrogenation for finished product, or handling of starting materials that are sterile filtered later.

Air flow between rooms must be controlled to ensure that air flows from the most critical processing rooms to the least critical rooms. Flow of air between rooms is controlled by room pressurization. Pressure differentials between adjacent rooms should be 0.05 inches of water and typically 3 pressurization levels are required in aseptic processing facilities.

3.6 FINISHES

- smooth crevices free, non-flaking
- no ledges
- minimum exposed piping

3.7 LAYOUT

- air locks
- unidirectional flows

3.8 HVAC DESIGN CONSIDERATION

- flush mount all control and sensors
- provide ports and access for DOP tests of HEPA
- use bacteriostatic sealant
- avoid too many levels of pressurization which can lead to high leakage rates, typically no more than 3 levels.
- Lighting: shadow less and uniform intensity at 100 to 150 foot-candles at work surface: 70 to 100 foot-candles at work station. Light fixtures should have cleanable surfaces and withstand sanitizing chemicals. Fixture materials must resist flaking, chipping, oxidizing and other forms of deterioration.
- Access To Clean Room(s):
  - Air lock or anti-room from a change room.
  - Change rooms are required with appropriate gowning materials.
  - Change rooms should be effectively flushed with filtered air.
- Electrical Design:
  - Installation of electrical panels devices control, boxes and conduits should be avoided in the clean room.
  - Electrical components, if installed, should be flush mounted into walls, ceilings or floors and be designed in such a way as to ensure cleanliness and integrity of the clean room.
  - Should be hard wired.
  - Electrical components on surfaces should be air tight.
  - Electrical junction boxes should be located outside clean area.

- Electrical panels, controls, distribution equipment and panels and starters/related components that do not have to be used for daily operation in clean room should be installed in unclassified areas conduits entering the clean room should have seal fittings attached to them just ahead of the entrance point to prevent outside air and vermin from coming into clean room through raceways of electrical components.
- Light switches should be installed outside clean rooms.
- If present all switches and receptacles should have gasket weather proof SS/anodized aluminum covers and located as high enough above the floor as possible and out of reach of hose-down-cleaning activities.

Diffusers Used Should Be

- stainless steel, if possible
- non aspirating
- flush with ceiling and sealed

Return Air Intakes should be:

- stainless steel especially if terminal HEPA's are not employed
- low level wherever possible
- as simple as possible
- flush with wall and sealed

Terminal HEPA Filters

- A greater assurance of air quality integrity.
- Generally less expensive duct work resulting from being able to use galvanized steel duct work, but of heavier wall thickness construction for the higher pressures.
- Cost of HEPA filters are high.

General

- no protrusions, ledges or exposed piping are allowed
- access doors in walls and ceilings should be limited
- no drains
- drains, if present should be designed with an atmospheric break, or check value to prevent back flow (trap seal primer is required)
- "process" drains and "sanitary" drains should be separated with a running trap
- cross connections between "process" and "sanitary" systems should be avoided
- all process pipe lines or service lines whose contents come in contact with product or product contact surface (such as steam and compressed air) should be sloped back to source or to a planned low point drain outside of controlled area

How many different classifications of clean room exit?

- BRITAIN - BS 5295
- AUSTRALIA - AS1386
- USA - STD 209E
- FRANCE - AFNOR X 44101
- GERMANY - VD 12083

Pressurization of Rooms

The purpose of pressurization is to keep the air flow in the proper direction.

There are three main approaches to pressurization of room:
- pressurized room - least space requirement, not optimal
- pressurized corridor
- pressurized room and airlock - most correct design

Air Handling Unit (AHU) Construction

Prefilters
- 30% ASHRAE or country's equivalent rating for dust spot efficiency
- 85% ASHRAE efficiency

Coils
- no more than 8 fins per inch
- no more than 6 rows of coils

Use of these values is known to minimize pressure drops.

Insulation

- External insulation such as fibreglass is generally used . Internal duct insulation is not recommended since it can not be cleaned, and can harbour microbes and can shed particles in to the air stream being carried into duct work.

3.10 AIR SUPPLY

The cleanliness of the clean room is conducted by three separate yet equally important parameters: air supply, air distribution and filtration. Decisions made on one aspect will influence the others.

The key question affecting air supply is one of quantity. How much air is necessary in each area? Obviously the volume of air moved increases as the classification decreases. This will influence the size of the air handling plant, size of utilities such as power, steam and chilled water and

ductwork. The height of the room is important. Typically if height is not an issue in terms of equipment, the height should be no more than 9.5 to 10 feet. At least 12-18" is taken up with ducting and ceiling, leaving an 8 ft. ceiling. This is ideal as it allows normal height individuals to work without feeling the "breeze." Too high a ceiling dilutes the sweeping effect where it counts the most (4-5 feet above floor level) and it becomes expensive to run.

Therefore, it is essential to consider at the outset of HVAC design how much air has to be moved in terms of air changes, what is the heat load which in turn will impact temperature and relative humidity and what volume of air is required to dissipate the heat load. How many air changes are required to meet the cleanliness level, nature of equipment, number of people and the state in which the room is to be tested (ie. at rest or in use).

An important factor in the prevention of particulate build-up within clean rooms is the use of significant over pressures. In suites of rooms with differing cleanliness levels, pressure gradients can be created and by subjecting the most sensitive areas to the highest over pressure ensure that the transfer of contamination from room to room is reduced to a minimum.

Air Distribution

There are 2 recognized methods of air distribution within the clean room.

Turbulent flow - Conventional design approach where terminal outlets represent only a proportion of the total ceiling area located to suit the individual process requirements. Exhausts may be located within the ceiling or at low levels within the walls.

For facilities requiring Class 100 and better, for example, in a filling suite a unidirectional downflow (laminar flow) air distribution pattern is essential, particularly when "in use" testing is required. With a vertical air flow of moderate velocity, (90 ft/min.) from a fully filtered ceiling, particle travel is easy to predict, there being no dead areas for contamination to build up. Air changes of 60/hr are not uncommon and both capital equipment and operating costs are significantly higher than is the case with turbulent flows.

Wherever practical, laminar flow should be restricted into small rooms, controlled zones or canopies within rooms and self contained work stations.

As cleanliness levels increase so does the importance of air exhaust location. Cleanliness of Class 100,000 can be maintained efficiently with exhaust air grill in the ceiling or at a high level in the walls. However, with higher cleanliness levels, low level exhaust becomes essential.

Predictability of air flow is the ultimate requirement. This way systems can be designed to protect the product and the operator from the effects of air borne contamination.

Air Filtration

Clean room technology is dependent on the use of High Efficiency Particle Arrester (HEPA) filters. Technology has advanced significantly since the first introduction of the HEPA's. The newer design has better advantages such as:

- much lower pressure drop, producing reduced system resistance
- higher cubic foot per minute (CFM) capacity
- greater loading capacity, resulting in larger service life
- reduced risk of pinhole leaks

The relative efficiency of HEPA filters is extremely important in the performance of the clean room. All filters must be tested at least once during the manufacturing process. While this provides an overall indication that a specified efficiency has been achieved, it gives no protection against damage during delivery or installation. For this reason HEPA's must be tested after installation for leaks using DOP (dioctylphalate) or bubble point test.

Requirement for containment of potential air borne contaminants within clean rooms may require HEPA filtration on the exhaust air system. Typically, for BL2 level and greater it is necessary to HEPA filter the air on the exhaust side. To be effective, filters should be located as close as practicable to the point of exhaust from the room, reducing the ductwork susceptible to contamination to a minimum. Filters must be capable of being changed without breaching the integrity of the duct work system.

Humidity Control

- Desiccant humidifiers are required for humidity control in cold room or low Relative Humidity (RH) environmental rooms.

- Where required, humidifiers must be specified as a maximum annual humidity variation of either $\pm$ 5% RH or $\pm$ 2% RH.

- 2% RH humidity control uses the same equipment, but measurement and control systems are different and add 10% to the cost.

- Dehumidifiers and controls add 25% to the cost.

- Humidifiers and controls add 15% to the cost.

Facility Microbial Load

Clean areas must be monitored routinely for presence of viable organisms. This environmental monitoring demonstrates the effectiveness of cleaning and disinfecting procedures, gowning and scrub-up procedures, clean room etiquette and quality of air introduced into the area.

Environmental Monitoring

An environmental monitoring programme should be developed for all manufacturing areas. This is a key component for ensuring that a controlled environment is maintained. An environmental monitoring program provides a measurement of the manufacturer's ability to isolate the various operating areas of the facility and demonstrates that the facility and its operations are under control. Monitoring should be conducted as appropriate for each stage of processing and may include air quality, including viable and nonviable particulate; bioburden for floors, walls, and surfaces; and personnel. Monitoring should be performed under static and dynamic conditions, including product manufacture, and to test the effectiveness of sanitization and/or cleaning procedures. The rigour of an environmental monitoring program will be highly dependent upon the stage of processing and the degree of product exposure. The data collected should be trended so that profiles of each area can be created. Stricter limits and classifications may be imposed where open processing steps occur. Monitoring data collected prior to facility start-up is desirable to establish a baseline.

Facility Cleaning Procedures

A system for cleaning and/or disinfecting the controlled room and appropriate equipment should be in place and approved by Quality Assurance.

- For Class 100:
  Comprehensive daily cleaning and/or routine cleaning.

- For Class 10,000 and 100,000:
  Thorough cleaning 2 or more times per week except when not in use.

- For all Classes:
  - Disinfectants and detergents should be monitored for effectiveness and validated.
  - Disinfectants should be used on an alternating basis.
  - Cleaning log for room and critical equipment must be kept.
  - Cleaning must be performed by personnel trained in controlled environment cleaning using dedicated cleaning materials.
  - Disinfectants must be prepared fresh daily with WFI in class 10,000 and lower areas, and with purified water in classification greater than 100,000.

- Exact cleaning sequences and routes are defined so that order of cleaning is always from surfaces least likely to be contaminated to those more likely to be contaminated

Facility Monitoring

Continuous Monitoring for:

- Class 100:
  - Non-viable particulate, viable monitoring, temperature and relative humidity monitoring at the critical site each day.

- Surface area sampling daily.

- Media fills should be conducted every 3 months on filling lines to assured integrity of equipment/personnel/air system. All filling personnel should take part in a media fill at least once per year.

- Media simulations of the Final filtration /final pooling/final formulation process should be conducted every 3 years.

- If a process change occurs prior to this, a media simulation will be conducted on the new process (3 studies).

- All utilities servicing the clean room should be validated and monitored routinely when appropriate. This includes gases (N, and compressed air), clean steam, vacuum systems, WFI water.

- HEPA filters in air systems supplying rooms should be integrity tested at least annually.

- HEPA filters in laminar flow units and in biocontainment cabinets should be integrity tested 2 times a year.

- All environmentally controlled areas must have alert and action limits for corrective actions.

• Class 100 Turbulent and Class 10,000:
  - Non-viable particulate, temperature and relative humidity monitoring of the room in static state once per month.

  - Viable monitoring each day.

• Class 100,000:
  - Viable monitoring once a week.

• All Classes:
  - Pressure differential monitoring each day.

Other Considerations

• Avoid too many levels or pressurization which can lead to high leakage rates.

• Any controls or sensors mounted in the controlled area should be mounted flush.

• Provide ports of DOP challenge to HEPA filters.

- Specify factory prescanned 99.99% HEPA filters and scan again after installation.
- Sealants must be bacteriostatic and not support biological growth e.g. GE silicone, Dow Corning RTV 732.
- Avoid/eliminated sound traps.

3.11 CONTAMINANTS OF PARENTERALS

For parenteral products, contamination in the form of particulate matter is defined as unwanted mobile insoluble matter. Particulate matter come from a number of sources and may be loosely defined into:

- Intrusive contamination: is material originally present in the solution which have not been removed by the classification and filtration stages of manufacture prior to filling. It can also be materials left on the final container and were not removed by the washing process.
- Extrusive contamination: is material from the environment falling into the product and its container during the filling operation.

Illustrative examples of mean particle sizes generated by various activities (Encyclopaedia of clean rooms, bio-clean rooms, and aseptic areas by Philip R. Austin).

Activity	Mean Particle Size (micron)
Rubbing latex painted surface	90
Rubbing epoxy painted surface	40
Rubbing Formica surface	10
Rubbing stainless surface	2
Manipulating standard paper	65
Manipulating plasticized clean room paper	10
Manipulating Tyvek clean room paper	5
Using hard product on standard paper	80
Using ballpoint pen on standard paper	20
Touching face having thin coating of cosmetics	50
Touching clean hair	25
Brushing clean skin	4

Note: The eye can see particles as small as 25 microns.

Detection of Contaminants

A UV light of specially selected frequency, will increase detection capability by a factor of 100. This can be achieved using CONTAM-A-LIGHT (Acorn Industries, Michigan). It should be used frequently (especially in the filling area) to inspect conditions of work surfaces product, containers, gloves, etc. The device is held approximately 4 inches away from the surface at an angle and it will illuminate the area to be inspected.

Bacteria and Particles carried by people:

BACTERIA	HANDS	100-1,000/cm^2
	FOREHEAD	10,000-100,000/cm^2
	SCALPS	approx. 1 million/cm^2
	ARMPITS	approx. 1-10 million/cm^2
	NASAL/SECRETION	approx. 10 million/g
	SALIVA	approx. 100 million/g
	FACES	> 100 million/g
PARTICLES	SURFACE OF SKIN	approx. 1.75 m^2
	SKIN REPLACEMENT	approx. every 5 days
	SHEDDING OF PARTICLES	> 10 million/day

Training for Clean room Personnel

All persons must be trained before they enter into the clean room. Training must be planned in such a way that the least amount of training is performed in the clean room to minimize the potential for contamination. When personnel are being trained in the clean room, treat them as you would treat a visitor who is unfamiliar with the operation.

For example: They should not touch anything: "What's this" as they pick up an item.

If personnel are grouped around an operation, they feel restless and start to lean, touch or sit on clean room benches.

The earliest training programme to make is a booklet training programme. In this booklet, list the rules that you wish the clean room personnel to obey. The next step is to explain each rule. If a booklet training programme is prepared, preface the explanation section of the booklet with a pre-test and the end with a post test.

The following are examples of a pre and post test questions:

Pre-test questions:
When donning clean room garments, the first item to put on is the:

a) head cover
b) coverall
c) shoe cover
d) gloves
e) face mask

Post-test questions:
When donning clean room garments, what is the proper order for putting on the following items of coverall, gloves shoe covers, head cover and face mask.

a)
b)
c)
d)
e)

Pre-test questions:
When working in a horizontal laminar flow clean bench, the hands of the operator should always be:

a) gloved
b) clean
c) downstream or to the side of the work
d) not moved abruptly
e) all of the above

Post-test questions:
Mark which statements are true or false.
When working in a horizontal laminar flow clean bench, the hands of the operator should always be:

a) upstream of the work
b) downstream or to the side of the work
c) gloved
d) moved quickly
e) fingers touching the bench top when resting

The training for clean room personnel should take into consideration the gender differences.

Training must also be a repetition and reinforcement of ideas. Checklists provide necessary reinforcements to employees of clean rooms and bio clean rooms. Checklist should be wall mounted in a large print poster. A signed copy of all check lists should be placed in the employees file, attesting to the fact that the employee has received, read, understands and will abide by the checklist. This establishes commitments on the part of the employee.

Personnel Operational Rules

The following is an example of rules to be observed by personnel entering and performing tasks in a clean room:

- keeps hands, fingernails, and face clean;
- never touch, adjust or comb your hair in the clean room;
- do not wear jewellery on wrists or hands;
- valuable items such as wallets may be moved into the clean room provided they are not removed inside the clean room;
- personal items such as keys, coins, cigarettes, matches, pencils, handkerchiefs, tissues, combs, etc. should not be carried into the clean room;
- no eating, chewing gum or tobacco or smoking in the clean room;
- nervous relief type mannerisms such as scratching the head, rubbing hands or playing with hair or similar actions, are to be consciously avoided;
- avoid wearing soiled or dirty street clothes in the clean room;
- never apply or wear cosmetics in the clean room;
- wear clean room garments in the specified manner;
- wear gloves or other hand protection as required;
- keep parts, tools and the work station clean and orderly;
- work only on a clean surface;
- make certain that parts are clean before assembling;
- do not leave exposed parts in the clean room;
- keep surplus parts in appropriate containers;
- make certain that tools and containers are clean before using;
- do not walk around unnecessarily;
- report adverse environmental conditions to your supervisor;
- when in doubt, contact your supervisor.

Contamination in Clean room

"Know your enemy." The enemy is contamination in the form of living and inert material. The battle is a continuous affair of preventing contamination from entering the product. Personnel are major sources of contaminants especially from skin and hair fragments. Tests have shown the extent of viable bacteria dispersion by overall body emissions. Normal activities release several hundred colony forming units per minute per person, even when clean clothing is worn. The emission rate increased with activity, indicating that a combination of higher breathing rates and bodily movements generated bacteria emission rates.

Austin Contamination Index

In an effort to better understand the contamination level in clean rooms, the Austin Contamination Index was created. Personnel emissions are stated for different types of garments as shown in the table below. In every case except the membrane garments, emissions are caused

by contaminants on the surface of the clean material which were not removed during laundering and particles then pass through the fabric of the garment as a function of its weave.

Austin Contamination Index in Particles/min 0.3 micron and larger

Personnel Activity	Snap Smock	Standard Coveralls	2 piece Coveralls	Tyvek Coveralls	Membrane Coveralls
No movement	100,000	10,000	4,000	1,000	10
Light movement	500,000	50,000	20,000	5,000	50
Heavy movement	1,000,000	100,000	40,000	10,000	100
Change position	2,500,000	250,000	100,000	25,000	250
Walk 2.0 mph	5,000,000	500,000	200,000	50,000	500
Walk 3.5 mph	7,500,000	750,000	300,000	75,000	750
Walk 5.0 mph	10,000,000	1,000,000	400,000	100,000	1,000

Change position means - standing up, sitting down, etc.

The above data includes all types of particles; inert and viable. The data was developed using automatic light scattering particle counters with personnel performing activities under controlled conditions. Thus a person garmented in a coverall made of Tyvek the contamination index of particles 0.3 micron in size and larger for various personnel activities are described below:

- An individual standing or sitting with no movement emits 1,000 particles/minute.
- A person sitting with slight hand and forearm movements emits 5,000 particles/minute.
- Changing from sitting to standing, or body flex, gives off 25,000 particles/minute.

Cown and Thomas of the BioEngineering Laboratories, Georgia Institute of Technology collected information over a period of several years regarding the number and size of the bacterial particles shed by people under various conditions. The values shown in the table below are in numbers of particles generated per minute, exactly as if the persons were producing the contamination at a steady rate.

Conditions	Quantity of Bacterial Aerosols
Surgical teams	
Good Practices	5,000
Average Practices	10,000
Poor Practices	50,000
Laboratory Personnel	
Slight Activity	4,000
Moderate Activity	8,000
Excessive Activity	15,000

An effective way to reduce the bio-burden of a facility is to require that personnel remove their street clothes before dressing with clean garments. Street clothes have billions of inert and biologically active particles on their surfaces; leaving these clothes outside the room reduces contaminant levels in the bio-clean room.

The true function of a clean garment is to act as a people contamination filter. Since filters are percentage devices, the less upstream contamination , the less downstream contamination. In the case of the clean garment, the upstream side of the garment is the inside of the garment. Thus, the less particles under the clean garment (no street clothes) the less particles will penetrate the garment fabric and appear on the outside surface of the clean garment during the use of the garment.

Clean Room Construction: Recent Additions

In addition to clinical wall panels, glazing is becoming an increasingly popular choice in clean rooms.

There are significant operational benefits from the extensive use of glazing. These include:

- greater unity between different sections of the manufacturing process
- supervision without the necessity or supervising staff to be continuously entering and leaving the clean room through a complex changing process
- improved work environment for production operations
- glass is actually an extremely suitable material for clean room use as it readily satisfies the principle requirements:
  - hard
  - smooth
  - impervious
  - easily cleanable

Disadvantages include contaminated air leaking around frames if not sealed properly and solar heat gain. Whenever possible, glazed areas should be flush with adjoining wall surfaces, and double glazed to meet this criteria on both sides of the wall where clean rooms adjoin one another. Glass should be located into tailor made frames in stainless steel or equivalent using silicone sealant.

Other Features used in Clean Rooms

A wide range of fixtures and fittings are required within the room if the manufacturing function is to be effective.

For example:

- light fixtures
- filter housings and return air grilles
- pass throughs
- piping and electrical services
- production equipment

All fixtures must be flush mounted and sealed into the foam fabric. Non-essential equipment should be located outside the room, allowing routine maintenance to be effected without any requirements for maintenance staff to enter the clean room or for the integrity of the room to be breached. Fluorescent light tubes and even HEPA filters can be changed in this way if service access above the ceiling is practical.

Long horizontal service runs should be avoided whenever practical. The zone above the suspended ceiling provides an ideal area for installing the service main from which individual services can drop directly to points of use.

Sanitization

Regular and careful janitorial activity using cleaning formulation such as sodium hypochlorite is an important part of this process and can be tested on a regular basis by QC analyzing swabs or settle plate samples taken within the room. However, whether as a matter of routine or as a safety procedure, after leaks or spillage of active products, it may be necessary to take more stringent measures.

The use of formaldehyde:
dynamic gassing - not recommended
pressure gassing - widely used

A solution is evaporated within a room where the air system has been turned off. The gas circulates in the room by natural convection which allows contact to all room surfaces. After a designated period, the rooms must be purged and the air handling equipment, which may normally recirculate a high % of air, must have a capability of supplying 100% fresh air and dumping 100% exhaust air during this period. System control is extremely important at this time to avoid over pressurizing rooms and permitting escape of gas through the room.

Clean Room Clothing

The single biggest source of contamination in the clean room is the people who work there. Clean room clothing must protect the environment from the wearer and should be designed to meet the highest standards. The state-of-the-art facilities require the use of one piece, coverall suits, normally with integral hoods, knee length over boots and gloves. Fabrics must be made from 100% synthetic continuous filament polyester and be constructed to act as filters as well as to be inherently low linting.

Access to Clean Room

- A key item of importance in clean room design is access into the clean room. Staff should follow, strict personal habits. This starts in the changing areas where the layout and "flow" should be progressive from "black" to "grey" to "white" zones. The black zone is used for changing and storage of outer clothing. The floor should be readily cleanable and the entrance must be guarded with contamination control mats. Internal footwear may be provided at this stage. The black zone change room may be located away from the clean room, close to the employee's entrance to the building, or it may form part of a double change procedure in the grey area where the coveralls, etc. are held.

- Facilities should be available in the grey area for staff to scrub-up and availability of the clean room garments. Flooring should be contamination controlled and lead to the white area.

- The "white" area is where staff change into their clean room footwear and step over into the clean room via a bench. Ideally, the air must flow from white to grey to black zones.

- Material movement throughout the pharmaceutical process are important, but their introduction to and removal from the clean rooms must be carefully controlled if they are not to introduce contamination.

- Wherever possible, even raw materials must be manufactured and packed in clean conditions. Polyethylene or similar material should be used in preference to paper.

- Materials must be transferred through air locks and whenever possible dedicated carts or trolleys to be used to avoid the need for different trolleys passing from grey to white areas.

Validation of Clean Room

Validation of Clean Room			
	IQ	**OQ**	**PQ**
DEHUMIDIFIERS	X	X	not required
HVAC AHU	X	X	not required
CENTRAL HEPA FILTERS	X	X	X
FANS	X	X	X
DUCTWORK	X	X	not required
COILS	X	X	X
CONTROLS	X	X	X
TERMINAL HEPA FILTERS	X	X	X

Installation Qualification (IQ)

- As built facility drawings accompanying a narrative description.
- Materials used in the construction, utility services provided, blowers, duct work, upstream prefilters and HEPA specification must be provided.
- Materials used to seal walls, doors, windows and fillers should be described.
- Finishes used for walls, floor and ceiling should be described.

Operational Qualification (OQ)

This phase is mostly concerned with calibration of temperature, humidity sensor, air velocity recorders, leak testing photometers, particulate monitoring equipment, etc.

Once the calibration is complete, the operation of the clean room is evaluated as follows:

- Integrity test the HEPA filters by releasing cold DOP (dioctylphthalate) into the air intake (80-100 μg/L of DOP) and monitor the face of the filter with a photometer. Scan the entire face of the filter, 1" to 2" from the filter face for leaks. A particulate concentration of greater than 0-.01% of the upstream challenge indicates a leak.
- Measure air velocities through all HEPA filters. The value to be 90 ft/min $\pm$ 20% is acceptable.
- Balance the system - balancing assures that pressure differentials between adjacent rooms meets specifications. There should be a minimum of 0.02 inches of water(recommended 0.05 inches of water).
- Test, balance and adjust the system to bring all parameters (RT, RH, air velocity, air changeover and AP) to within specified limits.
- Demonstrate air flow patterns in the rooms by releasing smoke and observing its flow and turbulence.
- Room recovery rate can be demonstrated by generating a known number and concentration of particles at the centre of the laminar flow room and measuring the time it takes for the room to return to class conditions.
- Particulate levels in the area should be determined for the room when it is empty and with permanent equipment in place.
- Routine cleaning and disinfection of the area should be qualified/validated during operational qualification.

Performance Qualification (PQ)

PQ must demonstrate that the room can maintain its class condition (ie. particulate's) T, RH, Bioburden, and delta P (pressure) when:

- permanent and temporary equipment is in operation
- during aseptic processing activities

When swabbing for Bioburden and particulate counts, the sample location, sample volumes, counts and statistical analysis of data should be described.

Modular Wall and Ceiling Systems

- Chemically inert
- Impermeable to moisture
- Cleanable and sterilizable
- Non-shedding
- Non-dust shelving
- Fully insulated for noise and thermal attenuation
- Non-combustible and fire retardant
- Non-outgassing
- "Monolithic" - smooth, crack free, homogenous
- Monoblock, non-progressive, de-mountable
- Integrated fittings, utility and HVAC chases

Benefits of Modular Design and Construction

- Lower start-up costs
- Earlier production and market entry
- Reduced interruption to existing operations (especially in expansions and modifications)
- Reduced congestion, construction infrastructure and outside labour on the plant side - higher labour productivity
- Improved site safety
- Improved quality control
- Advance planning and Firm Scope Definition eliminate "Cost Creep"

Humidity Controls in Pharmaceuticals

- Personnel Comfort and adherence to aseptic techniques
- Electrical/Mechanical/Chemical processing stability
- Corrosion and mould growth (> 50% R.H.)
- Electrostatic discharge control (< 40% R.H.)
- Humidity excursions in duct work can lead to unacceptably high bioburdens in the air handling systems.

Clean Room Mechanical Systems

For a parenteral facility, specifications are as follows:

- Pressurization:

  Typically ± 0.25 inches w.g.

- Temperature:

  Typical range: 65 - 75 degrees Fahrenheit
  Constant temperature setting more important than the setting
  Normal tolerance: ± 3 degrees F
  Where thermal stability is critical tolerance is: ± 1 degree F

- Humidity:

  Without control can vary between 40 and 60% RH
  Typically 45% RH, ± 5% RH
  For critical applications, ± 1% RH

- Air flow:

  Typical laminar flow room velocity: 50 - 110 fpm
  Average for class 100 is 70 fpm, with a normal 9 ft high ceiling
  Expect 150 - 450 air changes per hour

FEDERAL STANDARD 209D

Class limits in particles per cubic foot of size equal to or greater than particle sizes shown (micrometers)

Measured particle size

CLASS	0.1	0.2	0.3	0.5	5.0
1	35	7.5	3	1	NA
10	350	75	30	10	NA
100	NA	750	300	100	NA
1000	NA	NA	NA	1000	7
10000	NA	NA	NA	10000	70
100000	NA	NA	NA	100000	700

NOTE: The class limit particle concentrations above are defined for class purpose only and do not represent the size distribution to be found in any particular situation.

SECTION III

VALIDATION

1. HISTORY OF VALIDATION

In the early 1970s there were tremendous problems with the sterility of Large Volume Parenterals (LVP's) in the United States. Problems of sterility led to a number of deaths due to infections. As a result, validation of all sterilization processes such as steam sterilization, dry heat sterilization, depyrogenation, ethylene oxide sterilization, steam in place, filtration and radiation sterilization became mandatory.

By late 1970s, sanitization, water systems, media fills and environmental control were added to the validation list. In fact, the validation concept was so successful in reducing the above problems, that by 1983, the US FDA introduced the first guideline on process validation which was subsequently revised in 1987 and validation became one of the corner stones of GMP compliance.

GMPs say "special processes " must be validated. A **"special process"** is defined as one in which the quality or the effectiveness of processing cannot be **adequately** tested or evaluated in the final product.

Examples of special processes:

- Utility systems such as pure steam generator, equipment such as filling machines, test equipment such as filter integrity test and/or computer software controlling process purification. This is because failure of these could directly affect the safety of the product or its user.

- Validation should be performed on events which require routine, intensive, mandatory testing programmes to confirm their quality and effectiveness. Use of validation in such cases can minimize routine testing and improve productivity.

- Validation should be performed on equipment or software which is unique or custom designed for a particular process. Such systems do not benefit from widespread industrial use e.g. in-house developed software, in-house developed monoclonal antibodies for use in affinity chromatography.

2. VALIDATION AND VERIFICATION - MIX UP ?

During validation and verification, evidence is collected to demonstrate that specific requirements have been met by process or product. Verification on the other hand is usually carried out during the development phase to assure that the requirements for the product are met by the current version of the design, prototype or product. Validation is a terminal event to product

development and demonstrates that the manufacturing process will consistently produce a product that meets a predetermined specifications. Validation demonstrates consistency every time. During validation, the system is usually challenged. This is not the case with verification.

Thus, fundamental differences between verification and validation exist.

- Validation demonstrates consistency; meaning specifications are met multiple times. In addition to demonstrating consistency, the replicate runs must be identical which in turn means parameters must fall within predetermined limits of acceptability.

- Validation must be performed within a particular lot size. For verification this can change.

- During validation, the process is challenged.

3. FUNDAMENTAL ELEMENTS OF VALIDATION

Each validation event must:

- Document the validation plan and procedures in a controlled document BEFORE validation begins.

- Establish acceptance criteria for a particular validation event BEFORE the event commences. Thus, it is necessary to establish testing parameters, limits of acceptability, methods of analysis, etc.

- Demonstrate that the process meets an established range of operations for the chosen parameters consistently.

- Demonstrate the ruggedness of equipment or process performance by challenging equipment or process at the limits of established operating conditions.

- Demonstrate accuracy, precision, reliability of analytical test method used to assess the performance, identity, strength and potency of chemical substances, components, equipment and product.

4. HOW TO IMPLEMENT A VALIDATION PLAN

- Know what equipment and systems are present in the facility and understand their function with respect to the product being manufactured. Evaluate the consequences of failure of such equipment on the product.

- Based on this, prepare a list of items which need validation.

An illustrative example is given as follows:

Utility System :	-	clean steam
	-	compressed air
	-	purified water system
	-	chiller
Production Equipment:	-	vial washer
	-	dryer
	-	autoclave
	-	lyophilizer
	-	filling machine
Support Equipment:	-	depyrogenation oven
	-	pumps
	-	process holding vessels

5. VALIDATION STRATEGIES

5.1 INTRODUCTION TO VALIDATION PROGRAMME

In order to ensure that the facility, equipment, systems, services and utilities perform reliably, consistently and according to design intent, a validation programme must be implemented.

Validation programmes consist of three types of qualifications:

a. Installation Qualification (IQ) : Documented verification that all key aspects of the installation will be in accordance with design specification and applicable regulatory codes and guidelines.

b. Operational Qualification (OQ) : Documented verification that the systems and /or subsystems perform as intended throughout the anticipated operating ranges.

c. Performance Qualification (PQ) : This activity identifies the critical process parameters to produce the desired products, establishes acceptance operating ranges for those parameters and verifies that they can be consistently controlled and monitored. Performance qualification studies should be carried out in triplicate to assure reproducibility. Performance qualification is the heart of validation. Performance qualification must confirm that under routine and challenged conditions of operations, the equipment operates as expected and that the outcome of processing is acceptable. Consistency and reliability at the limits of acceptable operating conditions is fundamental for performance qualification. For example, when validating a heat sealing unit the most important parameters are temperature, pressure and elapsed time.

It would be acceptable to show two extremes which would be likely to result in a poor seal. For example, highest temperature, pressure and time and lowest temperature, pressure and time. The first set of conditions (highest) will provide a cut seal, the second set of conditions (lowest) will likely provide an incomplete seal. If in each case, the seals are acceptable, then provided the equipment performs within these operating boundaries, the sealing event can be judged as acceptable. Our limits of acceptability are cut seal and incomplete seal.

Validation is defined as an activity which assures that facilities, systems, procedures, processes and products are maintained in accordance with CGMP compliance.

5.2 LEVELS OF VALIDATION

Level 1

Lowest level of concern. Reliability of the item can be assured by Preventive Maintenance and Calibration Programme; these include items such as thermometers, weighing balance, etc.

Level 2

IQ/OQ required. However, challenging the performance is not required because the performance of the equipment during monitoring will provide performance data e.g. air compressor, chiller, plant steam, etc.

Level 3

Highest level concern and consequently need to completely validate i.e. IQ/OQ and PQ e.g. WF1 system, filling machine, pure steam generator, fermenters, purification systems, lyophilizers, autoclaves, etc.

Example of Validation Requirement of a Typical Vaccine Production Facility

Facility Suites	IQ
Facility	✓
Receiving and Quarantine	✓
Released Storage Suite	✓
Media Preparation Suite	✓
Inoculum Preparation Suite	✓
Fermentation Suite	✓
Downstream Processing Suite	✓
Purification Suite	✓

Facility Suites	IQ
In-Process Testing Laboratory	✓
Quality Control Laboratory	✓
Product Filling	✓
Product Quarantine	✓
Gowning Suite System	✓
Corridors	✓

Process Equipment	IQ	OQ	PQ
Sterilization Autoclave	✓	✓	✓
Decontamination Autoclave	✓	✓	✓
Biohazard Hood/Laminar Flowhood	✓	✓	✓
Glassware Washer/Dryer	✓	✓	✓
Inoculum Fermenter	✓	✓	✓
Production Fermenter	✓	✓	✓
Holding Vessels *	✓	✓	
Acid, Base and Antifoam Holding	✓	✓	
Microfiltration/Ultrafiltration	✓	✓	✓
Purification System	✓	✓	✓
Process Piping (Rigid)	✓	✓	✓
Process Piping (Flexible)	✓	✓	
Homogenization System	✓	✓	✓
Centrifugation	✓	✓	✓
Filling Unit	✓	✓	✓
Labelling Unit	✓	✓	
Lyophilizer	✓	✓	✓

*** PQ required if sterility is required.**

Utility and Support Systems	IQ	OQ	PQ
Floor Drainage	✓	✓	✓
Biodecontamination System (SIP)	✓	✓	✓
Dust Collection System	✓	✓	✓
Facility Access System	✓	✓	✓
Electrical System	✓	✓	
Utility Station Panels	✓	✓	
Instrument Air	✓	✓	
Process Air	✓	✓	✓
Purified Water System	✓	✓	✓
Plant Steam System	✓	✓	✓
Steam /Condensate Distribution	✓	✓	
Chilled Water System	✓	✓	
Pure Steam Generator	✓	✓	✓
Domestic Hot and Cold Water	✓	✓	
Filter Integrity Test System	✓	✓	✓

5.3 TYPES OF VALIDATION

Most widely accepted and practised is prospective validation.

- **Prospective**

  This is the simplest and most common approach. The product is developed and manufacturing process is validated before introducing the product into the market.

- **Concurrent**

  Validation is performed during production process. This type is common when prospective validation is performed on a small scale due to large expenses involved. The data from small scale are transferred to large scale and concurrent validation is performed.

- **Retrospective**

  This type is much more difficult and intensive and may not give conclusive results. In the US the following criteria must be met for retrospective validation:

- All batches made in the specified time period chosen for the study must be included.

- Only batches made in accord with the process evaluated can be included. Typically 20 - 30 batches are required for meaningful retrospective evaluation.

Process Validation

Examples of Manufacturing Processes:

Fermentation	Formulation
Primary Recovery	Decontamination
Purification	Cleaning
Depyrogenation	Sterilization

Examples of Support Processes:

Sanitization
CIP - Clean-In-Place
SIP - Steam-in-Place

Worst Case Challenge

"A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures which pose the greatest chance of process or product failure when compared to ideal conditions - such conditions do not necessarily induce product or process failure." FDA, 1987.

Cleaning Validation

Cleaning validation is an example of process validation. The cleaning process is defined as an interaction of chemicals, water, cleaning tools, objects/items to be cleaned and people performing the procedure to achieve cleaning. To define and control the quality of the cleaning process:

- Identify the raw materials that are used in the cleaning process, i.e. chemicals, water, buckets, sponges, mops, etc.

- Define how people are trained in cleaning techniques.

- Define the cleaning techniques that are appropriate for specific areas, equipment, etc.

- Define what is an acceptable result.

Thus, validation of cleaning process as described above becomes a simple demonstration of the interaction of materials, people and equipment in a controlled manner to achieve a measurable or observable result. Cleaning validation must also demonstrate that the process of cleaning is consistent, reproducible and rugged.

Utility Validation

The design and maintenance of utility systems is one of the most important facets of the plant operation. From a Quality Assurance perspective, utilities can be divided into the following major categories:

Utilities with Product Contact:

These are utilities used as part of a manufacturing process whereby there is an intimate and immediate contact with the process material. Examples include water (dilution), compressed air (agitation, sparging), medical gases (aeration) (CO_2, N_2, O_2) and sometimes steam.

Utilities with Indirect Product Contact:

These are utilities that are involved in a process that may eventually be exposed to a product (product contact surface). Examples include rinse water in a cleaning process and steam for the sterilization of a reactor or other equipment requiring autoclaving.

Utilities with no Product Contact:

These are utilities that, by the way they are installed and used, would never come into contact with the product. Examples include chilled water used in heat exchanger, plant steam in a sterilizer jacket or heat exchangers or effluent handling waste system.

Utilities with indirect or direct product contact are of paramount importance since these utilities and delivery systems need to be designed, constructed and maintained so as to ensure that the safety, quality or purity of the product is not at risk. These utilities require formal validation as any critical equipment supporting a manufacturing process. Once validated, these utilities need to be kept in a validated state with appropriate maintenance and monitoring programs so as to ensure that the systems produce and deliver the appropriate utility to conform to the requirements established. Procedures for operation, maintenance and monitoring (performance) need to be documented.

6. VALIDATION OF EQUIPMENT OR EQUIPMENT SYSTEMS

Whether equipment or equipment systems should be validated depends on how the equipment functions. For example, a depyrogenation oven functions independently from other processing equipment and therefore it should be evaluated independently.

On the other hand, Purified Water System (USP) should be evaluated as a system. This is because water is not removed from the system for use until it has been completely processed within the system. Therefore, softeners, carbon beds, ion exchange resin beds, filters, UV lights, storage tanks, recirculating pumps and distribution piping should be evaluated as a whole. In such a case, it would be more appropriate to perform IQ and OQ on individual components and PQ on the entire system. This is useful because if a pump breaks down and is changed it is not necessary to perform IQ and OQ on the entire system; just the pump.

7. PRODUCT VALIDATION VS DESIGN VERIFICATION

Validation of the product manufacturing event should only be performed when the product design is completed. This means validation is a terminal event to the development process. Validation is ***not*** a tool of the development group; it is a tool of the manufacturing group. The development group is trained to develop and improve process and products, therefore they are always changing things to achieve that objective. Validation is not a developmental process, neither an experiment. It is a planned evaluation of an established process which confirms that it can be performed as directed and produce acceptable products.

Thus, during validation, one cannot change the components, raw materials, processing events, process acceptance criteria, final product design or final acceptance criteria. Therefore, it is difficult for the development group to perform validation. Validation work must be performed in a location with the equipment that will be used for commercial manufacturing. Exceptions include virus removal validation. In this case, process is scaled down considerably and validation performed.

8. VALIDATION MASTER PLAN FOR VACCINE PRODUCTION

Objective:

To provide key facility design elements and the appropriate validation strategy so as to ensure that the facility is successfully qualified in meeting corporate or company specifications and all appropriate GMP requirements. The following sections outline essential elements and subject matter that should be included in a typical master plan, irrespective of the intended use (product type). It is aimed, however, at biological facilities.

Introduction

This should include the purpose of the facility and key regulatory (GMP) and containment/safety levels having to be achieved. A brief outline of any support or ancillary activities servicing the area should also be identified.

Facility Description

Building overview should be described including the following:

- Main overall structure (exterior surface, walls, number of floors, strategic location of utilities).
- Dedicated or campaigned (multiuse) facility.
- Key containment elements.
- Key utilities servicing the facility.
- Key manufacturing or process train.
- Key controlled environment finishes.

Utility Description

An overview of all utilities servicing the facility with appropriate capacities and key specifications. The following utilities should be described.

Domestic Water Supply

- Pressure
- Backflow preventers
- Points of use

Plant Steam

- Pressure/capacity
- Equipment serviced

Compressed Air

- Pressure/capacity
- Pretreatment, filtration
- Compressor type
- Instrument vs. Product Contact
- Details of Distribution System

Medical Gases (N_2, O_2, CO_2)

- Central or bottled system
- Filtration required
- Distribution System

Pure Steam

- Pressure/capacity
- Generator type
- Water Quality Feed
- Distribution System

HVAC

- Air handling units
- Duct work distribution (Supply and Return)
- Filtration (Prefilters and HEPA)
- Exhaust needs
- Interlocks, damper devices
- Special controls
- Special cooling/heating designs
- Special humidification/dehumidification
- Number of air changes

Water for Injection (WFI)

- Pretreatment design
- Distillation type (capacity, quality level)
- Distribution System (hot/cold loops, number of use points, material make-up)

Sanitary Drainage

- Backflow preventers
- Capacity
- Decontamination systems (as appropriate)

Electrical

- Back-up supply
- Special voltage
- Key facility finishes

Fire Protection

- Sprinkler system
- Emergency exits
- Fire doors/ratings

Environmental Support Systems

An overview of monitoring programmes (computer automated) that may monitor key facility specifications, i.e.

HVAC:	Temperature Pressure Differentials
WFI:	Flow rates Temperature Pressure
Security:	Access status

Equipment Overview

A description of all major equipment is required. A room by room listing would be beneficial. Each equipment description should include key specifications and design elements.

Building Floor Plans and Product/Personnel Flow

Facility layout showing controlled room layout

- All controlled rooms and appropriate clean room classifications (10,000, 100,000, etc.).
- Key equipment highlighted for each room and position.
- Room usage identified for each room.

Air Flow Direction

- All rooms identifying pressure relationships.
- Air flow directions (to demonstrate containment or product protection as appropriate).

Personnel Entry and Flow

- From street clothes to entry.
- To lab whites.
- To aseptic gowning.
- To proper exiting.

Product Flow

- Showing different product stages.
- Demonstrating unidirectional flow with no cross-over of clean vs. dirty or live vs. non-live activities.

Clean Material Flow/Dirty Material Flow

- Demonstrating unidirectional flow of clean supply material/reagents/glassware from dirty/soiled material.

Facility and Equipment Validation Programme

Overview of key components of validation strategy for the facility

- IQ, OQ, PQ (General Expectations)

Responsibilities during Validation

Engineering/Construction

- Construction and inspection procedures must be carefully monitored throughout the project to ensure compliance to design and specifications.
- Coordinates with Maintenance Department of Facilities to ensure a maintenance plan or programme is established to maintain the integrity of appropriate system.
- Assist production and maintenance departments in training of personnel for system operation and use (organizing/co-ordinating with the appropriate vendors).

Quality Assurance

- Develops a master validation plan and schedule in cooperation with Facilities and Production.
- Co-ordinates with Production Manager, Engineering Manager and QC Testing (when appropriate) in designing the validation protocols (IQ and OQ) and ensuring the documents are approved by all functional groups.

Designs and executes PQ validation protocols in cooperation with Production.

- Reviews all elements of the validation data (IQ, OQ, and PQ where appropriate). To ensure systems meets predetermined specifications and requirements of the protocol and prepares a validation report to verify this.
- Develops an on-going monitoring program (where applicable) to demonstrate that the system is being maintained and is under control.
- Reviews all design specification to ensure compliance to GMP.

Manufacturing

- Participates in the design and execution of the validation studies (IO, OQ, PQ).
- Develops Standard Operating Procedures in collaboration with QA and Facilities.

- Ensures operators receive the appropriate training to operate the system or equipment and that it is documented.
- Monitors the system/equipment according specifications approved by QA.
- Reviews design specifications to ensure production needs are met.
- Maintenance.

Acceptance Criterion

- Acceptance criterion are identified as specifications, test results or control limits that must be met before system, equipment or facility is considered validated.
- Each utility and equipment will have a unique acceptance criterion that IQ, OQ, and PQ will define.

Protocol Listing

- A listing of all protocol required to be written and reports to be concluded for the facility plan (pre numbering or identification is recommended at this stage).

Preventive Maintenance (PM), calibration and change control

Once a system or equipment is validated, it is necessary to assure that the performance matches the conditions of the qualifications or validation over a prolonged period. The only way to ensure this is to **monitor** and **use change control programmes** to confirm that the conditions of validation are routinely met. Such programmes include Preventive Maintenance, routine calibration and change control. Preventive Maintenance and calibration is reasonably well understood and implemented in most industries. Change control is less common.

For example:

- A maintenance technician should not be able to change the seal of a fermenter which has already been validated without prior approval from QA.
- A technician should not be able to change the point of use of sterilizing filter on compressed air without notifying QA.

One way of instituting change control is by controlled maintenance: Equipment ID # 7003-A where A - may mean do not touch the equipment without QA approval. This needs to be instituted during training.

Standard Operating Procedures (SOPs)

To support the facility, key standard operating procedures required to be identified and written. These include the following;

Environmental Monitoring

- Clean room monitoring (air classification, temperature, humidity, pressures)
- WFI
- Compressed air
- Pure Steam
- Medical Gases

Metrology Programme

- Annual recertification of all critical measuring instruments.

Change Control Procedure

- Prior to any change made to a validated system or equipment an assessment must be made if revalidation is required.

Maintenance SOPs

Preventive Maintenance Procedures/Frequency

- scheduled shut down
- spare parts program
- maintenance log books

Emergency and Contingency Plans

- HVAC failure
- Spills
- Operator Safety

Changeover Procedures

- Between campaigns for multiple use facilities.

Revalidation Programme

- Dictated either through change control or through routine scheduled studies based on the criticality of the system or process.

Training Initiatives

- General Education
- Biosafety Training
- Plant Training
- Medical Surveillance/Hygiene
- GMP

Process Validation

Not all facility validation master plans include this subject. Some choose to make this a separate plan as it relates to manufacturing activities.

Process Validation is defined as "*establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its' predetermined specifications and quality attributes*".

Elements of Process Validation should include the following:

- Process Simulation using Media Fills to demonstrate closed systems and aseptic manipulations for all sterile manufacturing steps.

- Manufacturing Performance Qualification whereby the performance specifications defined at each stage are clearly met in a consistent reproducible manner.

- Cleaning Validation to demonstrate cleaning procedures for all product contact equipment are adequately controlled to eliminate cross-contamination between products.

- Computer Validation of computerized systems that control or monitor processes require qualification for full validation depending on a system application.

- Sterilization Validation of any sterilization process that effect product quality, efficiency or safety is performed (includes thermal, chemical or filtration processes).

Levels of Process Validation

All processing events do not require validation. Processes should be categorized according to their potential impact on the safety and performance of the product.

Level III - Full Validation
In this level, the failure or inconsistent performance of these processes could adversely affect the safety, quality or efficacy of the product.

Examples: a. Sterilization, depyrogenation, aseptic processing, etc. are prime examples.

b. A diagnostic product which is a sole source of information to a critical treatment decision.

Level II
This requires qualification. Components interacting in the process must be identified and controlled so that the process itself must be established.

Example: An automated packaging process for a non sterile product requires qualification but not validation. In this case, it is necessary to demonstrate that the process can be performed effectively but there is no need to demonstrate process consistency under ideal and challenged conditions.

Level I
This process can be assured with controlled documentation, training of personnel, simple equipment Calibration and Preventive Maintenance procedures. Example of Level I process includes media mixing process for liquids. Example: Mixing.

9. WHEN TO REVALIDATE/CHANGE CONTROL?

The time element of once a year is generally a good time to review IQ and PQ of critical systems.

Effects of change examples are as follows:

- change in scale of operation
- change in manufacturing site
- change in equipment
- change in packaging
- change in subcontractors/vendors

In GMP change control must be instituted for:

- documents
- material specifications
- vendors
- contractors
- test methods
- processing steps
- processing equipment
- processing site
- final product packaging
- utility equipment
- software
- environment
- personnel

SECTION IV

DOCUMENTATION AND DOCUMENTATION CONTROL FOR CGMP COMPLIANCE

1. IMPORTANCE OF DOCUMENTATION

Documentation prepared during the production and testing of pharmaceutical products is the most complex and extensive of any industry that produces a consumer product. The records generated during production are exceedingly important because it is by the completion and accuracy of various documents that the true quality of the product can be determined.

A documentation system which meets **all** CGMP requirements should consist of at least as a minimum the following:

- Documents that will describe the entire process (ie: Master Batch Protocol, Product and In-Process Specifications, Standard Operating Procedures, Test Procedures, etc.).
- Data collection documents - these documents are usually in the format of forms which record information collected during processing (examples include: Test Method Forms, Monitoring Forms, Log of Use Forms, etc.).
- Traceability documents - these documents allow a complete tracking of all materials used in producing a batch (examples include: Part Number, Part Number Specification, Receiving Codes, Document Number).

When an inspector inspects a facility, he or she looks at the documentation system and documentation control to seek assurance that:

- The facility, utilities, equipment and instruments commensurate with their intended use and that they are properly calibrated and adequately maintained.
- A Material Control System is in place and functioning optimally, which shows that **only** tested and approved raw materials are used in all and any manufacturing operations.
- Processes used in the production of a batch are fully validated.
- Personnel are adequately trained to perform their required duties.
- A traceability system exists in the event when a product recall is required.
- An optimally functional and well trained QC/QA system exists so that testing of all components, closures, in-process and final products can be released if they meet their required specifications.

2. POINTS TO CONSIDER WHEN CREATING A DOCUMENTATION SYSTEM

2.1 LANGUAGE

The language and choice of words when preparing documents should be such that it is:

- Instructive and clear to the technician. This means that the information must be accurate, not vague or requiring guesswork or be interpretive.
- Informative to Regulatory Agency Inspectors.
- Confirm compliance with CGMP.

Documents must be written clearly, specifically and be informative yet flexible and practical. See example below:

> *A microbial cell suspension (fermentation broth) requires centrifugation. The technician typically places this broth in a Alpha Laval centrifuge set at # 4 setting and runs the centrifuge for 15 minutes. This event can be described in several ways in an SOP:*

For example:

1. Spin the fermentation broth at room temperature (R.T.) until a solid pellet is obtained.
2. Spin the fermentation broth for 15 minutes at R.T.
3. Spin the fermentation broth in an Alpha Laval centrifuge at setting #4 for 15 minutes.
4. Spin the fermentation broth at 2,000 revolutions per minute (RPM) (ie. setting #4) for 15 minutes at 20-25°C.
5. Spin the cells to form a solid pellet. Typically 1500 x g for 15 minutes is sufficient. This is achieved at a setting of # 4 in the Alpha Laval centrifuge model (# X42) with a rotor (size X42) at 2000 RPM.

Which of the above options 1-5 is most clearly written?

Option #1:

Good, because it informs the technician what an acceptable outcome should be, but is vague in how to achieve this outcome.

Option #2:

Totally vague; does not tell the technician how to perform this task.

Option #3:

Specific, accurate, and informative but inflexible. What happens if the Alpha Laval centrifuge is not working on the day the centrifuge is required? This means that the SOP will have to be written for a different kind of centrifuge!

Option #4:

Better than Option #3 but still not ideal. If the RPM is used, especially in the case of centrifugation, additional information such as g force must be accompanied.

Option #5:

Specific, accurate, informative and flexible. It directs the technician clearly what needs to be done and how to do it and yet remain flexible in case the centrifuge is replaced.

Another reason why the choice of words and clarity when writing an SOP is very important is in a case where a new employee comes on board. An example of such a situation is described:

> *"Wash the microfiltration unit with spectrum detergent (P/N # 2011) and rinse with water for irrigation (P/N # 4201). When the unit is completely dry, place a new filter (P/N # 6536) and switch off all remaining controls. Label the unit as clean, date of cleaning and initials."*

What is wrong with the above directions? There are two things wrong with the instructions:

- The writer of this SOP has assumed that the unit will be air dried. This is because in the class 100,000 clean room where the microfiltration is taking place, toweling or use of paper products is not allowed and therefore the rationale was that the unit will be air dried.

- The new employee reads this SOP and draws the conclusion that the dryness of the unit is more important.

A realistic outcome of such a situation is:

> *The technician leaves the clean room, gets paper towels and dries the unit with paper! Pieces of paper (very fine) collected on the downstream side of filter ultimately end up in the product. The lot is failed due to specification of the product calling for particulate free liquid!*

Thus, documentation must be written in a manner which is sufficiently flexible yet precise to minimize interpretations.

2.2 CHANGE CONTROL

Change Control is an option to use only when absolutely necessary. There are cases where SOPs have several revision numbers (for example TM 1081.27 - Test Method for Measuring Protein Concentration).

This SOP was two years old but had been revised 27 times! When an inspector sees 27 revisions in 2 years it does not create confidence in or credibility of an organization.

Issues to consider when implementing change control:

All changes must be reviewed by Departments affected by the change. Thus for example, a QC document change must be circulated through QC, QA and production. Since the change was in the QC department, the technician performing that task must be retrained.

- If the change is dramatic and it can affect the identity, strength, safety or efficacy of the vaccine, then Senior Management must be advised. It may also be necessary to contact the Inspecting Agency before the change is implemented. This is especially the case when a licence to market has already been obtained.

- One copy of the previous revision must always be kept on file and archived. Other outdated versions such as controlled copies must be collected and destroyed.

- At the time of inspection, a history of change must be available for each official document; all records and data to support the change must be complete and available for review to the Inspecting Agency.

2.3 DOCUMENTATION CONTROL DESIGN

Before implementing a documentation system, the QA Department must prepare an SOP on how to write SOPs. The information in such an SOP describes:

- How to prepare the many varied types of documents required for a complete documentation system in a CGMP facility.

- What the format of the document should be.

- Who will review and sign off for approval of different documents.

- How will the documents be controlled and distributed in the facility, and the number of controlled copies which will exist.

- How will they be numbered, identified and revised.

2.4 DOCUMENTATION FOR PLANNED AND UNPLANNED VARIANCES OR DEVIATIONS

Just as a variance report is required in the production area when a process step deviates from the Batch Protocol or when a method step deviates from the Test Method, the same scenario applies in a good, well controlled documentation system.

For example, if the QC department performs routine environmental monitoring on the 15th of every month as per SOP for environmental monitoring for Class 10,000 Purification Suite. If there is a heavy load of Lot Release testing of a batch being carried out in the QC department and there is an urgent need to complete this Lot Release, the QC Department may have to prioritize their workload and decide to delay the planned environmental monitoring by a few days to take care of the emergency mentioned. In this case, the QC department must send out a memo to Production and QA to inform of the planned delay thus:

> *"Due to urgent and heavy work load in the QC Department the environmental monitoring in the production area (Class 10,000 Purification Suite) scheduled to be carried out September 15, 1992, will be rescheduled to be carried out on September 22, 1992. A review of the last 12 environmental monitoring results have shown that we are well within our limits of bioburden and particle counts and it is not anticipated that a delay of one week will cause concern."*

This memo should be sent out to Production and QA and must be signed off by both departments and placed in the Environmental Monitoring Data File.

Thus, when a planned deviation from SOP occurs, it must be justified, and be accepted by all parties concerned. The deviation must be documented in the environmental monitoring data files. A good system to implement is CCN - Change Control Number. For example, for Measles Vaccine production, one can implement a Change Control Number as described below:

> *CCN-MV represents Change Control Number for Measles Vaccine. Every change made during the production of Measles Vaccine will be recorded in the CCN-MV log book for Measles.*

For example, when a deviation occurs, it would be recorded:

> *"CCN-MV-91-01-14, Sodium Phosphate, USP grade purchased from Fisher Scientific was changed to Sodium Phosphate, USP grade purchased from Merck." Change of approved vendor was agreed by QA and Production. Approved by QC Manager on 14/01/91.*

A yearly review of the Log book will show how the manufacturing process is changing and its potential impact on the specifications of the final product.

3. NUMBERING SYSTEM

The most important role of the numbering system is to provide identification, control and traceability of **all** materials and documents used in the production of a batch of vaccine. There are different kinds of numbers for different types of documents as described below:

3.1 MASTER DOCUMENT INDEX (MDI)

MDI is an index of all documents (Document Number and title of each document) currently in place and, those that have been retired at the facility. In addition the MDI also provides information on the revision number of the document and the effective date. It is not unknown to have MDI having between 1000 in small facilities to over 10,000 documents in large organizations. An MDI may be broken down into an alphanumeric form. One example is shown below:

SOP-001-999	Standard Operating Procedures
VA-001-999	Validation Protocols, Validation Assays
QA-001-999	Quality Assurance Documents
QC-001-999	Quality Control Documents
TM-001-999	Test Methods
TMF-001-999	Test Method Forms
MC-001-999	Material Control
S-001-999	Specifications
FE-001-999	Facilities and Engineering

For example:

SOP-001.0 Operation of the Beckman Model XJ3 Bench Top Centrifuge where:

SOP 001.0 means that it is a Standard Operating Procedure, Document Number 1 in the SOP system and 0 means this is the first approved version of Document Number 001. As revisions are made, the 0 changes to 1, etc. thus, SOP-001.3 indicates revision # 3 of the same document.

3.2 PRODUCTION BATCH NUMBERS (PBN) OR FINAL PRODUCT LOT NUMBERS (FPLN)

A batch according to the USFDA is defined as:

"a specific quantity of a drug that is intended to have a uniform character and quality within specified limits and is produced according to a single manufacturing order during the same cycle of manufacture."

A Production Batch Number is a combination of letters and numbers which signify something

about the Batch and from it, a complete history of the manufacturing, processing, packaging, holding and distributing of a batch can be obtained. Final Product Lot Number and Production Batch Number are one and the same. Although any combination of numbers can be used, the numbers chosen are such that they usually signify something about the batch. For example:

B in the PBN could denote a routine Batch
V in the PBN could denote a Validation Batch
R in a PBN could denote a Research Batch

The time of manufacture is also important and could be reflected in the Batch Numbering System. For example:

"V9103MV as PBN would mean a Validation Batch of Measles Vaccine produced in March 91."

A PBN is the most "public" number generated in a GMP facility. It appears on every vial and circulates in the consumer market. If a problem arises with the product, this number is cited on any complaint. In this respect, the documentation and documentation control must be such that the Producer of the Lot can trace accurately through all the records and documents and produce every piece of documentation involved from the testing of raw materials and components to Batch Records, final product testing, stability, inspection and packaging of this product.

The production Lot Number should be assigned by Quality Assurance in conjunction with the person in charge of scheduling production in the facility. A log of these numbers and their assignment plus the format must be maintained and shown to the inspector during an inspection.

3.3 PART NUMBERING SYSTEM, PART NUMBER AND PART NUMBER SPECIFICATIONS

The Part Numbering System is a basic block of GMP documentation. It consists of a Part Number and a Part Number Specification. A Part Number is a simple numerical number used to identify a critical item used in the manufacture of a product. A Part Number Specification defines the identity of the Part Number, describes the item in detail and generally includes a way to test the quality of that item. The purpose of a Part Number in a GMP system is to control quality. This quality control is fundamental to GMP operations. In a GMP environment, the use of a Part Number enables an item to be differentiated from another similar item by quality.

For example:

- Part Number of a 500g bottle of Sodium Chloride, ACS grade will be different from the Part Number of Sodium Chloride, USP grade because the quality of salt is different.

- A 500 g bottle of NaCl USP grade will have the same Part Number as 2.5 kg NaCl USP grade. This is because the quality of salt in both containers is the same.

- A 10 inch diameter gasket will have a different Part Number than a 7.5 inch diameter gasket made of the same material and quality.

Naming a Part

Part Numbers can be assigned randomly or organized into categories:

Generally smaller companies tend to be simple:

F-01	Part Number of a Inlet Air Filter
D-02	Part Number of a Dialysis Membrane
C-03	Part Number of a Chemical, e.g. NaCl
I-04	Part Number of an Intermediate in Drug Production
S-05	Part Number of a Solution

or categorization, is the case with larger companies for example:

P/N	1000-1999	is allocated for	Cell Lines
P/N	2000-2999	is allocated for	Raw Materials
P/N	3000-3999	is allocated for	In Process Intermediate
P/N	4000-4999	is allocated for	Finished Product
P/N	5000-5999	is allocated for	Components
P/N	6000-6999	is allocated for	Closures

Assigning Part Numbers

Part Numbers are generally assigned by the QC department. There should be only one Part Number for each unique item.

QC Department prepares a "Part Number Request Form." This form is provided to the "requestor" who completes information on the form. Typically, the form requests the following information:

- item in detail
- designated vendors
- catalogue numbers
- how and where about in the process will the item be used
- critical features which must be checked when the item arrives

QC uses this information to create a Part Number Specification Form and a Part Number is assigned to the item requested.

QA is responsible for preparing an SOP which should describe how to assign, retire and categorize Part Numbers, how the Part Numbering system should be operated, who assigns Part

Numbers, how should they be controlled and how to complete a Part Number Request Form. Part Numbers can be retired if the item is no longer used in a GMP environment but **NEVER** reassigned to another item.

Part Number Specifications

When a Part Number item is received at the facility, a Quarantine label is applied to the item. The Part Number and Receiving Code are then recorded on the quarantine label and the item placed into a quarantined area.

QC will inspect and/or test the item before it is released into the facility. In order for QC to inspect and/or test the item, the QC technician needs the Part Number Specification Form so that he/she can check the Part Numbered item against the Part Number Specification to see if it meets or fails the specification set for the Part Numbered item.

The Part Number Specification describes the Part Numbered item, purchasing information (e.g. approved vendors), chemical formulas, size, sample information, handling precautions, reference sample size, storage conditions, testing methods and acceptance criteria (where appropriate) and information on expiry date. In addition it should contain information on edition or revision number and approval signatures.

If there are several categories of Part Numbered items, it is usually convenient to set up Part Number Specification Forms which are also categorized as follows:

A Part Number Specification Form for a Cell Line may contain information whether it is a mammalian cell (further categorized into anchorage dependent or suspensions) or microbial cell lines cell line history, vectors and markers (if recombinant) passage level limitation if any (this may be important when the cell line is used for biological assay) isoenzyme analysis, phenotype and genotype characteristics, MSDS, storage and expiry date.

A Part Number Specification Form for a Chemical may contain information on the physical appearance, description of the chemical grade, formula weight, handling requirements, MSDS, storage and expiry date.

Generally, a Specification Form should be about one page long. Where testing is required, a procedure called the Test Method (TM) is supplied on the second sheet, or more appropriately, the TM could be referenced on the Specification Form. The TM will provide step by step information on how to perform the analysis, while the Part Number Specification Form should describe what an acceptable result should be.

When a Part Numbered item is received into the facility, the QC department checks to ensure that the item has not been damaged during shipment, the item ordered on the Purchase Order is indeed what was received and received from an approved vendor. All Part Numbered items are inspected against the Part Number Specification Form as a minimum before being released from Quarantine.

What items should have Part Numbers and Part Number Specification?

Generally only those items which are:

- critical ie. those items that are direct part of the final product or come into direct contact with the product during processing.

  Thus NaCl used in preparing buffer for a purification process to produce a vaccine will need to be fully tested; whereas NaCl used to regenerate a column after QC testing of an in-process intermediate located in QC laboratory need not be tested fully.

- items subject to deterioration should be tested.

- items purchased from a new or unknown vendor should be tested until the vendor is properly qualified.

The nature and extent of testing is dependent upon the end use of the item. For GMP Production, a Certificate of Analysis (C of A) and one identity test as per USP or equivalent is adequate.

The level of testing required is decided by considering the following:

- How will the failure of the item likely affect the quality or safety of the final product?
- Does the item come into direct contact with the product or become part of the product?
- What is the likelihood of failure and the impact of failure on product quality, safety and efficacy?
- How reliable is the vendor? Number of years the vendor has been in business? Vendor audit report, ISO 9000 certification?

Items which do not require to be tested include:

- Chemicals used to prepare assay reagents, (while they will have a Part Number), purchased from a well qualified or known vendor and a good grade(such as an ACS grade), it is generally acceptable and no further testing is required.

- Items like parafilm, aluminum foil, notebooks, pens, hand wipes, measuring cylinders, etc.

All Specification Forms must indicate an expiration date, to assure that the item maintains its original quality until it's last day of use. A vendor assigned expiration date must be honored unless in-house date is sooner. The expiration date is dependent upon light, temperature, and humidity, etc. It is important to store the items appropriately to ensure the item's quality is maintained (for example; in the absence of light, tightly closed, cool temperature 2-8°C).

In general, dry chemicals are stable for approximately five years. For sterile items, the expiration date must be validated.

When testing raw materials, containers and closures for the use in GMP Manufacture, a Retain Sample must be kept; the amount and number of samples tested must be established by the QC department and vigorously followed. A good resource for sampling guides is the MIL STD 105E.

Receiving Codes

The only way to completely identify an item used in CGMP Manufacture is to have a Part Number and Receiving Code combination. When a Part Numbered item arrives at a facility, it goes through a visual and Purchase Order verification inspection. Prior to being moved to in the quarantine area, a Number referred to as the Received Code is assigned to the Part Numbered Item. The purpose of this Receiving Code is to be able to identify between shipment of items having the same Part Number..

Thus, if a shipment of NaCl USP grade of 6 x 500 g bottles was received on Jan 2, 1996; it could be identified as follows:

Bottle # 1	P/N 6003	Receiving Code	960102-1
Bottle # 2	P/N 6003	Receiving Code	960102-2
Bottle # 3	P/N 6003	Receiving Code	960102-3

Where P/N 6003 is the Part Number for NaCl, USP grade. Receiving Code is the date of receipt 960102 and since there are six bottles, each bottle will be differentiated as 1,2,3,4,5 and 6. Thus each bottle is identified uniquely, so that in the event of a problem, the particular bottle of NaCl USP used in the problem Batch can be identified.

In addition to assigning a Receiving Code, an entry must also be made in "Receiving Log Book." A Receiving Log Book contains column entries for the Part Number, a description of the item, the amount received, supplier, manufacturer, manufacturer's lot #, purchase order#, Receiving Code and the initials of the individual logging in the item and comments if necessary.

Labeling Part Numbered Item

Each item received from the vendor is labeled with its Part Number and Receiving Code and placed into a locked quarantine area. QUARANTINE label is usually orange in color. The Quarantine date is entered on the label and the number of units eg. (1 of 6) recorded on the label. Once the item is in Quarantine, QC is notified for sampling and testing. When the item is released, QC prepares a RELEASE label (which is usually green in colour) and attaches the label so that almost 90% of the quarantine label is covered. The label must contain information such as Part Number, Receiving Code, date of release, storage conditions and expiration date. If the item is rejected, a REJECTION label, usually red in colour is applied and the item moved to a locked rejected area.

The QUARANTINE label is red in colour with yellow lettering:

QUARANTINE
Lot #:
_____
Date: _____
By:

The RELEASED label is florescent green in colour:

RELEASED
Lot # _____
Release Date: _____ By: _____
Expiry Date:

The REJECTED label is yellow in colour:

REJECTED
Lot # _____
Date: _____ By: _____

4. SOLUTION LOT NUMBERS (SLN)

Solutions are prepared daily in the GMP facility, especially in the Production and QC where testing is conducted. These solutions may affect the quality of the product test and therefore must be controlled and documented. Three types of documentation are required for this:

- Solution Specification Form (SSF) which tells the technician how to prepare a solution and what the acceptance specifications should be.
- Solution Preparation Log Book - This is a log of all solutions prepared in-house, in chronological order and assigned a Solution Number.
- A solution label which is applied onto the bottle.

The Solution Log Book should record the description of the solution, Part Number, date of preparation, volume prepared, pH (if appropriate), concentration, the solvent used, name of preparer, expiration date and storage condition. The solution label should contain the following information:

The SOLUTION label is usually white in color with green lettering:

SOLUTION
Name:
_____
Lot # _____ P/N: _____
Conc.: _____ pH: _____
Amt:
_____
Prep By: _____ Date_____
Store @: _____ Exp_____

5. INTERMEDIATE PART NUMBERS

There are several examples of Intermediate Part Numbers.

Media Part Numbers

In the case of fermentation media preparation, it is not unusual to make stock solutions of trace elements or vitamin solution which are filter sterilized and added aseptically to the fermenter prior to inoculation. In such cases, the final fermentation media may have a Part Number (NM4).

Where NM4 may be composed of:

NM1 Solution of Dry Chemicals at appropriate concentrations
NM2 Trace Elements Solution
NM3 Vitamin Solution

NM1 + NM2 + NM3 = NM4 which is the fermentation media. Each of these complex solutions will have a Part Number, Receiving Code, Expiration Date, Date of Preparation and Storage Conditions. It is usual to prepare these in bulk, aliquoted into small containers and store a frozen. The containers are labeled as 1 of 20, 2 of 20, etc.

In-Process Intermediate

Another example of where Part Number Intermediates are used is described in the example below:

> *In some cases of vaccine production, the entire cycle could be 30 days from beginning to end. There will have to be approved break points where the material is stored until an assay result is confirmed or due to weekends, etc. This means that the intermediate must be stored in an appropriate container under appropriate conditions. Under these circumstances, the Part Number, Expiration Date, Lot Number (equivalent to Receiving Code for a raw material) Date, and Description (example from DEAE column) must appear on the label as a minimum.*

Since the storage period may be quite long, the Part Numbered Intermediates must be tested prior to their release to ensure that it meets acceptance prior to further processing. Thus, an in-process test must be designed to check whether storage has had any deleterious effects. In case of a validated process, this test may not be necessary as during validation, the impact of storage must have been evaluated and challenged. Since an item may be stored at 2-8°C for prolonged periods of times, contamination is possible. Storing the in-process intermediate in a sterile container following sterile filtration shows Good Manufacturing Practices.

6. STANDARD OPERATING PROCEDURES (SOPS)

SOPs are directive documents which provide a step by step instruction to personnel on ***how*** to complete a given task reliably and consistently. There are several ways to prepare an SOP. One example of a format is described below:

Title: This should be brief and direct:

e.g.. Operation of Chemap FZ 2000 Fermenter
Calibration of Accumet 20 pH Meter

Use of words such as Operation, Calibration, etc. at the beginning of the sentence allows all "Operation" related SOP's to be located together "Calibration" related SOP's to be located together, etc. In a facility having several hundred SOP's, this categorization is helpful and makes for a user friendly system.

Purpose:

Usually restates a well written SOP title. It allows the writer to expand the procedure further which was not possible in the title.

Scope:

This is a very important section as it informs the person what a particular SOP does and does not apply to.

For example:

SOP on Measurement of Absorbance of Protein using a calorimetric assay at 590 mm. This SOP might apply to the double beam spectrophotometer, or to the spectrophotometer in the in-process laboratory area but not the spectrophotometer in the QC laboratory.

Responsibility:

This section declares who is responsible for training and maintaining the SOP.

Safety:

It is advisable that this section appear in all SOPs. For example, if dealing with BL2 or BL3 organism or product, safety precautions must be listed. If the SOP deals with harsh chemicals (such as phenol crystals), precautions on how to avoid contact with skin and what to do if contact is made must be included. This section may also include what to do in the event of a biological or chemical spill.

Preliminary Operation:

This section is optional and may or may not be relevant to the SOP. A check list is a good example; it may be necessary for a technician to go through a checklist before starting a procedure to ensure all the relevant materials required for the procedure are assembled prior to starting. Another example would be in the sanitization of biohazard hood before starting a procedure.

Procedure:

This is the heart of the SOP; it must contain simple and short step by step instructions:

a. Add this to ...
b. Pour solution
c. Label the flask ...
d. Observe color ...
e. Record the reading.

Calculation:

Step by step instructions on how to do the calculation. Example of a sample calculation must be shown; the results expected must not be listed in this section.

Documentation Requirements:

This section is optional. It should reference any log books. For example: when a solution is prepared, the Solution Log Book must be completed or if a pH meter is used, the LUMAC of pH meter should be completed during the procedure.

Since SOPs are usually more than one page long, the title, SOP Number and Revision, pagination, name of the Company must appear on all pages. This procedure is followed only if Approvals and dates of Approval are provided. These are only necessary on the front page. If not, Approvals and Dates of Approval will have to appear on every page.

An SOP is usually written by a person who knows the task or is going to perform the task. This person is referred to as the originator. The SOP is then reviewed by at least two other people. These can be either the supervisor of the originator, QC, QA, Facilities and Engineering or Regulatory Affairs as appropriate. One signature of the SOP must belong to either QC or QA. An SOP cannot be a controlled and approved document if it does not have either a QC or QA

signature. Personnel in the facility must have access to SOP's and appropriate Forms in order to perform their tasks. Usually, the Master Copy of the SOP is in say blue color. This copy is kept locked in a fire proof cabinet in the documentation department. Since Document Control is a QA function, all copies of the SOP must be made and accounted for by QA Department.

For example, if five copies of an SOP are required, each copy must be controlled as described below:

SOP 1052.3, Operation of Getinge Model X52 Sterilization Autoclave

Controlled Copy #1 QA Manager
Signature _____ Date Received _____

Copy #2 QC Manager
Signature _____ Date Received _____

Copy #3 FandE (Facilities and Engineering)
Signature _____ Date Received _____

Copy #4 Production Manager
Signature _____ Date Received _____

Controlled Copy #5 Production Area:
Name of Supervisor _____ Room # _____
Date Received _____

Each SOP must be stamped as controlled copy #1, #2, #3, #4, #5 and the date of issue.

7. DATA COLLECTION DOCUMENTS

Forms are an excellent vehicle to gather data on a task performed. Advantages of using Forms over Laboratory Notebooks include:

- The information required by the preparer of the form is gathered, not the information which the task performers deem to be necessary. This means no matter who performs the activity the kind of information will always be consistent. This is important to have consistency and reproducibility of the method.

- "Completeness" of information - by simple fill in the blanks all information required can be recorded with minimal effort.

- Signatures - the space for a second signature allows technicians to think their work through more carefully on what they are doing as their work will be countersigned. This allows an additional checkpoint.

The use of laboratory notebook should be discouraged as the sole recorder of information as entries are quite informal and usually incomplete. It may be useful to have a laboratory notebook to record some additional information not called for in the form. Best way to ensure "user friendly" forms is to avoid asking for detailed comments. It is more likely that a form will be completed fully by the technician if the form has:

- Simple fill in blank entries
- Checklists
- Tests to answers by circling
- Easy access to forms; for example, forms locked up in an area remote from where the technician is working is not likely to be productive.

Reminder in the actual SOP on which form to use (e.g.. use TMF 2019.2) to record data makes it easier for the technician to comply.

When the technician has completed the form, it must be reviewed for accuracy and completeness by someone who is knowledgeable about the operation. As in the case of SOPs, the original form must be of a different color stored in a locked, secure, place and copies may be filed in an appropriate location where easy access is possible.

8. MASTER BATCH PRODUCTION PROTOCOL (MBPP)

A Master Batch Production Protocol (MBPP) is an original document which provides a complete step by step instruction for the manufacturing of an intermediate or a final product. This document is not used in manufacturing but is stored in a safe place in the facility for review during an inspection. A copy of the MBPP is reproduced every time a batch of product is to be manufactured and is called the Batch Production Protocol (BPP). This copy of the BPP, when fully completed during the course of manufacturing becomes the official record of the product manufacture and is then called Batch Production Record or BPR. A record of all BPR's must be available at the facility during an inspection.

The BPP is used as a training guide to ensure all personnel involved in manufacturing understand the steps involved prior to commencing the production cycle. It must be available to all relevant personnel at all times during manufacturing and be signed and verified during the production process. A MBPP may contain several sections depending on the level and length of product processing. A general guide to a MBPP is as follows:

- Bill of Materials listing Part Numbers and providing space to record Receiving Codes or Lot Numbers of all items used during the manufacturing.

- Component preparation events such as cleaning of equipment, components, and closures and/or sterilization of equipment, component closures and relevant solutions.

- Environmental monitoring; scheduled monitoring and monitoring during critical operations.

- Formulation of Vaccine.
- Assembly and processing of raw materials to make the final product.
- In-process testing and schedule.
- Final product packaging and labeling.
- Product inspection.

In addition to providing step by step instructions for events as the process proceeds from start to finish, the Batch Protocol must also provide space to record information such as:

- component, raw material and final product accountability data. This means the quantity of material used, quantities returned to storage, quantities discarded and quantities of final product produced;
- results of in-process tests, instructions for alarm and alert in case of out of specifications (OOS) results;
- signatures of events performed at each processing step and verification signatures at every critical step;
- samples for reference materials, labels or intermediate drug substance, drug product and packaged material;
- fill-in-the blank spaces must be provided to input additional information/data not described above as the processing cycle proceeds from start to completion.

Before creating a MBPP, the beginning or ending of a manufacturing cycle must be determined. For example: with Biologicals a batch usually begins with inoculation and proceeds through to harvest and final purification. Thus, a MBPP in this case will involve al three unit operations - fermentation, harvest or primary recovery and purification.

In some cases where the fermentation broth contains very low level of product, it is common to perform several fermentation and primary recovery steps which are then followed by concentration. The concentrated material is stored at ultra cold temperatures (- 60°C or below). Five or six batches are then sent to QC for testing and if they meet the acceptance criteria, are pooled together for purification. In such an event, QC and Production may create the five or six BPP for production of the material from fermentation to the end of concentration step only and one BPP for the pooled concentrated material to the completion of final purification.

A MBPP should be at the minimum contain the following information:

1 Organization's Name

2 Product Name
3 Part Number
4 Document Number with Edition Number
5 Stamp for Confidential Information
6 Pagination
7 Yield Where Applicable
8 Space for filling in the Lot Number
9 Space for at least two additional signatures in addition to the signature of the QA person who released the BPP into production
10 Date of release of BPP into production

Items 1-6 must appear on every page. Items 7-10 on the first page only.

Points to consider with MBPP:

- A MBPP should be written as soon as all process specifics have been identified and defined. Usually, it is a good idea to perform the process at least once on a smaller scale in order to qualify the MBPP before a final version is made.

- Production and QC should write the MBPP.

- A MBPP should be written in a manner which achieves 2 objectives, it should provide a convenient, practical and efficient set of instructions for the line worker and ensure that fundamental principles of CGMP compliance are met.

- The completed BPR should be kept within QA Department and archived every year.

The language of the MBPP should be very similar to an SOP. All production employees involved with manufacturing must be trained and show evidence that they understand what is involved in the manufacturing process. Specifically:

- significance of reporting events which do not match written instructions;
- report of deviations and writing deviation report, availability of deviation form e.g.. to record equipment malfunction;
- lateness of sample removal that the outgoing technician must inform incoming technician the status of the manufacturing completed to date;
- data which looks suspicious;
- spills of any sort, etc.;
- change in SOPs;
- change of shifts;
- completion of Batch Protocol;
- importance of following the Batch Protocol.

Generally on the first page of the BPP, it is recommended to have a section where the technician can verify his/her understanding of the contents and requirements of the BPP as exemplified on the next page:

I have read and understand the content of this BPP

Technician's Signature and Date _____

Technician's Signature and Date _____

Depending on the number of technicians, the appropriate number of lines can be added. In the BPP, processing step (wherever possible) must be stated, with limits of acceptance.

For example:

Adjust the conductivity of the supernatant with WFI (P/N 2182) to 5.0 $\pm$ 0.5 mS/cm.

Information on traceability of the Batch should be included. For example:

- location or room number
- date/time entries
- identification of equipment by Tracking Number (T/N)
- sample #, size, time, method of sampling, location of storage
- calibration: pH, viscosity, conductivity
- processing parameters: temperature, pressure, vacuum, bubble point, CO_2, O_2, glucose, aliquot or other relevant metabolite, labels used, clearing tags, etc.

All this information is part of the BPP and must be recorded in the Batch Record.

Best Company in the World
BATCH PRODUCTION PROTOCOL

Date Effective:	**Batch Production Protocol for Tetracycline (Used in Culture Media only) BPP 9071.0**	**Confidential Information**
Supersedes: New		**Page 1 of 40**

Section A: Component Preparation
Product Tetracycline, USP
x units/vials

Product Part Number, 8665
Lot # _____
Theoretical yield = 20,000 vials

A1 BILL OF MATERIALS

Part #	Description	Receiving Code	Quantity Required	Quantity Received	Production Signature	QC Signature
4111	Vial, 10 ml 20 mm					
4261	Stopper, 20 mm red					
4814	Seal, 20 mm Grey					

A2 ACCOUNTABILITY

Item	A = Qty Received	B = Qty Sterilized	C = Discarded	D = Quantity Returned to Storage	% Gain/Loss
4111					
4261					
4814					

Calculation: A/(B + C + D) = % gain or loss _____/_____ = _____%
Acceptance Criteria = ± 5%
Calculated By: _____ Verified By: _____
Date: _____ Date_____

When the BPR is issued, the Lot Number of the Batch is filled in by QA. Each page of the BPP must be stamped by QA to indicate it is an official copy of the MBPP.

9. PRODUCT RECORD

The Product Record is a collection of all documents which support the production and control of a single batch of product. Typically it would include:

- Batch Production Protocol
- QC Records
- Sterilization Charts
- Move Tickets (if applicable)
- Reference Sample Storage (retain samples)
- Cleaning Documentation

- Environmental Monitoring Records
- Inspections Records
- Water Data
- Accountability Forms

When the information to make up the Product Record is all put together, Production Manager must review it for completeness and accuracy. Any variances from Batch Protocol are brought forward for discussion or investigation with QC and QA departments.

The entire package is then provided to QC to review for release or rejection with respect to analysis. QA approves the Product Record with respect to documentation.

10. MASTER FACILITY PLAN (MFP)

This is one of the most important documents in the CGMP facility. It is an overview of how the company plans to be in compliance with CGMP. The MFP is also known as a Commitment Document. It describes the company's product lines, whether it is going to operate as a multi purpose or dedicated facility, the layout of the facility with respect to material, personnel and product flow, an organigram, list of major utilities and equipment and plan to qualify the facility for GMP operations.

This document is not strictly required by GMP but provides a working policy of the commitment of the company to CGMP compliance. It is a document which brings a common objective to all departments within the facility. It is also a document an inspector likes to see prior to an inspection as it gives the inspector an impression of the company's commitment and understanding of CGMP. However, when such a document is written, it **must** be followed. The inspector who reads such a narrative will expect to find if it is being implemented fully.

Typical contents of a Master Facility Plan may be comprised of 7 major sections:

The first section is rather short. It provides the Company description, ie. whether it is involved with Biologicals, Vaccines New Chemical Entities, Generic, Ethical Pharmaceuticals, Diagnostics, etc. When and why was the company founded. Current and future product lines. Multipurpose or dedicated facility.

The second section should provide an organigram showing reporting structures and number of people in each structure. It describes the individual departments and their relative roles and responsibilities. It is important to note that QA/QC documentation departments must be separate from production and must report to the same level of hierarchy as production. In very large facilities, a task force known as Material Review Board (MRB) or Material Review Committee exists. This committee usually consists of representatives from QC, QA and the Production Department. Their function or purpose is to review complaints and critical deviations that occur during production, raw material components, finished products and environmental deviations which could affect product quality. This committee makes serious recommendations to senior management and their proposals are usually implemented. If such a MRB exists, it should also

report to the same hierarchy as Production and QA.

The third section is quite comprehensive. It describes the layout and flow of the facility. Different parts of the facility and their level of finishes are described. Thus, here one describes the individual rooms, their classification, adjacencies and features which help to assure product quality and safety. The flow in "new" facilities should be such that there is a logical (where possible) unidirectional flow from raw material to finished product to minimize the potential for mix-up and contamination. Separation of finished and in-process materials is important. So untested product must be Quarantined and never allowed to mix with approved released product or raw materials. Areas designated for locked room, cages and cabinets for storage is critical in GMP operations as is documentation of how components are documented and accounted for.

In retrofitting facilities, it may be difficult to obtain a smooth logical flow. In these situations it is important to implement procedural alternatives. Although, procedural alternatives are not ideal, they are better than no alternatives. For example, controlling access by instituting pass thru's or locking rooms, and material transfer by using sealed disinfected containers is better than "just not doing anything." In this section, attempts must be made to communicate that although design is not optimal, the company is still in control and aware of the potential source of errors and cross contamination which may result from the sub-optimal design by instituting creative procedural remedies and increase care and remedies to minimize the potential for things to go wrong.

The fourth section addresses all the major utilities and processing equipment, key specifications of these equipment, their capabilities and intended use.

The fifth section describes documents and document control. Thus for example: system of accountability, traceability, types of documents, Master Document Index, examples of copy of individual documents such as different types of Standard Operating Procedures (SOP), Validation Protocols, QA documents, Test Methods, etc. are examples of useful addition to this section.

The sixth section includes a Validation Plan. The purpose of this plan is to outline a schedule for validating the facility, utilities, equipment, processing environment, processes and personnel training. The acceptance criteria for each item should be listed, the level of validation (critical items to be extensively validated), audit of validated items, validation expiry date (revalidation) and member of validation approval and committee. The order of validation must be defined.. For example, validation of sterilizers must be completed before validation of an aseptic filling process. A mechanism to report deviations during validation which may occur must be in place.

The final section of the Facility Plan describes monitoring and control programme which would allow the organization to remain within CGMP compliance. Once the facility is built and validated it is critical that it remain in a validated state. This is achieved by QA through audits, Preventive Maintenance (PM) Programme, Calibration, Material Control, Cleaning Validation, Environmental and water monitoring, data trending and CGMP training.

11. DOCUMENTATION RELATED TO EQUIPMENT

Documenting Equipment Monitoring and Maintenance

Once the facility is validated, the validated state must be maintained so as to ensure compliance with CGMP. The regulations require routine cleaning, inspection and maintenance of equipment in a written commitment. Therefore, these records must be kept and be available for review. The basic documentation requirements in this section include:

Log of Use Maintenance and Calibration (LUMAC)

A LUMAC provides a chronological record of all equipment related activities and the status of a equipment at any given time. A LUMAC must exist for clean rooms, all utilities and major equipment used in processing. A LUMAC for a clean room will contain information on why was the room used, for how long, how and when was it cleaned, etc. A typical LUMAC book will contain the following:

Date	Client	Product Used	Activity Performed on Equipment	Performed By

The log book must be a bound book with numbered pages located very close to the equipment in question.

Work Orders for Preventive Maintenance (PM) and Calibration

Routine use of equipment creates a continuing need for replacement of worn O rings, gaskets, membranes, etc. Routine PM must be part of any compliance programme. Many facilities shut down on a yearly basis for the purposes of Preventive Maintenance. This period of time is also used for recalibration once the maintenance work is completed.

In addition to routine Preventive Maintenance, repairs can also occur during plant operations. However, precautions must be taken to minimize the frequency of emergency repairs. A typical example is the mechanical seal of a fermenter. If the vendor has recommended a change of seal at 5,000 hours, it is important to check and maintain the seal around 4,000 hours so that leak in the fermenter does not occur as a result of seal "expiry date" being too close to 5,000 hours. Proactive preventative and close visual inspection of equipment and utilities during routine cleaning can help minimize emergency repairs.

Use of work order forms are one of the most convenient ways of documenting maintenance.

A maintenance work order can look as follows:

Best Company in the World
Maintenance Work Order

Date Effective:	**FE - 001.0**	**Confidential Information**
Supersedes:	**Equipment Name**	**Page X of X**

WO # _____ Equipment /Utility_____
Name_____
Equipment Tracking # _____

Location of Equipment _____

Circle One: Emergency Routine
If Emergency, Date Needed
By_____

Is this equipment critical (circle one) Yes No
If critical, QA signature required _____

Summary of Repair or Maintenance Work

_____
_____
_____
_____
_____
_____

Performed By _____ Date _____

A log of equipment and utility Work Order must be maintained at Facilities and Engineering.

Once the work is completed and reviewed by the Maintenance Manager, one copy is entered into the Equipment History File for that equipment, second copy is maintained with Production, third copy with Facilities and Engineering and fourth with QA department.

If the equipment is listed as critical (this is easily denoted as a C following the tracking #). For example, if the equipment is a fermenter, it has a tracking # of T/N 1234 it is usually followed by a C indicating that it is critical equipment and any kind of tampering including maintenance is forbidden unless authorization is received from QA. The rationale behind such control is that

if the kind of maintenance performed may upset the validation of the equipment requiring to be revalidated; this is important for QA to know.

It is uncommon to see a Master PM checklist. This list is compiled by Facilities and Engineering, detailing the weekly, monthly and yearly PM assignments. All equipment must be identified with stickers to show PM has been performed, the next due date as is the case with calibration.

12. VALIDATION PROTOCOL

A Validation Protocol is a written plan that describes how to conduct validation and how to measure the success of validation, be it equipment, utility or a process. Validation Protocols are of three major types: IQ, OQ, PQ. Validation is only deemed complete when level of validation assigned (ie. IQ only, IQ and OQ or IQ, OQ and PQ) have been performed and all acceptable criteria have been met.

General Acceptance Criteria

Installation Qualification

Installation Qualification (IQ) shall demonstrate that the various systems and equipment conform to their purchase specifications, design drawing, vendor requirements as defined by validation project team, to the extent that prior documentation can be found in support of these systems, or shall be assembled for use in support of this project. Additions to existing systems must conform to these general acceptance criteria.

- The equipment and utilities/systems must be installed according to engineering documents and drawings. These records shall be retained in a master file of the facility documentation and drawings. The retained drawings and documentation may include but not limited to the following items:

  - Process and Utility Schematic Diagrams
  - Engineering Schematic Diagrams
  - Piping and Instrumentation Drawings
  - Equipment Specifications
  - Vendor Supplied Documentation
  - Electrical Drawings

- IQ drawings and other documentation provided by contractors during and after the construction effort. Other contractor supplied documentation shall be audited for accuracy during the IQ phase.

- All equipment: piping, wiring, and instrumentation must be clearly identified in the field and conform to the descriptions provided in the appropriate drawing or other documentation.

- All electrical and instrumentation wiring shall be completed in accordance with the design documentation and all loops must be functional.

- Where necessary, instrumentation must be calibrated using approved written procedures using standards traceable to NIST where possible.

- Piping and equipment intended to operate under pressure or vacuum must be tested and certified. ASME are required on any vessel greater that 20 L rated for an operating pressure 15 psi or greater.

- Materials of construction shall be checked for conformance against specifications.

- All protocols and required documentation for each system and piece of equipment shall be available on site and shall be circulated and approved in accordance with standard procedures.

- Change control on all equipment and systems in the facility shall be instituted from the start of IQ for each item. Any changes made subsequent to the start of the IQ must be made in accordance with change control procedure.

Operational Qualification

Operational Qualification (OQ) shall serve to demonstrate that the equipment or system functions as intended in the absence of production materials. The following criteria shall be utilized to approve the OQ of each equipment of system.

- All testing performed as part of the OQ must be completed in accordance with approved protocols and written procedures.

- All automated sequences, interlocks, alarms, timers, counters, etc. must operate repeatedly as specified in the design documentation.

- Systems and equipment must function reliably under environmental conditions approximating normal use.

- All instrumentation (indicating or recording) must be calibrated using written procedures. Calibrations shall be traceable to NIST where possible.

- Draft written standard operating procedures shall have been prepared for the operation of each system and piece of equipment. These procedures will be finalized and formally approved after completion of the PQ evaluation of each system.

- During full operation, the maximum machine noise level shall be 74dBA measured 6 feet from each machine.

Performance Qualification

The Performance Qualification (PQ) shall demonstrate that each system and piece of equipment will perform its intended function as desired resulting in components, materials, products and results that conform to their quality control specifications. Such performance shall include the documentation of parameters, measurements, conditions, etc. as specified in the design documents.

- Validation must include a challenge component.
- The critical processing steps for each system or piece of equipment shall be observed in three production scale trials. Essential data shall be reviewed and compared to the expected results.
- Critical operating parameters shall be independently measured and documented in each trial. Such measurements will be made with instruments which are traceable to NIST where possible.
- All testing performed as part of the PQ must be completed in accordance with approved protocols and written procedures.
- Key parameters for each system or piece of equipment must be maintained within the limits specified in the design documentation.
- Systems assembled from a number of individual pieces of equipment must be shown to operate successfully as an integrated whole.
- Equipment and system controls shall fulfill the functional requirements described in the design documentation.
- Components, materials and product processed by each system or piece of equipment shall conform to the appropriate in-process or finished good specifications.
- The PQ trials shall be performed using actual production materials, unless an individual protocol provides for the use of placebo or other materials.

Assay Validation

Prior to commencing individual assay validations it is important to have a Master Assay Validation Plan (MAVP). This is particularly important in a large facility where different assays or same assays are being conducted in different parts of the facility.

Typical sections of MAVP include:

Method Principles:

This section describes the general principles at work and assay sensitivity.

Method Suitability:

Describe how the assay will be used, and when appropriate, why it is preferred or superior to other methods.

Method Categorization:

Most analyzes are performed in the QC laboratory. All assays need to be qualified. But like equipment, there is a level of validation required. Thus each assay must be assessed on the impact of identity, strength, purity, safety and efficiency of the product. If the assay is unique or biological it is recommended that a full scale validation be implemented. This is especially true of biological assays which show considerable variability. On the other hand, a generally accepted method such as protein assay by Biuret or an existing compedial method, the "level" of validation may be less rigorous.

Revalidation:

Will be triggered when significant changes to reagents, vendors, instrumentation and technicians occurs.

The control of an assay is affected by the quality of raw materials used to prepare reagents. Thus, for example, it is necessary that when one uses Nanopure water or equivalent to make a reagent solution for HPLC, one does not use technical or lower grade salts. Thus, Part Number Specifications for these items must be assessed critically as the assay outcome may depend on such parameters. Additionally, the stability of prepared solutions is an important consideration as it has an impact on the success of the validation. All solutions must have an assigned expiration date.

Equipment or instruments used, their level of performance and calibration may have a profound impact on assay outcome. It is important to ensure that the equipment has been installed properly, operates reliably and is in a calibrated state prior to using it for assay validation. Finally, always start with a completely cleaned and flushed system; in the case of HPLC where a dedicated column does not exist for each product, a very rigorous regeneration and cleaning is important prior to starting assay validation. Technician training is another key to successful assay validation. The notion that "she or he only has to follow the SOP or Test Method" is irrational and should not be practiced. The principle of the assay, the outcome of the validation, schedule, buffer, sample and other requirements must be communicated and explained to the technician.

When evaluating a method the following must be considered as a minimum

- Precision:
  Measure of consistency or reproducibility. This is usually achieved by measuring the variation of a homogenous sample and determining the mean and relative standard deviation (RSD). A minimum of 6 replicates with RSD of No More Than (NMT) 2% is acceptable.

- Accuracy:
  This is used to demonstrate the ability of the assay to recover a known amount of analyte and expressed as a percentage. For samples at concentration lower than 100 ppb, recovery of 60-110% is acceptable while for more concentrated samples, recovery of 80-105% are the norm.

- Limit of Detection (LOD):
  This is the lowest concentration of a sample that can be detected by the method in question. The test article must always contain at least three times the LOD.

- Limit of Quantitation (LOQ):
  The lowest concentration of a sample that can be quantified with an acceptable degree of precision.

- Selectivity, Specificity and Interference:
  This is a measure of the assay's sensitivity to impurities, related chemical compounds and degradation products and this is usually achieved by spiking a known concentration of sample with known concentration of potential close contaminates and impurities.

- Linearity and Range:
  Linearity is usually demonstrated over a defined range of analyte concentration. The slope of a regression line and its variance provides a mathematical measure of linearity.

- Ruggedness:
  This is especially important when using a unique assay or a biological assay which can have a wide degree of variability to begin with. In face of validation provided by analysts, different instrumentation, different days, lots of reagents, etc. all contribute to ruggedness.

Each Assay Validation Protocol and Test Method should contain blanks, positive and negative controls, reagent testing (e.g.. measuring background of buffer), etc. This is called assay monitoring; performing small checks at the onset of every test ensures that the assay continues to meet the validation criteria.

Process Validation General Considerations

"Process Validation is establishing documented evidence which provides high degree of assurance that a specific process will constantly produce a product meeting its predetermined specification and quality characteristics."

What to Validate?

- All critical aseptic manipulations of a final product.
- Any product manipulation event whose failure could adversely affect the safety, efficiency or quality of the final product.
- Any process that cannot be adequately tested in the final product.

Vaccine production, in particular, requires rigorous process validation as proteins are highly susceptible to processing conditions and can degrade and/or change easily.

The reason for validation include:

- affect the quality of the product
- provide information from study which will be used to support another validation event
- scale-up exceeds ten fold
- change in components, equipment, formulation, site, etc.

The best way to qualify aseptic processing is by performing media fills. During a media fill, all equipment performs as it would during normal routine operation, except that the product which is being filled is microbiological medium. The media is designed so that is will support the growth of any bacteria or mold during processing thus demonstrating rigorously the qualification of aseptic processing.

This procedure also helps to obtain information on other part of the process operations such as, fill volume control in fillers, fill machine operation, stopping conditions, etc. Media fills are also used to evaluate container/closure integrity. To achieve this, the media filled vials are stored right side up and upside down for extended periods of time and observed for growth. This information is especially valuable when a process change has involved a change in container or closure.

The process qualification should be formatted as a Batch Protocol so that the same routine as real processing is followed. The element of challenge should be included in the Batch Protocol. For example, variables need to be evaluated in terms of upper and lower limits. The media fill should last as long as the routine processing time (ie. if 2,000 vials are normally being filled its important to media fill 2,000 vials). Some examples of challenge include sampling events, exchange of gas cartridge, etc.

14. PRODUCT QUALIFICATION

After demonstrating that a process can perform reliably and consistently, Product Qualification can start. A Product Qualification procedure usually starts with a formal Batch Protocol which describes the processing results in a step by step instruction. In addition, any unique observations or caution determined during Process Qualification can be written into the protocol. The

acceptance criteria for all processing parameters should be listed in Product Qualification Protocol. Product Qualification run should be used to finalize how to improve the flow or work. For example, approved break points could be better organized.

To complete a Product Qualification run, it is necessary to use three identical product runs using identical equipment and produce three batches of product that meet all processing parameters as well as final Product Specifications. However, Product Qualification is only regarded as complete when all three lots demonstrate good stability. These batches are usually used to support product expiration dating and labeling claims.

Choice of worse case scenario is not always at maximum load or fill. For example if one is assessing the interaction of a liquid product with its container, the smallest container often has the greater liquid to surface area ratio and as a result provides the greatest challenge to assessing change in container/closure system. Once validation cycle # 1 of 3 is complete, the document is reviewed for compliance. Deviation from failure to follow BPR must be investigated and failure identified and restored before validation cycle #2 starts. Once all three runs are complete, a Validation Certificate is issued for the process. It may be necessary at this point to review all relevant SOPs and other supporting documents to ensure that they are still valid as changes may occur to procedures during validation.

15. STANDARDS REFERENCE PREPARATIONS AND REFERENCE REAGENTS

Standards Reference Preparation and Reference Reagents must be characterized according to written procedures and stored under known conditions to preserve their integrity. In order to prove the in authenticity, complete records of all testing performed must be maintained. Documentation of reagents and test solutions and their expiry period is required. The records maintained should clearly identify the source of the material, its purity, its potency and the expiration period, as well as the person certifying the material as a standard.

WHO is keeping an updated list of International Biological Standards, International Biological Reference Preparations and International Biological Reference Reagents which is published in the reports of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series (Biological substances : International Standards and Reference Reagents, 1990, Geneva/WHO 1991). These substances are held and distributed by the following laboratories:

- International Laboratory for Biological Standards, Statens Seruminstitut, 5 Artillerivej, 2300 Copenhagen S, Denmark;
- International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts. EN6 3QG, England;
- Centers for Disease Control, Atlanta, GA 30333, USA;
- International Laboratory for Biological Standards, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Plesmanlaan 125, Amsterdam, Netherlands;

- International Laboratory for Biological Standards, Central Veterinary Laboratory, Weybridge, Surrey, England; and a few others.

16. MISCELLANEOUS RECORDS

Calibration Records

No matter which country's regulations are being followed, it is clearly stated in all GMP's that equipment and instruments used in the GMP production or testing must be calibrated, inspected, and checked according to a written procedure which is designed to assure proper performance. It is also required that a record of the work be maintained (ie. calibration records must be maintained in the equipment history file). Documentation must be prepared according to the suitability of the equipment for use. Suitability is defined as the equipment having the sensitivity or ability to measure parameters in range commensurate with the measurements to be taken and recorded.

> *For example: a thermometer used to measure temperature at 1°C intervals, should not only have 2°C markings on the scale.*

Calibration records must indicate the identity of the standard against which the equipment or instrument was measured. The standard must be traceable to a set by an Official Standard setting body such as: NBS (National Bureau of Standards) or equivalent. Certificates of such traceability should be retained in a permanent file. The time for retention of calibration data proposed by the FDA is 2 years after the expiration date of the product produced on equipment. Other agencies may have similar requirements. This information must be checked by QA prior to destroying calibration records.

Equipment Cleaning and Maintenance Records

The documentation of a cleaning programme must address as minimum:

- Assign responsibility
- Delineate schedule for cleaning
- Maintenance and sanitizing
- Identify how cleaning and sanitizing agents need to be used
- Specify how protection of equipment from contamination, after cleaning has been performed, is to be accomplished
- Direct that inspection for cleanliness, immediately prior to use, be performed

To verify that these actions have been accomplished as specified, logs are to be maintained in production for individual pieces of equipment which show for each batch processed:

- Date of Process
- Time of Usage

- Product Manufacture with the Equipment
- Lot Number of the Product Performed

This work must be independently checked by a second person in QC dated and signed. The log is documentation of the work performed. Entries must be made in chronological order.

Sanitization Record

In aseptic operations, not only must the equipment be sanitized but the facility surfaces (walls, floor and ceiling) must also be disinfected. The requirements for sanitization and documentation of such work are virtually identical to those described above for equipment.

Distribution Record

Records of distribution of vaccines must accurately reflect who received each batch of vaccines so that in the event of product recall, all units comprising the batch can be located in the market place.

Such records must contain:

- Name and strength of the vaccine
- A description of the dosage form
- The name and address of each consignee
- The date and quantity of material shipped
- Control number of the material shipped

The policy of FIFO (First in, First out) must be strictly adhered.

Returned Goods Documentation:

These records should indicate the:

- Identity (name and strength) of material returned
- Lot or Control Number
- Quantity of material returned
- Date of receipt
- Person and location from which the return is received
- Reason for return
- Appearance of goods

If the vaccine is destroyed immediately, this should be noted on the record of returned product together with the date of disposition.

Training Record

CGMP regulations require that a person be trained in a specific job and in the regulations as they relate to the job function. By having an accurate job description, one can define the training requirement. To document that the training has been received, a record for each employee should be prepared in which the person's name, job function, specific training courses or instruction received, date of such inspection, person performing the training and procedures governing the subject in which instruction was given.

Vaccine Manufacturing Audit Programme Checklist

Indicate by Y (yes), N(no), or NA (not applicable) for all observations. If necessary, comments can be written below the items or on a separate note pad.

Building Facilities

____ There is adequate lighting.
____ There is adequate ventilation.
____ There are adequate screens and controls to prevent infestation.
____ Physical separation exits for operations requiring dust collection, solvent control, and temperature and humidity controls.
____ There are adequate personnel washing, locker and toilet facilities.

Plant Space

There is adequate space provided for the placement of equipment and materials in the following areas:

____ Receiving, sampling and storage of raw materials.
____ In-process and production operations and materials.
____ Storage areas for containers, packaging materials, quarantined material, and released final product.
____ QC laboratory operations, equipment, retain samples, and records.

Equipment

____ There are no mechanical parts that come in contact with vaccine or vaccine components that will react, add to, be absorptive, or adversely affect the identity, strength, quality, or purity of the vaccine.
____ The equipment is constructed in such a manner that lubricants or coolants required for the operation of the equipment may be used without becoming incorporated into the drug product.
____ The equipment is constructed or located in such a manner as to permit necessary cleaning, adjustments and maintenance.
____ The equipment is constructed or located in such a manner as to exclude possible contamination from previous as well as current production operations.

____ The equipment is thoroughly cleaned before use and identified to indicate that it is ready for use.
____ The equipment is of suitable capacity and accuracy for use in the intended measuring, weighing, or blending operations.
____ The weighing equipment is properly calibrated.
____ Utensils and in-process containers are constructed in such a manner as to permit thorough cleaning.
____ Responsible supervisory or QA inspectors approve the equipment and areas prior to the start of production or packaging operations.
____ Responsible supervisory or QA inspectors are present while the equipment is in operation.

Responsible Individuals

____ Management supports the Quality Product Programme.
____ Management supports the *CGMP Programme*.
____ A documented *Training Programme* is utilized and kept current.

Receiving and Storage

Receiving records for raw materials or components include:

____ Name of component or material
____ Manufacturer or supplier
____ Receiving date
____ Manufacturer's lot number
____ Quantity received
____ Control or purchase number
____ A stock rotation policy is in place.
____ Proper storage conditions are used for all materials.
____ All the raw materials and components are properly labeled.
____ There is a receiving procedure that is followed and a list of personnel authorized to receive items.
____ There is an approved vendor list that is followed and a list of personnel authorized to approved vendors.
____ Raw materials and components are labeled, sampled and placed in a quarantine according to written procedures; only authorized personnel have access to the quarantine areas.
____ There are written procedures that indicate how rejected materials or components are handled.

Identification

____ Each component or raw material has a purchase order or control number that, when cross-checked to the receiving records, will identify the:
- product

- supplier
- quantity received
- purchase or control number
- date of receipt

____ QC labels are complete and affixed to each container, as appropriate.
____ There are procedures for sampling components and raw materials.
____ There are procedures for testing components and raw materials.
____ Accurate inventory records are kept for all approved components and raw materials.

Critical Production Steps

____ Each critical step in the production process is performed by a responsible individual, and checked by a second responsible individual.
____ The automatic, mechanical, or electronic equipment used in the processing is routinely checked and documented by responsible individuals.
____ There are documented records for the critical steps of selection, weighing, measuring, and addition of materials.
____ There are procedures that prevent the duplicate addition of materials.
____ There are written records of any deviation from the batch records, and of any corrective action taken.
____ There is documentation to show that adequate blending time was used, providing a uniform mixture prior to further processing.
____ There is adequate documentation to show that in-process samples were collected and tested as per batch records.
____ The determination of actual yield has been calculated and recorded on the batch records.
____ Fully competent and responsible personnel check the actual yield against the theoretical yield of each batch or lot.
____ In the event of a significant discrepancy, procedures exist that will initiate an investigation to determine the cause of the discrepancy.

Batch Investigation

____ All areas, equipment, and containers will be completely labeled at all times, to identify fully and accurately their:
- batch or lot number
- contents
- stage of processing

____ All previous identification labels have been removed.
____ The batch or lot is handled in such a manner as to prevent the cross-contamination of the material with any other material.
____ All in-process containers are labeled for use and all labels are removed prior to use.

Areas of Cross-Contamination

____ The formulation and processing areas are manned by competent, responsible, individuals who are trained in the procedures required to prevent cross contamination.
____ Weighing operations are carefully supervised and require two signatures on all weighing steps.
____ There are documented cleaning schedules for the equipment and areas used in production.
____ There is documentation to show that the cleaning of the equipment and the areas used for production are adequate to prevent cross contamination.
____ Approved cleaning compounds are used for the cleaning of all equipment used in production.
____ Procedures exist for the correct disposal of waste materials.
____ There are adequate filters to remove particles from the air.
____ Procedures exist for the maintenance and changing of all filter systems.
____ Product containers are not left open or unattended in the production areas for any length of time.

Packaging and Labeling of Final Product

____ There are documented specifications for all containers, closures, cartons, and component parts.
____ Only approved containers, closures, cartons, and components parts are used in the packaging operation.
____ The containers provide adequate protection for the product from deterioration or contamination.
____ There is adequate storage space and inventory control of all packaging materials prior to use.
____ Packaging and labeling operations are adequately controlled to assure that only those products that have met all the QC specifications and have been released will be packaged and labeled.
____ There is adequate physical separation of the packaging lines.
____ All packaged and unlabeled materials are under the control of QA inspectors and are locked in a caged area at the end of the day.
____ There is adequate physical separation of the labeling lines.
____ All labels and inserts are under control of the QA Department.
____ All label printing, counting, and reconciliation is the responsibility of the QA Department.
____ All labels and inserts are issued by the QA Department, any additional labels that are required must be requested in writing.
____ Each container is inspected by the QA inspector for appearance, lot number, and expiration date.
____ After inspection each carton or drum is sealed and a "QC Inspected" stamp placed on the carton or drum.

____ The final product has a lot or control number, that permits determination of the complete history of the product.

Warehousing

____ Finished products are stored under sanitary conditions and adhere to "First in First Out" procedures.
____ The shipping and storage areas are maintained under proper temperature and humidity conditions.
____ Stock rotation is used to prevent outdating of products to avoid product deterioration.
____ An approved rodenticide and insecticide programme is in place.
____ The warehouse area is maintained in a clean and orderly manner and is secured at all times.

Quality Control Laboratory

____ There are written specifications for raw materials used in production which include:
- sampling procedures
- sample size
- number of containers to be sampled
- identification system for samples
- tests to be performed

____ Procedures exist for the periodic retesting of materials that are subject to deterioration, or for materials that have exceeded their expiration date.
____ There are documented laboratory procedures for the release of raw materials from quarantine.
____ There are documented laboratory procedures for the release of final product from the quarantine area for packaging and labeling.
____ The laboratory is staffed with competent, responsible personnel and equipped with the appropriate instruments necessary to test raw materials, in-process samples, and final product in a scientific and accurate manner.
____ Representative samples are collected from the production operation and retained until the product is released.
____ Specifications for final product testing and release are documented; and validated protocols are on file that show the methodology is scientifically sound and accurate.
____ Documentation exist for all outside laboratory testing.
____ A calibration programme exist that checks the reliability, accuracy, and precision of laboratory instruments.
____ There are procedures for the acceptance or rejection of raw materials, in-process samples, and final product.
____ There are complete records of all laboratory tests performed, including dates and signatures of the individuals completing the assays, and the individuals who verified the assays for accuracy.
____ There are procedures for retain samples.
____ Stability studies have been performed on all products.

____ There are no errors in the laboratory records; and all test failures have been investigated and recorded.

Quality Assurance Responsibilities

____ There is proper documentation for the handling of all returned products.
____ If the material is to be destroyed, it will be documented and destroyed by two competent individuals under the supervision of the QA department.
____ A customer complaint system is in place and will be utilized to track all product complaints and to take the appropriate corrective action.
____ There is a recall procedure and documentation for all products involved in recalls.
____ A Material Review Board will review all discrepant materials and approve the corrective action to be taken.
____ All batch records and packaging and labeling records will be reviewed by Quality Assurance prior to the final release of the product for shipping.
____ There is a central file where all distribution records are maintained.
____ There is a documented CGMP and SOP training programme for all employees.

Personnel

____ All personnel are properly attired.
____ All safety equipment is used correctly.
____ There are no significant language barriers between supervisors and operators.
____ The employees are capable of reading and understanding all company documents used in the production of the products.
____ All injuries are immediately reported to the employee's supervisor.
____ Jewelry and cosmetics are worn in accordance with written company procedures.

Example of information required to prepare a report for the Release of a Final Product

1. **Product Identity**
   product number
   lot number
   manufacturing location
   date of manufacture

2. **Processing Document Availability**
   What was reviewed to support this decision

3. **Process Document Acceptability**
   document reviewed for accuracy/completeness
   processing specifications met
   environmental specifications met

4. **Product Acceptability**
   Certificate of Analysis

5. **Product Accountability**
   Units produced
   Unit to QC
   Units rejected
   Units subject to release

6. **Deviations and Investigations**
   materials
   processing
   testing
   product handling

7. **Options for Product Disposition**
   ( ) released for commercial use
   ( ) released for investigational use
   ( ) released for destruction
   ( ) rejected; used for developmental work only

Finished product can be released only if the product meets predetermined specifications and the documentation to support the production and testing of the product is accurate, complete and retrievable.

Thus, there are two products from the facility for every batch produced:

product itself
documents

Neither can be sold without the other.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 001.0 CURRENT GOOD MANUFACTURING PRACTICES	Confidential Information
Supersedes: New		Page 1 of 2

1.0 PURPOSE:

To provide a system for the complete documentation of all required records, logs, and instructions necessary for compliance with 21 CFR parts 58, 211 and 606.

2.0 SCOPE:

Applies to all written and approved systems for document compliance used in GMP.

3.0 RESPONSIBILITIES:

3.1 QA will be responsible to assure all documents are maintained according to CGMP compliance.

4.0 APPROVALS:

QA APPROVAL:	QC APPROVAL:	MANUFACTURING:
DATE:	DATE:	DATE:

5.0 PROCEDURE:

5.1 Written procedures shall exist for all production, quality control, packaging and labeling processes, that occur during the production of a controlled product.

5.2 Production batch sheets shall be written, to provide adequate instruction, indicate critical parameters, and provide documentation of the manufacturing operation.

5.3 Support documentation for cleaning, maintenance, and raw material control shall exist; they shall verify that the components and equipment used during the production operations are acceptable for use.

5.4 Quality Control (QC) records shall exist to support and document all laboratory testing of raw material, in-process material, and final product parameters.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 001.0 CURRENT GOOD MANUFACTURING PRACTICES	Confidential Information
Supersedes: New		Page 2 of 2

5.5 All trash will be disposed of in a proper manner that is in keeping with the local ordinances for trash containers and trash removal. No dumping of rejected or outdated drug products into the trash containers will be permitted.

5.6 Packaging and labeling procedures and documentation shall exist to provide accurate records of all final product released and shipped out of the facility.

6.0 FORMAT FOR DOCUMENTS:

6.1 All departmental procedures must be in the form of this example, properly titled and given an appropriately assigned procedure number, which is preceded by the department code.

6.2 The codes are as follows:

BPR	Batch Production Record	TMF	Test Method Form
QA	Quality Assurance	MC	Material Control
QC	Quality Control	S	Specification
SOP	Standard Operating Procedures	VA	Validation
TM	Test Method	CP	Client Protocol

6.3 Each procedure will be assigned a number from the Master Document Index which will be maintained by the QA Manager and will be sequential in nature.

6.4 If a revision of an existing procedure is written, it will be assigned a new revision or edition number as follows:

QA 001.0 QA 001.1

6.5 All procedures will be written and approved by two management level personnel; one of whom must be the supervisor affected by the procedure and the other QC or QA.

6.6 All procedures will follow this format and must be typewritten on a word processor. The original file copy will be maintained by Quality Assurance and signed for approval. Controlled copies will be distributed to all designated facility areas.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 002.0 GENERAL HOUSEKEEPING AND SANITATION	Confidential Information
Supersedes: New		Page X of X

1.0 PURPOSE:

To provide a system for the complete and timely cleaning and sanitizing of the packaging, labeling and shipping departments.

2.0 SCOPE:

Applies to all parts of the facility, involved in the packaging, labeling and shipping of drug product.

3.0 RESPONSIBILITIES:

It is the responsibility of QC to maintain this SOP.

4.0 APPROVALS:

ORIGINATOR:	QC APPROVAL:	QA APPROVAL:
DATE:	DATE:	DATE:

5.0 PROCEDURE:

5.1 Each individual area is responsible for the removal of all trash and debris, that results from the ordinary course of operation during normal work hours.

5.2 Each area is responsible for the routine cleanup of the equipment and the surrounding areas used during normal work hours. Also, cleaning logs will be kept current and verified daily for accuracy and completeness by the area supervisor.

5.3 An approved cleaning product list and inventory will be kept, no substitutions to this list will be made without written approval from Quality Assurance.

Best Company in The World
CONTROL FORM

Date Effective:	**CF 2024.0** **HOUSEKEEPING LOG**	**Confidential Information**
Supersedes: **New**		**Page 1 of 1**

Room: _____ Week of: _____

Day of week	Sweep by	Mop by	Sanitize by	Trash removed
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				

Comment: _____

_____

_____

_____

_____

_____

_____

Reviewed by: _____ Date: _____

Best Company in The World
QUALITY ASSURANCE

Date Effective:	QA 003.0 MASTER AND WORKING BATCH RECORDS	Confidential Information
Supersedes: New		Page 1 of 2

1.0 PURPOSE:

To provide a system for the control and use of Batch Records.

2.0 SCOPE:

Applies to all products manufactured for clients and in-house products.

3.0 PROCEDURE:

3.1 The Master Batch Production Protocol will be written and approved before a Production Batch Protocol is issued.

3.2 The MBPP will be prepared to provide specific operating instructions for the final product.

3.3 The MBPP will be approved for use and dated by a responsible individual and then independently checked, approved, and dated by a second responsible individual. Usually the Production and QA Directors are responsible for the approval of Master Batch Records.

3.4 The MBPP does not allow for typographical corrections. If a typographical error is made the MBPP must be retyped.

3.5 The MBPP is retained for a period of at least one year after distribution of the last production lot manufactured using a BPP record.

4.0 MASTER BATCH PRODUCTION RECORD INCLUDES:

4.1 The name of the product and in-process materials used in the preparation of the product, and the specifications required to obtain acceptable quality product.

4.2 A complete list of all the raw materials, designated by names or codes, that sufficiently indicate any specific quality characteristics.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 003.0 MASTER AND WORKING BATCH RECORDS	Confidential Information
Supersedes: New		Page 2 of 2

4.3 Lot number of each raw material obtained from the QC release sticker.

4.4 Statement of the weight or volume required of the primary ingredient per batch or lot, or the "calculating factor". This is used to compute the quantity of other raw material used in relationship to the units of the significant or primary ingredient.

4.5 Instructions to follow during each operating step in the production, processing, testing, and controlling of the batch.

4.5.1 Batch number
4.5.2 Date
4.5.3 Major Equipment employed
4.5.4 Key raw materials used and their lot numbers
4.5.5 Weights or measures of raw materials used in manufacturing
4.5.6 In-process tests and laboratory controls
4.5.7 The endorsement of Production QC and QC

5.0 BATCH PRODUCTION PROTOCOL:

5.1 As the need rises for the production of a particular product, the Master Batch Production Protocol is photocopied. This photocopy serves as the actual working Batch Production Protocol.

5.2 The Batch Production Protocol is retained for at least one year after the expiration date.

5.3 Each Batch Production Protocol has a lot number identifying all production and control documents relating to the history of the lot.

5.4 The Production Batch Protocol, containing all production and control records, is reviewed and approved by Production, QC and QA.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 004.0 TRAINING PROGRAMME AND DOCUMENTATION	Confidential Information
Supersedes: New		Page 1 of 2

1.0 PURPOSE:

To provide guidelines for the implementation and documentation of an internal training programme, for all employees involved in the manufacture, testing, packaging, and shipment of GMP products.

2.0 SCOPE:

Applies to all existing employees and to all future employees that are hired to work in the designated areas.

3.0 PROCEDURE:

3.1 The training programme will consist of three separate and distinct sections:

- **3.1.1** Current Good Manufacturing Practices
- **3.1.2** Current Good Manufacturing Practices for Quality Control Laboratories
- **3.1.3** Standard Operation Procedures competency

3.2 The CGMP training programme will be developed from the regulations promulgated in 21CFR parts 211.1-211.208 (USFDA).

- **3.2.1** The CGMP regulations will be explained and discussed with the employees so that a working knowledge of the regulations is understood by all of the individuals who work in Production.
- **3.2.2** Examples will be given on interpretation of the regulations and how they apply to the existing operations. Practical applications and implementation of the regulations will also be discussed.
- **3.2.3** Additional training materials, handouts, and slide presentations will also be used to increase the comprehension of the individuals.

3.3 The CGMP regulations will be explained and discussed with the employees of the QC and QA Departments so that a working knowledge of the regulations is understood by all of the individuals and how the regulations apply to the QA, QC and Production Departments.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 004.0 TRAINING PROGRAMME AND DOCUMENTATION	Confidential Information
Supersedes: New		Page 2 of 2

3.3.1 Examples will be given on interpretation of the regulations and how they apply to the existing operations. Practical application and implementation of the regulations will also be discussed.

3.3.2 Additional training materials, handouts, and slide presentations will also be used to increase the comprehension of the individuals.

3.4 The written and approved SOPs for the Production Department will serve as primary documents for the SOP training programme.

3.4.1 The SOPs which are used on a daily basis for the operation of all of the equipment and instrumentation, will also be used for the training of employees.

3.4.2 Each supervisor will be instructed in the training procedures necessary for correct and consistent training of employees in his or her respective areas.

3.5 For each different type of training programme there will be a certificate packet (training documentation sheet), which will detail the kind of training received, the date, time and signature of the trainer, and the signature of the trainee indicating that he or she has understood the training received.

3.6 The Training Documentation Sheet will be filed by the Personnel Department in the training programme file for each individual.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 005.0 TRAINING PROGRAMME FOR THE PRODUCTION FACILITY	Confidential Information
Supersedes: New		Page 1 of 2

1.0 PURPOSE:

To provide the guidelines and format for the systematic and documented training of all employees in the Production, QA and QC Departments.

2.0 SCOPE:

Applies to all new employees and existing employees who are learning new methodologies or the operation of new equipment.

3.0 PROCEDURE:

3.1 The supervisor will provide the new employee with the current copy of the SOPs and adequate time to carefully read all of the appropriate documents.

3.2 Upon completion of the reading assignment, the supervisor will review the SOP documents with the employee and answer any questions the employee has concerning the documents.

3.3 The supervisor next will demonstrate the required procedures for the employee and will watch and guide the employee through the procedure. The employee will then repeat the procedure without any help, but under supervision from the supervisor.

3.4 When the employee has demonstrated to the supervisor a verbal and functional knowledge of the procedure, then and only then will the employee be permitted to perform the procedure without supervision.

3.5 The supervisor will randomly check the quality and accuracy of the employee's work and will provide constructive criticism or praise, as appropriate.

3.6 When the supervisor is satisfied with the employee's knowledge and proficiency, he or she will sign off on the Training Documentation Sheet to show that both the employee and the supervisor agrees that the training provided has been mastered by the employee.

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QUALITY ASSURANCE

Date Effective:	QA 005.0 TRAINING PROGRAMME FOR THE PRODUCTION FACILITY	Confidential Information
Supersedes: New		Page 2 of 2

3.7 The Training Documentation Sheet, includes all of the procedures and duties performed by the operators in the Production Facility.

3.8 The Training Documentation Sheet lists the procedure or duty by group, or specific function, and provides a place for the signature and date of the employee and the signature and date of the supervisor.

3.9 The Training Documentation Sheet is kept in the Personnel Office and a copy is kept by the Production Director. The form is kept up-to-date at all times.

Best Company in the World
Quality Assurance

CGMP Training Documentation Sheet

Area of Assignment

_____

Employee Name _____ Date Started _____

Job Title _____ Supervisor _____

Area or Assignment

	Initials/Date Employee	Initials/Date Supervisor
	_____	_____
	_____	_____
	_____	_____
	_____	_____
	_____	_____

1. As indicated by my initials, I have read and understood the CGMP documents, that are relevant to this area or assignment.

2. I have demonstrated to the satisfaction of my supervisor that I am competent and knowledgeable of the CGMP responsibilities described above and can perform them without supervision in a manner consistent with CGMP regulations and company policy.

Signature _____ Date _____

Supervisor Signature _____ Date _____

Best Company in the World
Quality Assurance

SOP Training Documentation Sheet

Area of Assignment

_____

Employee Name _____ Date Started _____

Job Title _____ Supervisor _____

Area or Assignment

	Initials/Date Employee	Initials/Date Supervisor
	_____	_____
	_____	_____
	_____	_____
	_____	_____
	_____	_____

1. As indicated by my initials, I have read and understood the CGMP documents, that are relevant to this area or assignment.

2. I have demonstrated to the satisfaction of my supervisor that I am competent and knowledgeable of the CGMP responsibilities described above and can perform them without supervision in a manner consistent with CGMP regulations and company policy.

Signature _____ Date _____

Supervisor Signature _____ Date _____

Best Company in the World
Quality Assurance

CGMP Training Documentation Sheet for Quality Control

Subject

_____

Employee Name _____ Date Started _____

Job Title _____ Supervisor _____

Area or Assignment

Initials/Date Employee	Initials/Date Supervisor
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

1. As indicated by my initials, I have read and understood the CGMP documents, that are relevant to this area or assignment.

2. I have demonstrated to the satisfaction of my supervisor that I am competent and knowledgeable of the CGMP responsibilities described above and can perform them without supervision in a manner consistent with CGMP regulations and company policy.

Signature _____ Date _____

Supervisor Signature _____ Date _____

SECTION V

UTILITY SYSTEMS FOR THE VACCINE PRODUCTION

Process Utility Systems have to be designed to satisfy the requirements of the facility and are based on the operational philosophy of the company, ie. single shift, double shift or 24 hour shift. The capacity requirements of the various utility processes and process equipment are estimated by using existing in-house data, data from vendors and allowing for expansion in the future. This chapter discusses some general considerations for design of Utility Systems. The most typical utilities encountered in vaccine production facilities include:

- High Purity Water - (WFI, Purified, Deionized Water)
- Clean Steam
- Process Air
- Clean-In-Place (CIP)
- Product Contact Steam
- Product Contact Water
- Product Contact Air
- Product Contact Cleaning Solutions

1. PHARMACEUTICAL WATER SYSTEMS

Water is the most difficult component to maintain to the standard requirements. This is especially true as higher quality water is required. In addition, it is almost one of the most expensive components to maintain. Thus it is important to identify the quality of water for each part of the process so as not to use, for example, WFI for media preparation in vaccine fermentation where cells have to be subsequently broken to isolate and purify antigen.

Purified water (at least USP grade) must contain no added substances and therefore microbiological control of this water is difficult unless it is handled as WFI, which is very expensive. Purified water should be limited in use whenever possible. Purified water is usually used during fermentation and primary recovery steps and as a final rinse when cleaning fermentation and primary recovery equipment.

1.1 DESIGN APPROACHES

- Analyse Feed Water Quality
- Establish Product Water Quality Requirements
- Apply Appropriate Unit Operations to Achieve the Desired Results
- Incorporate Good Design Practices for Storage and Distribution
- Design for Ease of Validation

1.2 FEED WATER QUALITY

3 Major areas where feed water is obtained from :

Municipal Water — Potable Quality

Well Water — No Seasonal Variation
- High Hardness
- High Bicarbonate Alkalinity
- High Silica
- High Iron
- Free of High Molecular Weight Organics

Lake and River Water — Seasonal Variation
- High Turbidity
- High Silica
- High Molecular Weight Organics

(Low Molecular Weight Organics can be present in all types of water)

Water System Components

- Feedwater Pretreatment
- Production
- Storage and Distribution
- Cooling for Use

Carbon Adsorption

- Removes chlorine and low molecular weight organics
- Should be heat sanitizable

1.3 PRODUCT WATER SPECIFICATION

	Purified Water	WFI
pH	5-7	5-7
TDS	< 10 ppm	< 10 ppm
Resistivity	< 3 MegOhms	< 1 Meg Ohm
Heavy Metals	< 0.1 ppm	< 0.1 ppm
Bacteria	< 100 cfu/ml	0.1 cfu/ml
Pyrogens	Not Applicable	<0.25 EU/ml

Purified Water (USP) can be generated by either dual bed ion exchange or reverse osmosis.

Reverse Osmosis (R.O.) is the most common method. There are several types of Reverse Osmosis membranes:

- Cellulose Acetate
- Cellulose Triacetate
- Polyamide Thin Film Composites
- Polysulfone

Polysulfone membranes are gaining wide acceptance in industry due to their ability to resist a variety of cleaning agents and strength.

1.4 MICROBIAL CONTROL IN PRETREATMENT

Multimedia Filters	Backwash Raw water chlorination
Carbon Filters	Backwash Sanitation
Ion Exchange	Frequent regeneration Continuous flow
Reverse Osmosis	Chemical sanitation Continuous flow
Ultraviolet Lamps	Used in recirculating loops Limited sanitizing capacity

1.5 WATER FOR INJECTION (WFI) GENERATION SYSTEMS

- Single Effect Stills
- Multiple Effect Evaporation (usually 3 are sufficient)
- Vapour Compression Stills
- Reverse Osmosis

1.6 STORAGE AND DISTRIBUTION SYSTEM MATERIALS

Distribution System Materials:

Deionized Water(DI)	-	Unpigmented Polypropylene
		- PVDF
		- Stainless steel

Storage Vessel Requirements:

Water for Injection (WFI) usually stored in electropolished stainless steel vessels. Other requirements for storage vessels include:

- Stainless steel vessel rated for minimum 15 psig and full vacuum
- Non-rusting 316 L stainless steel with internal finish of Grade No. 4.
- Sterilizing vent filter
- Flanges and nozzles are to be sanitary type
- All parts are to be sterilizable

'6D Rule'

The system shall be constructed with no dead legs greater than six pipes diameters, measured from the point of connection to the adjoining flow conduit.

2. PROCESS COMPRESSED AIR

Compressed air that directly contacts the product or directly contacts material that come into product contact.

Design Criteria

Item	Process
Temperature	Less than 100°F
Dew Point	Less than -40°F (100 psig)
Hydrocarbons	Less than 1 ppm
Particles	99.9% removal @ 1 micron

Process Air System Components

- 'Oil Free' Compressor
- Receiver
- Filtration
- Air Dryer
- Distribution Piping System

Generally, air is supplied through a filtration and compressor unit which draws in atmospheric air and compresses it to approximately 12% of its volume. This air will contain oils, carbon, yeast, bacteria, dust and water vapour. At some point this air will be in contact with the product during the manufacturing process.

The standard for the quality of air required is:

Hydrocarbon, NMT (Not More Than) 1 ppm
Particles, NMT 100/m^3 of 5μ or larger
Moisture < 1.0 %

- Compressed Air Systems must be well designed from compressors through to points-of-use.
- There must be a well engineered compressor room with back up compressor.
- All pipework must be correctly sized to slopes and be drainable.
- There must be a simple well laid out distribution pipework.
- A complete system which can be cleaned, tested and documented.

Types of Compressed Air

- Process Air - free of particles and oil free suitable for product contact after terminal filtration.
- Plant Air - particle free, dry and suitable for pneumatic equipment.
- Breathing Air - as process air but HEPA filtered.
- Instrument Air - as breathing air.

3. CLEAN STEAM PIPING

3.1 CLEAN STEAM APPLICATIONS

- Autoclave operations
- Lyophilizer sterilization
- Humidification for HVAC systems
- Equipment sterilization
- Conventional stainless steel piping (schedule 10, 304L, 316L)
- Sanitary tubing not required
- Butt welded joints
- Pitched to drain with adequate steam traps
- Sample cooler to test quality

3.2 CLEAN STEAM CGMP REQUIREMENTS

Proposed LVP GMP requirements CFC-21 Sections (FDA Regulations) 212.227

- Free of boiler activities.
- Free of volatile amines or hydrazine.
- Steam, if considered, should meet WFI specification for constituents such as pyrogens, bacteria and dissolved solids.

4. CIP - CLEAN IN PLACE

A Technique for Cleaning Process Systems and Equipment Without Dismantling.

Cleaning is mandated by CGMP 21 CFR 211.67

" equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements."

CIP Advantages

- Reproducible cleaning
- Cleaning monitoring and documentation
- Use of aggressive cleaning conditions
- No equipment damage due to disassembly
- No potential recontamination during assembly
- Increased equipment availability
- Labour savings
- Personnel safety
- Validation

CIP System Components

- CIP Unit
- Circuit
- Supply Line
- Return Line

Objectives of Automated CIP Systems

- Eliminate human error
- Eliminate accidental contamination
- Improve personnel safety
- Improve productivity
- Automated documentation
- Validation
- Cost reduction

CIP System Design Steps

- Identify equipment and systems to be cleaned.

- Establish level of cleanliness - Define how clean is clean?
- Investigate cleaning compounds.
- Develop cleaning compounds.
- Design equipment to facilitate cleaning.
- Arrange equipment to facilitate cleaning.
- Design piping to facilitate cleaning.
- Design CIP fluid circulation system.

Typical CIP Cleaning Approach

CLEANING STEP	FUNCTIONAL DESCRIPTION
Pre-Rinse	Remove residual process fluids and reduces the "soil' load
Alkaline Wash	Solubilizes proteins that remained on equipment surfaces
Rinse	Flushes out traces of the alkaline wash
Acid Wash	Solubilize remaining dirt and to neutralize residual alkaline
Final Rinse	Remove residual traces of alkaline and acid washes

SECTION VI

PROCUREMENT

Procurement is defined as the action of obtaining materials or equipment to meet with standards set out for pharmaceutical production or usage.

1. SPECIFICATIONS

1.1 STANDARDS

- International Pharmacopoeia (IP)
- British Pharmacopoeia (BP)
- European Pharmacopoeia (EP)
- United States Pharmacopoeia (USP)
- ISO 9000
- DIN
- American Society for Testing and Materials (ASTM)
- American Society of Mechanical Engineers (ASME)
- Canadian Standards Association (CSA), etc.

1.2 GOVERNING AGENCIES

- World Health Organization (WHO)
- Food and Drug Administration (FDA)
- Local Governing Agencies, etc.

1.3 PROCESS OF PROCUREMENT

Written specifications which are drawn up to determine what is it that needs to be purchased. The specification should be inclusive and clear with no ambiguity. The following examples are of two completely different items your company may order. A procurement system for both items is described below:

(these illustrative examples are used for demonstration purposes only)

Example #1 - Purchase of Bottled Water for Injection (WFI)

Many organizations are not able to maintain WFI Systems due to expense and lack of expertise. It is not uncommon to purchase WFI for fill and finish involving very small amounts of WFI.

For example, Injectable 1 ml vials may be more cost effective if bottled WFI is used. If one is purchasing bottled WFI, the procurement specifications may be:

- 5,000 units at 0.5 litre per bottle;
- containers to comply with Type I glass container;
- product to comply with USP XXIII Water for Injection;
- produced under CGMP of the country;
- produced in an accredited facility inspected by such as FDA (USA), HPB (Canada) agencies;
- product to be sterile filled and packed in accordance with USP XXIII, unless otherwise specified;
- labelling to comply with USP XXIII specifications.

Example #2 - Purchase of Pure Steam Generator

This is an example of a purchase of a utility system. The specifications can be drawn up as follows:

- 400 kg/hr at 60 psig, condensate to meet USP specifications for WFI water.

- ASME Section VIII Division I Specifications for pressure vessels.

- CRN approved (Canadian Registration Number) for pressure vessels. This means that the vessel is to be made in such a manner so that it could be CRN approved. The purpose of asking for CRN is to communicate to the vendor the importance of quality. Each country has its own standards. In Canada we have CRN Number while in US it will be a National Board Number. By communicating this information you have set a specification and the vendor is therefore obliged to meet it if it wants the business.

- CSA approved (Canadian Standards Association) for all electrical and electronic components. The rationale here it is to state that the wiring should be of a certain quality. In the US it will be UL approved where UL= Underwriters Laboratory. Defining such specifications forces the vendor to ensure that quality wiring is used for electrical materials.

- All stainless steel to meet ASTM Specifications for either 304L or 316L (for all wetted parts).

- Surface finish shall be average 15 to 20 Ra (Ra= Roughness average) and be treated by electro polishing. Ra is a measure of smoothness. Lower the number, smoother the surface. If you do not specify, it may arrive as a mill finish and will not be as easily cleanable.

- Welding procedures and documentation to comply with ASME Section IX for gas tungsten arc welding (GTAW) procedures. This gives a specification for welding which is recognized around the world.

- Testing procedures and documentation to comply with ASME Section V. This section specifies the method for testing, which again is universal, forcing a manufacturing standard, the vendor must comply with.

2. VENDOR QUALIFICATIONS

By rendering tight, specific and clear specifications one is conveying to the vendor that the purchaser knows the meaning of quality, how to assign quality and where quality can be obtained. This may help put vendors in a position of perhaps not sending a product different in quality from what the purchaser had specified. Remember it is the purchaser's prerogative to specify and insist on the item the way the purchaser requires it to be and not the way the vendor wants to sell it.

2.1 Why is it Necessary to Qualify Vendors?

- To ensure that you are dealing with reputable companies which are and can be in compliance with the standards that your company desires and requires to be able to market your products where you want.

- To increase your comfort level that these companies have the professional and technical expertise to deliver the required products in a timely fashion to your facility; that they understand the needs of your company and appreciate the tight specifications a pharmaceutical company operates under.

2.2 Which Vendors to Qualify

Qualifications should be conducted on all companies you intend to do business with. Thus in the case of WFI system there could be many vendors. For example, some providing membranes, others providing piping and yet another providing tanks. This means one could be dealing with:

a. contractors and/or equipment suppliers;
b. material and product supply companies;
c. testing facilities;
d. shipping and freight companies.

2.3 What to Investigate When Choosing Vendors

Expertise in the field:

- Does the company have properly trained personnel on staff, professional (Ph.D, Engineers, etc.) and technical staff with appropriate supporting certifications?

- What standards does the company comply with in terms of CGMP's

Proven track record in the field:

- If time and money are the usual critical factors, it is always better to deal with well established companies in the field. Some smaller companies may give you a better price but may not be able to supply in time or may have cash flow problems.

References of recent sales or completed projects:

- If it is necessary to deal with new companies you have never worked with before ask for their listing of recent customers, call their customers to check for their experience. It may cost a little but you can learn a lot from their experience.

- Any company that is unwilling to supply a listing should be removed from your qualified vendors list as suspect regarding its ability to do business in a professional manner.

Financial investigations to ascertain the viability of the companies long term operations

- If you are contemplating a long term supply contract or about to invest in the manufacture of equipment where you will be required a substantial capital investment in advance of shipment of the goods.

Example #1 - With respect to Purchase of Water for Injection System; items to look for in vendor qualifications include criteria such as:

- Level of manufacturing experience in the field. How many litres have they produced? What is the success record?
- Documentation programmes, in-house QA and QC.
- Testing practices to USP XXIII or BP, etc.
- FDA or equivalent approved facilities (last inspection report).
- QA inspection of the vendor site is the ideal way to audit, however, this is not always possible.

Example #2 - Purchase of a Pure Steam Generator

- Engineering experience in the field of pharmaceutical equipment manufacturing.
- Documentation; QA/QC system in place (welding documentation).
- Approved coded shop (following ASME, DIN or ISO 9000 standards).
- Testing programmes (video scope of welds, x-ray and hydrostatic testing).
- Electro polishing capabilities.
- Inspection of the fabrication site (as noted before, may not be possible, but if you are using a local shop, it will be well worth the effort).

3. PURCHASING AGREEMENTS

In an ideal world one would pay for materials upon receipt of the products as they would arrive at your manufacturing facility, but this is seldom the case. Therefore purchasing agreements must be negotiated with the various suppliers. At this stage your company can either be in a position to take advantage of impending purchases, due to the scale of capital value or be at a disadvantage if the value is low and location may be remote. In any of these cases it is imperative that you have specified the product fully before negotiations start because these negotiations maybe out of your direct control since discussions may be taken over by purchasing departments or purchasing agencies such as World Bank.

In the case of our example #2 (the Clean Steam Generator), you will have investigated all the suitable units available on the market during your vendor qualification phase and have most likely decided on which unit you would prefer to purchase. In drawing up your specifications, you would be advised to use the vendors own specifications along with your own modifications to attempt to ensure when you present your request to purchase that you will most likely receive that product. If your company is building a large project as in the case of the steam generator or contracting for a long term stable supply of WFI over several years, you may have a greater advantage in writing the purchasing agreement and may be able to put the conditions your company needs.

For example:

We built a $15,000,000.00 manufacturing facility and had a secured source of funding for the entire project which the Provincial Government paid for. Suppliers and contractors were aware of the grant we had received from the Government. To the suppliers and vendors this was a golden opportunity to make real money that was guaranteed, as they knew we were serious and the project was going ahead. We used this to our advantage to dictate the terms of agreement for purchase and were very successful with most companies.

What to Expect from a Vendor during Price Negotiation

Example #1 - Purchase of Water for Injection

- Payments will be Freight on Board (FOB) to the suppliers warehouse.
- Payment is usually net 30 days upon receipt of the materials (provided you are an established client with adequate financing). If not, 100% payment before shipment of materials is likely. Try to hold back 25% until goods are checked and approved by QA, if possible.
- Long term contracts could be established to have a continuous monthly supply and monthly billing to reduce the initial total out lay of funds (this may also be an advantage for expiration dates if applicable).

- Remember, if shipping is your responsibility, you must contract a carrier that has passed the vendor qualification to ensure that they are reliable, have the proper storage facilities etc.

Example #2 - Purchase of a Pure Steam Generator

- Again if you are a large purchaser you will have advantages in the purchasing agreement as discussed before.
- Usually 20% payment on signing the contract.
- 20% payment on approvals of all drawings and specifications.
- 40% upon receipt of the equipment.
- 20% hold back, for QC inspection of equipment, documentation before release of funds

4. QUALITY CONTROL and QUALITY ASSURANCE

Your company must have an established set of procedures usually in the form of (SOPs) for receiving all incoming materials and equipment to your facility. Equipment must be "quarantined" and released as per approved SOPs.

All documentation must be inspected, reviewed by the appropriate groups, and approved as received in the specified conditions of the original purchase order.

Testing of materials will be conducted on the Lot Numbers of materials supplied to meet with the specifications your company has decided to set for the materials. (ie. for WFI was to specification of USP XXIII).

Example #1 - WFI Water

- container inspection
- label inspection
- Lot Numbers inspection
- testing (water supplied must meet USP XXIII)
- documentation from supplier as to Lot Number testing

Example #2 - Pure Steam Generator

Equipment inspection (have all the parts specified been delivered)

Documentation

- drawings
- ASME approvals or equivalent
- CSA approvals or equivalent
- CRN number approvals or equivalent
- welding documentation
- Materials Test Reports (for the steel used in the construction)
- all pertinent testing data
- manuals - operation, maintenance and spare parts
- installation and operational qualification documents (IQ, OQ)
- spare parts (supplied as ordered), etc.

SECTION VII

ROLES, RESPONSIBILITIES, AUTHORITY AND ACCOUNTABILITY OF PERSONNEL WORKING IN GMP ENVIRONMENT

An example of an organigram of a typical vaccine production facility is shown on the next page. It must be emphasized that there are several ways to organize personnel. Different company culture and philosophy may dictate the different organizational structure.

Each department has a key role to play in terms of GMP. The roles, responsibilities, authority and accountability of each department is described below. These are general and by no means all inclusive or the only descriptions. As mentioned earlier, roles and responsibilities may vary depending on the culture of the company. Therefore, the rest of this chapter should be viewed as a guide.

1. DEPARTMENT OF RESEARCH AND DEVELOPMENT (R & D)

R & D Department has several roles to play:

- It can trouble shoot problems in production, analytical or QC test. For example if a test reproducibility is a problem in QC Department, personnel from R & D Department who had developed the test can be an excellent resource to help QC with technology transfer, set-up, trouble shooting and assisting in validation.

- Must keep excellent records during product development cycle with the help of QA for inspection purposes of new product. Inspectors like to see R & D data from research to the final production process and review how the product and methods were developed and the scientific rationale behind such issues.

- Work with Production Department to implement technology transfer of the process and scale up issues.

- Work with Production and QC Department to check specification of materials used in GMP production set-up, approved break points in the production process, and help in the write-up of the Batch Protocol.

- Train Production and QC staff to run the production process.

- Be aware of choices of process and materials used in R & D as it may affect production and QC downstream when the process moves from R & D to manufacturing

2. DEPARTMENT OF PRODUCTION

The major functions of the Production Department are to manufacture, formulate, fill, package and label final product under the following constraints of CGMP:

- must be performed by trained personnel;
- using equipment and personnel who are validated;
- operating variables must be controlled within acceptable limits;
- all events must be fully documented;
- any deviations or variances must be investigated and reported.

In order to achieve a successful run in the Production Department, QC and Production must work hand in hand. Together they must assure control of all processing operating variables so that the final product is produced by a controlled process which meets strict specifications.

- Environmental variables such as dust, microbial contaminants, air pressure, temperature, humidity may affect the "fitness for use" or quality of the final product and must therefore be strictly controlled. Usually QC monitors the conditions, but production is responsible for maintaining the quality of the environment with the help of Facilities and Engineering Department.

- Production Department is also responsible for accountability which indirectly controls the process. Thus, the number of components or weight of raw materials for each step must be accounted for as this ensures that there is no quality problem. Traceability practices ensure that the testing, approval, use and effectiveness or suitability of specific critical components can be documented.

- Production Department controls processing by following established SOPs and then documenting that these procedures have been followed routinely. Always, a Batch Record must accompany a processing event. Verifying signatures at critical steps are compulsory and any deviation from this requirement is a violation of GMP. Deviations must be addressed with QC and QA, unilateral decision by production should not be allowed.

There are several variables which must be controlled during manufacture of a product, these include but are not limited to and fall under the auspices of production.

- Quantity of materials - ie. lot size. The lot size is determined by validation. The upper and lower limit should not be surpassed. For example, if the operating volume of the fermenter is set at 900L $\pm$ 50L for a 1500L name plate fermenter, the volume should not exceed 950L even though the fermenter has the capability to go to 1,100L of operating volume.

- Time limits for processing should be set within acceptable limits. If an ultrafiltration step takes 3 hours to complete, and ends up taking 5 hours the reason for this must be investigated.

- Limits should be established for the number of processing events. For example: *"concentrated supernatants from up to 4 batches may be loaded into the DEAE Flow column."* This means no more than 4 batches as the process is validated to 4 batches and not more.

- Time limits for storage. If a process intermediate is given an expiration date, it must be processed before its expiration date.

3. DEPARTMENT FOR QUALITY ASSURANCE

Key function of the QA Department are:

- Documentation
- Compliance Auditing
- Validation
- External Inspection
- Training

CGMP training is required by regulations.

Depending on the job description of the person, it can include one, some or all of the following:

- Principles of GMP
- General facility training
- Department specific training
- Task specific training

A successful training programme should include a combination of in-class study and on the job training.

GMP training programme should be scheduled periodically throughout the year and must be documented. Generally, several shorter training sessions spread throughout the year are the best and most cost effective way to train. Training should be customized. For example, only employees required to work in contained areas should be trained in containment. Training of purchasing personnel in such areas is not warranted. Training personnel for task specific duties is not sufficient. There must be a thorough understanding of product similarities, product hazards and product characteristics.

An employee in a GMP facility is an integral part of the QA requirement. The employee must have the proper education and experience to perform the duties required by the job description. The employee must not contribute to product contamination or be contaminated by the product. All new employees must pass a health and physical. These physicals should be updated yearly and include blood tests to detect toxins or infectious agents present in the work place.

An example of general training programme may include:

Facility and Product Overview:

This section could include a review of the layout of the facility, flow of materials and personnel, controlled area access, products, production schedules and departmental organization.

CGMPs:

This section should include a review of the appropriate regulations especially those pertinent to the employee's job description and how the employee can affect quality.

Documentation:

This section should review the proper use of forms, log books, SOPs, Batch Records, the company policy of crossing out mistakes, use of black pens, copy of documents, etc.

Material Handling:

This section must include requirements for controlled movement and use of material throughout the facility, safety precautions and use of MSDS sheets.

Contamination Control:

In this section, the trainer may review safe handling of toxin and infectious agents. Identify hazardous agents in the facility and demonstrate proper handling, safety and clean-up procedures. It should demonstrate the proper use of safety clothing and equipment.

Aseptic Techniques:

This section must include, at a minimum, the basic principles of aseptic technique, such as proper use of biohazard laminar flow hoods, clean room gowning, etiquette in clean rooms, use of aseptic equipment, etc.

4. DEPARTMENT OF QUALITY CONTROL

Material Control

This can be a separate department known as Material Handling Department, if the organization is very big. However, this function is a QC function and must evolve as a QC function which is then transferred into a Material Handling Department which can be regarded as a sub department of QC. The function of Material Handling is to control the receipt of raw materials, chemicals, components, closures and other items involved in GMP manufacture. Further, it controls the movement, storage and distribution of raw material, intermediate and final product within the facility. There must be areas within Material Handling Department to ensure adequate and appropriate space for:

- Quarantine of raw materials, components, closures and labels;
- Release/approve components, raw materials and labels;
- Rejected raw materials, components, closures and labels;
- Quarantine of final product;
- Release of final product.

All materials coming into the facility must be accounted for and there must be a complete traceability system in place (e.g. use of move tickets). Materials must be stored in a manner to accommodate FIFO (First In/First Out).

Microbial Monitoring and Testing

This is required in several areas by monitoring and testing:

- Purified water and condensate at every point of use
- Process air
- Environmental - particulate and bioburden
- Personnel - cleanliness, contaminants
- Surfaces - cleanliness, bioburden and particulates
- Equipment - cleanliness
- Incoming materials, raw materials containers and closures

Master Cell Bank/Working Cell Bank (MCB/WCB)

Involves preparation and maintenance of Cell Banks so that they are contaminant free. Viability and ability to produce products must be tested every six months to ensure use of healthy culture when preparing an inoculum.

Testing Intermediates and Final Product for Endotoxin, Sterility, and General Safety

Physical and chemical testing may include:

- Identity, testing, inspection and characterization of all incoming items to be used in GMP
- Lot Release
- Reference Standards - production and maintenance
- Assay Validation
- Stability testing - during clinical production and following field use to support expiration date claims

Validation

To provide support for testing during validation. For example, sterility testing during PQ of Fermentation Validation, USP criteria for High Purity Water Testing, Environmental monitoring for PQ of clean room, etc.

Other Duties

Establish a particular library of known contaminants. For example, known slides of pathology studies of vaccine potency are useful to compare as references in the future for trouble shooting. In addition, during production retained samples are taken and these must be maintained appropriately. Appropriate calibration standards for laboratory instrumentation is also a QC function. The actual calibration is generally a Facilities and Engineering function but appropriate use of standards, their quality, expiration date, etc. fall under the auspices of QC.

5. DEPARTMENT OF FACILITIES AND ENGINEERING

The primary function of Facilities and Engineering is to provide support to the Production, QC and QA Departments.

It must keep the facility, utility and equipment running reliably and consistently with a minimum of downtime, in a manner in which the identity, strength, purity, performance, safety or effectiveness of the vaccine is not compromised and it will not adversely affect the critical operating parameters of the equipment.

The key functions (not all inclusive) of this department are to:

- Maintain the facility, equipment and utilities in a validated state. This means that there must be written procedures which are followed for equipment operation, cleaning, calibration, preventative maintenance and written procedures to document the same.

- Perform all equipment and utility system operations as well as repair/maintenance activities. There must be approved written operating procedures for new equipment installation, routine and emergency maintenance, start-up operation, monitoring, checking of the facility, utility and equipment.

- Documentation Requirements for Facilities and Engineering Department include:
  - Catalogues
  - IQ and OQ files
  - P & ID's and as builds
  - Company SOPs
  - Equipment history files which contain calibration repair and maintenance
  - Equipment inventory for all spare parts

- This department must have working space for spare parts and storage of tools.

- All personnel working in Facilities and Engineering department must be trained in CGMP and be proficient in trouble shooting of equipment, assigned responsibility for major equipment and then cross train for back-up.

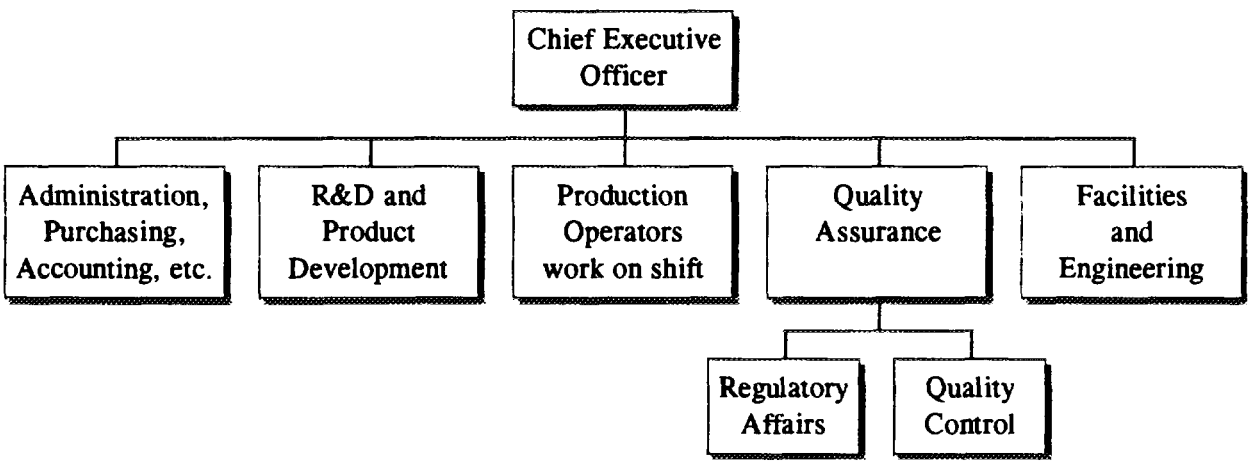
- Facility upkeep functions such as clean and orderly organization of non-essential and essential equipment, providing a pest free environment, routine inspections to check for cracks, peeling paint, roof leaks, changing filters, maintaining pressurization, disposal of general "refuse."

- Maintaining the alarm systems for unauthorized entry, emergency procedures such as equipment failure, power outages, fire, earthquake, etc.

- An emergency response manual must be created by Facilities and Engineering Department. All personnel must be trained in the event of an emergency.

- Facilities and Engineering personnel must work hand in hand with QC to review results of environmental and water monitoring so as to service areas falling within alert limits, with QA to ensure all equipment, utilities and facilities, remain in a validated state and with Production Department to ensure that all equipment is functionally as per specifications.

ORGANIZATIONAL CHART



PART III

FACILITY DESIGN WORKSHOP MATERIALS

FACILITY DESIGN WORKSHOP

One of the most important parts of the workshop was the facility design workshop which comprises four modules. The participants could, based on their professional experience, voluntarily join any of the following modules:

Group A: Project design for a production plant for 10 million doses of DPT vaccine

Group B: Project design for a production plant for 100 million doses of DPT vaccine

Group C: Project design for a production plant for 10 million doses of Oral Polio vaccine

Group D: Project design for a production plant for 100 million doses of Oral Polio vaccine

The groups have chosen their group leaders. The task, with the assistance of the faculties, was to prepare a project document, technically as detailed as possible, on the above-mentioned facilities.

A simple criterion for the facility design workshop was to prepare the project design in compliance with the GMP. The workshop introduction was made on the third day and the work started in the afternoon during the site visits. The groups continued their job after the training workshop hours, in the evening, sometimes very late as well as in the very early mornings. All participants showed great enthusiasm and competitive spirit. Points for technical clarification were discussed during the breaks of the training workshop.

The facility design workshop presentations were held on the last day and the presentations in their current forms were submitted for this publication shortly after the training workshop finished. The submissions were not changed, an attempt was, however, made to present them in a more standardized way in order to have a better comparative value for the audience of this publication.

IVI/UNIDO/BIO FARMA Training Workshop on QA/GMP/QC
for Vaccine Manufacture in Developing Countries
Bandung, Indonesia, 8-15 July 1996

PROJECT DESIGN

PRODUCTION PLANT FOR 10 MILLION DOSES OF DPT VACCINE

GROUP A REPORT

Group Leader	:	Dr. L.R. Sood
Members	:	Dr. Mai Nguyet Thu Hong
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Executive Summary

This report describes the preliminary design of a DPT (Diphtheria, Pertussis, and Tetanus) vaccine manufacturing plant of 10 million doses annual output and with the expansion capacity to 20 million doses per year. The plant includes two fermentation facilities, and a bulk mixing facility. One of the fermentation facilities is designed for campaign manufacturing of Diphtheria Toxoid and Pertussis vaccine, and the other fermentation facility is designed for Tetanus Toxoid manufacturing.

The design of the plant is based on the Biological Laboratory Safety Level 2 Large Scale (BL2-LS) guidelines set by National Institute of Health, USA, and the design of the plant will be in compliance with the CGMP requirements set by the Food and Drug Administration (FDA), USA.

DESIGN CRITERIA

General

The entire plant will be built on a grassroot area. It is estimated that a total of 520 square meters will be required for this purpose. An additional area, approximately 300 square meters has been reserved for future CGMP manufacturing expansion. High bay areas have been allocated for tall utility equipment (fermentors), and some smaller areas have been built out to accommodate known utilities such as electrical system, emergency power system, and fire protection systems.

Installed Plant Capacity

According to the various functions of the DPR manufacturing plant, the plant is divided into three major facilities including the Diphtheria Toxoid and Pertussis Vaccine Production Facility, the Tetanus Toxoid Production Facility, and a Bulk Mixing Facility.

The plant will be designed in such a way that it can produce 10 million doses of DPT annually and have the expansion capability to 20 million doses per year.

Quality Control/Quality Assurance (QC/QA)

QA in-process QC laboratory and Production offices will be located within the plant.

Finishing

Sterile purified bulk of DPT vaccine will be prepared and mixed in the Bulk Mixing Facility.

Regulatory Compliance

BL2-LS containment provisions will be supplied for the production facilities. The design will be in compliance with CGMP requirements set by the Food and Drug Administration, USA.

Expansion Capacity

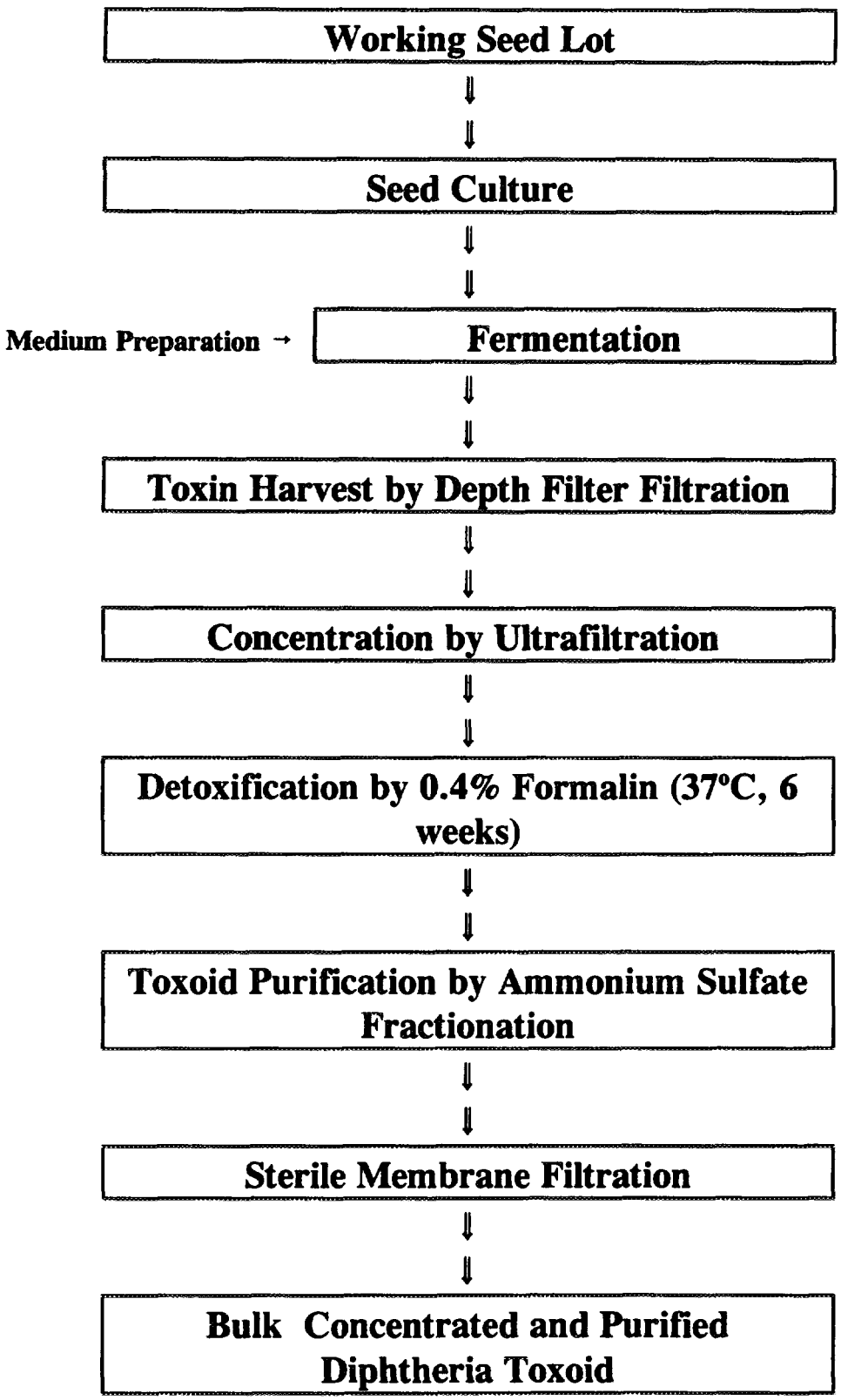
The plant will have some expansion capacities.

Composition of Vaccine

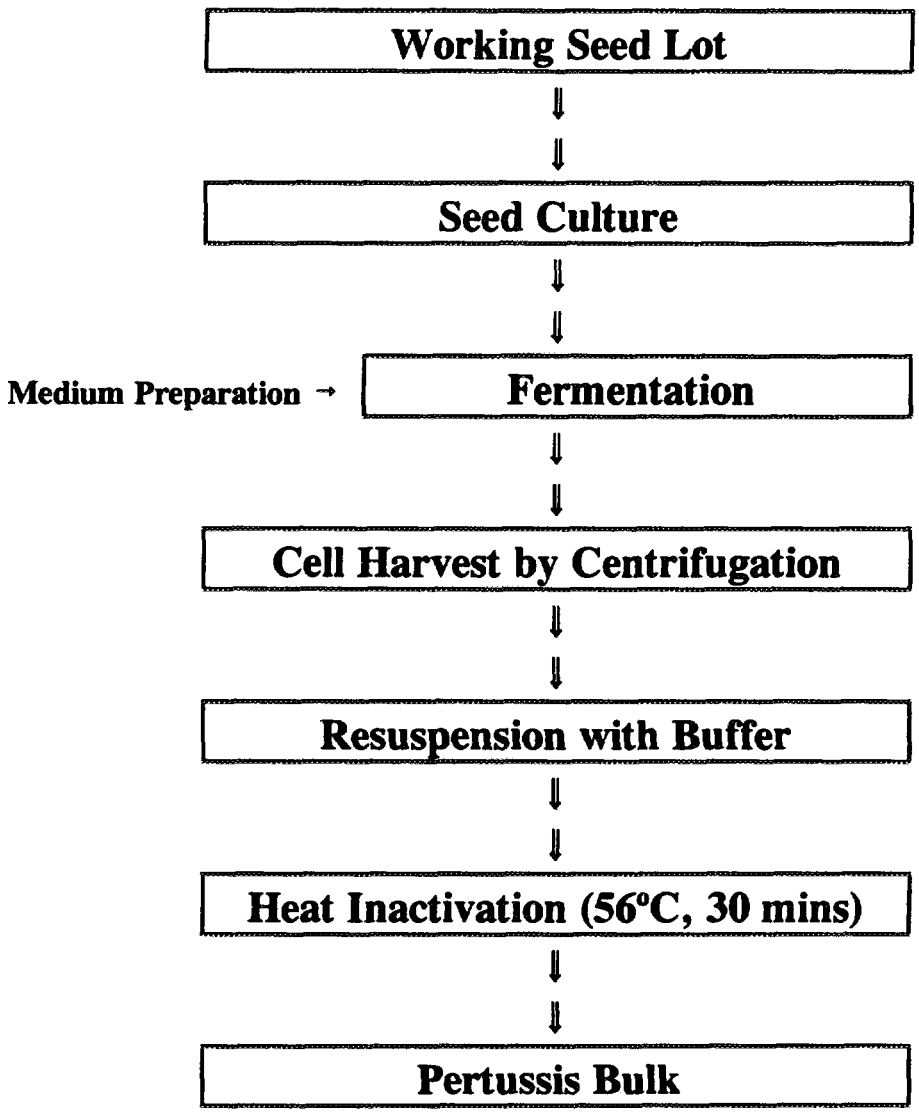
One dose per ml:

Tetanus Toxoid:	10Lf
Diphtheria Toxoid:	15 Lf
Pertussis	15 O.U.
Adjuvant:	$AlPO_4$ Gel
Preservative:	Merthiolate (0.01% w/v)
pH:	6.5 +/-0.2

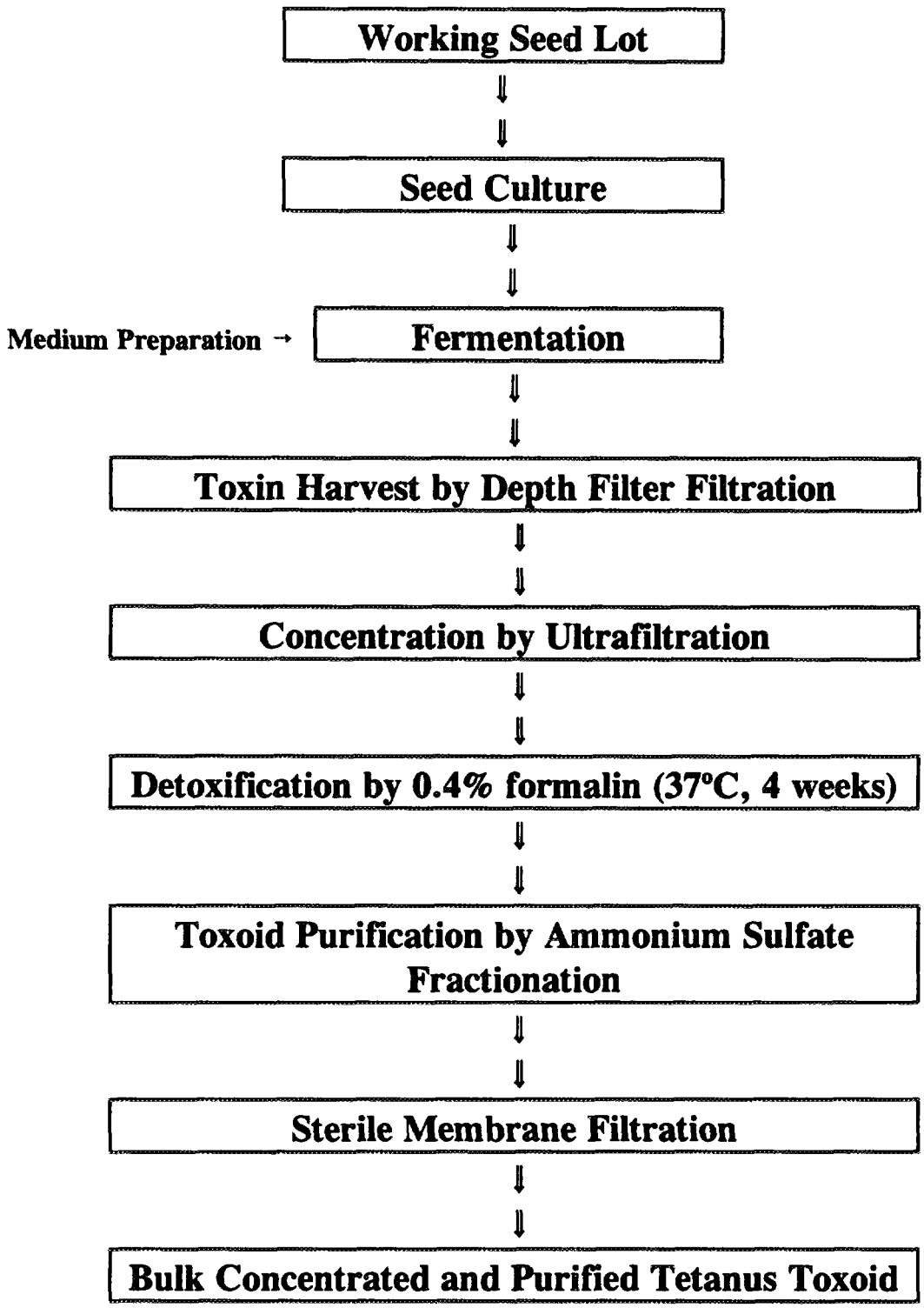
Diphtheria Toxoid Production



Pertussis Vaccine Production



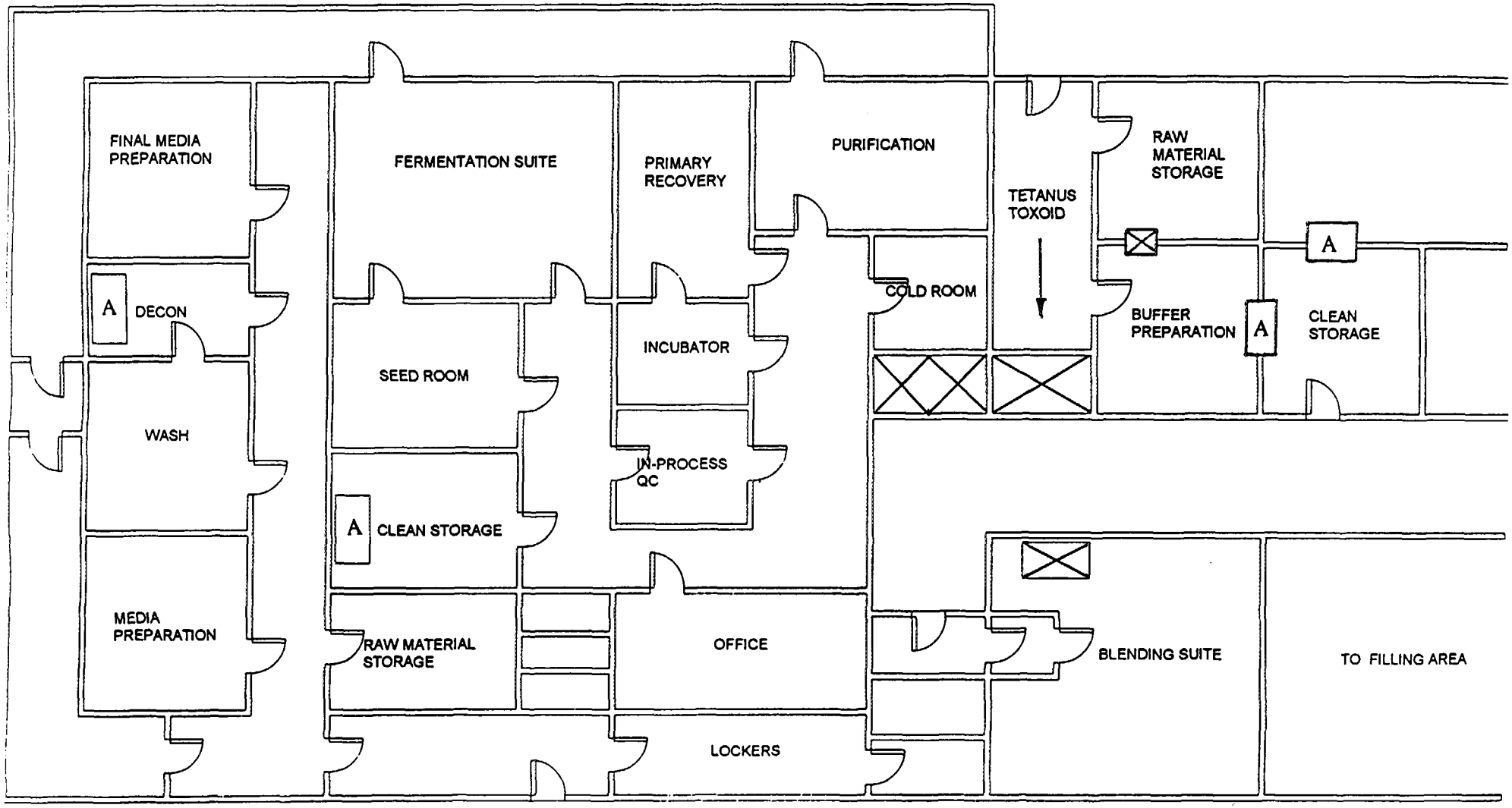
Tetanus Toxoid Production



REQUIREMENT OF DIPHTHERIA, TETANUS AND PERTUSSIS COMPONENTS FOR MANUFACTURING 10 MILLION DOSES OF DPT VACCINE

	DIPHTHERIA	TETANUS	PERTUSSIS
Requirement for:			
1 dose	15 Lf	10 Lf	15 OU
10×10^6 doses	$15 \times 10 \times 10^6$ Lf	$10 \times 10x\ 10^6$ Lf	$15 \times 10 \times 10^6$ OU
	$= 150 \times 10^6$ Lf	$=100 \times 10^6$ Lf	$= 150 \times 10^6$ OU
Yield from each batch:	70L x 120 Lf (200 Lf - 60%)	140L x 36 Lf (60 Lf - 60%)	70 L x 36 OU (45 OU - 80%)
	= 70 x 120 x 1000	= 140 x 36 x 1000	= 70 x 36 x 1000
	$= 8.4 \times 10^6$ Lf	$= 5.04 \times 10^6$ Lf	$= 2.52 \times 10^6$ OU
No. of batches	150/8.4 = 20 (approx.)	100/5.04 = 20 (approx.)	150/2.54 = 60 (approx.)

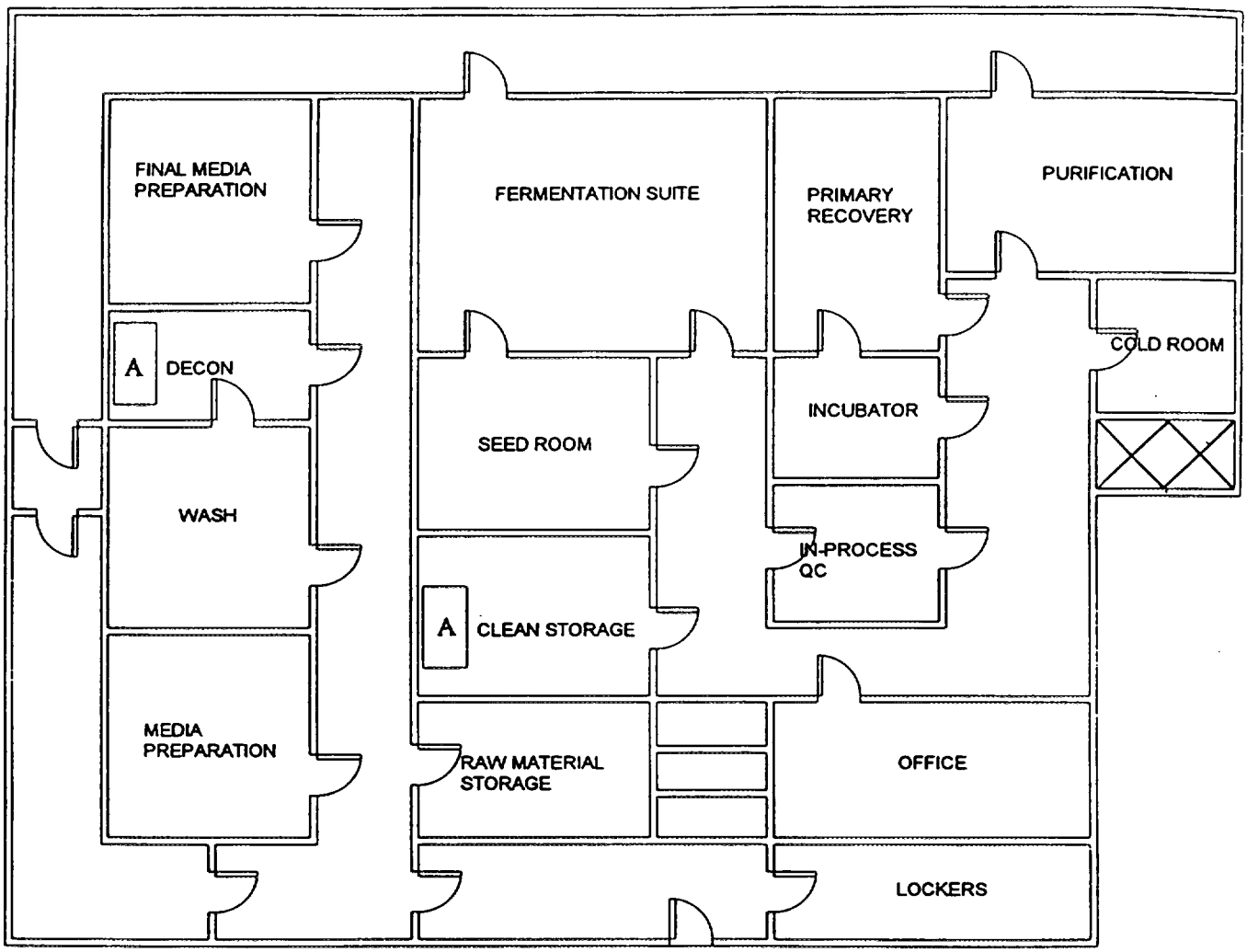
DIPHTHERIA AND PERTUSSIS LABORATORY



⊠ - compressor for cold room

A - double door autoclave

TETANUS LABORATORY



A - double door autoclave

☒ - compressor for cold room

Equipment List and Budget

Equipment	Numbers	Total Budget (US$,000)
Autoclaves	5	400
Depth filter vessels	2	50
Ultrafiltration units	2	150
Millipore separator	1	25
Fermenter 100 l	2	400
Fermenter 200 l	1	250
Mixing Vessel	1	50
Transfer pumps	3	75
Westphalia Centrifuge	1	200
Double jacketed media - Vessels	4	200
Membrane filter holders	5	50
Bottle washers	2	40
Tube washers	2	40
pH meters	4	4
Microscopes	2	10
Stainless steel double-jacketed closed vessel with stirrer	1	50
Vertical Laminar Flow Platforms	4	40
Rotary Shaker	2	10
Meat mixing machine	2	60
Refrigerated centrifuge	2	30
Balances	8	12
Stainless steel closed vessels	3	39
Water Bath	4	3
Spectrophotometer	1	20
Total Equipment Budget		**2,208**

Total Cost of a 10 Million Doses Bulk DPT Vaccine Plant

Shell and Facility Construction (520 m^2)	US$ 1,560,000
Total Equipment Budget	US$ 2,208,000
Total Cost of Bulk DPT Vaccine Plant	**US$ 3,768,000**

VALIDATION MASTER PLAN

1. Facility Description

    1.1 Facility
    1.2 Equipment

2. Validation Programme

    2.1 Strategy
    2.2 Protocols
    2.3 Acceptance Criteria

3. Standard Operating Procedures

    3.1 Policy
    3.2 SOPs
    3.3 Batch Production Records

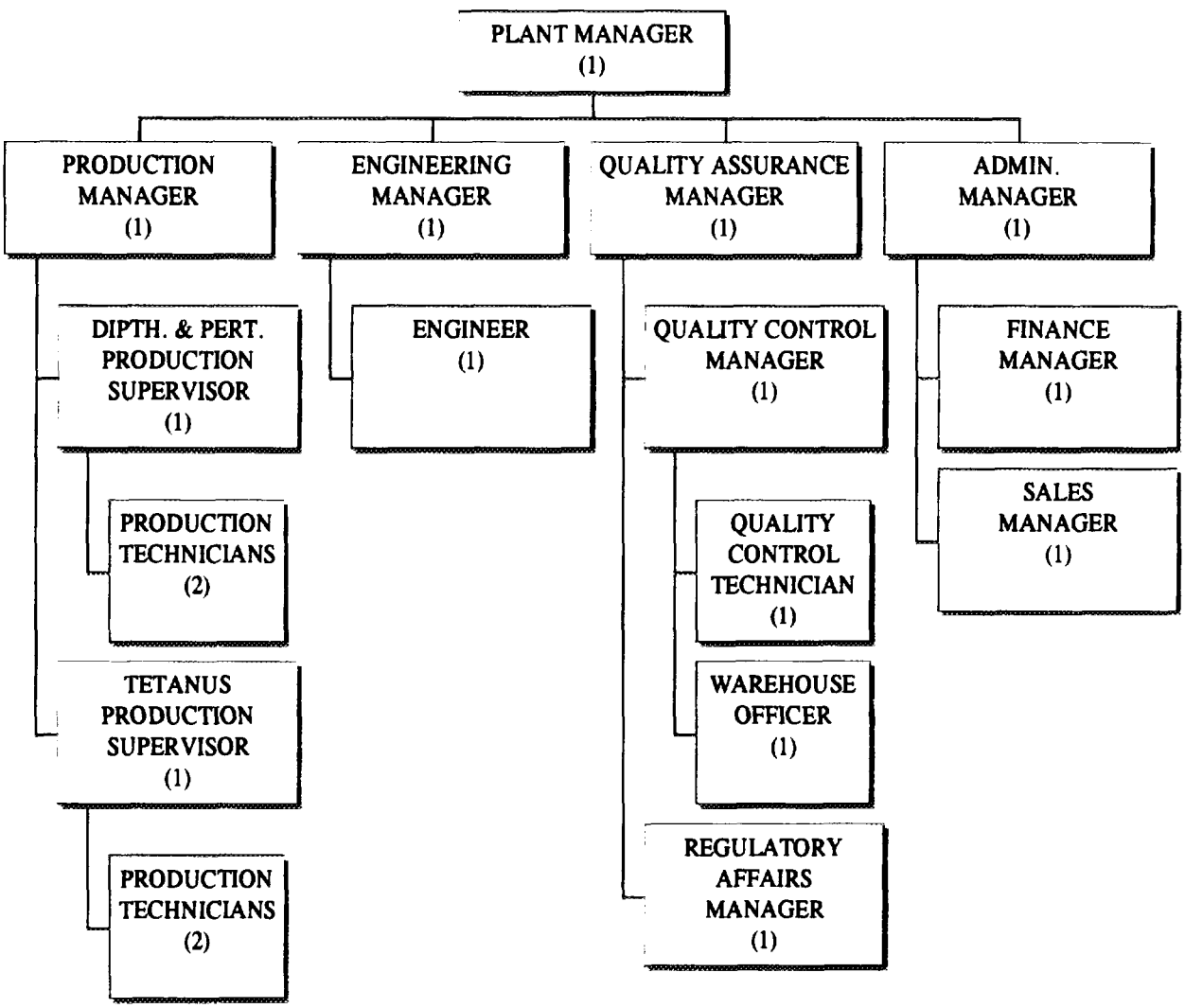
4. Training

5. Maintenance Programme

6. Planning Schedule

7. Facility Plans and Material/Personnel Flow

ORGANIZATION STRUCTURE



TOTAL PERSONNEL REQUIRED : 18

IVI/UNIDO/Bio Farma Training Workshop on QA / GMP / QC
of Vaccine Manufacture in Developing Countries
Bandung, Indonesia, 8-15 July 1996

PROJECT DESIGN

PRODUCTION PLANT FOR 100 MILLION DOSES OF DTP VACCINE

GROUP B REPORT

Group Leader : Dr. Ravetkar
Members : Dr. Sokhey
Dr. M. Jayasheela
Mrs. Teeranart Jivapaisarnpong
Dra. Antonia Retno Tyas Utami
Dr. Y. Udaya Bhaskara Rao
Drs. Suhaeri S.

CONCEPTUAL DESIGN STUDY
100 MILLION DOSES OF DTP

Identification of Product :

100 million doses of DTP vaccine

Identification of Technologies :

Bio fermentation

Identification of Capacity Requirement :

100 million doses of DTP

- Facility designed to produce 100 M doses of DTP Vaccine
- Using FERMENTER TECHNOLOGY for the three components
- Fermenter cultures clarified using *cross filtration technology* to obtain supernatants of '**D**' and '**T**' and cell suspension of '**P**' components.
- Supernatants
  a. Concentrated using *Pelican Cassette system* and
  b. purified by *salting procedures*
  c. detoxified by formalin ;
  '**P**' cell suspension inactivated at 56 °C for 30'.
- Composition of DTP Vaccine (1 dose)

Diphtheria toxoid	: 15 Lf
Tetanus toxoid	: 10 Lf
Pertussis	: 15 OU
Aluminum phosphate	: 1.5 mg
Thimerosal	: 0.01 %

- Working capacity of the fermenters

	Working capacity	Volume of Medium
Diphtheria	500 L (1)	350 L
Tetanus	1 000 L (2)	700 L
Pertussis	500 L (1)	350 L
	1 000 L (1)	700 L

- Separate building for each component and each building will have 300 m^2 of built up area and critical area (BL-2 is 20 % of built up area.

- **Time schedule**

Preparation of detailed engineering drawings and obtaining license from civic authorities including environmental clearance and Arriving at memorandum of understanding for supply of power, water and sewage connections	6 months
Actual civil construction work	6 months
Procurement and installation of utilities and equipment.	3 months
Validation of utilities and equipment.	3 months
Trial run	3 months

- **Schedule of Production**

one year after trial run	40	million doses
two year after trial run	80	million doses
three year after trial run	100	million doses

- **Staff structure**

  Total of 45 persons in all the three units at different level of position

- Air conditioning - 120 TR for each building
  Coldroom (15 C.M.) - capacity 10 tonne each
  Water - 100,000 L/day for 3 units

- Effluent Plant has been designed with settling tower and aeration

- Total cost of building and utilities is US $ 6,361,000

EQUIPMENT LIST

No.	Equipment	D	T	P	Cost/unit US $	Total Cost US $
1.	Double door autoclave (4 x 4 x 6')	2	2	2	10,000	60,000
2.	Hot air oven (4 x 4 x 6')	1	1	1	5,000	15,000
3.	Media vessel SS 316 with stirrer					
	1000 L	-	2	1	5,000	15,000
	500 L	1	-	1	2,500	5,000
4.	Centrifugal pump 1/8 HP	1	2	2	500	2,500
5.	Beef Cutting Machine	1	2	-	500	1,500
6.	Digestion Kettle 1 000 L	-	2	-	5,000	10,000
	500 L	1	-	-	3,000	3,000
7.	Pressure vessel or unit process vessel					
	200 L	2	4	4	5,000	50,000
	100 L	2	2	2	2,500	15,000
8	Vertical Laminar Flow (4 x 4 x 4')	2	2	3	5,000	35,000
9.	Shaker Incubator	1	1	1	5,000	15,000
10.	Fermentor					
	1000 L	-	2	1	1,000,000	3,000,000
	500 L	1	-	1	500,000	1,000,000
11.	SS 316 Media vessel 500 L	1	1	-	10,000	20,000
12.	SS Vessel with stirrer 500 L (double jacket)	-	-	1		
13.	Prostak system (tangential) to process 1000 L or Westfalia centrifuge	1	1	1	200,000	600,000
						4,866,000

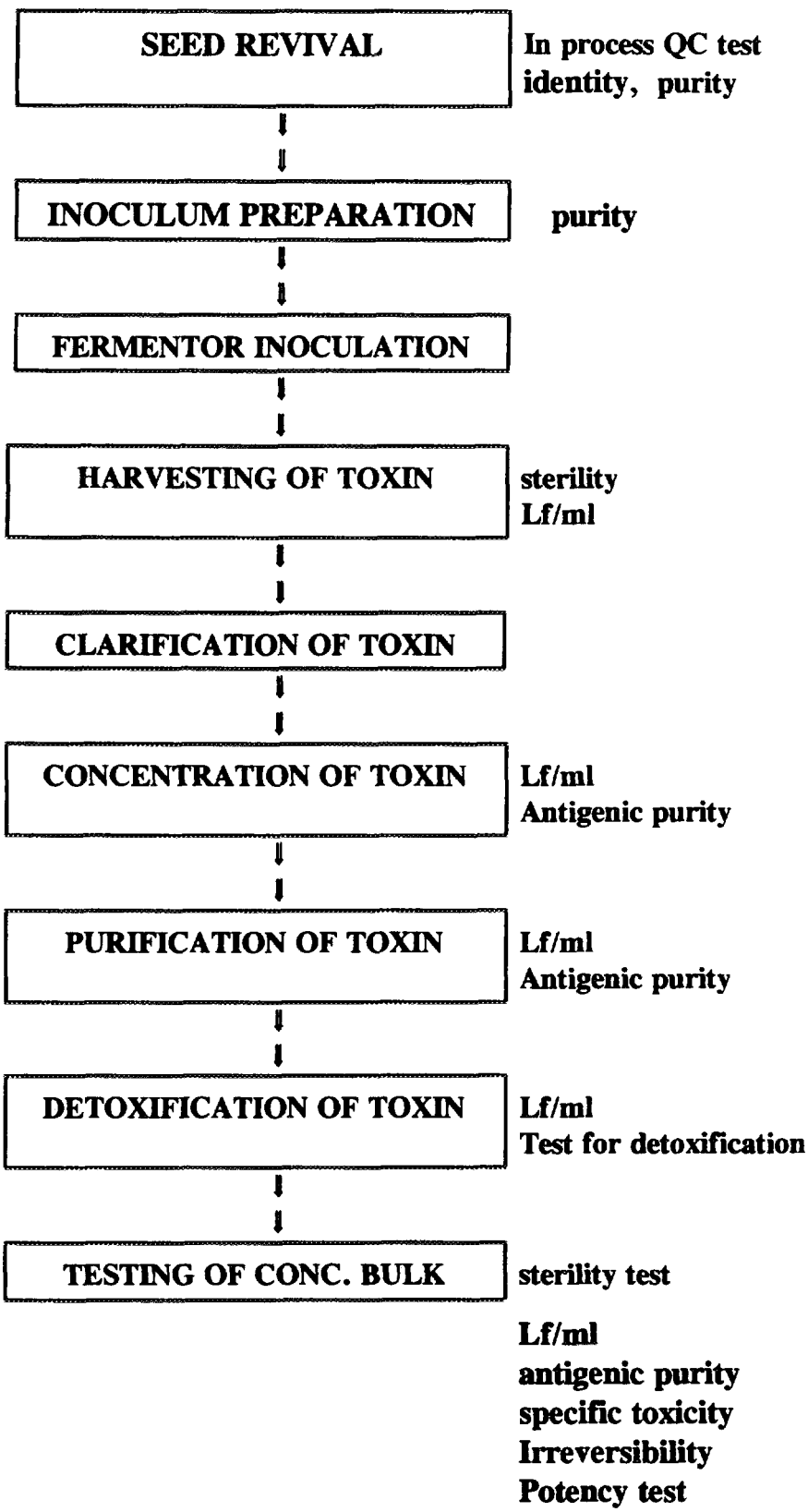
EQUIPMENT LIST (Continue)

No.	Equipment	Cost (US $)
		4,866,000
14.	Generator 300 KVA x 2	120,000
15.	Effluent Treatment Plant	60,000
16.	Pure steam boilers x 2	80,000
17.	Refrigerated centrifuge 6 Na	120,000
18.	Pelican system 6 Na	1,500,000
19.	pH meter 6 Na	10,000
20.	Water bath 3 Na	5,000
21.	HVAC system	600,000
22.	Demineralised and Distilled water plants	100,000
23.	Cost of building at the rate of US $ 3,000 / m^2 1,000 m^2	3,000,000
	GRAND TOTAL	**6,361,000**

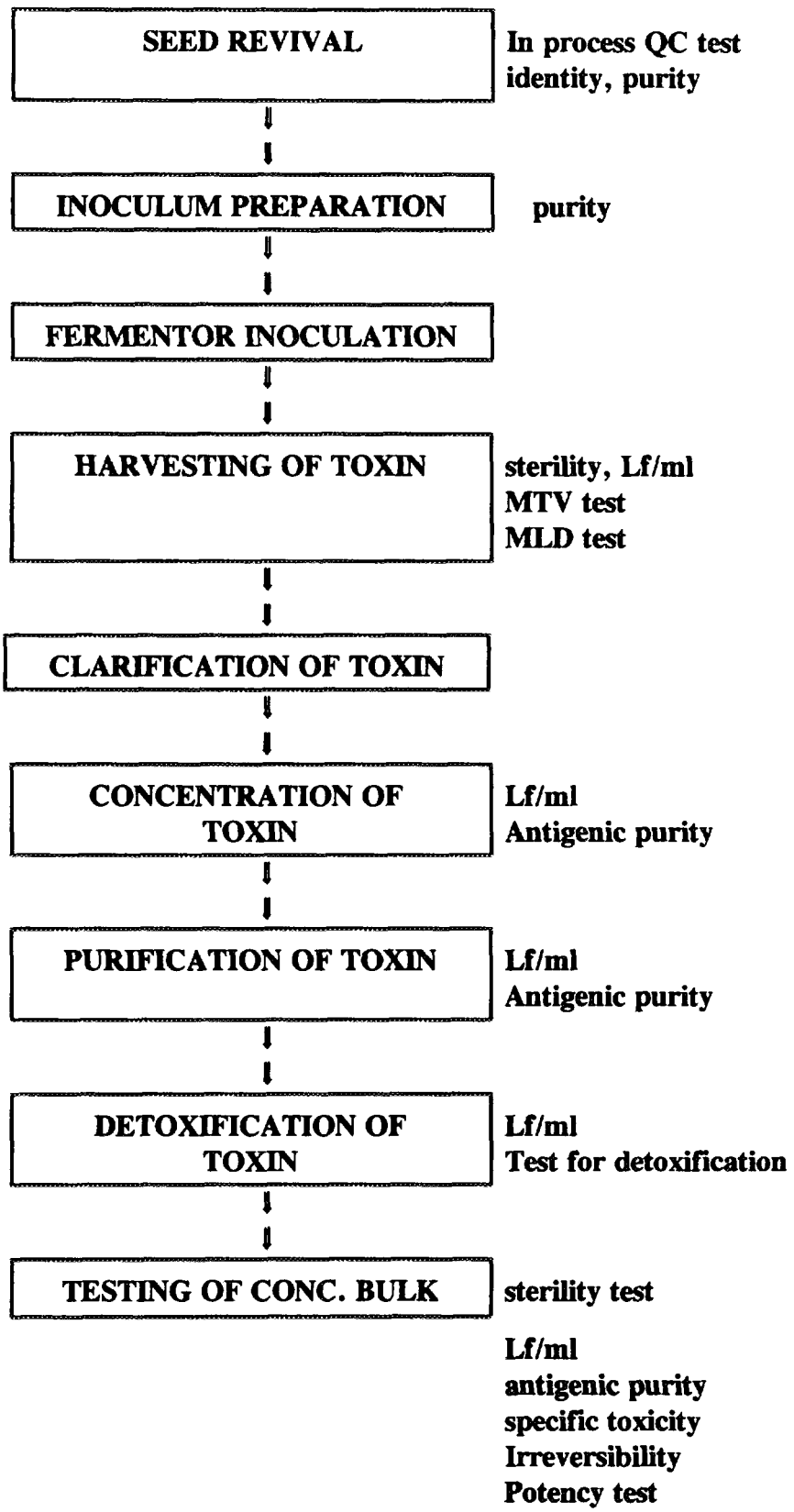
OUTPUT = PRODUCTION CAPACITY **$\underline{100 \times 10^6}$ doses**
[100 million doses]

	Diphtheria	Pertussis	Tetanus
Composition of 1 Dose/ml	15 Lf	15 OU	10 Lf
Demand	150 x 10^6 Lf	150 x 10^6 OU	100 x 10^6 Lf
Antigen conc. at harvest	200 Lf	45 OU	60 Lf
Yield of Downstream Processing	60%	80%	60%
Fermentor Volume Required (Total)	1.25 x 10^6 ml	4.2 x 10^6 ml	3.0 x 10^6 ml
Fermentor Volume Required for 100 million doses	12,500 L	42,000 L	30,000 L
Requirement of Fermentors	1 x 500 L fermentor	1 x 500 L + 1 x 1000 L fermentor	2 x 1000 L fermentors
Yield/run	350 L	350 + 700 L	2 x 700
No. Run	1 / wk	1 / wk	1 / 2 wks
No. of working week	46	46	46

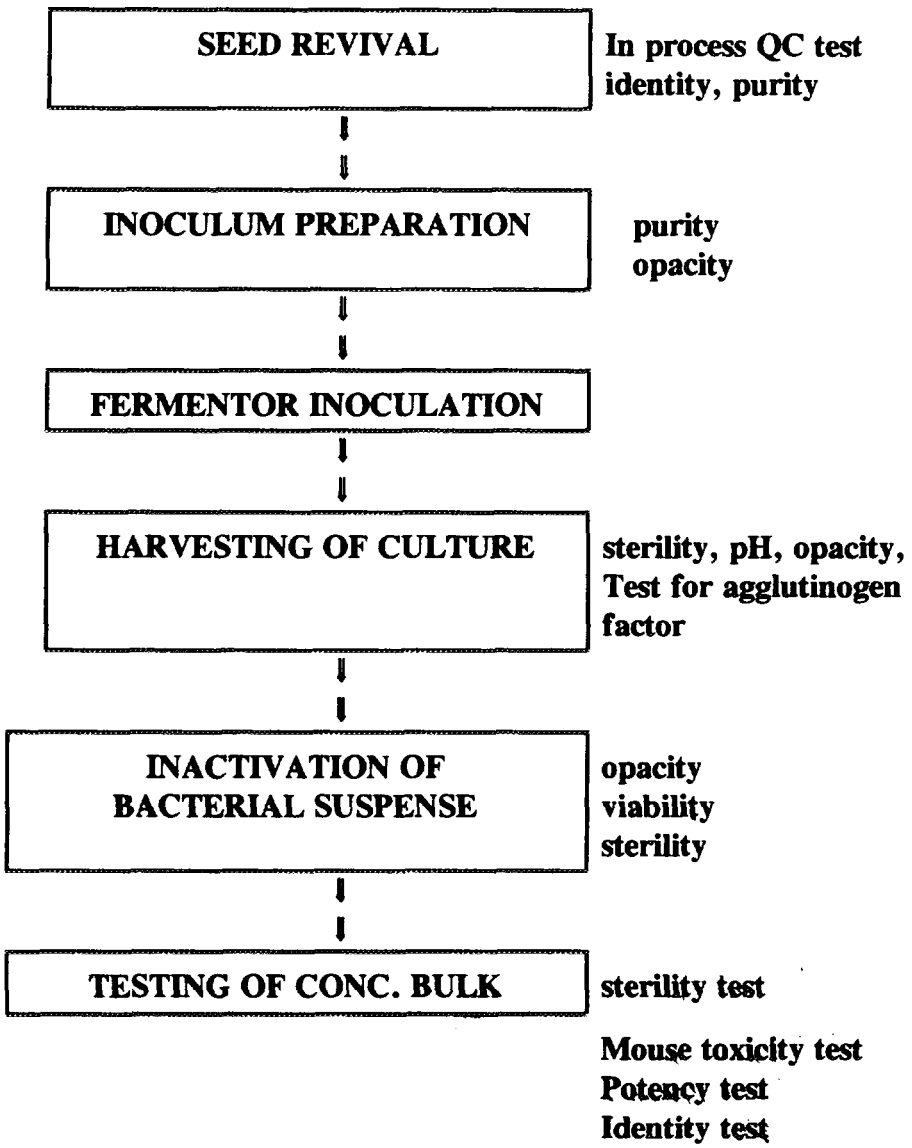
DIPHTHERIA


SEED REVIVAL
In process QC test
identity, purity
INOCULUM PREPARATION
purity
FERMENTOR INOCULATION
HARVESTING OF TOXIN
sterility
Lf/ml
CLARIFICATION OF TOXIN
CONCENTRATION OF TOXIN
Lf/ml
Antigenic purity
PURIFICATION OF TOXIN
Lf/ml
Antigenic purity
DETOXIFICATION OF TOXIN
Lf/ml
Test for detoxification
TESTING OF CONC. BULK
sterility test
Lf/ml
antigenic purity
specific toxicity
Irreversibility
Potency test

TETANUS

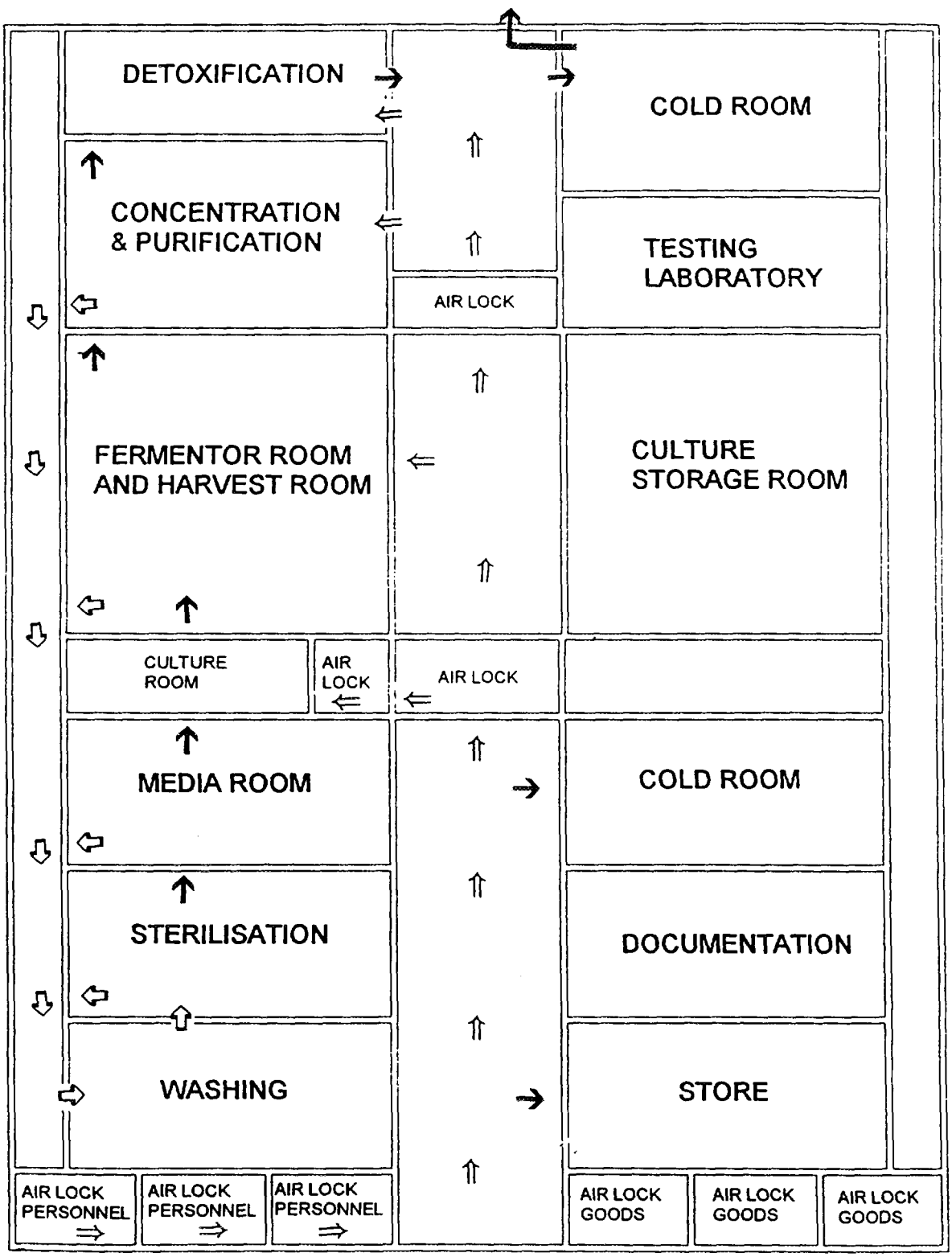

SEED REVIVAL
In process QC test
identity, purity
INOCULUM PREPARATION
purity
FERMENTOR INOCULATION
HARVESTING OF TOXIN
sterility, Lf/ml
MTV test
MLD test
CLARIFICATION OF TOXIN
CONCENTRATION OF TOXIN
Lf/ml
Antigenic purity
PURIFICATION OF TOXIN
Lf/ml
Antigenic purity
DETOXIFICATION OF TOXIN
Lf/ml
Test for detoxification
TESTING OF CONC. BULK
sterility test
Lf/ml
antigenic purity
specific toxicity
Irreversibility
Potency test

PERTUSSIS


SEED REVIVAL
In process QC test
identity, purity
INOCULUM PREPARATION
purity
opacity
FERMENTOR INOCULATION
HARVESTING OF CULTURE
sterility, pH, opacity,
Test for agglutinogen
factor
INACTIVATION OF
BACTERIAL SUSPENSE
opacity
viability
sterility
TESTING OF CONC. BULK
sterility test
Mouse toxicity test
Potency test
Identity test

BACTERIAL VACCINE LAY OUT PLAN

WITH SOME OF MAIN FLOWS



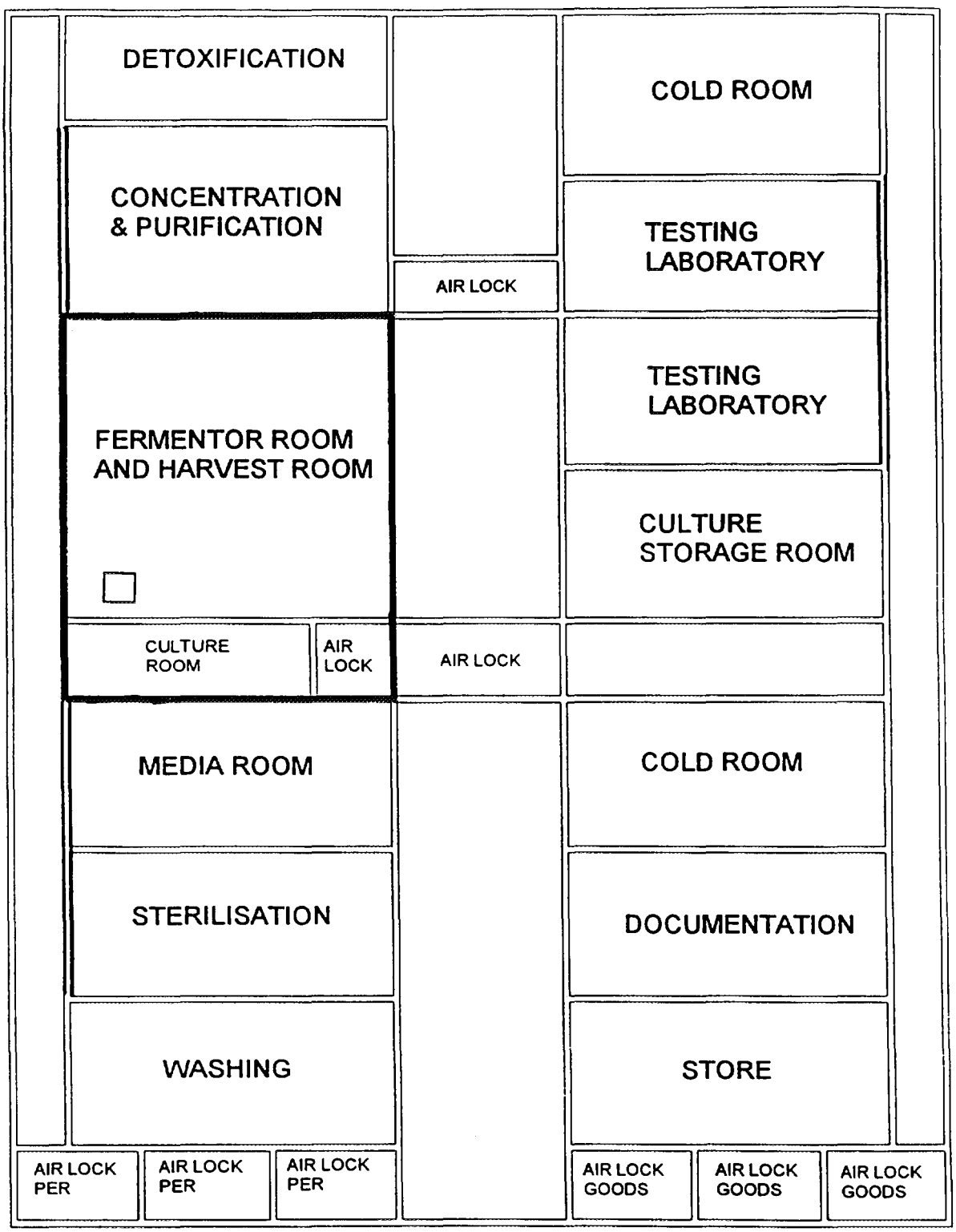
→ - Clean material flow

⇦ - Dirty material flow

⇒ - Personnel flow

BACTERIAL VACCINE LAY OUT PLAN

DOOR / WINDOW / FINISH SCHEDULE



double glass window

single glass window

epoxy sealed levelled floor

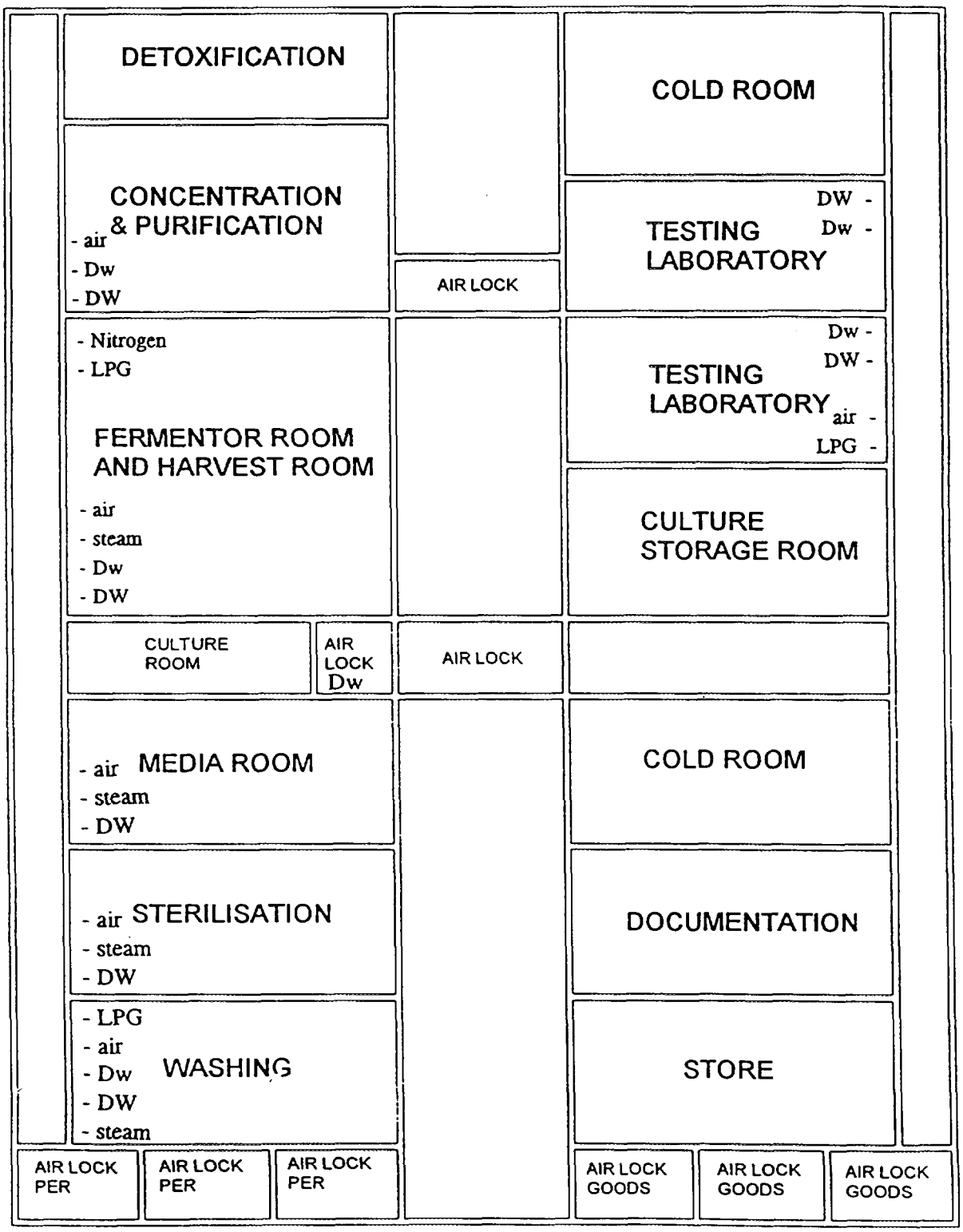
other areas:
vinyl flooring
epoxy painted walls and ceiling

pass box

PER - personnel

BACTERIAL VACCINE LAY OUT PLAN

FACILITIES, SERVICES, PLUMBING AND GASES

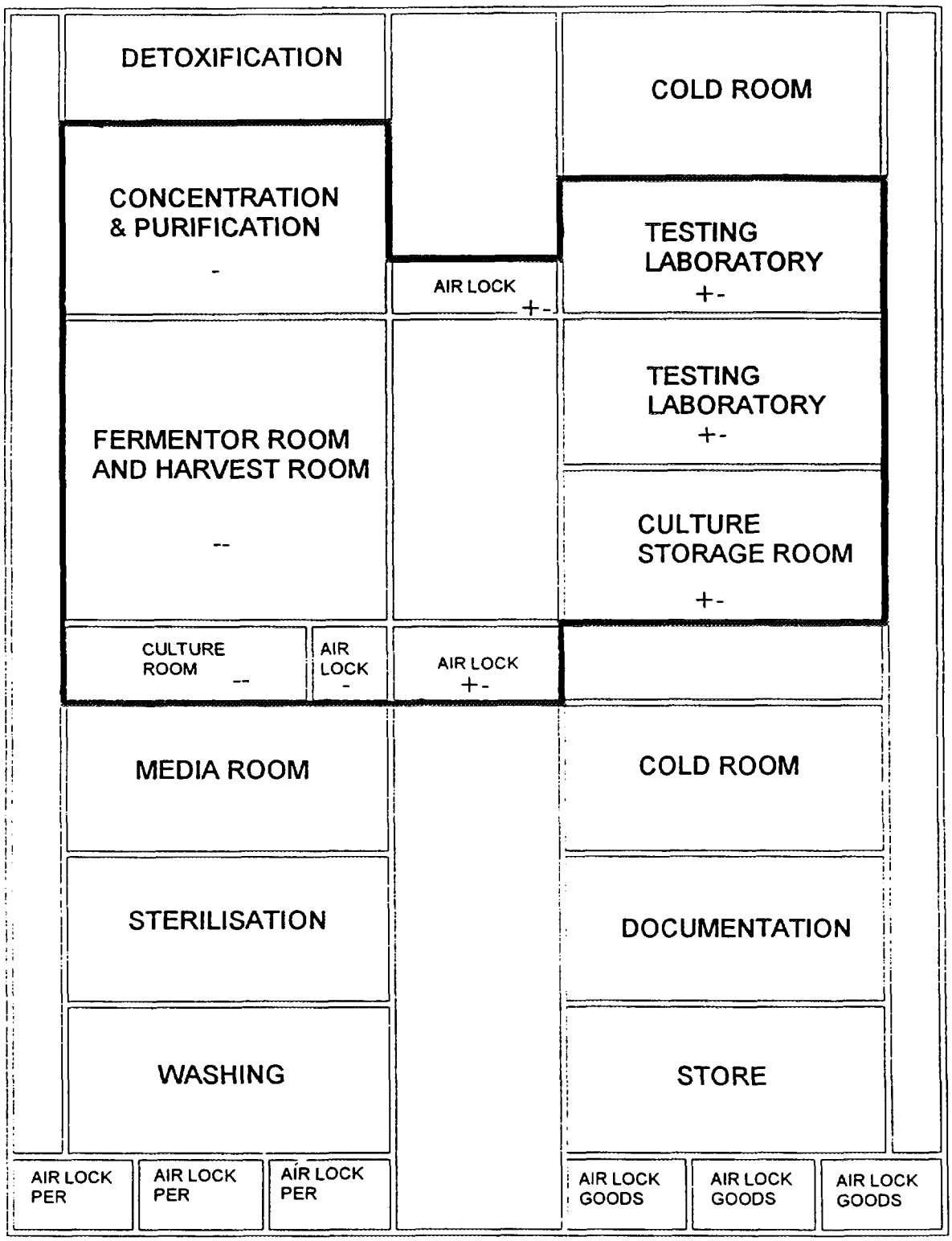


PER - personnel Dw - demineralized water

DW - distilled water

BACTERIAL VACCINE LAY OUT PLAN

HVAC



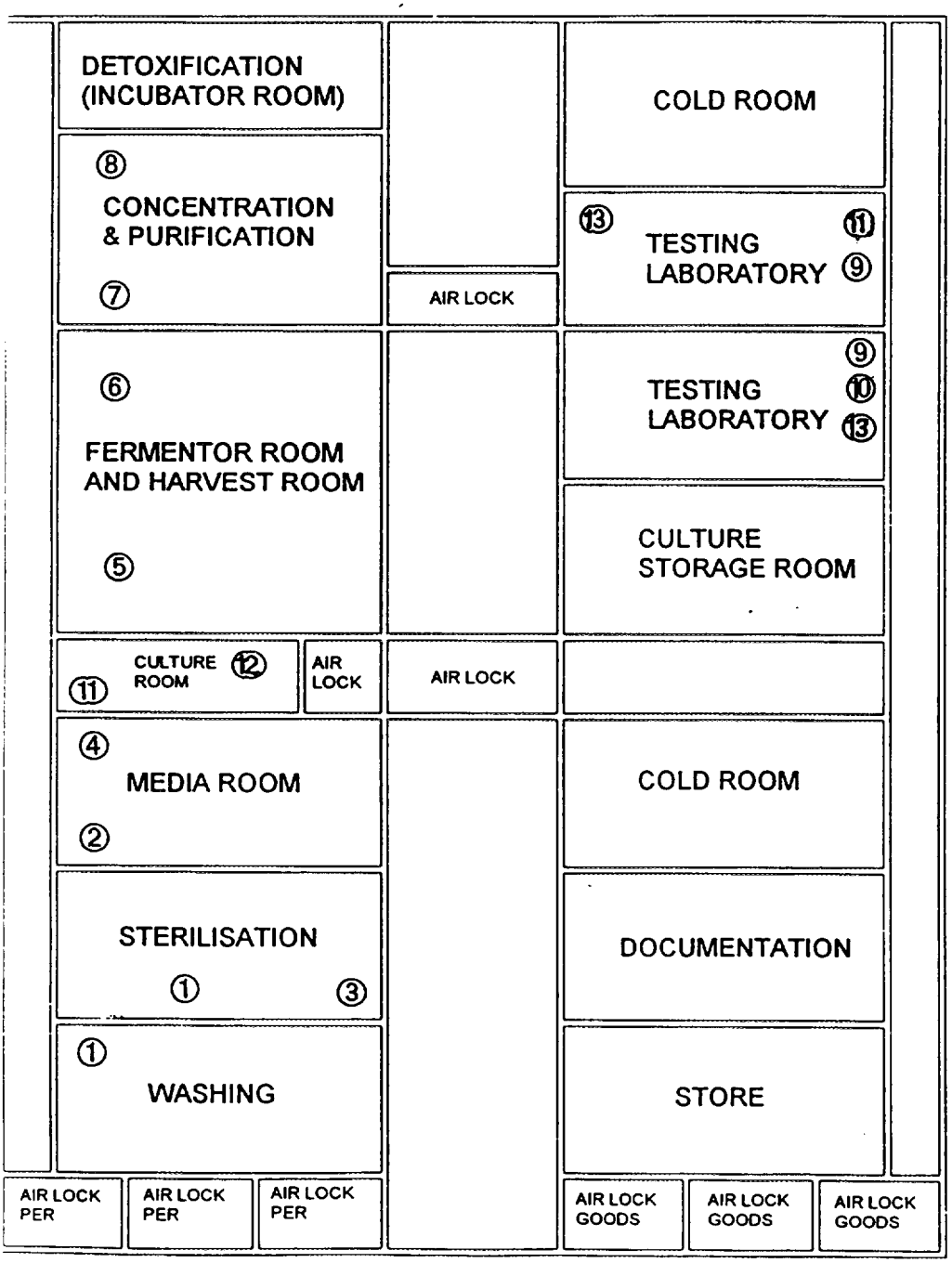
CLASS 100000

PER - personnel

-- }
- } AIR PRESSURE
+- } DIFFERENTIALS

BACTERIAL VACCINE LAY OUT PLAN

EQUIPMENT ARRANGEMENT



① - Autoclave
② - Mincing machine
③ - Hot air steriliser
④ - Media kettle
⑤ - Fer
⑥ - Prostak
⑦ - Pellicon
⑧ - Centrifuge
⑨ - Water bath
⑩ - Microscope
⑪ - Laminaire bench
⑫ - Shaker incubator
⑬ - Refrigerator

PER - personnel

IVI/UNIDO/Bio Farma Training Workshop on QA / GMP / QC
of Vaccine Manufacture in Developing Countries
Bandung, Indonesia, 8-15 July 1996

PROJECT DESIGN

PRODUCTION PLANT FOR 10 MILLION DOSES OF ORAL POLIO VACCINE

GROUP C REPORT

Group Leader	:	Dra. Yenni Siti Chaerani, MSc.
Members	:	Dr. Otavio F.P. de Olivia
		Dr. Yu Yong Xin
		Mr. Tang Sheng wen
		Dr. Guo Xin-chan
		Dr. Lim Wei-ling Wilina
		Dr. Ina Ray
		Dr. Bui Van Son

INTRODUCTION

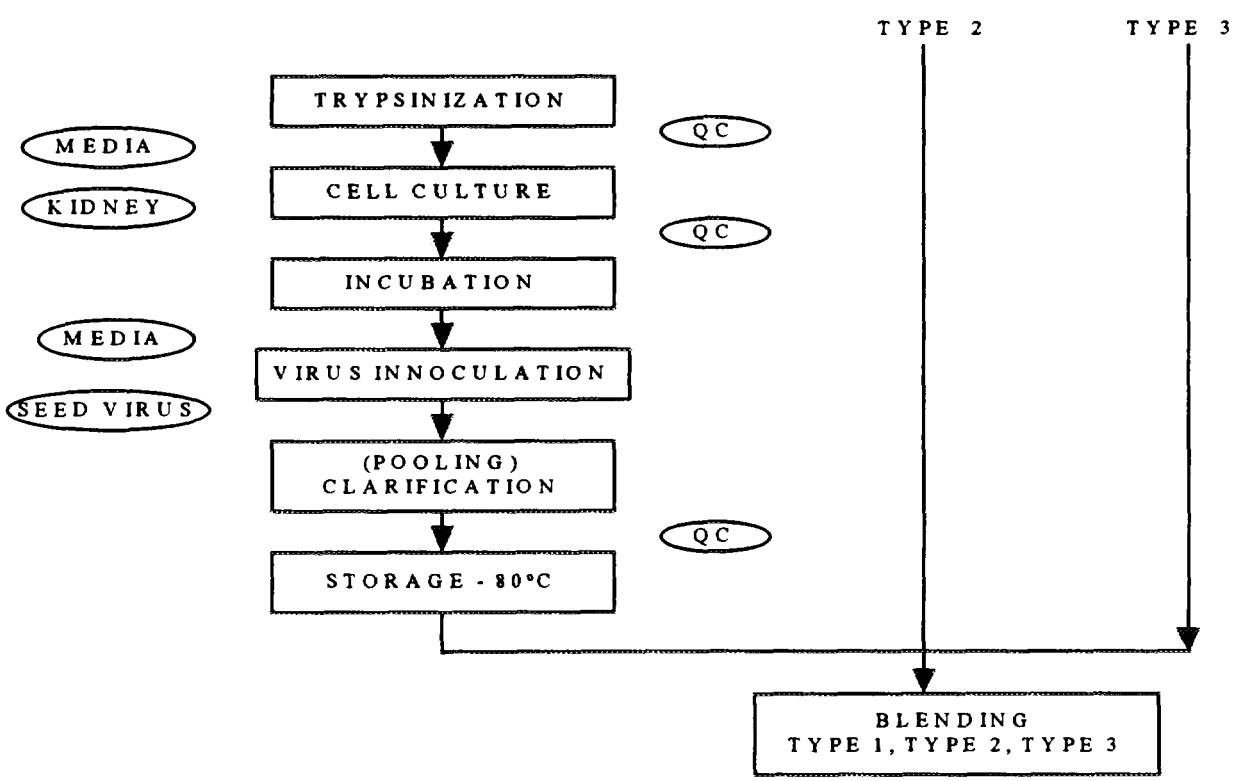
The aim of this project is to design a production facility which will produce 10 million doses of trivalent OPV per year with final concentration of 10^6 $TCID_{50}$ per dose for type 1, 10^5 $TCID_{50}$ for type 2 and $10^{5.5}$ $TCID_{50}$ for type 3 from monovalent bulk vaccines which have concentration of 10^8 $TCID_{50}$ per ml.

Assuming the bulk vaccine concentration of 10^8 TCI D_{50} volume of bulk vaccine required, theoretical calculation has been made for producing 10 million dose/year of polio polyvalent to be 100 litre of type-I, 70 litre type-II and 30 litre type-III.

STEP OF PRODUCTION

Starting from fresh monkey kidneys, production involves processes including trypsinization, preparation of monolayer cells, inoculation of cell culture with polio 1, 2 and 3, harvesting, pooling, clarification and bulk preparation.

PRODUCTION FLOW CHART



REQUIREMENT DESIGN

- Condition
  Legal and regulation aspect : Company policy and GMP
  Economical aspect : Investment level

- Starting Point: New Building on New Site (inside manufacturing area)

- Building and provisions
  - Type of building : Polio Production Facility (BL2-LS)
  - Process : include GMP/Quality requirement
    * Specification of Raw Material
    * Production capacity : 10 million dose/year
    * Lines speeds : optimum
    * Operation according to SOP
  - Building
    Civil : Site level, construction methods for building, piping bridges, architectural details painting description, etc.
    Equipment : Capacity, dimension, noise level, etc.
    Piping system : Diameter, specification of material coding of pipe lines, welding, etc.
    Electrical : Voltage, installation, distribution unit emergency power supply, lighting, etc.
    Room : With entrance, corridor, locker, offices, meeting room, wash room, shower, air shower production room, etc.
    HVAC : Temperature, pressure, humidity, air change, fresh air, etc.

EQUIPMENT

A list of equipment required is drawn up in Appendix 1. It is estimated that US$ 674,000 is necessary to purchase the equipment.

DESIGNING THE PRODUCTION FACILITY

Having determine the steps involved in production and equipment required, taking into account the requirement of space, flow of personnel, goods, production materials, waste, HVAC and containment, a layout as shown in Appendix 2 is proposed.

The facility will need to be built on an area of 560 m^2. Working on the premise that US$ 3,000 is required to build per square meter, the cost of the facility would come up to US$ 1,680,000.

Design of Lay out :

In order to prevent contamination and cross contamination, each type of products (bulk) should be carried out at one time in each room. Each room should preferably have its own entrance and partitions to separate all of those rooms. QC and other supporting facilities are not included in the design.

Costing of Building and Equipment

Cost estimate

Building facility	560 x $ 30.000	=	16,800,000
Draw Up lay out, equipment location,		=	7,000
equipment facility		=	674,000
Engineer activity			
(basic design, detail design)		=	15,000
Construction supervision		=	5,000
Training cost		=	10,000
Cost of insurance		=	40,000
Technical validity		=	9,000
Start up cost		=	25,000
Available local of employees		=	15,000
Proposal for waste handling		=	10,000
Contingency cost		=	220,000
Total			**US$2,700,000**

STAFF REQUIREMENT

To meet the operational needs, it is estimated that a qualified person experience in Polio Vaccine Production, one qualified staff (supervisor), two technicians, three laboratory assistants and one administrative secretary would be required.

IMPLEMENTATION TIME SCHEDULE

Starting from drawing preliminary equipment list and determining scientific steps, to finally production could be started, many activities including facility design, seeking approval from authorities, tendering for construction, construction, tendering for equipment, commissioning and validation are expected to take place consecutively or concurrently as shown in Appendix 3. It is estimated that 5 - 6 years are necessary to complete the project.

PRODUCTION SCHEDULE

OPV is produced using primary monkey kidney cells. Based on the assumption that each monkey kidney can provide 10 litre of bulk vaccine, it is estimated that 16 monkeys are required for the production of 10 million doses of OPV. The facility can handle 2 monkeys at each operation. The production schedule as shown in Appendix 4 is arranged to take this into account. It can be seen that the facilities is used for 30 weeks in a year. The utilization is thus, much lower than the 46 weeks during which the facility is permitted to operate.

CONCLUSION

From our study, we conclude that :

1. It would require US$ 1,680,000 to build the production facility for 10 million doses of OPV on an area of 560 m^2 with additional US$ 674,000 required to purchase the necessary equipment.

2. The facility could not be fully utilized for the whole year. It would be advisable to produce some other viral vaccines such as measles, rubella, etc. in the same facility.

3. It would not be cost effective to produce OPV at this level of requirement.

PROJECT PHASE

1. Pre-investigation
2. Project Definition
3. Basic Design
4. Detail Design
5. Construction
6. Technical Validation
7. Pharmaceutical Validation
8. Plant Start Up
9. Plant Acceptance

Pre-Investigation

Economical feasibility : Useful life of capital investment
Evaluation of govern and company policies
Capacity utilization
Product positioning versus competitions

Technical Feasibility : Product characteristic, capacity, equipment, etc.

Project definition

1. Project plan
   * Organization (project, chart)
   * Responsibilities working procedure (time, planning, control and overall)
   * Communication
   * Contractual data
   * Execution of the project

2. User Requirement
   * Budget estimate

Basic Design

- Architecture design
- Layout Design
- Equipment list
- Facility requirement
- Civil
- Piping
- Instrumentation
- Electric
- Plumbing
- HVAC
- Cost estimate
- etc.

Detail Design

- Specification
- Contract for contractors and supplier (civil, HVAC, Electrical, P &I, etc.)
- Final design
- Schedule of flow finishes, etc.

Construction

- Foundation, concrete, steel, etc.
- Delivery and installation of equipment
- Installation (P&I, electric, instrument, etc.)
- Wall, floor, ceiling, etc.
- Coding (piping, installation, etc.)
- Loop testing
- Calibration of instrumentation
- Rotation direction
- Rotation equipment

Technical Validation

a. Installation Qualification
b. Operational Qualification
c. Technical Training (operator, maintenance, engineering, personnel involved in manufacturing, processing, etc.)

Pharmaceutical Validation

Determination
The critical process parameter
Acceptable range of the variable
Continuous control

Plant Start Up

First production runs
1. Protocol
   - IQ, OQ
   - Process description
   - Preventive maintenance
   - Validity programme

2. Protocol Procedure : keys S.O.P

Plant Acceptance

User requirement :

- Condition
  Legal and regulation aspect : Company policy and GMP
  Economical aspect : Investment level

- Starting Point : New Building on New Site

- Building and provisions
  - Type of building : Polio Production Facility (BL2-LS) (with regard to safety, human health comfort and efficiency)

  - Process : With emphasis on special process
    - Specification of Raw Material
    - Production capacity, lines speeds, efficiency
    - Capacity of utilities and availability factor
    - Safety precautions operating personnel
    - Transport way
    - Operation condition, etc.

- Requirement design : include GMP/Quality requirement
- Location : New building In the manufacture inside area
- Building

Civil : Site level, construction methods for building, piping bridges, architectural details painting, description, etc.

Equipment : Capacity, dimension, noise level, etc.

Piping system : diameter, specification of material, coding of pipe lines, welding, etc.

Electrical : voltage, installation, distribution unit, emergency power supply, lighting, etc.

Room : with entrance, corridor, locker, offices, meeting room, wash room, shower, air shower production room, etc.

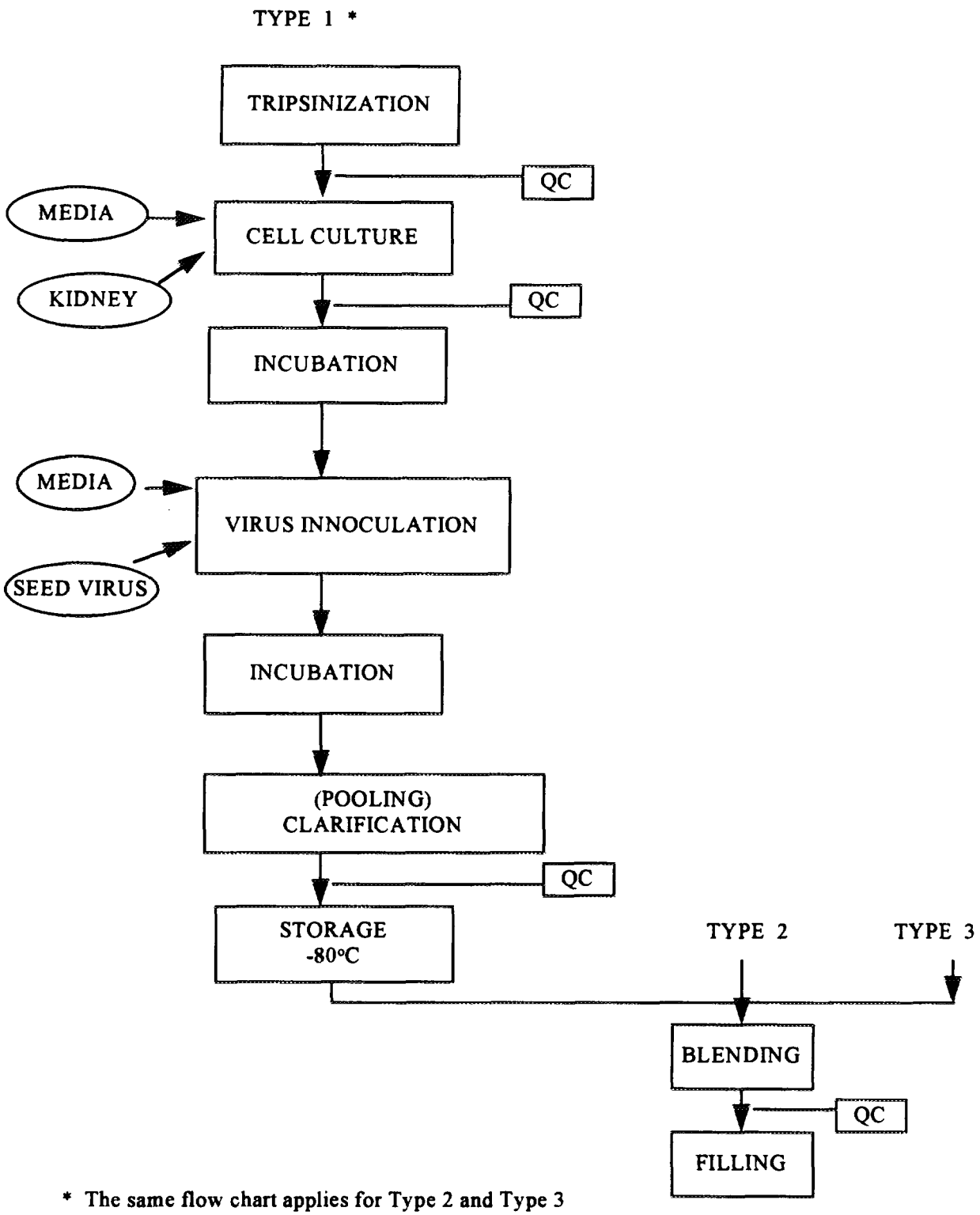
HVAC : Temperature, Pressure, Humidity, Air change, fresh air, etc.

Appendix 1

List of Equipment

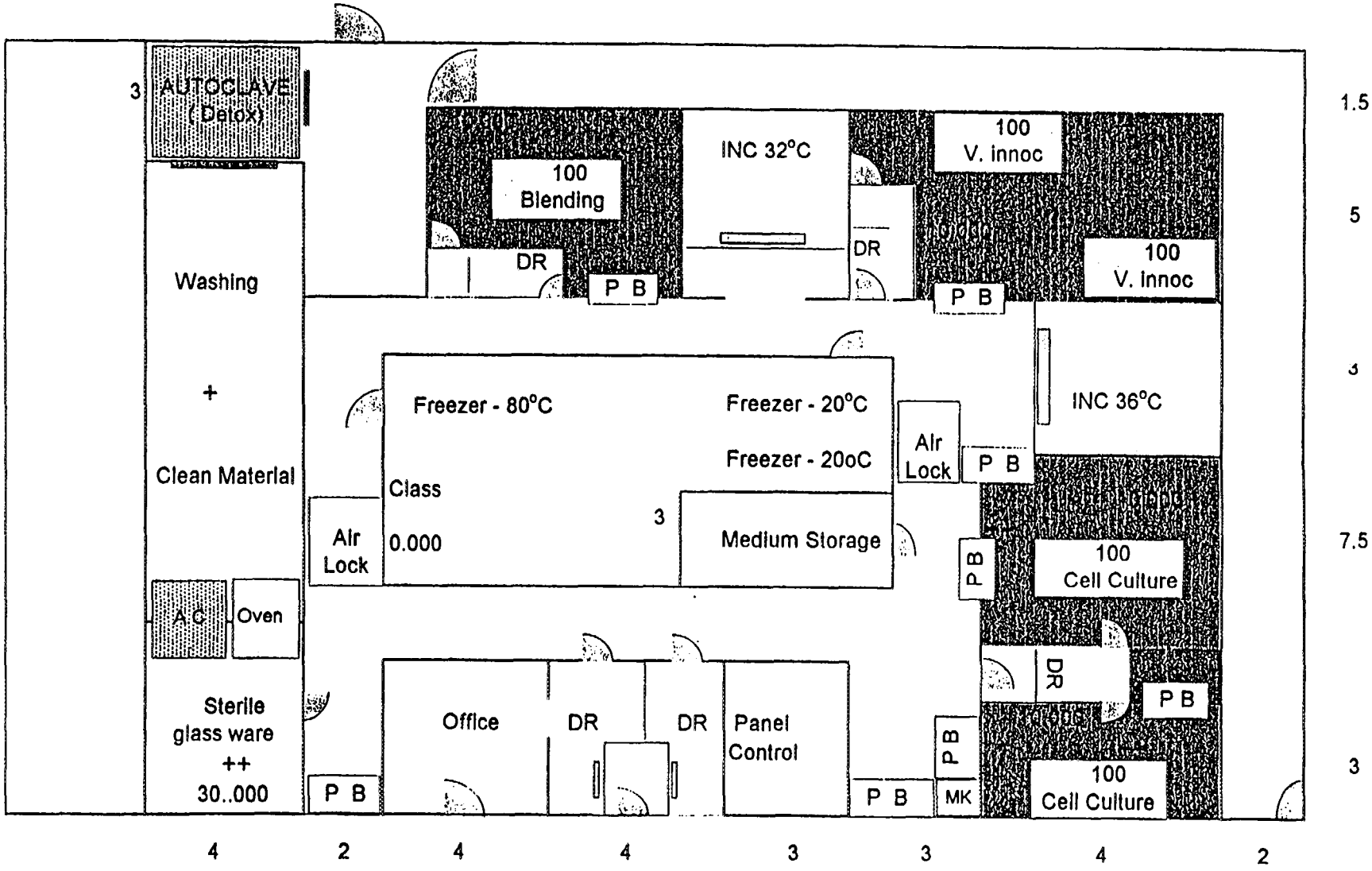
ROOM	TYPE	SIZE (m^2)	MAIN EQUIPMENT	AMOUNT	PRICE
Cell Culture	10.000	30	LAF	1	15,000
			Clean bench	2	22,000
			Inverted microscope	2	24,000
			Refrigerated Centrifuge	1	14,000
			Automatic Dispenser	3	9,000
Virus Culture	10.000	30	LAF	1	15,000
			Clean bench	1	11,000
			Inverted microscope	1	12,000
			Automatic Dispenser	2	6,000
Trypsinization	10.000	12	LAF	1	15,000
			Clean bench	1	11,000
			Inverted microscope	1	12,000
			Automatic Dispenser	1	3,000
			Water Bath	2	26,000
INC 36°C		15		1	30,000
INC 32°C		15		1	30,000
Blending	1000	20	Tank	1	8,000
			LAF	1	15,000
			Stainless steel table	1	30,000
			Electric balance	1	13,000
			pH meter	1	10,000
Washing		150	Ice maker	1	4,000
			Electric balance	1	7,000
			Dry Oven	1	9,000
			dryer	1	4,000
			washing machine	2	5,000
			Double door autoclave	1	30,000
			Roux bottle washer	1	20,000
			Ultrasonicator	1	30,000
Storage	30.000	20	Freezer -80 °C	3	60,000
			Freezer - 20 °C	6	90,000
Media Storage	30.000	20	Stainless Steel Rack	8	7,000
Utility		40	pure water machine	2	12,000
Pass Box				10	35,000
L. Production					30,000
TOTAL BUDGET (Equipment)					**674,000**

Appendix 2

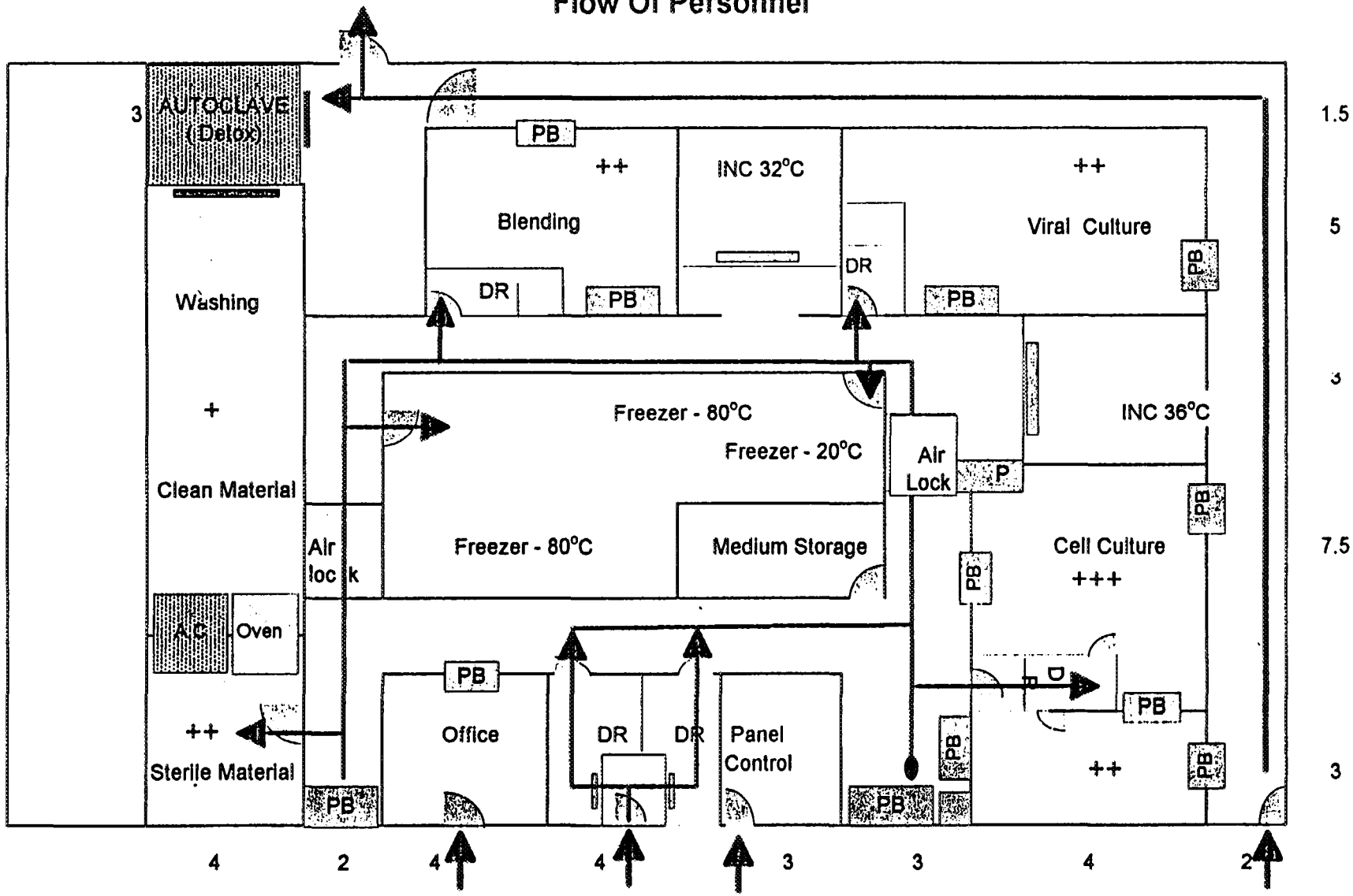


* The same flow chart applies for Type 2 and Type 3

Building & Equipments Facilities

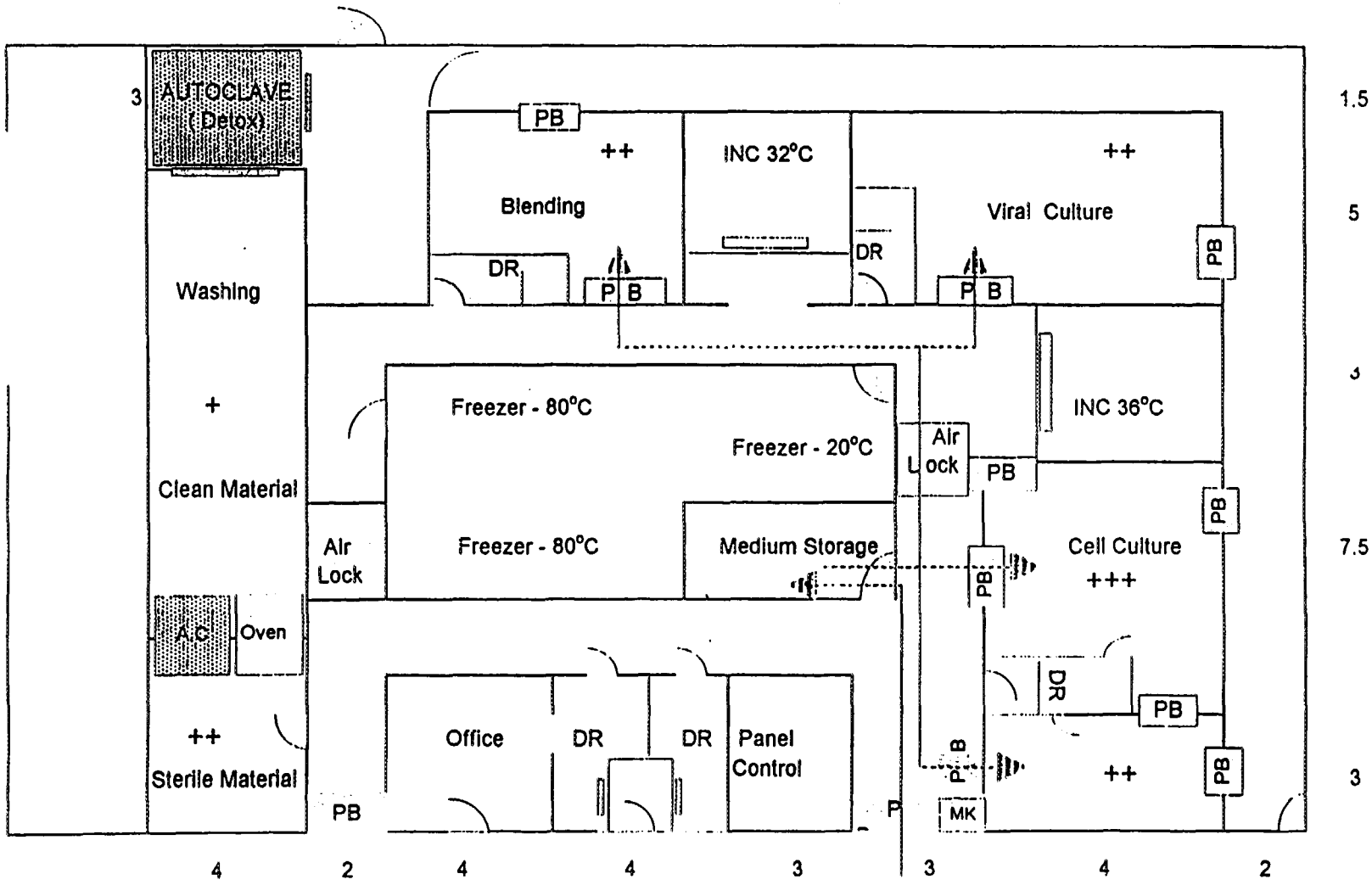


EQUIPMENT FACILITIES



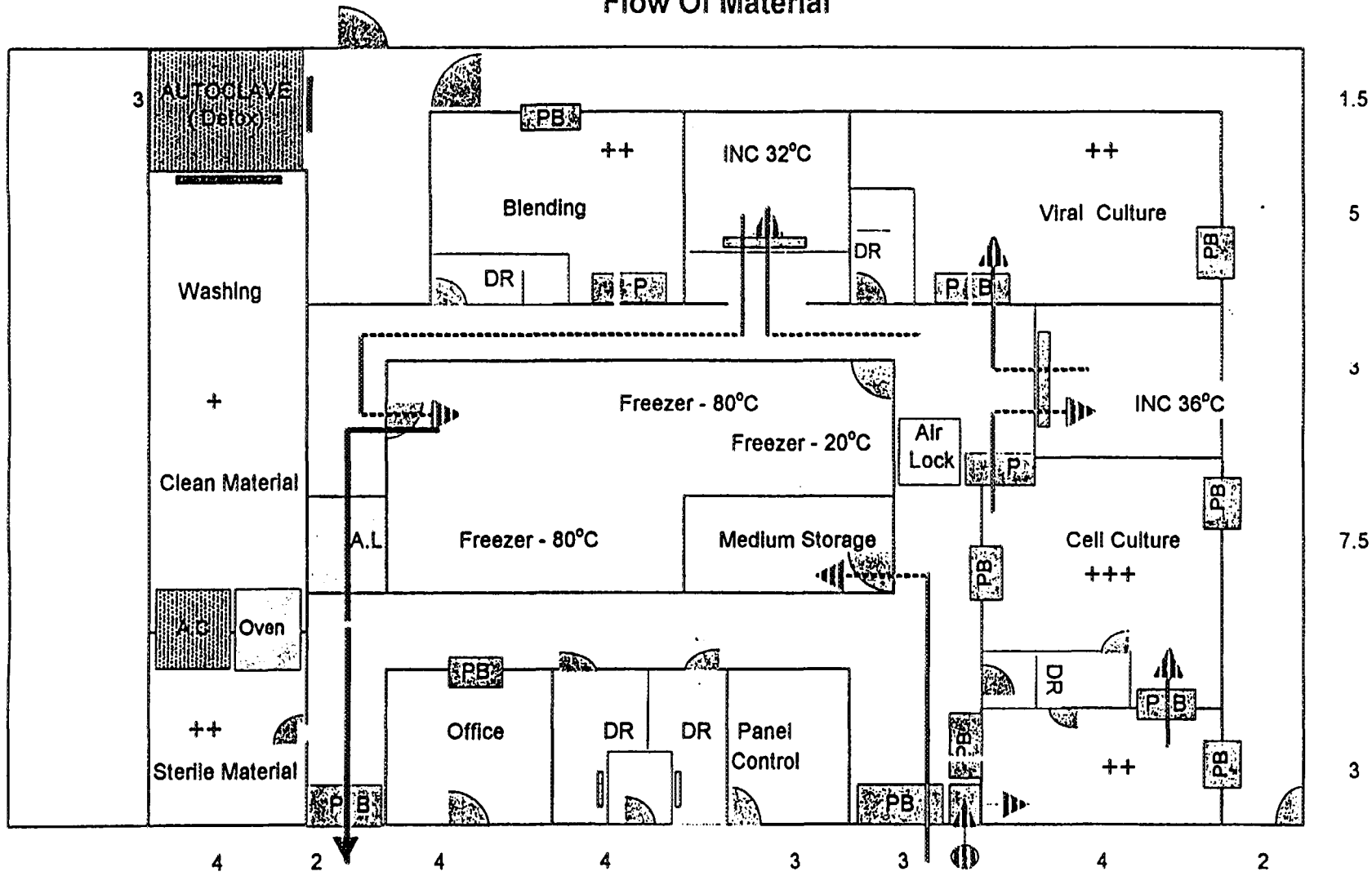
FLOW OF PERSONNEL

FLOW OF MEDIUM



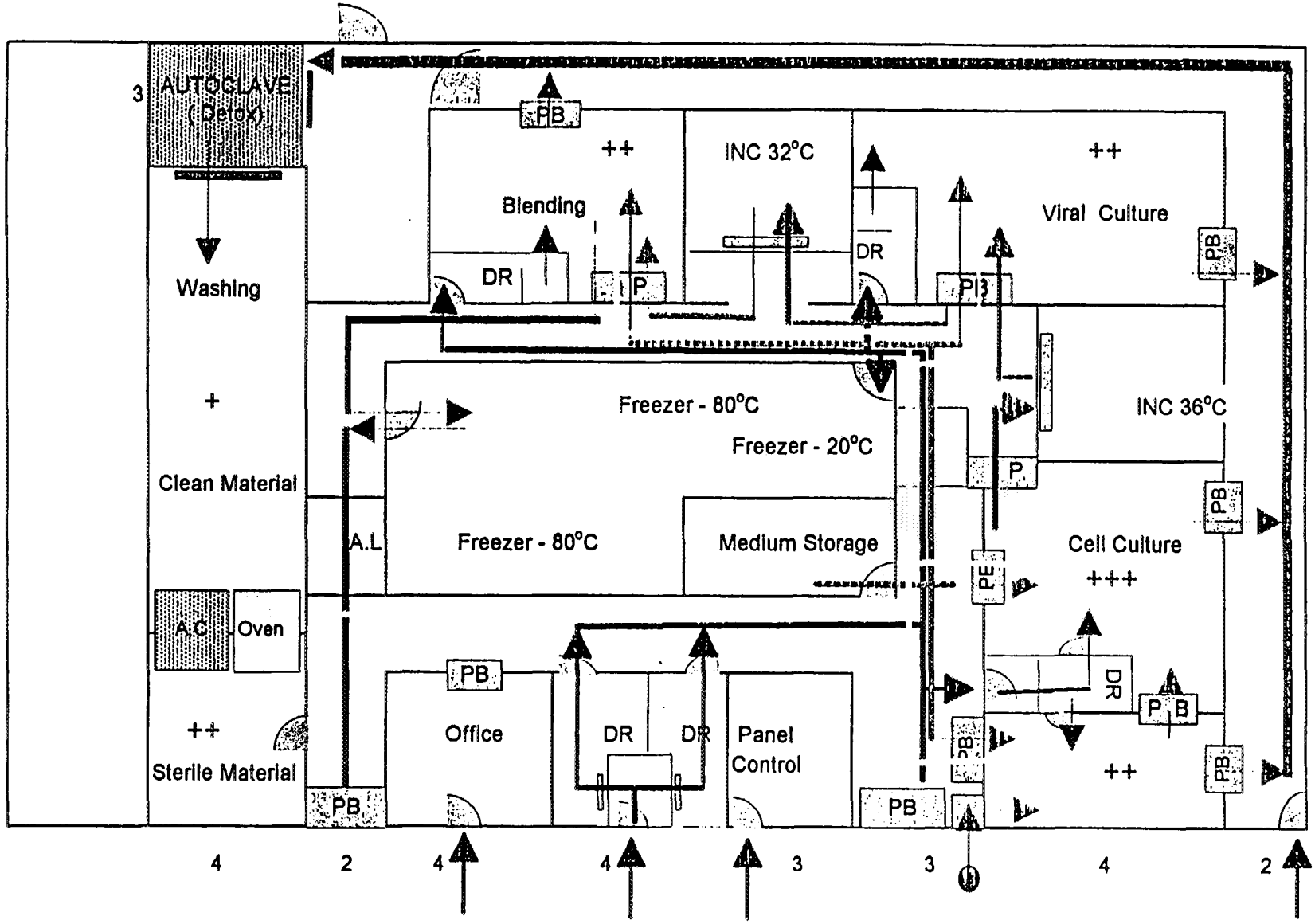
FLOW OF MEDIUM

Flow Of Material



Media Monkey Kidney & Process Glassware Final Product

FLOW OF MATERIALS


AUTOCLAVE (Detox)
Washing
Clean Material
Sterile Material
A.C
Oven
A.L
Blending
INC 32°C
Viral Culture
Freezer - 80°C
Freezer - 20°C
Freezer - 80°C
Medium Storage
INC 36°C
Cell Culture
Office
Panel Control
DR
P
PB
PE
++
+++
3
1.5
5
3
7.5
3
4
2
4
4
3
3
4
2
Personnel
Medium
Proses
Media
Product

Appendix 3

Implementation Schedule of Polio Production

Project activity	Year 1	Year 2	Year 3	Year 4	Year 5
Scientific step					
Design (Basic design)					
Design (Detail design)					
List of equipment					
Approval					
Tendering of Construction					
Finalization list of equipment					
Construction					
Finalized (P&I, HVAC, Elect. etc)					
Tendering of equipment					
and procurement					
Supplier Installation					
Commissioning Validation					
Production start up					

Appendix 4

Time Schedule Production of Polio Monovalent Bulk (Type 1, Type 2 and Type 3)

Activity	Week																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Cell Culture	P1	P1	P1	P1	P1					P2	P2				P3	P3														
Virus Culture			P1	P1	P1	P1	P1				P2	P2				P3	P3													
Harvest				P1	P1	P1	P1	P1				P2	P2				P3	P3													
Pooling								P1					P2					P3												
Monovalent Bulk																				P1				P2					P3	

Monkey : Type 1 : 10 monkeys
Type 2 : 3 monkeys
Type 3 : 3 monkeys

Capacity : 2 monkey kidneys / week

Times for Production of Bulk Polio Type 1, Type 2 and Type 3 = 30 weeks

IVI/UNIDO/Bio Farma Training Workshop on QA / GMP/ QC
of Vaccine Manufacture in Developing Countries
Bandung, INDONESIA, 8-15 July, 1996

PROJECT DESIGN

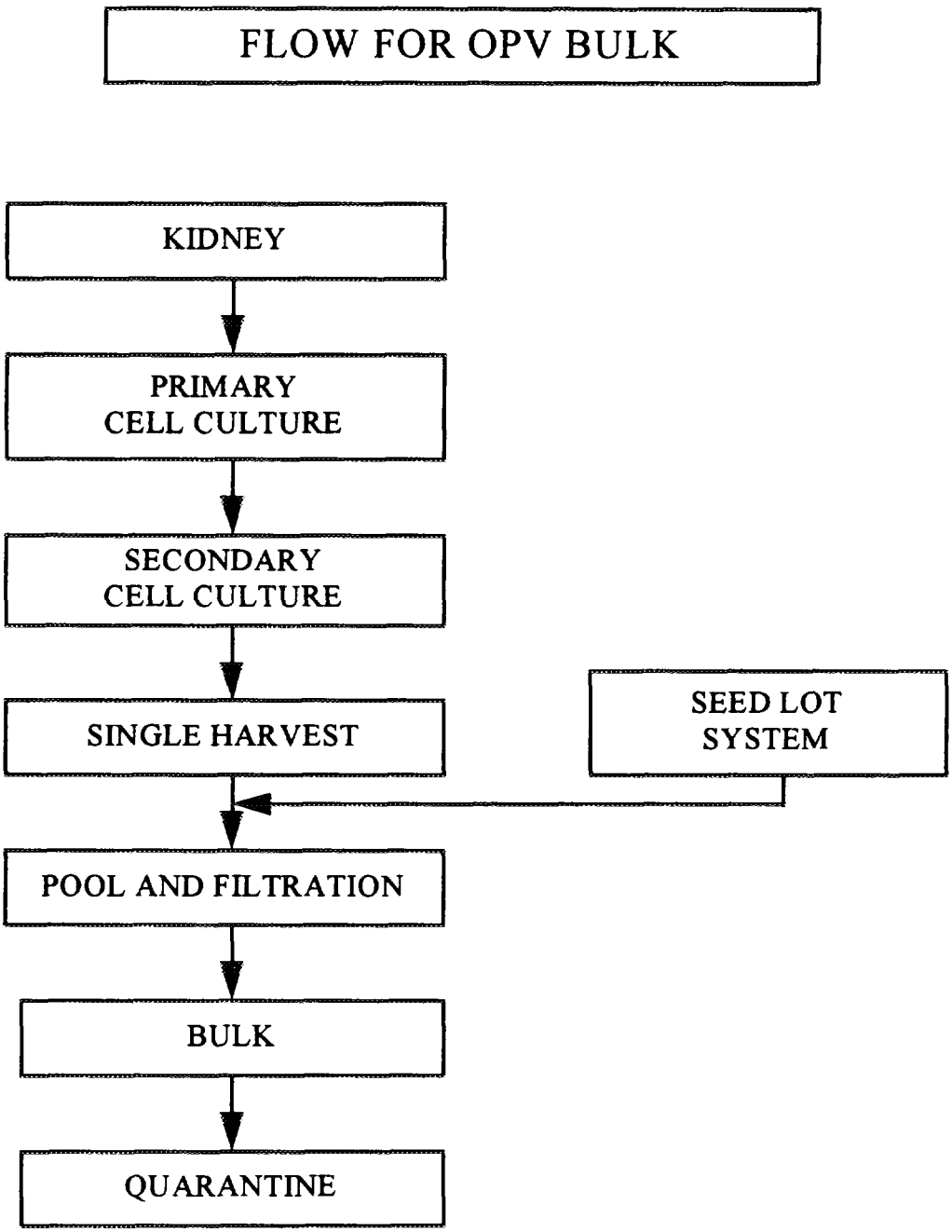
PRODUCTION PLANT FOR 100 MILLION DOSES OF ORAL POLIO VACCINE

GROUP D REPORT

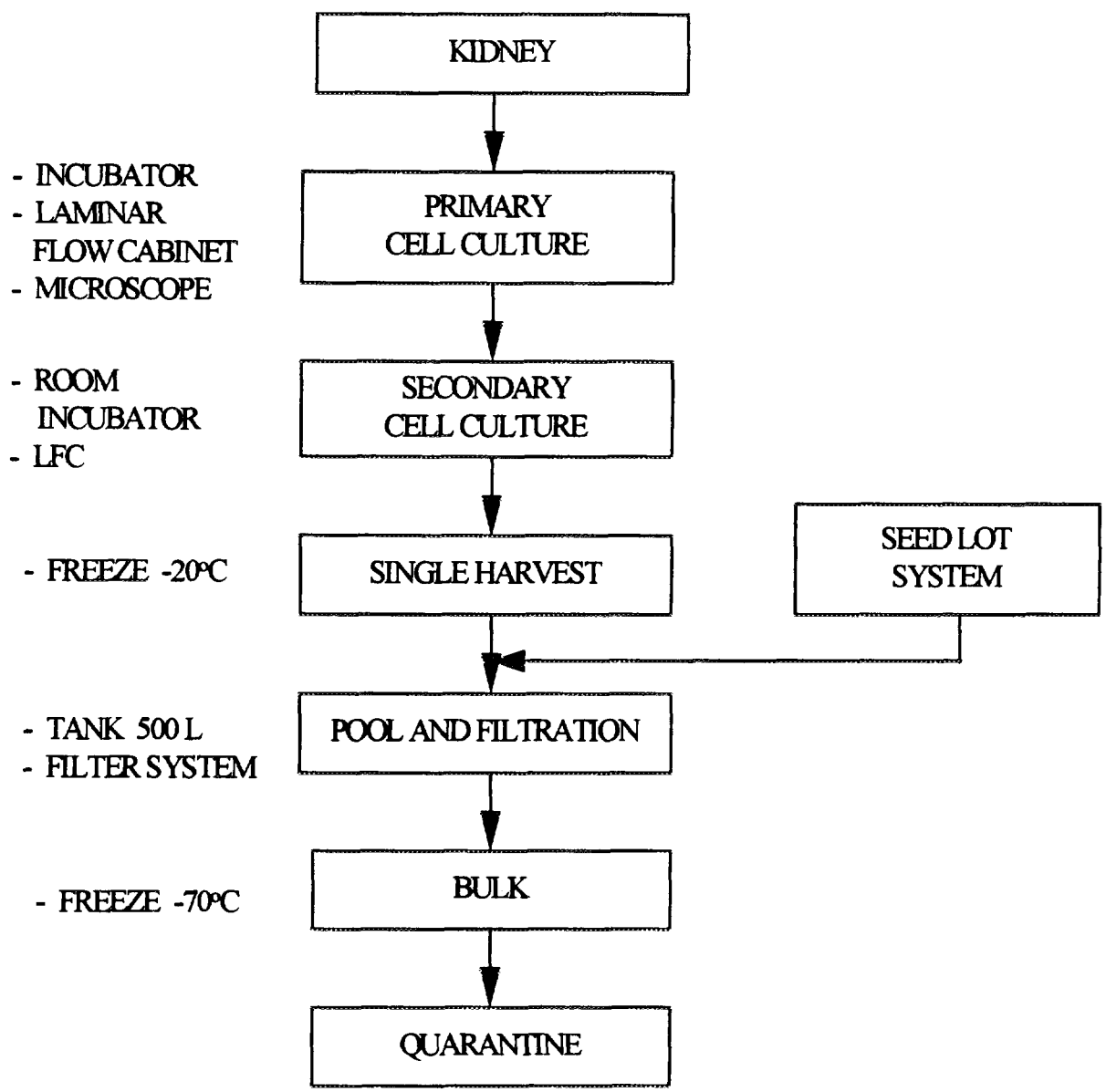
Group Leader	:	Dr. Jorge Gomez
Members	:	Dr. Nawal F. Mostefai
		Mr. Chen Xue Kin
		Dr. A.M.T. Shoushtari
		Ms. Sri Endreswari
		Dr. Choi Wan Gyu
		Mr. Yao Tongli

INTRODUCTION

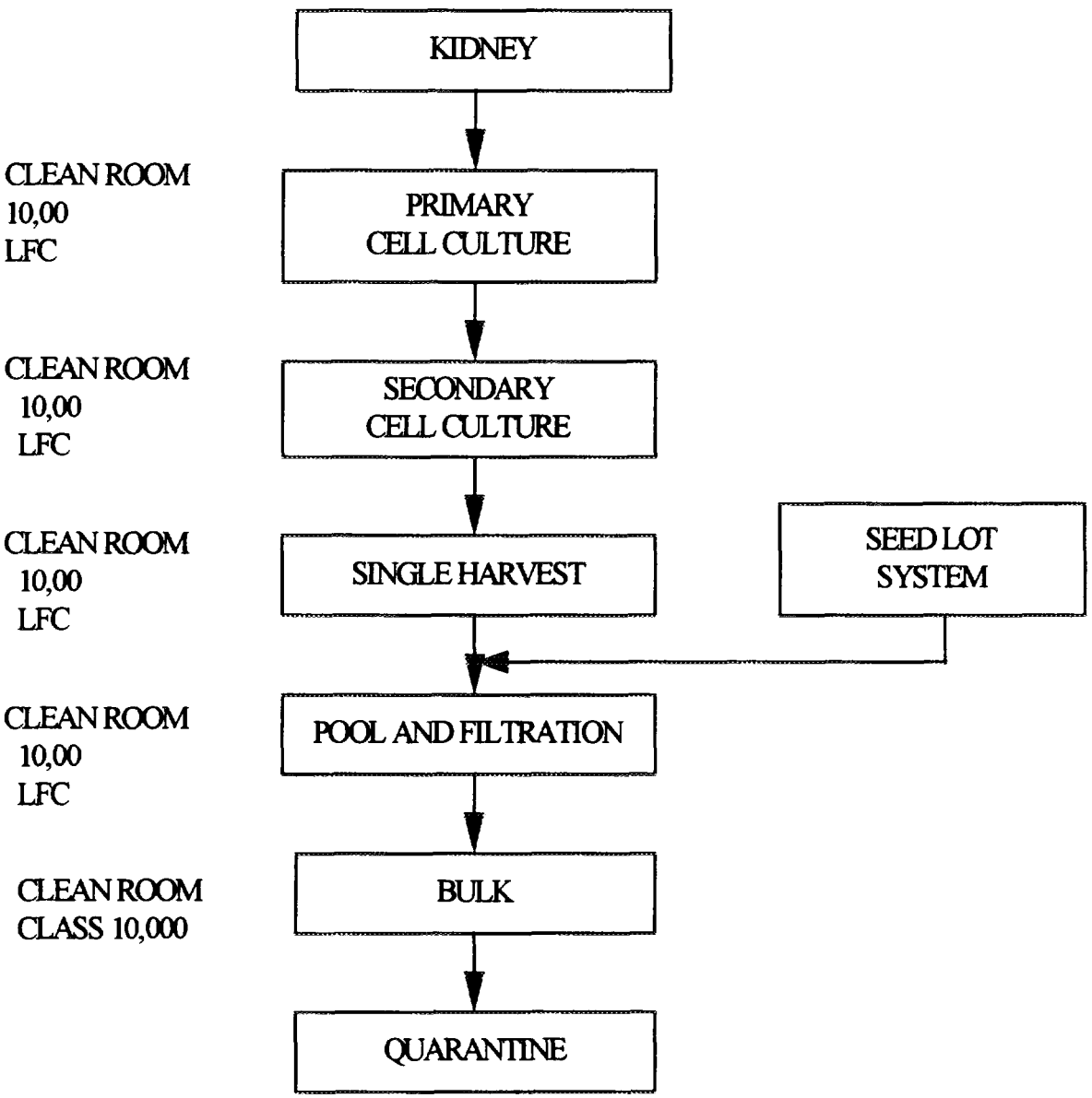
OPV-1OOM produces biological for human use and belongs to the pharmaceutical industry. OPV- 1OOM is a new dedicated facility which will produce 1OOM doses of OPV a year and employ 54 persons. It is a BL-2 Facility designed with respect to GMP in order to provide at its best ability, safety for its personnel, its product, and its environment. This facility is built in accordance with the regulation of the country and is in process of getting its building-license-the equipment, the necessary utilities as well as the production technology and the quality control procedures are in the validation phase.


FLOW FOR OPV BULK
KIDNEY
PRIMARY CELL CULTURE
SECONDARY CELL CULTURE
SINGLE HARVEST
SEED LOT SYSTEM
POOL AND FILTRATION
BULK
QUARANTINE

FLOW FOR OPV BULK



FLOW FOR OPV BULK



1. PRODUCT CHARACTERISTICS

LIVE ATTENUATED TRIVALENT VACCINE FORM LIQUID

DOSAGE	:	0.2 ml
USAGE	:	2 drops oral route
EXPIRATION DATE	:	6 months at +2 to 4°C
	:	2 years at -20°C

2. DEFINITION

Trivalent attenuated poliomyelitis vaccine is a mixture of attenuated poliomyelitis virus Type 1, Type 2, Type 3 at a concentration of:

TYPE I	1,000,000 DICT/50	6
TYPE II	100,000 DICT/50	5
TYPE III	600,000 DICT/50	5.8

NO. OF BULK PRODUCTION
FOR 100 MILLION DOSES PER YEAR OPV

Bulk No.	Polio Type
1	I
2	II
3	III

3. FORMULATION

TYPE I	1,000,000	DICT/50	0.2 ml
TYPE II	100,000	DICT/50	0.2ml
TYPE III	600,000	DICT/50	0.2ml

HUMAN SINGLE DOSES

0,2 ml - 2 drops

RAW MATERIAL FOR BULK

- WATER WFI	300 Litres
- CULTURE MEDIA (MEM)	300 Litres
- CELL FACTORIES	40 pieces
- SERUM	15 Litres

EQUIPMENT FOR PRODUCTION

5	Laminar Flow Cabinet
1	Tank 500 Litres
1	Filter System 400 Litres
20	Freezers
2	Invert Microscope

EQUIPMENT FOR WASHING-STERILISATION-CULTURE MEDIA PREPARATION

4	Autoclaves
1	Osmoses Reverse Unit
4	Ovens
2	pH-metres
2	Balances
1	LFC
1	Filter System
1	Ultrasonicator

UTILITIES

1	Steam generator
1	Pretreat water system
1	Electric and power generator
1	Air compressor
2	HVAC
	Sewage system
	Gas station

4. SCHEDULE

Assume : Blue print done

Building construction (2100 m^2)	}	18 months
Validation		
Installation	}	
Utilities	}	
Equipment	}	18 months
Production	}	
(5 batches with 1 MK)	}	
Ideal time frame		36 months
Realistic time frame		42 months

Validation Plan Schedule

1. Building Validation
2. Utility Validation
3. Equipment Validation
4. Processing Environment
5. Process Training
6. Personnel Training
7. Preventive Maintenance Programme
8. Calibration
9. Material Control
10. Cleaning Validation
11. Environmental Monitoring
12. GMP Training

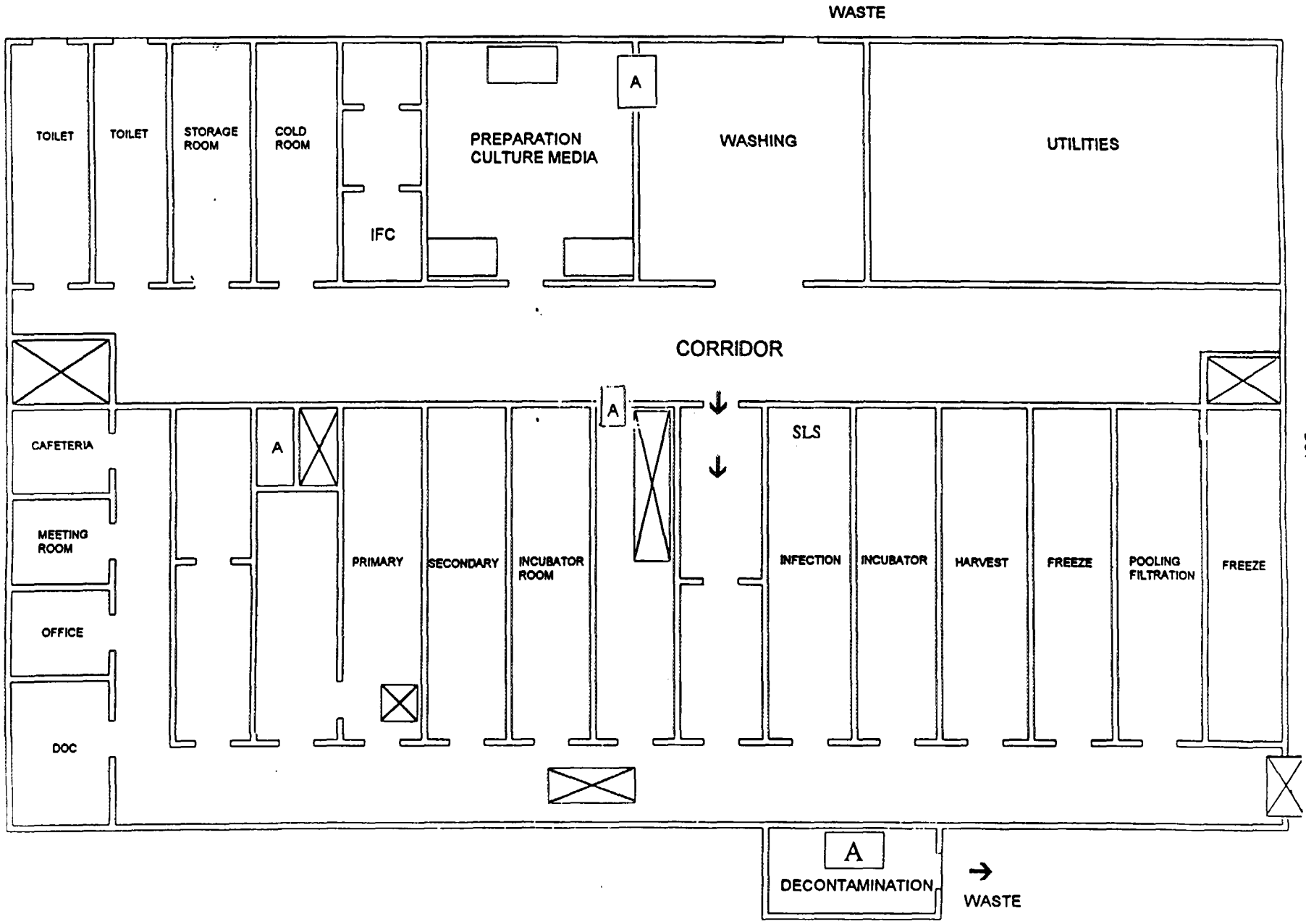
OPV - 100m

COST

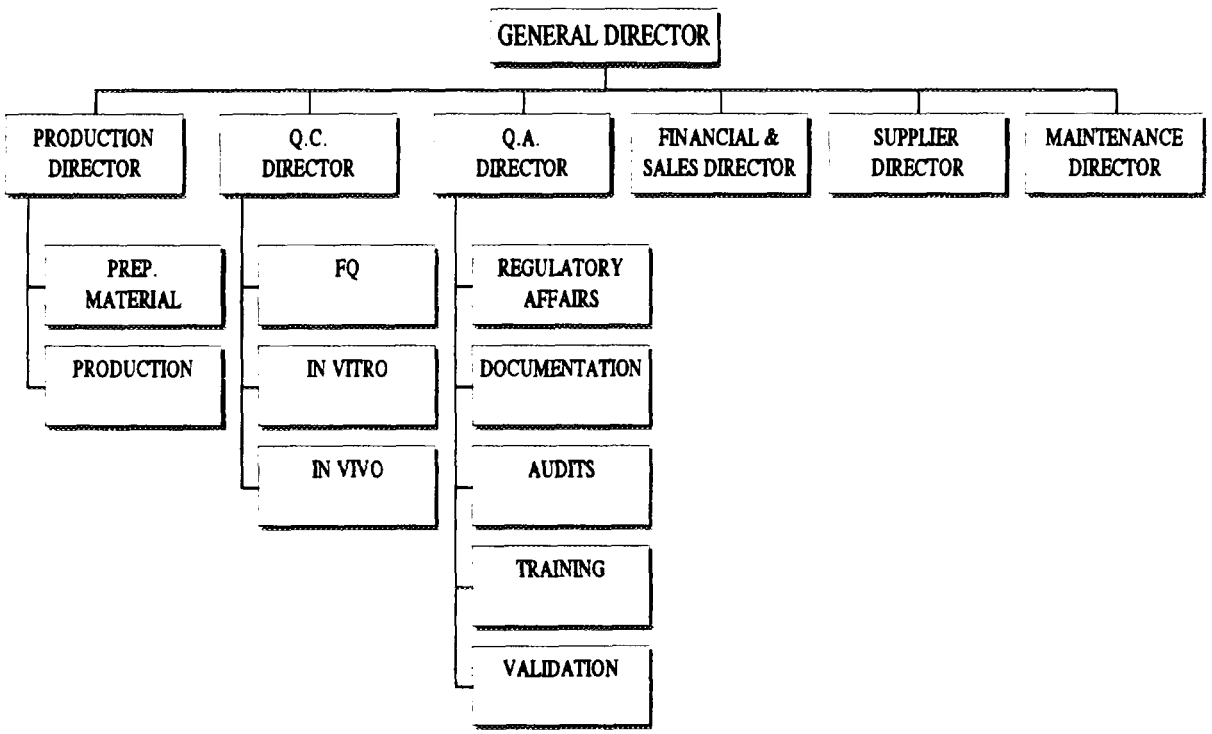
US$ 3000/m^2	Laboratory production
US$ 1000/m^2	QC, QA, Administration, storage R.M., etc.

LABORATORY PRODUCTION	800 m^2 x US$ 3,000 =	US$ 2,400,000
QC	300 m^2 x US$ 1,000 =	300,000
QA	200 m^2 x US$ 1,000 =	200,000
ADMINISTRATION	300 m^2 x US$ 1,000 =	300,000
STORAGE R.M.	200 m^2 x US$ 1,000 =	200,000
UTILITIES MAINTENANCE	300 m^2 x US$ 1,000 =	300,000
SUB TOTAL		**US$ 3,700,000**
EQUIPMENT 30 %		1,110,000
		4,710,000
VALIDATION COST 10 %		471,000
GRAND TOTAL		**US$ 5,181,000**
		======

PRODUCTION LABORATORY OPV BULK 100M



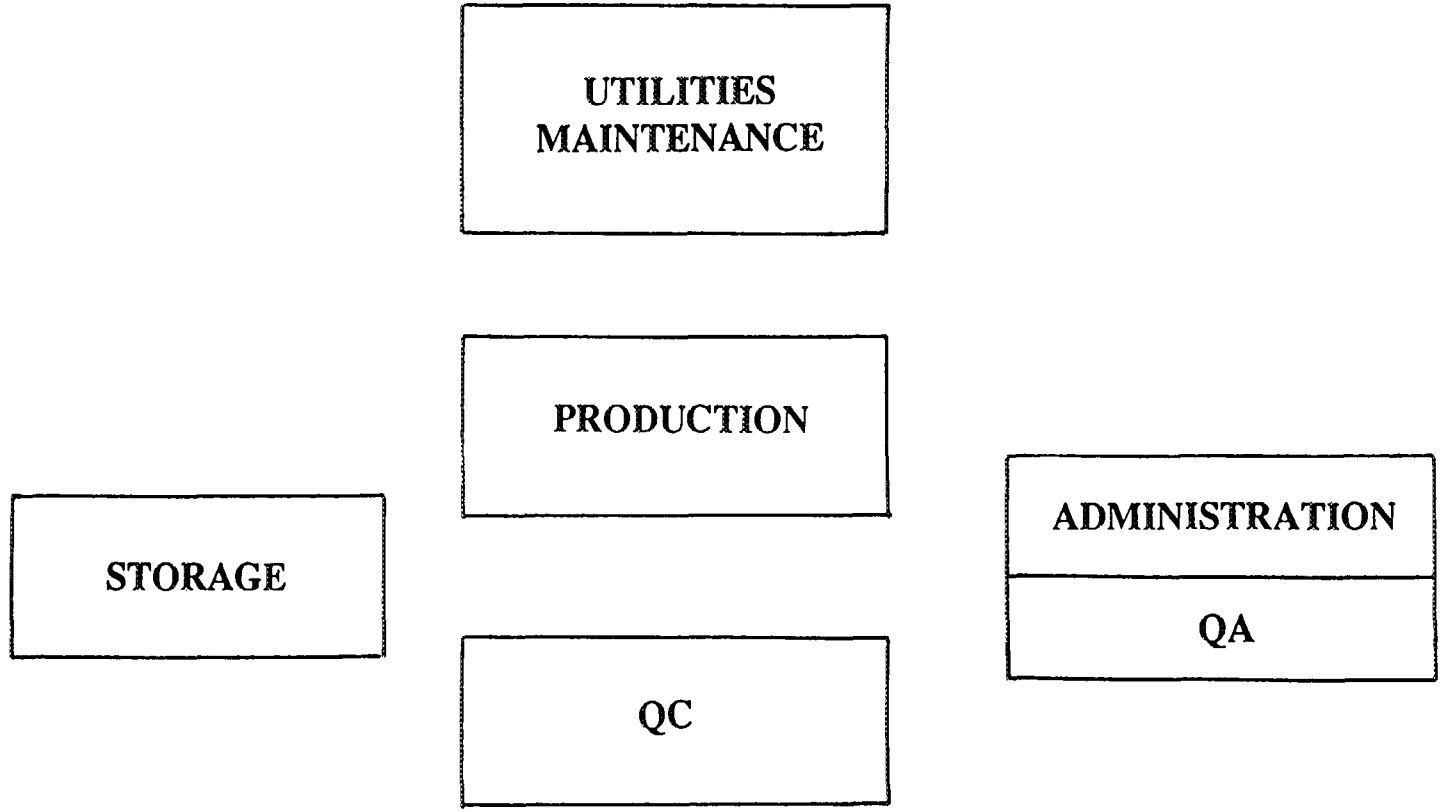
ORGANIZATION STRUCTURE



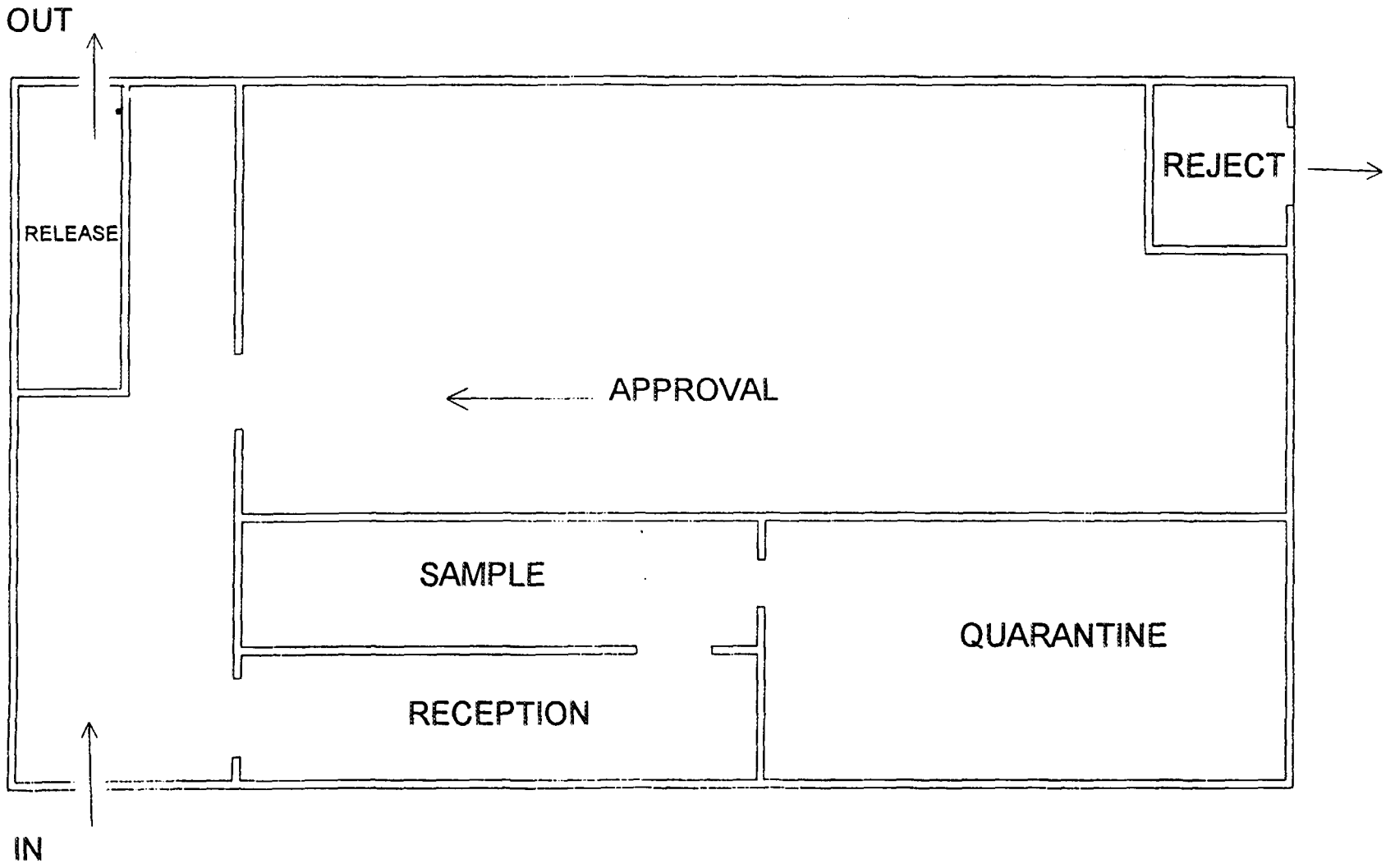
TOTAL PERSONNEL : 54

PRODUCTION PERSONNEL : 14

GENERAL PLAN DISTRIBUTION FOR PRODUCTION OF OPV BULK



STORAGE RAW MATERIAL



310

PART IV

COURSE PROGRAMME

COURSE EVALUATION AND FEEDBACK

LIST OF PARTICIPANTS

LIST OF FACULTIES

COURSE PROGRAMME

July 8 - 15, 1996

IVI/UNIDO/BIO FARMA TRAINING WORKSHOP QA/CGMP/QC FOR VACCINE MANUFACTURE IN DEVELOPING COUNTRIES

DAY 1 - July 8, 1996

08:30-10:00 : Dr. Zoltan Csizer / Dr. Gurinder Shahi
Opening Session Speeches from:
- Director General FDA (Indonesia)
- Provincial Health Officer
- Director of Bio Farma
- IVI Project Leader
- UNIDO Representative

10:00-10:30: Coffee Break

10:30-11:30: Rosemina Merchant
Introduction to the Course
- Course Layout
- Expectations
- Workshop Requirements
- Site Visits
- GMP Action Plan

11:30-12:30: **Section 1**- Rosemina Merchant
Introduction to CGMP
- Rationale
- Concept
- Philosophy

12:30-14:00: Lunch

14:00-15:00: Section 1 - Rosemina Merchant
Introduction to CGMP
- Basic Elements of QA Programme
- CGMP Regulations and Guidelines of WHO
- Differences between Quality approaches on North America and Europe

14:30-15:00: Coffee Break

15:00-17:00: **Section 2** - Rosemina Merchant
Facility Design for CGMP Compliance
- Pharmaceutical Facility
- Room Data Sheets
- Building Project Checklist
- Site Survey Checklist
- Design and Project Management

DAY 2 - July 9, 1996

08:30-09:30: **Section 2** - Rosemina Merchant
Containment and Biosafety Considerations in Designing BioPharmaceutical Facilities

09:30-10:30: **Section 2** - Rosemina Merchant
Clean Room Part I:
- What is a clean room?
- Clean room design

10:30-11:00: Coffee break

11:00-12:00: **Section 2** - Rosemina Merchant
Clean Room II
- Contamination Control in Clean Room
- Gowning

12:30-13:30: Lunch

13:30-14:00: **Section 3** - Nikola Cucakovich
Introduction to Validation

14:00-14:30: Nikola Cucakovich
Validation issues in the clean room:
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

14:30-15:00: Coffee break

15:30-16:30: **Section 3** - Nikola Cucakovich
Facility Qualification
Documentation Requirements during Facility Qualification
Interlocking Systems
Special Design Considerations

DAY 3 - July 10, 1996

08:30-10:30: Section 5 - Rosemina Merchant
Utility Systems for the Pharmaceutical Industry
Pharmaceutical Water System; Design Approach
Clean Steam
CIP

10:30-11:00: Coffee Break

11:00- 12:00: Section 3 - Nikola Cucakovich
Introduction to Site Visit and Workshop on Facility Design
Individuals will be split into four groups to design a plant for:

10 Million DPT - BL2-LS
100 Million DPT - BL2-LS

10 Million OPV - BL2-LS
100 Million OPV - BL2-LS

The issues to be covered in this workshop include:
Containment
Design
QA and QC
Technological
Operational
Yields and Time Lines
Equipment Specifications

12:00-13:30: Lunch

13:30-17:30: Section 3 - Nikola Cucakovich

Workshop on Facility Design and Site Visit

To prepare for Site Visits, Bio Farma personnel should prepare for groups to see the following:

Material Control, Warehousing, Production Area, QC Area, QA Documents, Testing and Stability Area and Record Keeping and Archives. Some examples of SOPs would be good.

DAY 4 - July 11, 1996

08:30-10:30: **Section 3** - Nikola Cucakovich
Critical Elements in Vaccine Manufacturing Systems
Seed Bank Production
Large Scale Production
Primary Recovery
Purification
Fill and Finish

10:30-11:00: Coffee Break

11:00-12:30: **Section 3** - Rosemina Merchant
Roles, Responsibilities, Accountability and Authority of Personnel in CGMP Operations
Procurement of Materials for GMP Operation, Validation of Personnel

12:30-14:00: Lunch

14:00-15:30: **Section** 7 - Rosemina Merchant
Role of QC and QA in CGMP Operations:

15:30-16:00: Coffee Break

16:00-17:00: **Section 3** - Nikola Cucakovich
Case Study BL3-LS Facility Design

17:00-17:30: **Section 6** - Rosemina Merchant
Procurement

DAY 5 - July 12, 1996

08:00-10:00: **Section 3** - Nikola Cucakovich
Equipment Validation, Preventive Maintenance and Cleaning Validation

10:00-10:30: Coffee Break

10:30-12:00: **Section 3** - Nikola Cucakovich
Utility Validation:
- HVAC
- Steam
- Air Compressor
- Drainage and Electrical Systems

12:00-13:30: Lunch

13:30-17:30: **Section 3** - Nikola Cucakovich
Master Validation Plan Workshop

DAY 6 - July 13, 1996

08:30-10:00: Section 2 - Rosemina Merchant
Introduction to Documentation System
Documentation and Documentation Control)

Points to Consider:
a) Importance of Documentation
b) Effect of Language/ Choice of Words
c) Preparation Format: Distribution, Approval, and Archiving
d) Deviation and Investigation

10:00-10:30: Coffee Break

10:30-12:30: Section 4 - Rosemina Merchant
Types of Documents:
Master Production Batch Protocol/Production Batch Protocol
SOP
Part Number and Part Number Specifications
Receiving Codes
Equipment Tracking Number
Master Document Index
Facility Master Plan
Master Validation Plan
Production Batch Numbers
Solution Lot Numbers
Intermediate Part Numbers

12:30-14:00: Lunch

14:00-16:00: Section 4 - Rosemina Merchant
Master Document Index (MDI) Workshop

16:00-16:30: Coffee Break

16:30-17:30: Section 4 - Rosemina Merchant
Presentation of MVP Workshop

DAY 7 - July 14, 1996

09:00-15:00: Bandung tour and individual meeting with Faculty

15:00-18:00: Open discussion with Faculty

18:00-20:00: Dinner with the Experts

DAY 8 - July 15, 1996

08:30- 10:30: **Section 2** - Rosemina Merchant
Facility Design Workshop Presentations

10:30-11:00: Coffee break

11:00-12:30: Dr. Zoltan Csizer
The GMP Action Plan

12:30-13:30: Lunch

13:30-14:30: Dr. Zoltan Csizer
Course Evaluation and Wrap-Up

COURSE EVALUATION AND FEEDBACK

A Course Evaluation Questionnaire (see attached) was handed out at the end of the workshop to enable faculty and organizers to benefit from the feedback and suggestions of participants.

Feedback

Participants generally reported that they found the workshop extremely useful and seemed to find the facility design exercise particularly beneficial. One participant, for example, reported that she now saw her own facilities with new eyes, and realized many ways in which facilities, practices and procedures could be improved. Several participants also reported that they felt much more confident now in their ability to troubleshoot and rectify problem areas in their own facilities.

Participants filled out evaluation questionnaires at the end of the workshop. The mean score of their evaluations (on a scale of 0 to 10) are summarized below:

Organization/Planning	8.5
Support Facilities	8.7
Course Materials/Handouts	8.3
Subject Matter	8.4
Faculty	8.3
Overall Rating for Course	8.4

Approximately 4 weeks subsequent to the course, participants were asked if their institutions had either taken, or intended to take, any action as a consequence of their participation in the workshop. Most indicated that their institutions now had a better appreciation for what it would require to achieve internationally acceptable standards of GMP. Many also said that their institutions had agreed to implement several improvements in approach to documentation and validation, for example, in accordance with what was learnt at the workshop. Several institutions were also in the process of establishing GMP Task Forces and initiating the process of developing GMP Action Plans. It is to be anticipated that substantial improvements in operation and practice are likely to result from these efforts by the various institutions.

Course Evaluation Questionnaire

Please take the time to fill in this evaluation form questionnaire which is designed to help us help you.!!

==========

Scoring Scale

0 1 2 3 4 5 6 7 8 9 10

very poor ---------- poor ---------- average ---------- good ---------- excellent

==========

A. Pre-Meeting Arrangements

Information/Correspondence from Organizers _____

Visa Application Process (if applicable) _____

Travel Agent [Jetspeed] Services (if applicable) _____

Airport Pick Up Service _____

Comments and Suggestions: _____

_____

_____

_____

_____

B. Accommodation and Meals

Hotel Facilities and Service _____

Meals/Breaks at Hotel _____

Meals/Breaks at Bio Farma _____

Comments and Suggestions: _____

_____

_____

_____

_____

C. Workshop Organization and Programme

Meeting Room and Facilities _____

Workshop Schedule _____

Technical Content _____

Course Handouts and Contents _____

Lectures _____

Working Groups _____

Facility/Site Visits _____

Opportunity to Interact with Speakers _____

Opportunity to Interact with Other Attendees _____

Comments and Suggestions: _____

_____

_____

_____

D. Course Subject Matter

Please provide your assessment of course subject matter according to the following criteria:

	Principles	**Practical Orientation**	**Relevance to your needs**
General GMP Issues	____	____	____
Facility Design Considerations	____	____	____
Validation	____	____	____
Documentation	____	____	____
Others: _____	____	____	____

Comments and Suggestions: _____

_____

_____

_____

_____

E. Faculty

Please rate faculty according to the following criteria (where applicable):

	Notes/Handouts	Presentation	Relevance	Approachability
Key Faculty				
Rosemina Merchant	____	____	____	____
Nicola Cucakovich	____	____	____	____
Support Faculty				
Benny Kaligis	____	____	____	____
Stanford Lee	____	____	____	____
_____	____	____	____	____
_____	____	____	____	____

F. Self Evaluation

How would you rate your knowledge of QA/GMP/QC prior to Workshop? (please tick as appropriate)
__ Very knowledgeable
__ Knowledgeable
__ Somewhat Knowledgeable
__ Slightly Knowledgeable
__ Not Knowledgeable

How would you rate your knowledge after completing this Workshop?
__ Very knowledgeable
__ Knowledgeable
__ Somewhat Knowledgeable
__ Slightly Knowledgeable
__ Not Knowledgeable

Comments: _____
_____
_____
_____

G. Overall Assessment

Rating for Organization/Planning	_____
Rating for Support Facilities	_____
Rating for Course Materials/Handouts	_____
Rating for Course Subject Matter	_____
Rating for Faculty	_____
Overall Rating for Course	_____

Comments and Suggestions: _____

_____

_____

_____

H. Quotable Quotes (comments and suggestions regarding this workshop or possible training initiatives of the IVI in general. These will be considered for possible inclusion in the next issue of the IVI Newsletter): _____

_____

_____

_____

_____

_____

_____

_____

_____

Name (optional): _____

THANK YOU!!!

IVI/UNIDO/Bio Farma Training on
QA/GMP/QC for Vaccine Manufacture in Developing Countries

Bandung, Indonesia
July 8-15, 1996

Course Evaluation Questionnaire

Please take the time to fill in this evaluation form questionnaire which is designed to help us help you.!!

==========

Scoring Scale

0 1 2 3 4 5 6 7 8 9 10

very poor ---------- poor ---------- average ---------- good ---------- excellent

==========

A. Pre-Meeting Arrangements

Information/Correspondence from Organizers	8.6
Visa Application Process (if applicable)	7.8
Travel Agent [Jetspeed] Services (if applicable)	8.2
Airport Pick Up Service	7.9

Comments and Suggestions:

_____
_____
_____
_____
_____

B. Accommodation and Meals

Hotel Facilities and Service	8.2
Meals/Breaks at Hotel	8.3
Meals/Breaks at Bio Farma	9.1

Comments and Suggestions:

_____
_____
_____
_____

C. Workshop Organization and Programme

Meeting Room and Facilities	8.2
Workshop Schedule	8.1
Technical Content	7.9
Course Handouts and Contents	8.3
Lectures	8.3
Working Groups	7.8
Facility/Site Visits	7.9
Opportunity to Interact with Speakers	8.3
Opportunity to Interact with Other Attendees	8.4

Comments and Suggestions: _____

_____

_____

_____

D. Course Subject Matter

Please provide your assessment of course subject matter according to the following criteria:

	Principles	**Practical Orientation**	**Relevance to your needs**
General GMP Issues	8.3	7.6	7.9
Facility Design Considerations	8.2	7.7	7.9
Validation	8	7.4	7.9
Documentation	8.5	7.8	8.4
Others: _____	____	____	____

Comments and Suggestions:

_____

_____

_____

E. Faculty

Please rate faculty according to the following criteria (where applicable):

	Notes/Handouts	Presentation	Relevance	Approachability
Key Faculty				
Rosemina Merchant	8.8	9.1	8.9	8.5
Nikola Cucakovich	7.5	7.7	7.9	8.0
_____	____	____	____	____
Support Faculty				
Benny Kaligis	7.5	7.5	7.9	8.0
Stanford Lee	7.9	7.8	7.9	7.9
_____	____	____	____	____
_____	____	____	____	____

F. Self Evaluation

How would you rate your knowledge of QA/GMP/QC prior to Workshop? (please tick as appropriate)

__ Very knowledgeable
__ Knowledgeable
__ Somewhat Knowledgeable
__ Slightly Knowledgeable
__ Not Knowledgeable

How would you rate your knowledge after completing this Workshop?

__ Very knowledgeable
__ Knowledgeable
__ Somewhat Knowledgeable
__ Slightly Knowledgeable
__ Not Knowledgeable

Comments: _____

G. Overall Assessment

Rating for Organization/Planning	8.5
Rating for Support Facilities	8.7
Rating for Course Materials/Handouts	8.3
Rating for Course Subject Matter	8.4
Rating for Faculty	8.3
Overall Rating for Course	8.4

Comments and Suggestions: _____

_____

_____

_____

_____

I. Quotable Quotes (comments and suggestions regarding this workshop or possible training initiatives of the IVI in general. These will be considered for possible inclusion in the next issue of the IVI Newsletter):

_____

_____

_____

_____

_____

Name (optional): _____

THANK YOU!!!

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