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TRAINING MANUAL FOR

IVI/UNIDO/BIOFARMA TRAINING WORKSHOP QA/cGMP/QC FOR VACCINE MANUFACTURE IN DEVELOPING COUNTRIES

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CHAPTER 1

INTRODUCTION TO cGMP

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

A. Rationale
B. Concept
C. Philosophy

A. 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/she is not able to determine whether or not a drug product 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, dietheylene glycol. Generally an elixir is designated as an alcohol based product, but this particular formulation was of dietheylene glycol. Upon ingestion, the 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."

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

LVP - Large Volume Parenterals

Intravenous fluids became contaminated with microbes during the production process. After sterilization, the intravenous fluid containers were cooled using potable water. Microbes present in the water were introduced into the space between the liner and the metal cap of the container. Organisms remained dormant until they were inoculated into the fluid at the time of preparation of the container for administration. Once transferred into the solution, the microbes proliferated rapidly and causing septicaemia and death in a large number of hospitalized patients.

1995 - 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 step.
- Active live virus production process which used heat inactivation step. For virus; scale of heat inactivation step may not have been sufficient.

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

Result: ***Safety evaluation of drugs and biologics 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 1,000, thousands of babies 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 was to remove the undesired enantiomer by a validated purification process assured by 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 cGMP's (i.e. production using a validated process).

1970 - Contaminated Caps (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
378 infected but survived

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 died from 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. By October 1, 1982, 6 more people died.*

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

1987 - Tryptophan

ShowaDenko 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/day! It is speculated that unexpected process contaminant/impurity present at less than 0.0089% is 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 Industry today 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 in-coming 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 contaminates 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 pharmaceuticals or vaccines and because of this potential, it is important to test many different physiochemical 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 drug product, an estimate 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 bad lots will pass the tests applied to them. In this case, bad lots of product 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 of 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 which is the same as the UQL.

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 drug or 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 contain 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.

B. Concept of cGMP

The objectives of cGMP are to be able to manufacture pharmaceutical and vaccines **consistently of** high quality and to be able to **detect** defects whenever they are found. The quality of a pharmaceutical and 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 nine key areas in pharmaceutical manufacture. Specifications are therefore a very important criterion to be considered as early as possible in pharmaceutical and vaccine development as it will provide a goal to work toward. Specifications must be developed in conjunction with production, QA and QC and 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 stability approved formulation candidates which are samplings for the final market requirements. Product

attributes must be made with stability in mind, many vaccines and pharmaceuticals show excellent attributes when first prepared, however, after a few months the story can be different.

c) Valid Compatibility/Stability Data

d) Process Specification

Validation and documentation during GMP production is where the production of contamination free and defect free pharmaceuticals and vaccines **consistently** and **reproducibly** is the goal.

e) Process Validation

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

> *to attain and document sufficient evidence to give reasonable assurance, given the current state of art of state manufacturing, that the process under consideration will do what 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.

f) Documentation; the most critical documents include:

1. MPR (Master Production Records)

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

2. SOP's - Standard Operating Procedures

Certain procedures in the manufacturing plant which are not related to the production of a specific batch of a pharmaceutical or vaccine is made reproducible through constant adherence to SOP's.

g) 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 drug." 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 towards producing a defect free pharmaceutical or vaccine.

h) QA Strategy

The strategy for assuring that every unit of drug product 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 is based on **screening all incoming shipments** and the **testing of all completed lots before releasing** them for distribution.

Screening of all in-coming materials starts with the preparation of adequate specifications and the 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 in-coming 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 tested before releasing the lot for distribution.

i) Post Marketing Surveillance Strategy

Three principle attributes comprise this event:

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

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

C. Philosophy of cGMP

- Definition

The United States definition for GMP is "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." The US definition of GMP is also strongly influenced by Industry Standards set by individual companies.

UK definition of GMP is it " 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 whether it is to be treated as a fundamental professional ethical matter.

Earlier on I had described certain customary practices in the pharmaceutical industry, like the end product testing, in-process testing and raw materials testing, each of these practices carry a significant risk of failure, and they are clearly

inadequate to guarantee the provision of defect-free pharmaceutical or vaccine. To date, the singular known solution to avoid manufacturing and distributing defective pharmaceutical or vaccine is the adoption of full cGMP; specifically process validation to establish accuracy and documentation to assure precision and reproducibility.

With respect to the issue of cost; typically in organizations where cGMP is implemented fully, it is not uncommon 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 cleanrooms, monitoring, etc. can add a significant cost to capital and operations.

- Cost

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 drug and consequently its availability to the various population?

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

- 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 biologics for example, 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 while the vaccine is on the market. Another aspect of the GMP dealing with scope, is in the level of the economy of the environment in which the practice is in use; this for example:

> GMP measures applied in industrialized countries may be more elaborate that those in developing countries. There is **only 1 GMP**, but the practical levels which are implemented may vary from one environment to another.

- 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 products performance while the product is in the field.

CHAPTER 2

BASIC ELEMENTS OF QA PROGRAMME

The function of the Quality Assurance (QA) is to design a programme to meet the expectations of cGMP.

For pharmaceuticals and vaccines, this translates to:

- identity
- purity
- potency
- stability
- uniformity
- safety
- efficacy
- quality

Quality:

- Establish the quality. Determine the attributes of the raw material, and how will it impact the process or performance of a product, i.e. choice of the raw material, if the raw material is not chosen properly.
- Determine what could go wrong that could significantly impact the safety, uniformity, reliability and performance of final product.
- Then go on to choose quality parameters and test methods that are scientifically rigorous.
- Finally set limits for these attributes; express as:

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

Set the specifications 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.

Monitor Quality:

- Monitor quality so that you assure that the standards you have set in #1 are routinely met, this is already 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.

Control Change:

- Change is inevitable; however uncontrolled change is dangerous. This is because there is always the potential that a 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.

Document It:

- Document the quality standards you have established (item 1).
- Document the monitoring programs and the monitoring data that you collect (item 2).
- Document any changes that occur (item 3).
- Documentation is the **CURRENCY** of a pharmaceutical company; without it, it can not market the product it has made.

QA in Pharmaceutical Organizations:

- Establish quality = set specifications
- Confirm quality = validation
- Assure quality = monitoring/control programmes
- Control change = minimize change

Always Document These Commitments

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 work will be performed in accordance to quality requirements and documented consistently and reproducibility. The statement is the heart of GMP and validation.
- Assures the accountability and traceability of information.
- Assures access to an integration of 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.

Example of Quality Systems:

ISO International Standard Organization

GMP's Good Manufacturing Practices

TQM Total Quality Management

CHAPTER 3

FACILITY DESIGN FOR cGMP COMPLIANCE

1. WHAT DO THE REGULATIONS SAY ABOUT FACILITY DESIGN? Some examples are described below:

Plant Lockers

- "personnel engaged in the manufacture, processing, packaging or holding of a drug product shall wear clean clothing, appropriate for the duties they perform. Protective appeal, such as head, face, hand and arm covering shall be worn as necessary to protect the drug products 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 in to 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 so such as to prevent potential contamination. *Thus one must design for uni-directional 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
- ejected 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

HVAC

- adequate ventilation to be provided
- equipment for control of over air pressure, microorganisms, dust, humidity and temperature is to be used when the operations dictate
- 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 shall be opened into a manufacturing area
- Germicidal hand washing

Sanitation

- Building used in the manufacture of vaccines are 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 is 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 rodenticides, 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)

- flow out of an operating area
- vials must be crushed and labels removed or destroyed from the products which cannot be salvaged

Live Vaccine Processing

- Space used for processing live vaccines shall not be used for any other purpose during the processing period for that vaccine and such space shall be decontaminated prior to initiating processing.
- Live vaccine processing areas shall be isolated from and independent of any space used for any other purpose by either in a separate building, in a separate wing of a building or in quarters at the blind end of a corridor and shall 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 quantity cannot be completely tested in the final product and therefore it must be built into the process used to create the vaccine. Additionally, 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 campaigned basis). Thus measures to prevent cross contamination of products and demonstrations of sufficient control of 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.

General Considerations for Facility Design

- The design of the facility should include the 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, rather enclosed to prevent build up of dust, etc.

- The facility design should provide for the 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 sufficient storage of supplies and equipment, this means sufficient for the campaign. 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 turn reduces the chances of contamination. Space issue should be must that there is approximately 20 square meters per operation.

- Use of separate air handling systems is required to establish isolated manufacturing areas fermentation where line operation are carried out must have a separate air handling system. Purification is usually performed in Class 100,000 environment. Final filtration and filling is 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 air-borne 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, the higher the quality of the room finish and air quality is required.

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

Containment Considerations In Facility

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 level 2 manufacturing activities which require GMP and containment:

Air Handling System

Room Air Supply

- Air supply must be independent from adjoining facilities for different manufacturing operations.
- Air supply HEPA filtered with magnehelic gauges to monitor pressure drop of the HEPA
- Directional inward, non-recirculated airflow for live, pathogenic manufacturing i.e. fermentation must be implemented

- Must be interlocked with exhaust ventilation to prevent pressurization.
- Equipped with audible alarms to detect pressurization failure.
- Ductwork must be sealed reasonably airtight and independent from others in facilities and accessible from outside containment laboratory in case of repairs.
- 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 hazards 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, these are over and above regulations and must be respected.
- Exhaust verification can be equipped with manual damper to permit sealing for decontamination if necessary.
- Exhaust from laboratory must meet a minimum of at least ten room volumes per hour.
- Recirculated HEPA filtered may be air permitted if it is not coming from a live area.
- Air exhaust system should be designed to be isolated to permit decontamination . For example, to avoid back flow of organisms in the event of a fan failure.

HEPA Filters

- HEPA filter be of a design to be tested and installed in-situ and decontaminated in-situ.
- HEPA filters to have minimum particle removal of 99.97 % for particles of 0.3um.
- HEPA filters to be installed as close as possible to source of hazard to minimize length of contaminated ductwork.
- HEPA filters to be installed in housing with leakproof junctions between filter frame and ducting.

Directional Air Flow

- An air flow indicator (magnehelic gauge for example) is required to ensure that exhaust/supply systems are functioning properly.
- Air pressure in lab should be maintained at a lower pressure than less contaminated areas.
- 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

- Laboratory is 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 labs near exit.
- Foot or elbow operated wash hand basin should be provided at 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.
- Lab 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 decontamination.
- Open drains should be closed when not in use.

Facility Equipment

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 in place in 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 bi-annually 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 system 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 40cm at the exhaust filter discharge to permit testing.
- HEPA filters in biological safety cabinets must be monitored by magnehelic gauges at all times.
- Use safety centrifuge buckets safety cups or sealed heads.

Ultracentrifuges

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

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/ gasketseal in the lid.

Culture Stirrers, Shakers and Agitators

- Operate in containment equipment.
- Use of heavy duty, screw capped culture flasks, filtered with filter protected outlets, if necessary and well secured.

Freeze-drying Apparatus

- Unit must be sealed throughout using o-ring connectors for example.
- 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 incineration
- 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 sanitizable.
- Where possible, monitors, recorders, printers and similar monitoring equipment should be located away from containment area.
- Surface area of equipment should be sanitizable and all ancillary equipment in contact with product should be sterilizable.

3. PHARMACEUTICAL FACILITY DESIGN PROJECT MANAGEMENT

There are four main stages in a project:

A. Feasibility Study - Economic Technical and Regulatory
B. Process Engineering - Personnel flow and Process Utilities
C. Project Review and Layout Considerations
D. Construction and Validation (Validation - this section will be discussed elsewhere)

A. FEASIBILITY STUDY; What is the purpose?

Economic Feasibility

The objective of an economic 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. Market requirements must be studied in detail and may include the following considerations:

- What is the product Definition?
- How many units are required per year? How does this translate in operations, number of shifts etc.?
- What are the range of product sizes/contents/materials? This impacts the size of equipment.
- What are the foreseen future market trends ?
- Inputs of production planning

  Market forecast
  Expiration date
  Process description
  Inventory levels

- Output of production planning

  Optimum batch size
  Number of production lines
  Equipment sizes
  Warehouse sizes

The input and output production planning decides how well your production works.

Financial Constraints must be evaluated with respect to: What is the return on investment (ROI) expectation? What are the capital constraints/limits? What is the foreseen market price for the production/profit margins/maximum acceptable cost of production?

Finally timing is also an important criterion, for example When is the product expected on the market and at what volume? Define a realistic time frame for the project (neither pessimistic or optimistic) and rigidly plan and control the project against this schedule. Typically, an economic feasibility study takes approximately 8 weeks.

- **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 ? What is the expected life cycle of the plant under the Condition of Operation?

- **Regulatory Feasibility**

Regulatory feasibility; what regulation will the plant or new facility have to operate under? Can the plant afford the regulatory constraints imposed by the country in which the product needs to be sold? Regulations depend on global

market, for example if you want to sell your product in Europe, regulation of European Union must be followed. Other regulatory requirements to consider include: Which regulatory authority will approve the product and inspect the operations? What are the anticipated standards required for the design, validation and documentation of the process and its operative environment? What will the regulations be like in the next 10 years?

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)?

The next step following the completion of the steps defined above, is termed the macro process review.

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 services demands?
- What are the regulatory constraints?
- ancillary plant and services

Ancillary Plant and Services

- What type and size of ancillary plant is 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, WFI
- Steam - house or process, clean
- Compressed air - grades
- Electricity
- Vacuum/special gases
- Effluent

- Inert gases
- Support area and storage needs

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 rooms.
- Offices.
- Cafeteria and personnel needs.
- Goods receiving area.
- Warehousing.

Future Operating Costs

- labour
- materials
- services
- other overheads

C. Project Review and Layout

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 on board 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 length of the construction programme.

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 which personnel need offices, where will documents be stored?

Material Flow

Material Flow needs to be identified with reasonable accuracy at an early stage as the viability of a location 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. The completes the macro process review. This next step after the macro process review is to prepare an initial plant or process layout.

Layout Analysis include the following:

- personnel flow
- material flow
- product flow
- biowaste flow

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 cGMP's

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

A full understanding of the operations in order the process area and flow of personnel and material through the facility is imperative under to design an acceptable layout. The definition of the operation must come from the user groups in the form of written description or logic diagrams. This is a step wise description of operation from one step to another.

Spatial requirements and relationships should be identified with input from users and 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 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 pharmaceutical facilities, engineering systems are present throughout the room, above the ceiling, below the ceiling, running horizontally, vertically, exposed and concealed. It cannot be emphasized too sharply that the space provided by the architect must also 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 as a criteria minimum:

- Flow patterns must be logical and simple
- Route lengths 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

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

Process Flow Diagrams 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 as is 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 the development of the 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 and pressure and material balance information is important. Separate diagrams are preferred for each utility systems 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 the air and air flow volume. In addition, the route of disposal for the effluents must be shown.

Following 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

Schedule of Finishes

eg. clean room data sheets (see later); these would specify, by the classification of area, acceptable types of finishes and the design details. New materials should be evaluated with care before major installations are undertaken. The architect must work with the uses 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 paint 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 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 levelling (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) with no recess or grooves and be smooth, acid an cleaning agent resistant surface.

- Epoxy coating - low cost, durable and impact resistant, best in high traffic areas. Because of the hardness of the material, the 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, can create headaches. Not recommended in high impact areas.
- Welded PVC - same as seamless but thicker, most durable but most expensive. It is a material of choice in aseptic areas more.
- Prefabricated wall panels (see cleanroom section).

Ceilings

Smooth, acid and cleaning agent resistant surface.

- Class 100,000 - non shedding tiles with hand drawn clips is sufficient. Simple ceilings over structural concrete, painted or vinyl covered gypsum plaster or modular is adequate for this classification.
- Class 10,000 require a cleaner epoxy painted finish.
- Class 100 environment filters and lighting fixtures usually occupy the entire ceiling grid work.

The quality of ceiling material must reflect pressurization within the room, a more stronger ceilings 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 joint between dissimilar materials).

Windows & Doors

Windows and frames should be 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 can cause bacteria to grow.

Example of a Clean Room Data Sheet

Project _____ Room number_____
Room name _____ Area_____

Specifications and locations of required services

Electricity
Voltage & number of outlets _____
_____
Horse power _____
Phase _____
Resistance _____

Air-conditioning
Temperature _____
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 _____ Special _____

Oil free _____ Other _____

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 _____

Room data sheets are an integral part of the facility design and is an invaluable source of information for Architect and Process Engineers. Once this information is complete, then only can one decide whether all the required number of rooms fit into the building. Should the existing building be a retrofit of an existing building or a new one to constructed. If new building is desired. This brings us to site selection.

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 to 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 facilities 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 need to be taken 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 MBO's). 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 are 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 are the objectives times to more realistic levels.

SITE SURVEY CHECK LIST

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 Municipal authorities Should be consulted	_____ ltr _____ PSIG _____ C _____ cents/m _____ ltr	_____ ltr _____ PSIG _____ C _____ cents/m _____ ltr
B.	Well what has been the experience in the area	_____ ltr _____ PSIG _____ C	_____ ltr _____ PSIG _____ C C
C.	Tower, Pond or River	_____ ltr _____ PSIG _____ C	_____ ltr _____ PSIG _____ C C

V. Telephone Service

Describe current or future status.

VI. Power

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

A. Natural or manufactured _____ _____

B. Heating value _____ Btu/cu _____ Btu/cu

C. Volume _____ cu.Ft. _____ cu.Ft.

D. Cost _____ $/M cu. Ft. _____ $/M cu Ft.

VIII. Sewage

		Requirements	Availability
A.	Flow	_____ GPD	_____ GPD
B.	Type	_____	_____
C.	B.O.D.	_____ ppm	_____ ppm

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

IX. Building Site

A. Topography of land _____
B. Fill or cut required _____ Cu.Yd.
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:

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 _____ Ft
E. Prevailing Wind _____ mph

XII. Neighbourhood

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

XIII. Transportation Facilities

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

XIV. Eating Facilities

A. Are restaurants or cafeterias near
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 Pharmaceutical 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

4. HVAC - HEATING VENTILATION AIR CONDITIONING DESIGN

Air Handling System - HVAC Systems

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 Class 100,000 or 10,000. A critical environment is Class 100.

- The degree of control or specification required depends on differing 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 done in Class 100.

- Controlled areas are categorized usually into room classifications, (i.e. 100,000, 10,000, 1,000 or 100). Each clean room or specification will dictate the design or HVAC particular needs 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 electronic while values higher than 60% promotes mold growth. In tropical countries, it is very expensive to maintain RH to 40-50%. In such cases, RH of 55% may be acceptable provided mold control is adequate.

- 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 cenntral HEPA's as each filter has to be certified.

- The exhaust air is then returned through a return duct and may be 100% exhausted by a fan or a % returned to the supply system. (The % varies with the design aspects typical 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 so as to sweep or purge the rooms so that it removes particulate generation. This means 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 louvred 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 from clean room for maintenance.

Installation Qualification

- 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 operate and any interlocks operate
  All HEPA filters have been certified
  All pressure monitoring devices, temperature monitoring and humidity monitoring devices should be certified

Operation Qualification

- 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 does interlocks between supply and exhaust fans react?

- Start-up operates as designed.

Process Qualification

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

- Validation or process 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 particles size of 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 5.0 micron and larger.

CLASS 100,000: Particle count not to exceed a total of 100,000 particles per cubic foot air of particle of a size 0.5 micron and larger and 700 particles per cubic foot of 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 preventative 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:

- the design of doors and windows
- service penetrations
- special fittings
- corners and joints
- ventilation duct

As 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 are:

- Quality of air the number of air changes per hour, this translates the correct quantity of air necessary to displace from the environment, pressurize the space and control to temperature and humidity. Pressurization of enclosed space; always move from cleanest to dirty.

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
In AHU bag filters	are used in a class 300,000
Terminal HEPA filters	are used in a class 10,000

- Flow pattern of air

Symmetrical supply and exhaust configuration is optimal, especially as classification decreases (lower than Class 100,000) low level exhausts become much more important.

Other Considerations

- avoid too many levels or 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 # of controls and sensors in the controlled areas and locate remotely to facilitate monitoring activated
- 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

CHAPTER 4

CLEAN ROOM

Definition of a Cleanroom

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 to 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.

When considering clean room design and construction the major criteria which need to be evaluated include:

- Room size & 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
  Items to consider here are, is the operation dust generating? Is there going to be shift work? Number of people per shift as it 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-thrus
  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 mold 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

- Cleanliness level; as discussed above

- Future expansion or relocation

What Are The Main Criteria For Clean Room Design For Vaccine Manufacture?

- effectiveness

- functional/reliability

- cost efficiency

Clean Room Air Flow Characteristics:

Three most common types of air flow encountered in Cleanrooms 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 flow (air usually returns through low level exhaust vents). A vertical flow of clean air, keep activities occurring on the horizontal plane within the room separate.

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 of a Class B or 100 Turbulent is the background environment for the critical manufacturing process (Class 100). 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 ± 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 in the process 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 a minimum of 3 pressurization levels are clean rooms; required in aseptic processing facilities.

What is The Basis For Clean Room Design

- cleanliness
- containment
- prevention of cross contamination

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

How Does One Design For Containment?

- negative pressurization
- entrance and exit air locks
- filtration
- glove box technology

How Can Cross Contamination Be Prevented?

- no air recirculation between areas
- HEPA filters in room exhaust registers
- positive pressurization
- locate Air Handling Unit intake upstream of building exhaust

Finishes

- smooth crevices free, non-flaking
- no ledges
- minimum exposed piping

Layout

- air locks
- unidirectional flows

When Designing A Clean Room, What Sort of Specifications Are Required?

- air quality - particulate count/microbial count
- temperature
- humidity
- room pressurization
- air velocity or changes
- directional flow pattern
- room finishes
- lighting

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 , shadowless 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 Cleanroom(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 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 prevents 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 high enough above the floor as possible, 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 very 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

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 fiberglass 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.

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 & 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." To high a ceiling dilutes the sweeping effect where it counts the most. Four to five feet above floor level and it becomes expensive to run.

Therefore, it is essential to consider at the outset 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, 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 cleanroom.

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, 90ft/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 600/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 grille 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.

Filtration of Air Supply

Cleanroom 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, BL2 level and greater 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 ductwork 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 5 % RH or 2 % RH
- 2 % RH humidity control uses the same equipment, but measurement & control systems are different-add 10 % cost
- dehumidifiers and controls add 25 % to costs
- humidifiers and controls add 15% to costs

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 program 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 operations are under control. Monitoring should be conducted as appropriate for each stage of processing and may Include air quality, including viable and nonviable particulates; 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 are 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 is performed by personnel trained in controlled environment cleaning using dedicated cleaning materials
  disinfectants are made fresh daily with WFI

- 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 particulates, 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 assure integrity 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 particulates, 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

Parenteral Contaminants

For parenteral products, contamination in the form and particulate matter is defined as unwanted mobile insoluble matter. Particulate matter from a # of sources and may be loosely defined into:

- intrusive
- extrusive

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 its real that were not removed by the wasting process.

Extrusive contamination is material from the environment falling into the product and its container during the filling operation.

Example of mean particle sizes generated by various activities (encyclopedia of clean rooms, bio-clean rooms, and aseptic areas by Philip R. Austin)

Note: The eye can see particles as small as 25 microns

Activity	Mean Particle Size
Rubbing latex painted surface	90
Rubbing epoxy painted surface	40
Rubbing Formica surface	10
Rubbing stainless surface	2
Manipulating standard paper	65
Manipulating plasticized cleanroom paper	10
Manipulating Tyvek cleanroom 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

Detection of Contaminants

A UV light of specially selected frequency, will increase detection. Capability by a factor of x 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
	SCALP	approx. 1 million/cm^2
	ARMPITS	approx. 1-10 million/ cm^2
	NASAL/SECRETION	approx. 10 million/g
	SALIVA	approx. 100 million/g
	FECES	> 100 million/g
PARTICLES	SURFACE OF SKIN	approx. 1.75m^2
	SKIN REPLACEMENT	approx. every 5 days
	SHEDDING OF PARTICLES	> 10 million/day

Training For Cleanroom

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 cleanroom to minimize the potential for contamination.

When personnel are being trained in the cleanroom, 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 cleanroom 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.

Pre-test questions:

When donning cleanroom 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 cleanroom 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) gloves
d) moved quickly
e) fingers touching the bench top when resting

Psychological points to consider:

Some differences between men and women are applicable to cleanroom operations include:

- women in general, have better control of their hands than men. For example application of cosmetics is an exacting application.

- women tend to be more conscious of their physical appearance than men and take care to see that clothing is worn properly.

- women generally prefer a warmer environment then men. The reason is physiology and clothing. The weight of women's clothes is tighter and the amount of surface area of body covered is different between men and women. Thus women tend to cool better that men and prefer a higher room temperature.

- men generally have "less cleaner" hands and nails than women. Women generally on the other hand touch their hair and face more often than men. Each touch results in contamination.

- in terms of personal habits, women tend to touch themselves when referring to themselves. This may automatically happen in a conversation when she says "I" or "one."

Both men and women must be made aware of the appropriate actions to be taken if such a contamination of the gloves takes place.

Training must also be a repetition and reenforcement of ideas. Check lists provide necessary reenforcements to employees of clean rooms and bio clean rooms. Check list 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 and understands, I will abide by the client list. 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 cleanroom:

- keeps hands, fingernails, and face clean
- never touch, adjust or comb your hair in the cleanroom
- do not wear jewellery on wrists or hands
- valuable items such as wallets may be moved into the cleanroom provided they are not removed inside the cleanroom
- personal items such as keys, coins, cigarettes, matches, pencils, handkerchiefs, tissues, combs, etc. should not be carried into the cleanroom
- no eating, chewing gum or tobacco or smoking in the cleanroom
- 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 cleanroom
- never apply or wear cosmetics in the cleanroom
- wear cleanroom 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 cleanroom
- 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 Cleanroom

"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 secure 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, a Austin Contamination Index was created. Personnel emissions are stated for different types of garments as shown in the table below. In every use but the membrane garments, emissions are caused by contaminants on the surface of the clean material which were not removed during laundering and particle then pass through the fabric of the garment as a function of its weave.

Austin Contamination Index in Particles/min 0.3 μ 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 date 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 μ 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 of 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 producting the contamination at a steady rate.

Conditions	Quality of Bacterial
Surgical teams	**Aerosols**
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 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 contaminants levels in the bio-cleanroom.

The true function of a clean garment is to act as a people contamination filter. Since fillers 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 and the downstream side. If no garment is the exterior 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.

Cleanroom Construction; recent additions:

In addition to clinical wall panels, glazing is becoming an increasingly popular choice in cleanrooms.

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 cleanroom through a complex changing process
- improved work environment for production operations.
- Glass is actually an extremely suitable material for cleanroom use as it readily satisfies the principle requirements:

  hard
  smooth
  impervious
  easily cleanable

Disadvantages include contaminated air can leak 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 cleanrooms adjoin one another. Glass should be located into tailor made frames in stainless steel or equivalent using silicone sealant.

Other Miscellaneous Items Used in Cleanrooms

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 thru's
- piped 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 cleanroom 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 practicable.

Long horizontal service runs should be avoided whenever practicable. The zone above the suspended ceiling provides an ideal area for installing 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 matte 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 invention being allowed to contact 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 room fabric.

Cleanroom Clothing

The single biggest source of contamination in the cleanroom is the people who work there. Cleanroom 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 Into Cleanroom

- A key item of importance in cleanroom design is access into the cleanroom. 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 cleanroom, close to the employee's entrance to the building, or it may form part of a double change procedure the grey area in where the coveralls, etc are held.

- Facilities should be available in the grey area for staff to scrub-up and dependency of the cleanroom garments. Flooring should be contamination controlled and lead to the white area.

- The "white" area is where staff change into their cleanroom footwear and step over into the cleanroom via a bench. Ideally, the air must flow from white to grey to black zones.

- Materials movements throughout the pharmaceutical process are important, but their introduction to and removal from the cleanrooms 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 paper 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 Cleanroom			
	IQ	OQ	PQ
DEHUMIDIFIERS	X	X	
HVAC AHU	X	X	
CENTRAL HEPA FILTERS	X	X	
FANS	X	x	x
DUCTWORK	X	X	
COILS	X	X	X
CONTROLS	X	X	
TERMINAL HEPA FILTERS	X	X	X

Validation of Cleanroom

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 declared.
- Finishes used for walls, floor and ceiling should be declared.

Operational Qualification (OQ)

This section is mostly concerned with calibration of temperature, humidity sensor, air velocity recorders, leak testing photometers, particulate monitoring equipment.

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 ± 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:

a) permanent and temporary equipment is in operation
b) 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 & Ceiling Systems

- Chemically inert
- Impermeable to moisture
- Cleanable & sterilizable
- Non-shedding
- Non-dust shelving
- Fully insulated for noise & thermal attenuation
- Non-combustible & fire retardant
- Non-outgassing
- "Monolithic" - smooth, crack free, homogenous
- Monoblock, non-progressive, de-mountable
- Integrated fittings, utility & HVAC chases

Benefits of Modular Design & Construction

- Lower start-up costs
- Earlier production & market entry
- Reduced interruption to existing operations (especially in expansions & modifications)
- Reduced congestion, construction infrastructure and outside labour on the plant side - higher labour productivity
- Improved site safety
- Improved quality control
- Advance planning & Firm Scope Definition eliminate "Cost Creep"

Humidity Controls in Pharmaceuticals

- Personnel Comfort & adherence to aseptic techniques
- Electrical/Mechanical/Chemical processing stability
- Corrosion & mould growth (> 50% RH)
- Electrostatic discharge control (< 40% RH.)
- Humidity excursions in duct work can lead to unacceptably high bioburdens in the air handling systems.

CLEANROOM MECHANICAL SYSTEMS
THE KEY TO CONTROLLING CLEANLINESS

eg. Parenteral facility:

- Pressurization

  Typically +/- 0.25 inches w.g.

- Temperature

  Typically range 68 - 75 degrees Fahrenheit
  Constant temperature setting more important than the setting
  Normal tolerance +/- 2 degrees F
  Where thermal stability critical +/- 0.1 degree F

- Humidity

  Without control can vary between 30 and 60% RH
  Typically 10% RH, +/-
  For critical applications, +/- 0.5

- Air flow

  Typical laminar flow room changes 50 - 10 fpm
  Average for class 100 is 70 fpm, with normal 9 ft high
  ceiling expect 480 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.

CHAPTER 5

PROCUREMENT

Procurement is defined as the action of obtaining materials or equipment to meet with standards set out for pharmacological production or usage.

1.0 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)
- Federal Drug Administration (FDA)
- Local Governing Agencies, etc.

1.3 The Process

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Example #2 - Purchase or

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  wants t
- CSA app
  rationale here
  approved
  ensure t
- A

- 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.

2.0 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 perogative 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:

  contractors and/or equipment suppliers
  material and product supply companies
  testing facilities
  shipping and freight companies

2.3 What to Investigate When Choosing Vendors

- **Expertise in the field**

  ie. 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

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 programs 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 programs (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)

3.0 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 discussion 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 these suppliers and vendors this was a golden opportunity to make real money that was guaranteed, as they know 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
- usually net 30 days upon receipt of the materials (provided you are an established client with adequate financing), if not, by 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 reliable 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

4.0 Quality Control & Quality Assurance

Your company must have an established set of procedures (SOP's) for receiving all incoming materials and equipment to your facility. Equipment must be "quarantined" and released as per approved SOP's.

All documentation must be inspected, reviewed by the appropriate groups, and approved as received in the specified conditions for the original 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

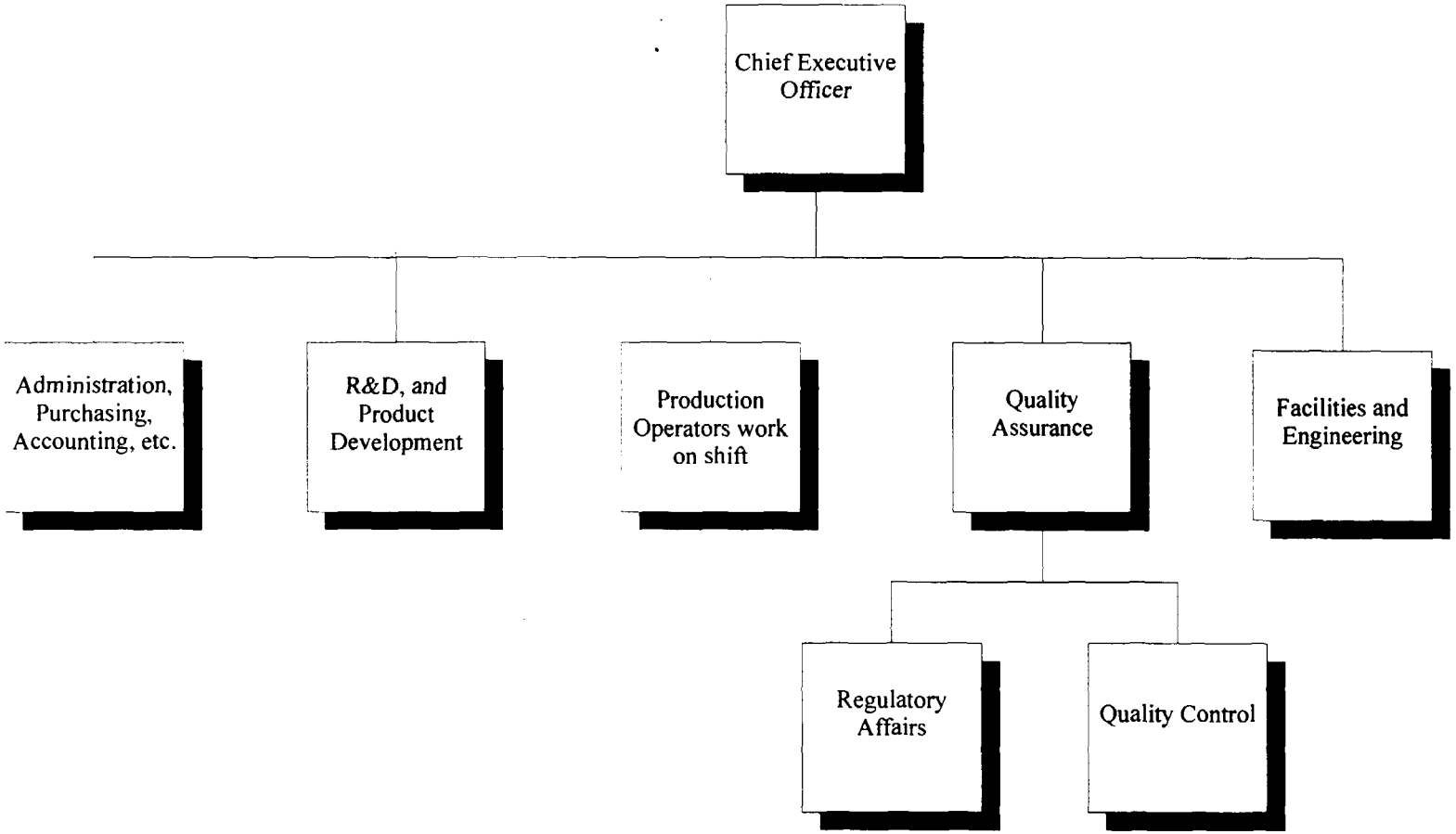
- drawings
- ASME approvals or equivalent
- CSA approvals or equivalent
- CRN number approvals or equivalent
- welding documentation
- Materials Test Reports (for the steel used in the construction)
- all pertinent testing data
- manuals - operation, maintenance and spare parts
- installation and operational qualification documents (IQ, OQ)
- spare parts (supplied as ordered) etc.

CHAPTER 6

ROLES, RESPONSIBILITIES, AUTHORITY AND ACCOUNTABILITY OF PERSONNEL WORKING IN GMP ENVIRONMENTS

An example of an organigram of a typical biologics 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.


Chief Executive Officer
Administration, Purchasing, Accounting, etc.
R&D, and Product Development
Production Operators work on shift
Quality Assurance
Facilities and Engineering
Regulatory Affairs
Quality Control

Department of Research and Development

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

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. All of these operations:

- 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 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 an 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 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 SOP's 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 900 L ± 50 L for a 1500 L name plate fermenter, the volume should not exceed 950 L even though the fermenter has the capability to go to 1100 L of operating volume.

- Time limits for processing should be set within acceptable limits. If an ultra filtration 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 supernatents from up to 4 batches may be loaded into the DEAE Flow column."* This means no more than 4 as the process is validated to 4 and not more.

- Time limits for storage. If a process intermediate is given an expiration date; it must be processed before its expiration date.

Department for Quality Assurance

Key function of the QA Department are:

- Documentation
- Compliance Auditing
- Validation
- External Inspection
- Training

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 Programs 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 program 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.

- cGMP's

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, SOP's, 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.

Department of Quality Control

1. 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 product, 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 (eg. use of move tickets). Materials must be stored in a manner to accommodate FIFO - First In/First Out.

2. Microbial Monitoring and Testing

This is required in several areas by monitoring and testing

- purified water and condensate 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

3. 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 product products must be tested every six months to ensure use of healthy culture when preparing an inoculum.

4. 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

5. 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 cleanroom, etc.

6. Other Duties

Establish a particular library of known contaminants for example, known slides of pathology studies of vaccine potency studies to compare as References in the future for trouble shooting, etc. In addition, during production, retain samples are take and these must be maintained appropriately. Appropriate calibration standards for laboratory instrumentation is also a QC function. The actual calibration is generally a Facilities & Engineering function but appropriate use of standards, their quality, expiration date, etc. fall under the auspices of QC.

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 drug is not compromised it will not adversely affect the critical operating parameter 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 there must be written procedures which are followed for equipment construction, cleaning, calibration, preventative maintenance and written procedures to document the same.

- 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 builts
  Company SOP's
  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 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 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 to ensure that all equipment is functionally as per specifications.

CHAPTER 7

HISTORY OF VALIDATION

In the early 1970's 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 sterilization and radiation sterilization became mandatory.

By late 1970's, sanitization, water systems, media fills and environmental control was 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.

GMP's 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 e.g. pure steam generator equipment such as: filling machines, test equipment such as: filter integrity test and 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.

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 can change.
- During validation, the process is challenged.

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.
- Demonstrates that the process meets an established range of operations for the chosen parameters consistency.
- Demonstrates the ruggedness of equipment or process performance by challenging equipment or process at the limits of established operating conditions.
- Demonstrates accuracy, precision, reliability of analytical test method used to assess the performance, identity, strength and potency of chemical substances, components equipment and product.

How to Implement A Validation

1. 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.

2. Based on #1, prepare a list of items which need validation.

   For example: (This is not a complete list)

Utility System

- clean steam
- compressed air
- purified water system
- chiller

Production Equipment

- fermenter
- homogenizer
- lyophilizer
- autoclave
- vial washer
- filling machine
- centrifuge

Support Equipment

- depyrogenation oven
- pumps
- processing holding vessels

Validation Strategies

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:

Installation Qualification (IQ)
Operational Qualification (OQ)
Performance Qualification (PQ)

Each apply where appropriate.

Validation is defined as an activity which assures that facilities, systems, procedures, processes and products are maintained in accordance with cGMP compliance.

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.

Operational Qualification (OQ)

Documented verification that the systems and /or subsystems perform as intended throughout the all anticipated operating ranges.

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 operate as expected and that the outcome of processing is acceptable. Consistency and reliability at the limits of acceptable operating conditions is a fundamental for performance qualification e.g. when validating a heat sealing unit the most important parameters are temperature, pressure and elapsed time. It is not necessary to show:

Highest temperature, lowest temperature, lowest time, lowest temperature, highest pressure, lowest time etc.

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.

Categorize the items in the list according to level of concern

Level 1

Lowest level of concern. Reliability of the item can be assured by Preventative 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 Biotechnology Facility Producing Parenteral Product

Facility Suites	IQ
Facility	✓
Receiving and Quarantine Suite	✓
Released Storage Suite	✓
Media Preparation Suite	✓
Inoculum Preparation Suite	✓
Fermentation Suite	✓
Downstream Processing Suite	✓
Purification Suite	✓
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 & Antifoam Holding Tanks	✓	✓	
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 System	✓	✓	
Chilled Water System	✓	✓	
Pure Steam Generator	✓	✓	✓
Domestic Hot and Cold Water	✓	✓	
Filter Integrity Test System	✓	✓	✓

What kind of validation can be performed ?

- prospective
- concurrent
- retrospective

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.

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, 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 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.

PREVENTATIVE MAINTENANCE, 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 Preventative Maintenance, routine calibration and change control.

Preventative 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.

PROCESS VALIDATION

Candidates for 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:

Firstly, identify the raw materials that are used in the cleaning process:
i.e. chemicals, water, buckets, sponges, mops, etc.

Secondly, define how people are trained in cleaning techniques.

Thirdly, define the cleaning techniques that are appropriate for specific areas, equipment, etc.

Fourthly, 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:

1. 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, N, O) and sometimes steam.

2. 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.

3. Utilities With No Product Contact

These are utilities that, by the way they are installed and used, would never come into product contact. Examples include chilled water used in heat exchanger, plant steam in a sterilizer jacket or heat exchangers or effluent handling waste system. Categories 1. and 2. 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.

The following sections will identify design requirements and specifications for these utilities as well as key validation needs.

Each utility system will be discussed with the following parameters critical to the successful validation and on-going operation of the utility.

- Definition of System (differentiation between differing applications)
- Typical System Description
- Key Design and Fabrication Requirement
- Installation Requirements and Procedures
- Cleaning/Passivation/Sanitizing
- Operational Qualification
- Testing (Process Qualification)
- Key Maintenance Requirements

The utilities discussed will include the following:

Water Systems

- Water systems can be divided into that used for manufacturing purposes or for general use or initial cleaning. The most acceptable water used for manufacturing is made by distillation.
- The important components requiring validation of a water or distillation system includes the preteatment, the still, the holding tank and the distribution system.

Pure Steam Systems

- Pure steam is produced from high purity water systems. Similar to water for manufacturing or distillation systems, a pure steam distribution system is required from the pure steam generator.
- Design and fabrication requirements are also similar to high purity water systems.

Compressed Air Systems

- System typically consist of pretreatment, the air compressor and a distribution system.
- Compressed air can be divided into Product Contact Air (air used for agitation, aeration, pressurization) or non-Product Air (air used for instrumentation or machine functions (solenoid valves).

HVAC (Heating Ventilating and Air Conditioning System)

- Special HVAC systems are required for those manufacturing activities requiring controlled environments.
- Air supplied through the HVAC utility must be HEPA filtered and at volumes delivered so as to give and maintain air pressure differentials, air cleanliness (to give appropriate clean room classifications) and conditioning (to give appropriate temperature and humidity needs).

Plumbing and Drainage Systems

- Drainage systems designed to handle both liquid and gaseous wastes must be carefully designed and maintained so as not to cross contaminate facilities or product paths.

Electrical

- Back-up systems for electrical power are pivotal to the success of any manufacturing environment.
- A key element to the successful completion of this system is the finish/location of the electrical outlets.

Water Systems

Definition of Water Quality System

- Each water system should be specified and designed in accordance with what the system purports to do.
- Water to be used in a manufacturing process, shall generally meet the requirements outlined in the U.S.P. for Water For Injection (WFI) and be defined as "Water for Manufacturing or Final Rinsing". Typically these systems are water produced through a distillation process.

Added directly to product.
Used to prepare media for a product.
Used for final rinsing of equipment, containers or other components having surface contact with the product.

- Water used for other applications such as initial rinses or non-product contact surfaces should have some quality standards identified and monitored accordingly.

Typical System Description

- Generally, water systems used for manufacturing consists of a potable quality supply of water from a municipal system (allows maximum CFU/ml) that feeds a pretreatment system. The pretreatment system may consist of any number of filtration, (sand, membrane filters) deionizing (to remove cations and anions), beds, carbon bed (to remove chlorine) or other treatment devices so as to ensure the water quality pre distillation meets the manufacturer's requirements of the still. (These requirements may vary with the type of still (multiple effect, single effect, vapour compression etc.) It is important the requirements are met so as to ensure proper functioning of the still and to reduce maintenance.
- The selection of the still depends on many factors including capacity needs, available steam supply, quality of municipal or city water supply and purity or quality of water desired.
- A distribution system is required to continuously circulate water to the point of use that is fed by a holding tank. It is important to size the holding tank according to still capacity and usage required (number of points in system and length of distribution system). Water should be circulated at elevated temperatures (greater than 80 C) to reduce biofilm build-up. An alternative approach is to " batch" or collect water in holding tanks, test or certify and then release for use. Again, water should be kept at elevated temperatures to reduce bioburden build-up.

Key Design and Fabrication Requirements For WFI Systems

Distribution System

- Water is continuously circulated and maintained at an elevated temperature (80 C) or more to prevent microbial contamination.
- Water may be reduced to a lower operating temperature during working hours (i.e. 65 C) but must be returned to 80 C or more during non-working hours (evening).
- If not continuously circulated, water may be stored in an intermediate tank or vessel at ambient or lower temperature for no longer than 24 hours.
- Dead legs must be avoided wherever possible. If present "dead legs" must be no more than six pipe diameters in length. Connections of portable hoses or permanent piping from WFI drops in system must be maintained/operated so that water does not sit for an extensive period of time. Valve at the drop should be closed (when not in use) and the hose/pipe drained.

- The entire system is sloped to allow for drainage and easy cleaning.

- Should be steam sterilized so as to ensure adequate sanitization.

- Stainless steel should be 316L grade or better.

- Heat exchanger should employ the following;
    - The cooling side of heat exchangers should not be drained at any time to reduce potential for corrosion.
    - Pressure of coolant must be maintained below that of the WFI loop and monitored to reflect this.
- In-line filters within the distribution system are not permitted.
- Only pure steam (from a pure steam generator) should be used to sanitize the WFI storage and distribution system and capable of achieving sterilizing temperatures.
- Circulating pumps of WFI shall be designed to utilize WFI as a lubricant of the seals.
- The holding tank should employ the following;
    - A hydrophobic vent filter that is steam sterilized and can be integrity tested.
    - Jacketed to maintain heat.
    - Level sensors to determine water level in tank.

Pre-treatment Systems

- Feed water from pre-treatment systems should be monitored for microbiological quality prior to distillation. An action level and steps to be taken should be defined when routine microbiological quality levels are exceeded. Access for sampling must be available for all major components.
- The system should be sanitized on a routine basis.
- R.O. units shall;
    - have non-working hours utilizing a timed internal flush cycle
    - have periodic disinfection of the entire system via a scheduled program
    - have a reduction in stagnant water in pipes downstream of the membrane
- Sanitization and recharging of portable DI units, should be easily performed.
- All pre-filters must be sized appropriately, inspected and replaced according to a written program.
- Water treatment equipment should be located in an area of controlled access to minimize tampering or adjustment by untrained personnel.
- Carbon beds should be sanitized and easily accessed for recharging or replacement.

Instrumentation For WFI Systems

- Instrumentation should be kept to the minimum amount necessary and used;
    - for the proper operation of the system
    - as an aid to preventative maintenance
    - to provide documentation that the proper conditions have been maintained.

- Temperature monitoring/controlling instruments should be of the type which has been installed into a well, so that the primary element can be removed from the system for certification without risking contamination to the system.

- Pressure-sensing devices should be of the type that have a sanitary stainless steel diaphragm, to isolate instrument internals from process fluid.

- Flow measurement and all instruments should be designed so that the primary element that is in contact with the WFI water, has no crevices and is easily cleaned by the natural circulation of the water.

Installation Requirements, Qualifications

Equipment Design and Appropriate Configuration

- Equipment and system design should include the following information;

    - flow schematics for the water system showing all instrumentation, controls and valves necessary to operate, monitor and control the system.
    - complete description of features and functioning of storage and distribution systems including specifications and equipment used for water treatment and pre-treatment.
    - specifications for construction assembly techniques where quality is of critical importance (i.e. welds, sanitary connections).
    - detailed specifications for all systems components such as storage tanks, heat exchangers, pumps, valves, piping, as well as their construction/installation techniques and identification of all major components (serial numbers, etc.).

Operating Plan

- Operating plans are defined in SOP's and should include the following;

    - procedures detailing the operation of the pre-treatment equipment such as carbon beds, water softeners, DI columns, filters etc.
    - procedures detailing the operation of the still and associated holding tank/distribution system.
    - a routine maintenance programme outlining equipment in the system requiring routine maintenance, cleaning, servicing, and any activities associated with any component of the distilled water system.
    - procedure detailing operation of all instrumentation/monitoring equipment present on the system and their appropriate documentation.
    - training programme to ensure personnel responsible for the operation have a complete understanding of the equipment and capabilities of the system.

Qualification Phase

- The Qualification Phase covers pre-validation activities and includes three categories;

    Installation Qualification (IQ)
    Certification and Operation Qualification (OQ)

Installation Qualification

- This step is mainly documented verification of the entire system and its initial installation.
- All specifications, equipment models, serial numbers, materials of construction and passivation records, are cross checked against the original design print and filed.
- Documentation and the results of inspections and tests performed by outside contractors, in-house, Physical Plant and or government bodies are filed.
- Cleaning passivation and final sanitization of system must be documented and verified.

Certification

- Instrumentation and mechanical controls must be certified prior to any validation studies to be initiated.
- Items to be included are those devices that measure, indicate or control pH, temperature, pressure, conductivity, flow, etc.
- Following initial certification, re-scheduling for routine certification must be set-up so as to maintain the system in a state of control.

Operation Qualification

- This step is documented verification that the system or subsystem performs as intended.
- Items to be include are pump discharge rates, alarms respond as designed to appropriate signals, heat exchangers operate as designed, valves close, seal and open properly, etc.

Process Qualification

- The Validation or Process Qualification Phase is typically comprised of a "prospective" phase followed by a "concurrent/retrospective" phase. The validation exercise consists mainly of a monitoring programme according to specifications required (for USP see Section 6.0).

- Prospective Validation Phase

  - The prospective phase involves the development of a preliminary microbial, endotoxin, particulates and chemical profile of the system.
  - This phase involves a rigorous sampling and testing regimen of the system for 2 to 3 weeks, simulating usage conditions.
  - All use points as well as additional monitoring sites (drain points, water treatment points, still) must be included in the test regimen for chemicals, endotoxin, microbes and particulates.

- Concurrent/Retrospective Validation Phase

  - Once the system "reliability" has been established in the prospective phase, additional monitoring is required for an extended period of time (i.e. minimum 6 months up to 1 year).
  - Testing may be reduced based on the prospective phase. This may vary with the individual systems.
  - Microbial alert and actions levels are established based on test data accumulated over a period of time (minimum 6 months).
  - Following completion of this later phase of validation and having demonstrated that the system is preforming consistently to standards required, a routine monitoring programme is established.

- Upon completion of the above, the system is considered initially validated. The system should be evaluated over an interval of one year, to ascertain if there are any seasonal fluctuations affecting the system. When a recognized change is determined to have a potential effect on validation, the revalidation or requalification measures can be identified and implemented immediately.

Water To Meet "Water For Injection" Requirements

- The water should meet the following test requirements.
  - Water sampled (as established in appropriate water monitoring programme) must meet the Water For Injection USP requirements.

    Pyrogen: Contains not more than 0.25 USP Endotoxin Unit per 1ml.

    Chemical: Pass all tests for Chemicals (USP).

  - Bacteriological purity of water should be no more than 10 microorganisms per 100ml and should not indicate the presence of any gram negative organisms. Bacteriological purity of water from a still should be no growth per 100ml.
  - During validation, each outlet should be evaluated.

Control Plan

- Once the system is initially validated, a control plan or monitoring programme should be set-up that includes routine testing and preventative maintenance.
- The entire system should be carefully monitored to ensure all of the operational requirements of the system are continuously being satisfied as originally designed. Control plan should be documented and include the following;
  - routine water sampling for microbial and chemical analysis from throughout the system to obtain a total profile of system operation. The sampling programme should be designed to monitor the equipment operations, the preventative maintenance programme as well as to determine the chemical endotoxin and microbial quality of the water.
  - alert and action levels established with appropriate strategies for response to any deviations to these levels.
  - a "change control" modifications procedure whereby any changes to the system (i.e. equipment modification, SOP revisions, sanitization procedures, etc.) are identified and evaluated with respect to a potential effect on the system. This may result in a revalidation or requalification of the system being necessary.
- A spare parts programme should be identified.
- The distribution system should be repassivated as necessary to avoid the build-up of "rouge" in the system.

Compressed Air Systems

Definition of Compressed

- Each compressed air system is specified and designed in accordance with what the system is proposed to do.
- Compressed air used for the following purposes at any stage of the manufacturing process is defined as: Product Contact Air.
    - Direct contact with product through such processes as agitation, sparging, aeration and product movement (pressurizing of vessels).
    - Direct contact with components or manufacturing surfaces which themselves later come into direct contact with the product (incidental product contact).
- Compressed air which is used in instrumentation or other machine functions (i.e. actuating solenoid valves) is defined as Non-Product Contact Air.
    - This air must not be exhausted into the controlled environment in which the product is being manufactured.

Typical System Description

Generally, compressed air system consists of an intake supply of ambient air to an air compressor. The compressed air then may be fed to a conditioning system (as required) and then distributed through a copper piping system for use points. Each use point would then typically have reducing valves and or various filtration devices to meet individual use point needs.

- Each air compressor and associated distribution system is defined with respect to the design of equipment and its appropriate configuration, the operating plan and control plan.

Qualification and/or Validation

- A qualification or validation protocol is prepared by Validation Services personnel and implemented to assure that the air system performs as designed and further to assure consistency in the operation of equipment and controls to meet the established requirements.
- A specific protocol is written for each system design.

Key Design and Fabrication Requirements

- An oil-free compressor is used to minimize the level of hydrocarbon aerosols generated and is selected to have enough capacity so that the proposed usage is 60 to 75% of rated capacity (maximum).
- The location of the air intake to the compressor is strategically located to avoid additional intake of contaminants, e.g. hydrocarbons. This preferably, is a fresh air intake.
- The moisture levels are controlled with the use of an appropriate desiccant dryer system.

- The distribution system employs features as follows;

    - Dead legs are minimized wherever possible.
    - The entire system is sloped to allow for drainage of any condensate which is formed due to a dryer malfunction.
    - Particle filters with a pore size of one (1) micron are required to eliminate gross particulates originating from compressor, drier or hydrocarbon absorber.
    - Use points involved in aseptic processes have a local 0.2u sterilizing grade filter. Any piping beyond this filter is 316L SS. The filters are integrity tested prior to installation.
    - Distribution piping does not pass through areas above 105 F (40.5 C) or below 32 F (0 C).
    - Piping shall consist of Type "L" hard drawn, degreased copper and joints made silver brazing alloy with a melting point of at least 535 C.
    - Careful attention is given to temperatures of filters in gas systems to prevent the accumulation of condensation (increase in bioburden and potential grow-through).

Installation Requirements, Qualification

- Equipment and system designs include the following information;

    - flow schematic for the air systems showing all instrumentation, control valves necessary to operate, monitor and control system (as built drawing) with sample points.
    - complete description of pretreatment and post treatment of compressed air.
    - specifications for construction assembly techniques where quality is of critical importance (i.e. welds, valves).
    - detailed specifications of all system components (compressor, filter, dryer, valvings, instrumentation).

- Operating plan is defined in an SOP which includes the following:

    - procedures detailing operation of compressor
    - procedures detailing operation of auxiliary equipment such as air dryers
    - procedure for routine maintenance programmes outlining equipment in system requiring maintenance, cleaning and servicing and its appropriate documentation (this includes filter change frequency)
    - instrumentation requiring calibration and its frequency

Qualification

- The Qualification plan covers three categories;

    IQ (Installation Qualification),
    Certification,
    OQ (Operational Qualification)

    For full details see WFI overview.

Process Qualification

- The air (used for product, or product contact surfaces) should meet the following test requirements.

  Moisture; Generally, a maximum dewpoint of -18 C at line pressure. If any portion of the distribution system located downstream of and including the dryer is at any time exposed to ambient temperature lower than 0 C, the dewpoint is required to be a maximum of -40 C at line pressure.
  Particulate Level; The test for oil and particulate levels does not exceed 1 mg/m.
  Microbes; provide microbial free air following sterile filtration (.2u filter) where required.
  Pressure; Maintain the required pressure at maximum delivery rate.
  Hydrocarbons: The system does not introduce hydrocarbons. The test for total volatile non-methane hydrocarbons, shows results based on methane equivalents which do not exceed 25 ppm.

A hydrocarbon absorber (activated carbon) post drying for trace Hydrocarbon removal is installed if tests indicate the necessity.

- During validation, each use point should be tested a minimum of 3 times.

Control Plan

- The entire system is carefully monitored to ensure all of the operational requirements of the system are continuously being satisfied as originally designed. A control plan is documented and includes the following;

  routine sampling for moisture and hydrocarbons
  sampling microbes as required
  alert and action levels established with the appropriate strategies for response to any deviation.

- Any changes to the system (equipment modification, SOP revisions etc.) are identified to Quality Assurance for evaluation and an action plan.

- A preventative maintenance programme is established to ensure the compressor continues to function as designed. All filters on the system should be changed routinely.

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, validation is scale down considerably and validation performed.

Levels of Process Validation

The level of Process Validation is also related to the concern level. 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:

Sterilization, depyrogenation, aseptic processing, etc. are prime examples. A diagnostic product on the other hand because it is a sole source of information which could be critical to treatment decision which is not part of the drug can be just as important.

Level II

This requires qualification, components interacting in the process must be identified and controlled that the process itself must be established.

An example of Level II concern is an automated packaging process for a non sterile product requires qualification but not validation. In this case, it is demonstrated that the process can be performed effectively but there is no demonstration of process consistency under ideal and challenged conditions as it is not necessary.

Level I

This process can be assured with controlled documentation, training of personnel, simple equipment Calibration and Preventative Maintenance procedures. Example of Level I process media mixing process for liquids.

Validation Master Plan for Biologics Facility

Objective: To provide key facility design elements and the appropriate validation strategy so as to ensure the facility is successfully qualified in meeting corporate or company specifications and all appropriate GMP requirements.

The following outlines 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 preventors
- 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, O, CO)

- Central or bottled system
- Filtration required
- Distribution System

Pure Steam

- Pressure/Capacity
- Generator type
- Water Quality Feed
- Distribution System

HVAC

- Airhandling Units
- Ductwork 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

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 programs (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 Program

Overview of key components of validation strategy for the facility

- IQ, OQ, PQ (General Expectations)

Responsibility During Validation

- Engineering/Construction
- Construction and inspection procedures must be carefully monitored throughout the project to ensure compliance to design and specifications.
- Co-ordinates with Maintenance Department of Facilities to ensure a maintenance plan or program 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).

Standard Operating Procedures

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 Program

- 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 SOP's

Preventative Maintenance procedures/Frequency

- scheduled shut down
- spare parts program
- maintenance logs books

Emergency and Contingency Plans

- HVAC failure
    - spills
    - Operator Safety

Changeover Procedures

- Between campaigns for multiple use facilities.

Revalidation Program

- 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.
- Definition: " 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;

  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.)

WHEN TO REVALIDATE/CHANGE CONTROL?

The time element, once a year, it is a good idea 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

CHAPTER 8

UTILITY SYSTEMS FOR THE PHARMACEUTICAL INDUSTRY

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 - Eg. USP, Deionized Water
- ProcessSteam
- Process Air
- Clean-In-Place (CIP)
- Product Contact Steam
- Instument Air
- Product Contact Cleaning Solutions
- Water for Injection WFI

Pharmaceutical Water Systems

Water is the most difficult component to maintain to the standard requirements. This is especially true as the quality increases. In addition it is almost one of the most expensive components to maintain. Thus is important to identify the quality of water for each part of the process so as not to use for example, WFI to use as media in vaccine fermentation where cells have to be broken to isolate and purify antigen.

For example 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.

Design Approaches:

- Analyze 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

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 & River Water	Seasonal Variation High Turbidity High Silica High Molecular Weight Organics

(Low Molecular Weight Organics can be Present in all types of Waters)

Water System Components

- Feedwater Pretreatments
- Production
- Storage and Distribution
- Cooling for Use

Carbon Adsorption

- Removes Chlorine and Low Molecular Weight Organics
- Should be Heat Sanitizable

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, 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 to a variety of cleaning agents and strength.

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

WFI Generation Systems

- Single Effect Stills
- Multiple Effect Evaporation (usually 3 are sufficient)
- Vapour Compression Stills
- Reverse Osmosis

Storage Vessel Requirements

- Stainless Steel vessel rated for minimum 15 psig and full vacuum
- Non-rusting 316L 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.

STORAGE & DISTRIBUTION SYSTEM MATERIALS

Deionized Water(DI)
- Unpigmented Polypropylene
- PVDF
- Stainless steel

Water for Injection (WFI) usually stored in electropolished stainless steel vessels.

Distribution System Materials

Deionized Water (DI)
- Unpigmented polypropylene
- PVDF
- Stainless Steel

Water For Injection is distributed through electropolished s tainless steel piping with orbital welds at joints.

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 1ppm
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 compresssor 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) 5 mg/mL
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 pneumatic equipment
- Breathing Air - as process air but HEPA filtered
- Instrument Air - as breathing air

Applications:

- Autoclave Operations
- Lyophilizer Sterilization
- Humidification for HVAC Systems
- Equipment Sterilization

Clean Steam Piping

- Conventional Stainless Steel Piping (schedule 10, 304 L, 316 L)
- Sanitary Tubing not Required
- Butt Welded Joints
- Pitched to drain with Adequate steam Traps
- Sample Cooler to test Quality

Clean Steam cGMP Requirements

Proposed LVP GMP Requirements CFR 21 Sections (FDA Regulations) 212.227

- Free of boiler additives
- Free of volatile amines or hydrazine
- Steam, if considered, should meet WFI specification for constituents such as pyrogens, bacteria & dissolved solids

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 - Clean in Place ; Definition of Cip

A Technique for Cleaning Process Systems and Equipment Without Dismantling

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 Systems 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?
- Investigating 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

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 Cycle parameters
- Design Equipment to Facilitate Cleaning
- Arrange Equipment to Facilitate Cleaning
- Design Piping to Facilitate Cleaning
- Design CIP Fluid Circulation System

CHAPTER 9

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 documentation control to seek assurance that:

- The facility, utilities, equipment and instruments are 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 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

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 a # 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 below:

> *"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 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 filler 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.

Change Control

Change Control is an option to use only when absolutely necessary. There are cases where SOP's 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 ie. it can affect the identity, strength, safety or efficacy of the pharmaceutical or 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.

Documentation Control Design

Before implementing a documentation system, the QA Department must prepare an SOP on how to write SOP's. 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 and identified and revised.

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 CNN - Change Control Number. For example, for Measles Vaccine production, one can implement a Change Control System 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 CNN-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 drug. There are different kinds of numbers for different types of documents as described below:

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 & Engineering

For example:

SOP-001.0 *Operating 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

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.

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 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, eg. 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 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 and on the quarantine label 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 eg. 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 mammalion 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) isoenzymes 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 pharmaceutical or 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 vendors 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, handwipes, 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 honoured 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 the 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.

Labelling Part Numbered Items:

Each item received from the vendor is labelled with its Part Number and Receiving Code and placed into a locked quarantine area; Quarantine label is usually orange in colour. 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 flourescent 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 colour 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, aliquot into small containers and store frozen. The containers are labelled 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 (SOP'S)

SOP's 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:

1. Title: This Should Be Brief and Direct:

eg. Operation of Chemap FZ 2000 Fermenter
Calibration of Accumet 20 pH Meter

The SOP may be about:

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.

2. Purpose: usually restates a well written SOP title. It allows the writer to expand the procedure further which was not possible in the title.

3. Scope: this is 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 colorimetric assay at 590 nm. 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.

4. Responsibility: this section declares who is responsible for training and maintaining the SOP.

5. Safety: it is advisable that this section appear in all SOP's. For eg. if dealing with BL2 or BL3 organism or product; safety precautions must be listed. If the SOP deal with harsh chemicals such as phenol crystals, for example, precautions on how to avoid contact with skin and what to do if contact is made with skin. This section may also include what to do in the event of a biological or chemical spill.

6. 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.

7. 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 colour ...
e. Record the reading

8. 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.

9. Documentation Requirements: this section is optimal, 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 SOP's 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 Approvals and dates of Approval 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 & 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 colour, 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 F&E (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

1) 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 assay 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, etc. 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.

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, technicians wo write large sections or use of questions which are vague and require input of a large amount of information. 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 (eg. 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 SOP's, the original Form must be of a different colour 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 is called the Production Batch Protocol. This copy of the PBP, when fully completed during the course of manufacturing becomes the official record of the product manufacture and is then called Production Batch Record or PBR. A record of all PBR's must be available at the facility during an inspection.

The PBP is used as a training guide to ensure all personnel involved in the 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 Bulk Drug Substance
- Assembly and processing of raw materials to make the final product.
- In-process testing and schedule.
- Final product packaging and labelling.
- 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 results (OOS).
- 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 Biologics 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 PBP for production of the material from fermentation to the end of concentration step only and one PBP 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 PBP into production

10 Date of release PBP into production

Items 1-6 must appear on every page. Items 7-10 on the first page only.

Example of MBPP for a Lyophilized Product; Key Unit Operations involved in lyophilization involve:

- component preparation which includes - cleaning and sterilization of vials, stoppers, seals and appropriate equipment
- formulation and filtration includes: weighing, mixing and sterile filtration of the product
- filling - aseptic fill of vials
- lyophilization - freeze drying of the vials
- sealing - crimping of the vials and application of aluminum over seals
- inspection - labelling, packaging, and final inspection

The above are the key unit operations in the lyophilization of the drug product. Each unit operation may be carried out in the same general area or perhaps in a different area. It is quite likely that operation a, b & c would be performed in the same area. d is most likely to be carried out in the lyophilizer room, e in another area and f in yet another area. In such a case, it is important to provide instructions in the PBP on movement and storage of the product as it moves through the manufacturing event.

Points to consider with MBPP:

- When to Write One?

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.

- Who Should Write It?

Production and QC should write the MBPP.

- How Should It Be Written?

It should be written in a manner which achieves 2 objectives:

- provides a convenient, practical and efficient set of instructions for the line worker
- ensure that fundamental principles of cGMP compliance are met
- Who should keep the completed BPR?

It 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 eg. 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 SOP's
- change of shifts
- completion of Batch Protocol
- importance of following the Batch Protocol

Generally on the first page of the PBP, it is recommended to have a section where the technician can verify his/her understanding of the contents and requirements of the PBP as exemplified below:

I have read and understand the content of this PBP

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 PBP, processing (wherever possible) must be stated, with limits of acceptance.

For example:

Adjust the conductivity of the supernatent with WFI (P/N 2182) to 5.0 ± 0.2 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
PRODUCTION BATCH PROTOCOL

Date Effective: February 20, 1995	Production Batch Protocol for Tetracyline	Confidential Information
Supersedes Date: New	PBP 9071.0	Page 1 of 40

Section A: Component Preparation
Product Tetracyline, USP
x units/vials

Product Part Number, 8665
Lot # _____
Theoretical yield = 20,000 vials

AI 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/Logs
4111					
4261					
4814					

Calculation: A/B + C + D = % gain or loss _____/_____ = _____%
Acceptance Criteria = ± 5%
Calculated By: _____ Verified By: _____
Date: _____ Date _____

When the PBR is issued, the Lot Number of the Batch is filled in by QA. Each page of the PBP 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:

- Production Batch 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; 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 as document is written, it **must** be followed. The inspector who reads such a narrative will expect to find 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 describes the Company description, ie. whether it is Biologics, Vaccine New Chemical Entities, Generics, 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 must untested product 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 retrofit 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, Preventative 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:

- LUMAC
- Work Orders for Preventative Maintenance and Calibration
- PM Schedule

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 cleanrooms, all utilities and major equipment used in processing.

A LUMAC for a cleanroom 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

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 Preventative Maintenance. This period of time is also used for recalibration once the maintenance work is completed.

In addition to routine Preventative Maintenance, stays 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** **Equipment Name**	**Confidential Information**
Supersedes Date:		**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 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 not 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.

Example of calibration sticker will be scanned to appear in the next edition.

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, IQOQ or IQ OQ & 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:

  a. Process and Utility Schematic Diagrams
  b. Engineering Schematic Diagrams
  c. Piping and Instrumentation Drawings
  d. Equipment Specifications
  e. Vendor Supplied Documentation
  f. 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 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 individuals 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 and why it is preferred or superior to other methods.

Method Categorization:
most analyses 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. 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 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.

- 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 (eg. 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 processes that cannot be adequately tested in the final product.

Biologics production in particular, requires rigorous process validation as proteins are highly susceptible to processing conditions and can degrade and/or change easily.

- Reason for validation, for example, it could be because it can:
- 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 mould during processing thus demonstrating rigorously the qualification of aseptic processing.

This procedure also helps to obtain information on other part of the process operations for example: 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.

13. 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 labelling claims.

Choice of worse case scenario is not always 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 PBR and 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 SOP's and other supporting documents to ensure that they are still valid as changes may occurred to procedures during validation.

14. REFERENCE STANDARDS

Reference Standards must be characterized according to written procedures and stored under known conditions to preserve their integrity. In order to prove the authenticity of a Reference Standard, 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's certifying the material as a standard.

15. 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. calibrations 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 2nd person in QC dated and signed or critical 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 drug products must accurately reflect who received each batch of drugs so that in the event of product recall, all units comprising of the batch can be located in the market place.

Such records must contain:

- Name and strength of the product
- 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 materia 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 drug is destroyed immediately, this should be noted on the record of returned together with the date of disposition.

Training Records:

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 performance of a job, one can define the training requirement. To document that training has been received, a record for each employee should be prepared 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.

Drug Manufacturing Audit Program 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 drugs or drug components that will react, add to, be absorptive, or adversely affect the identity, strength, quality, or purity of the drug.
____ 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 Program.
____ Management supports the *cGMP Program.*
____ A documented *Training Program* 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 labelled.
____ 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 labelled, 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 compound prior to further processing.

____ There is adequate documentation to show that in-process samples were collected and tested as per the 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 labelled 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 labelled 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 drug 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 Labelling 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 labelling 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 labelled.
____ There is adequate physical separation of the packaging lines.
____ All packaged and unlabelled 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 labelling 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 program 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 labelling.
____ 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 program 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 tested 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 labelling 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 program 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: **February 20, 1995**	**QA 002.0**	**Confidential Information**
Supersedes Date: **New**	**CURRENT GOOD MANUFACTURING PRACTICES**	**Page 1 of 3**

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:

Date Effective: February 20, 1995	QA 002.0 CURRENT GOOD MANUFACTURING PRACTICES	Confidential Information
Supersedes Date: New		Page 2 of 3

5.0 PROCEDURE:

5.1 Written procedures shall exist for all production, quality control, packaging and labelling 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.

5.5 Packaging and labelling 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: **February 21, 1995**	**QA 003.0** **GENERAL HOUSEKEEPING AND SANITATION**	**Confidential Information**
Supersedes Date: **New**		**Page X of X**

1.0 PURPOSE:

To provide a system for the complete and timely cleaning and sanitizing of the packaging, labelling and shipping departments.

2.0 SCOPE:

Applies to all parts of the facility, involved in the packaging, labelling 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:

Date Effective: **February 21, 1995**	**QA 003.0** **GENERAL HOUSEKEEPING AND SANITATION**	**Confidential Information**
Supersedes Date: **New**		**Page X of X**

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.

5.4 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.

BEST COMPANY IN THE WORLD
CONTROL FORM

Date Effective: October 15, 1996	CF 2024.0 HOUSEKEEPING LOG	Confidential Information
Supersedes Date: New		Page 1 of 3

Reference SP-2024

1.0 Location of laboratory - circle one: QC, Purification Suite, Fermentation Suite

Day: _____ **Month:** _____ **Year:** _____

Item	Activity	Performed By
Counter Tops	Remove unnecessary paperwork, tools and equipment. Wipe surfaces with sanitizing agents, 70% ethanol or stainless steel cleaner applied to clean wipes.	
Sanitization of laminar biohazard air flow work stations. (as applicable)	Remove unnecessary items from cabinet and sanitize with 70% ethanol.	
Plasticware and glassware washing	Decontaminate glassware everyday using the Castle Decontamination Autoclave.	
Tools	Pick up tools and clean if necessary. Return tools to appropriate places in toolbox.	
Balances	Wipe surfaces with damp sponge. Wipe dry with wipes. Level by adjusting leg screws until air bubble is centered.	
Solid waste (nonbiological)	Discard in lined trashcan. Empty daily.	
Liquid waste (nonbiological)	Solvents and chemicals are collected in approved storage containers. Other nonbiological liquids are poured down the drain and flushed with very large excess of water.	
Solid and small volumes of liquid waste (biological)	Deposit in double autoclave bag for autoclaving. Glassware may contain biological materials and can be autoclaved. Remove from room daily.	
Gowning supplies	Check daily and fill bins adequately with coveralls, labcoats, gloves. Order supplies when necessary. Sanitize boxes every week.	
Equipment, instruments glassware, and equipment skids	Sanitize skids weekly. Sanitize instruments daily.	

BEST COMPANY IN THE WORLD
CONTROL FORM

Date Effective: October 15, 1996	CF 2024.0 HOUSEKEEPING FORM	Confidential Information
Supersedes Date: New		Page 1 of 3

Item	Activity	Performed By
Safety Glasses	Wipe with sanitizing agent, 70% alcohol daily.	
2-8°C Fridge	Remove and decontaminate or discard items no longer required.	
Freezers	Remove and decontaminate or discard items no longer required.	
Incubators	Remove and decontaminate or discard items no longer required.	
Drying ovens	Remove and decontaminate or discard items no longer required.	
Solutions and Reagents	Discard or autoclave (as necessary) solutions which are expired	
Floor	Sweep daily	
Floor	Mop with sanitization agent daily	

Quality Control Review: _____ **Date:** _____

BEST COMPANY IN THE WORLD
QUALITY ASSURANCE

Date Effective: **February 22, 1995**	**QA 004.0** **MASTER AND WORKING BATCH RECORDS**	**Confidential Information**
Supersedes Date: **New**		**Page 1 of 3**

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 RESPONSIBILITIES:

It is the responsibility of QA to maintain this SOP.

4.0 APPROVALS:

ORIGINATOR:	QC APPROVAL:	QA APPROVAL:
DATE:	DATE:	DATE:

Date Effective: February 22, 1995	QA 004.0 MASTER AND WORKING BATCH RECORDS	Confidential Information
Supersedes Date: New		Page 2 of 3

5.0 PROCEDURE:

5.1 The Master Batch Production Protocol (MBPP) will be written and approved before a Production Batch Protocol is issued.

5.2 The MBPP will be prepared to provide specific operating instructions for the final product.

5.3 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. Production, QA and QC Directors are responsible for the approval of Master Batch Records.

5.4 The MBPP does not allow for typographical corrections. If a typographical error is made the MBPP must be retyped.

5.5 The MBPP is retained for a period of at least one year after distribution of the last production lot manufactured using a PBP record.

6.0 THE MASTER BATCH PRODUCTION RECORD INCLUDES:

6.1 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.

6.2 A complete list of all of the raw materials, designated by names or codes, that sufficiently indicate any specific quality characteristics.

6.3 Lot number of each raw material obtained from the QC release sticker.

6.4 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.

6.5 Instructions to follow during each operating step in the production, processing, testing, and controlling of the batch.

6.5.1 Batch Number
6.5.2 Date
6.5.3 Major Equipment employed
6.5.4 Key raw materials used and their lot numbers
6.5.5 Weights or measures of raw materials used in manufacturing
6.5.6 In-process tests and laboratory controls
6.5.7 The endorsement of Production, QA and QC

7.0 PRODUCTION BATCH PROTOCOL:

7.1 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 Production Batch Protocol.

7.2 The Production Batch Protocol is retained for at least one year after the expiration date.

7.3 Each Production Batch Protocol has a lot number identifying all production and control documents relating to the history of the lot.

7.4 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: **February 20, 1995**	**QA 005.0** **TRAINING PROGRAM AND DOCUMENTATION**	**Confidential Information**
Supersedes Date: **New**		**Page 1 of 3**

1.0 PURPOSE:

To provide guidelines for the implementation and documentation of an internal Training Program, 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 RESPONSIBILITY:

3.1 I t is the responsibility of QA to maintain and implement this SOP.

4.0 APPROVALS:

ORIGINATOR:	QC APPROVAL:	QA APPROVAL:
DATE:	DATE:	DATE:

Date Effective: February 20, 1995	QA 005.0 TRAINING PROGRAM AND DOCUMENTATION	Confidential Information
Supersedes: New		Page 2 of 3

5.0 PROCEDURE:

5.1 The Training Program will consist of three separate and distinct sections:

5.1.1 current Good Manufacturing Practices
5.1.2 current Good Manufacturing Practices for Quality Control Laboratories
5.1.3 Standard Operation Procedures competency

5.2 The cGMP Training Program will be developed from the regulations promulgated in 21CFR parts 211.1-211.208 (USFDA).

5.2.1 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

5.2.2 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.

5.2.3 Additional training materials, handouts, and slide presentations will also be used to increase the comprehension of the individuals.

5.3 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.

5.3.1 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.

5.3.2 Additional training materials, handouts, and slide presentations will also be used to increase the comprehension of the individuals.

5.4 The written and approved SOP's for the Production Department will serve as primary documents for the SOP Training Program.

5.4.1 The SOP's which are used on a daily basis for the operation of all of the equipment and instrumentation, will also used for the training of employees.

Date Effective: February 20, 1995	QA 005.0 TRAINING PROGRAM AND DOCUMENTATION	Confidential Information
Supersedes: New		Page 3 of 3

5.4.2 Each supervisor will be instructed in the training procedures necessary for correct and consistent training of employees in his or her respective areas.

5.5 For each different type of Training Program 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.

5.6 The Training Documentation Sheet will be filed by the Personnel Department in the Training Program file for each individual.

Best Company in the World
QUALITY ASSURANCE

Date Effective: **February 20, 1995**	**QA 006.0** **TRAINING PROGRAM 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 RESPONSIBILITIES:

It is the responsibility of QA to maintain this SOP.

4.0 APPROVALS:

ORIGINATOR:	QC APPROVAL:	QA APPROVAL:
DATE:	DATE:	DATE:

Date Effective: February 20, 1995	QA 006.0 TRAINING PROGRAM FOR THE PRODUCTION FACILITY	Confidential Information
Supersedes: New		Page 2 of 2

5.0 PROCEDURE:

5.1 The supervisor will provide the new employee with the current copy of the SOP's and adequate time to carefully read all of the appropriate documents.

5.2 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.

5.3 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.

5.4 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.

5.5 The supervisor will randomly check the quality and accuracy of the employee's work and will provide constructive criticism or praise, as appropriate.

5.6 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 agree have been mastered by the employee.

5.7 The Training Documentation Sheet, includes all of the procedures and duties performed by the operators in the Production Facility.

5.8 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.

5.9 The Training Documentation Sheet is kept in the Personnel Office and a copy is kept by the Production Director. The form is kept current 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

cGMPTraining 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 _____

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COURSE MANUAL FOR

IVI/UNIDO/BIOFARMA TRAINING WORKSHOP QA/cGMP/QC FOR VACCINE MANUFACTURE IN DEVELOPING COUNTRIES

TABLE OF CONTENTS

COURSE PROGRAMME

July 8, 1996- July 15, 1996

IVI/UNIDO/BIOFARMA TRAINING WORKSHOP QA/cGMP/QC FOR VACCINE MANUFACTURE IN DEVELOPING COUNTRIES

***DAY 1* July 8, 1996**

08:30-10:00: Dr. Zoltan Csizer/Dr. Shahi
Opening Session Speeches from:
- Director General FDA (Indonesia)
- Provincial Health Officer
- Director of BioFarma
- IVI Project Leader
- UNIDO Representative

10:00-10:30: Coffee Break

10:30-11:30: Nina Merchant
Introduction to the Course
- Course Layout
- Expectations
- Workshop Requirements
- Site Visits
- GMP Action Plan

11:30-12:30: Section 1- Nina Merchant
Introduction to cGMP
- Rationale
- Concept
- Philosophy

12:30-14:00: Lunch

14:00-15:00: Section 1 - Nina 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 - Nina 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 - Nina Merchant

*Containment and Biosafety Considerations in Designing BioPharmaceutical Facilities

09:30-10:30: Section 2 - Nina 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 - Nina Merchant

Clean Room II:
- Contamination Control in the Clean Room
- Gowning

12:00-13:30: Lunch

13:30-14:00: Section 3 - Nik Cucakovich
Introduction to Validation

14:00-14:30: Nik 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 - Nik Cucakovich
Facility Qualification
Documentation Requirements during Facility Qualification
Interlocking Systems
Special Design Considerations

***DAY 3* July 10, 1996**

08:30-10:30: Section 5 - Nina 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 - Nik 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 & Time Lines
Equipment Specifications

12:00-13:30: Lunch

13:30-17:30: Section 3 - Nik Cucakovich

Workshop on Facility Design and Site Visit

To prepare for Site Visits, BioFarma 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 SOP's would be good.

***DAY 4*July 11, 1996**

08:30-10:30: Section 3 - Nik 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 - Nina 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 - Nina Merchant
Role of QC and QA in cGMP Operations:

15:30-16:00: Coffee Break

16:00-17:00: Section 3 - Nik Cucakovich
Case Study BL3-LS Facility Design

17:00-17:30: Section 6 - Nina Merchant
Procurement

***DAY 5*July 12, 1996**

08:00-10:00: Section 3 - Nik Cucakovich
Equipment Validation, Preventative Maintenance and Cleaning Validation:

10:00-10:30: Coffee Break

10:30-12:00: Section 3 - Nik Cucakovich
Utility Validation:
- HVAC
- Steam
- Air Compressor
- Drainage & Electrical Systems

12:00-13:30: Lunch

13:30-17:30: Section 3 - Nik Cucakovich
Master Validation Plan Workshop

***DAY 6* July 13, 1996**

08:30-10:00: Section 2 - Nina 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 - Nina 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 - Nina Merchant

Master Document Index (MDI) Workshop

16:00-16:30: Coffee Break

16:30-17:30: Section 4 - Nina Merchant
Presentation of MVP Workshop

***DAY 7*July 14, 1996**

9:00-15:00:
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 - Nina 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

1:30-2:30: Dr. Zoltan Csizer
Course Evaluation and Wrap-Up

SECTION 1

1. INTRODUCTION TO cGMP

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

A. Rationale
B. Concept
C. Philosophy

A. RATIONALE

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/she is not able to determine whether or not a drug product has failed specifications and is defective.

1938 - Sulphanilamide, the elixir of death

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

203 gallons produced in 1938
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."

Regulation:

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

LVP - Large Volume Parenterals

The case of intravenous fluids which became contaminated with microbes during the production process. After sterilization, the intravenous fluid containers were cooled in water. The microbes present in the water were introduced into the space between the liner and the metal cap of the container. There organisms remained dormant until they were inoculated into the fluid at the time of preparation of the container for administration. Once transferred into the solution, the microbes proliferated rapidly and causing septicaemia and death.

1995 - Polio Vaccine (Cutter Labs, USA)

51 Children paralyzed
10 Deaths

Possible reasons:

- Inconsistent viral inactivation processes.
- Quick scale up of production without proper validation.
- Active live virus production process which used heat inactivation step. Scale of heat inactivation step may not have been easy.

Regulation:

Batch by Batch testing and release programme.

Result:

Safety evaluation of drugs and biologics by FDA as well as factory inspections.

(Lambert, E.C., Medical Mistakes, Indiana University Press, 1978)

1962 - Thalidomide

Thalidomide was commonly prescribed for insomnia and nausea in pregnant women in Europe.

1,000, Thousands of babies 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:

Remove the undesired enantiomer by a validated purification process assured by Assay Validation.

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 cGMP's (i.e. production using a validated process).***

1970 - Contaminated Caps

In the 1970's, patients in several hospitals in the USA developed bacteraemia:

40 died
378 infected but survived

Cause:

Abbots Labs (Chicago) 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

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

(Lambert, E.C., Modern Medical Mistakes Indiana University Press 1978)

1982 - Tylenol Poisoning

7 people died from taking Cyanide-laced tylenol (acetaminophen) capsules

12 year old girl complained of a scratchy throat to her parents who gave her tylenol (extra strength). Three hours later, she died.

By October 1, 1982, 6 more people died.

Result:

All medications must have tamper resistant packaging.

1987 - Tryptophan

ShowaDenko 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/day!

It is speculated that unexpected process contaminant/impurity present at less than 0.0089% is 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.

Currently, the situation in the Pharmaceutical Industry is such that it is not possible to provide unequivocal assurance of Quality. This is because:

a) Presumptive Testing

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

These tests are and can be performed for unforseen contaminates for example:

Contaminants which are introduced as a result of inadequate precautionary measures in the manufacture of different products in physically adjoining areas, and contaminants which are incorporated into the formulation as a result of inadequate environmental controls.

b) Samples Testing

In lieu of 100% testing for a desired attribute in a drug product, an estimate of the lot is made by performing the test for the attribute on a small number of items (sample) 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 bad lots will pass tests applied to them. In this case, bad lots of product 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 of lot must possess before it may be accepted

- Risk is the probability that a producer'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 which is the same as the UQL.

Weight Balance Check

A common current practice is to verify the addition of all components required in the formulation 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 if as it should be, that is, that the formulation contain all and only the components of the formulation.

B. CONCEPT

The objectives of cGMP are to be able to manufacture drug products of consistent high quality and to be able to detect a defective item whenever it is found. The quality of a drug product, 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 nine key areas in drug product manufacture:

a) Component Attributes

- all 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 stability approved formulation candidates which are samplings for the final market requirements.

c) Valid Compatibility/Stability Data

d) Process Specification

Validation and documentation are valid for cGMP where the production of contamination free and defect free drug products consistently and reproducibly is the goal.

e) Process Validation

The complete process for manufacturing the product item is first accurately defined. Each critical step is identified then each critical step is validated:

In context of pharmaceuticals, validation means:

> to attain and document sufficient evidence to give reasonable assurance, given the current state of art and state manufacturing, that the process under consideration will do what is expected to do.

Validation can be defined as a process of verification which consists of 4 phases:

- qualification
- challenge
- monitor
- requalification

f) Documentation; the most critical documents include:

1. MPR (Master Production Records)

The MPR is a document which embodies the 4 quality elements of manufacturing: Personnel, Materials, Equipment/Facilities and Methodology required for accurate and precise preparation of a specific drug product.

2. SOP's

Certain procedures in the manufacturing plant which are not related to the production of a specific batch of a drug product are made reproducible through SOP's.

g) 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 drug". Therefore production should scrutinize and challenge heavily any MPR that is presented for approval.

h) QA Strategy

The strategy for assuring that every unit of drug product 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 is based on screening all incoming shipments and the testing all completed lots before releasing them for distribution.

The screening of all in-coming materials starts with the preparation of adequate specifications and the 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 in-coming shipments are quarantined and inspected before being transferred to a Released Material warehouse. Lots in process are sampled at critical stages and tested to determine if the manufacturing process in progress is progressing as expected. Completed lots are reviewed before releasing the lot for distribution.

I) Post Marketing Surveillance Strategy

Three principle attributes comprise this event:

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

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

C. PHILOSOPHY

1) GMP Definition - USA definition for GMP is "the minimum necessary level of operation and administration of methods, facilities and controls to assure that the product meets the requirements of safety and the identity, strength, quality and purity which the product is represented to possess."

UK definition it is a guide which describes the special precautions and checks are 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 whether it is to be treated as a fundamental professional ethical matter.

Earlier on we described certain customary practices in the pharmaceutical industry, like the end product testing, sample testing and presumptive testing, each of these practices carry a significant risk of failure, and they are clearly inadequate to guarantee the provision of defect-free drug. To date, the singular known solution to avoid manufacturing and distributing defective drug products is the adoption of GMP specifically process validation to establish accuracy and documentation to assure precision and reproducibly are refined.

2) GMP - Cost

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

- Relationship between GMP and profitability
- Is there an optimum cost of GMP/profitability ratio?
- How much does it cost?
- Who can afford it?

3) 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 biologics cGMP starts right at the beginning of the process, at the Cell Bank stage and all the way to the Final Release of the product for distribution. Another aspect of the GMP dealing with scope, is in the level of the economy of the environment in which the practice is in use; this for example: GMP measures applied in industrialized countries may be more elaborate than those in developing countries. There is only 1 GMP, but the practical levels which are implemented are allowed to vary from one environment to another.

4) 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 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 firm 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 products performance in the field.

2. BASIC ELEMENTS OF QA PROGRAMME

The function of the Quality Assurance (QA) is to design a programme to meet the expectations of GMP.

For drugs and biologics, this translates to:

- identity
- purity
- potency
- stability
- uniformity
- safety
- efficacy
- quality

1. QUALITY

- Establish the quality. Determine which attributes of the raw material, process or performance e.g., choice of raw material.

- Determine what could go wrong that could significantly impact the safety, uniformity, reliability and performance of final product.

- Choose quality parameters and test methods that are scientifically rigorous.

- Set limits for these attributes; express as :

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

  Set wide enough so that you don't routinely trigger deviation but tight enough to have respect.

2. MONITOR QUALITY

- Monitor quality so that you assure that the standards you have set in #1 are routinely met, i.e., Quality Assurance. This means setting up a 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 factory i.e. to monitor its established quality routinely.

3. CONTROL CHANGE:

- Change is inevitable; however uncontrolled change is dangerous. This is because there is always the potential that a product improvement which is in fact product change will have an anticipated adverse impact on the safety or effectiveness of the final product.

- Regularly agencies do not expect a manufacturer to stop change, only to control change.

4. DOCUMENT IT:

- Document the quality standards you have established (item 1).
- Document the monitoring programs and the monitoring data that you collect (item 2).
- Document any changes that occur (item 3).
- Documentation is the **CURRENCY** of a pharmaceutical company; without it, it can not market the product it has made.

QA IN BIOLOGICS FACILITIES:

- Establish quality = set specifications
- Confirm quality = validation
- Assure quality = monitoring/control programmes
- Control change = minimize change

DOCUMENT THESE COMMITMENTS

3. MOST WIDELY USED GMP REGULATIONS ARE

A. United States

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

B. World Health Organization

Good Manufacturing Practices for Pharmaceuticals, 1992.

C. European Community

Current Good Manufacturing Practices.

Good Manufacturing Practice for Medicinal Products in the European Community, January 1992

D. United Kingdom

The Orange Guide, 1993.

MAJOR DIFFERENCES TO QUALITY APPROACHES BETWEEN NORTH AMERICA AND EUROPE

1. In North America:

An American manufacturer believes he has a right to market a product; in America **only** medical products must be proven safe and effective before market authorization.

In the European Community:

A European believes that it is a privilege to gain access to the economy; **all** products must be safe and they must do what the manufacturer claims they do.

2. In North America:

A regulatory agency, the Food and Drugs Administration (FDA) is authorized to approve products for the market and enforce regulations. FDA write the regulation and enforces them; the regulations are written, as a result in an enforceable language.

In the European community:

The Competent Authority, usually the government accredits certification bodies to work with manufacturers; these certifications bodies test products, register quality systems and grants markets authorization for products.

3. In North America:

The FDA is a large minimally funded organization that is open to direct pressures from Congress, consumer groups, the medical community and industry.

In the European Community:

The certification bodies are private, profit or not-for-profit organizations that serve manufacturers and are paid for these services. Pressures from special interest groups are involved in the standard setting process.

Example:

BSI is a standard setting organization for Britain

TOV is a standard setting organization for Germany

ANSI is a standard setting organization for Americans

ISO is a standard global setting organization

CEN is a standard setting organization for the European Community

4. In North America:

Product testing is performed by the manufacturer, FDA believes these results. Contract testing laboratories are NOT certified by the government or third parties.

In the European Community:

Product testing is performed by third parties. The testing facilities are accredited by the Competent Authority i.e. The National Government.

Europeans rely heavily on standards to determine product safety and performance. Products that meet standards are marketed.

5. In North America:

Inspectors retire and go to industry.

In the European Community:

European inspectors usually come from previous industrial positions.

QUALITY SYSTEMS

Due to global harmonization practices, the emphasis from QA (Quality Assurance) and QC - (Quality Control) is shifting to QS - Quality System.

Thus, instead of a department within an organization or factory being charge of assuring quality and controlling quality, quality is now the responsibility of the entire factory.

What does a quality system do?

- Assures that work will be performed in accordance to quality requirements and documented consistently and reproducibility. The statement is the heart of GMP and validation.
- Assures the accountability and traceability of information.
- Assures access to an 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 factory can respond to change effectively and efficiently.

Example:

ISO, GMP's, TQM, Malcolm Baldridge etc.

DIFFERENCES NORTH AMERICAN GMP's 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.

Current North American GMP's are production orientated.

New proposed GMP's will be design, purchasing, production and service orientated.

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 to 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 facilities 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 need to be taken 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 MBO's). 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 are 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 are the objectives times to more realistic levels.

SECTION 2

FACILITY DESIGN FOR cGMP COMPLIANCE

REGULATORY ASPECTS OF PHARMACEUTICAL FACILITY DESIGN

What do the Regulations say about Facility Design?

Examples:
Plant Lockers

- personnel engaged in the manufacture, processing, packaging or holding of a drug product shall wear clean clothing, appropriate for the duties they perform. Protective appeal, such as head, face, hand and arm covering shall be worn as necessary to protect the drug products 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 in to 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.

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

- where interruption of power is frequent

Adequate Space

Adequate space for the placement of equipment and material must be allocated to prevent mix-ups between items. The flow of components is to be such as to prevent contamination.

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:

- receipt, identification, storage and withholding components and closures
- rejected components and closures
- release components and closures
- 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

Lighting

Adequate lighting is to be provided

HVAC

- adequate ventilation to be provided

- equipment for control of over air pressure, microorganisms, dust, humidity and temperature is to be used when the operations dictate

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

Penicillin Operations

- Operations related to the manufacturing, processing and packing of penicillin are to be performed in facilities separate from those used for other human drug products. Air handling systems servicing penicillin areas are to be separated from other air systems.

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 backsiphonage, 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

Washing and Toilet

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

Sanitation

- Buildings used in the manufacture of drugs are 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 is 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 rodenticides, fungicides and fumigating agents. All of these materials must be registered and used in accordance with Federal or equivalent (country) regulations.

Building Maintenance

- All buildings performing pharmaceutical work must be maintained in a good state of repair.

Spore Bearing Organisms

- All work with spore bearing microorganisms shall be carried out in an entirely separate building (undergoing revision at the FDA).

Live Vaccine Processing

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

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

PHARMACEUTICAL FACILITY DESIGN PROJECT MANAGEMENT

There are four main stages in a project:

1. Feasibility Study

- Economic
- Technical
- Regulatory

2. Process Engineering

- Personnel flow
- Process Utilities

3. Project Review

- Layout

4. Construction and Validation

FEASIBILITY STUDY; What is the purpose ?

- **Economic Feasibility**

The main objective of a feasibility study is to provide OOM (Order of Magnitude) cost estimate; all projects must be constrained with strict financial limits based on the ROI (Return On Investments) and an expenditure ceiling must be applied on the operating costs of the plant, i.e. economic feasibility.

- **Technical Feasibility**

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

- Can it operate satisfactorily in terms of producing a consistent product within the defined specifications and produce the required quantified and range of products?

- Can it be operated reliably during its expected life cycle and within defined operating conditions ?

- **Regulatory Feasibility**

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 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.

MARKET REQUIREMENTS

- What is the product Definition?
- How many units are required per year? How does this translate in operations, number of shifts etc.?
- What are the range of product sizes/contents/materials? This impacts the size of equipment.
- What are the foreseen future market trends ?

- Inputs of production planning

  Market forecast
  Expiration date
  Process description
  Inventory levels

- Output of production planning

  Optimum batch size
  Number of production lines
  Equipment sizes
  Warehouse sizes

The input and output production planning decides how well your production works.

REGULATORY REQUIREMENTS

- Which regulatory authority will approve the product and inspect the operations?
- What are the anticipated standards required for the design, validation and documentation of the process and its operative environment?
- What will the regulations be like in the next 10 years?

FINANCIAL CONSTRAINTS

- What is the return on investment (ROI) expectation?
- What are the capital constraints/limits?
- What is the foreseen market price for the production/profit margins/maximum acceptable cost of production?

TIMING

- When is the product expected on the market and at what volume?
- Define a realistic time frame for the project (neither pessimistic or optimistic) and rigidly plan and control the project against this schedule.

CONCEPTUAL LOCATION

- A specific green field site?
- A space in the existing operating area?

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, vibration free)?

The next step following the completion of the steps defined above, is termed the macro process review.

MACRO PROCESS REVIEW

A macro process review entails a review of the project on a macro scale and starts with process flow diagram. A process flow diagram is prepared by considering the following:

- manufacturing process
- ancillary plant and services
- support area and storage needs

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 services demands?
- What are the regulatory constraints?

Future Operating Costs

- labour
- materials
- services
- other overheads

PROJECT ASSESSMENT

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 on board the following aspects:

PROCESS ROUTES

Well defined process flow diagrams which include all existing products and any that may be in the R and D 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 length of the construction programme.

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 cleanrooms.
- Layout of equipment to facilitate personnel movement.
- Changing facilities for personnel.
- Number of offices, which personnel need offices, where will documents be stored?

Ancillary Plant and Services

- What type and size of ancillary plant is 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, WFI
- Steam - house or process, clean
- Compressed air - grades
- Electricity

- Vacuum/special gases
- Effluent
- 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 rooms.
- Offices.
- Cafeteria and personnel needs.
- Goods receiving area.
- Warehousing.

MATERIAL FLOW

This needs to be identified with reasonable accuracy at an early stage as the viability of a location will depend on this information.

- raw materials
- receiving/quarantine
- released materials
- manufacturing-fermentation, primary recovery, downstream processing
- subassemblies
- in-process materials
- in-process bulks
- partly processed materials
- 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. The next step after the macro process review is to prepare an initial plant or process layout.

LAYOUT ANALYSIS

- personnel flow
- material flow
- equipment flow
- HVAC pressurization
- biowaste flow

LAYOUT EVALUATION

Primary

- efficient material flow
- efficient personnel flow pattern
- compliances with NIH (containment guidelines eg. live vaccine, pathogenic organisms)
- compliance with building codes
- compliance with cGMP's

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?

Approach

- Entry and exit corridor layout arrangement
- Utilization of pass through and pipe transfers or raw materials and in process materials.

LAYOUT

Spatial requirements and relationships should be identified with input from the user. Equipment sizes, services and clearance must be established at this stage. In addition to space for the 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 must be developed to establish the organization of the facility, suite or rooms. The next step is to develop 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, be easily maintained and be cost effective.

In pharmaceutical spaces, engineering systems are present throughout, above the ceiling, below the ceiling, running horizontally, vertically, exposed and concealed. It cannot be emphasized too sharply that the space provided by the architect must be a well engineered space.

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

- Flow patterns must be logical and simple.
- Route lengths 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 (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

The basic criteria from which any plant is designed is 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

A Process Flow Diagram is 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 as 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, to permit a critical review of the process design with minimum reference to other documents.

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 systems 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 the air and air flow volume. In addition, the route of disposal for the effluents must be shown.

Each PFD has a separate set of tables which show the quantitative and qualitative data for any process system. This is the minimum information required for sizing the lines and the development of the P & ID's from the PFD. In addition to the heat and material balances, the working documents need to be developed from the PFD's to record the engineering operating and safety criteria of the plant design.

BUDGET COSTS

Budget costs can be prepared as foreseen:

Project capital costs

- equipment and installation costs
- facility construction
- utilities and their installation
- validation

Future operating costs:

- labour
- materials
- services
- other overheads

PROJECT ASSESSMENT

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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 length of the construction programme.

In pharmaceutical spaces, engineering systems are present throughout above the ceiling, below the ceiling, running horizontally, vertically, exposed and concealed. It cannot be too strongly emphasized that the architect space provided is also a well engineered space.

While layouts are being developed, actual wall thickness rather than single line delineation must be shown.

CONSTRUCTION DETAILS AND SCHEDULES OF FINISHES

eg. clean room data sheets (see later); these would specify by the classification of area, acceptable types of finishes and the 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.

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.

Typical finishes are:

- epoxy paint finish over concrete - medium cost range, moderately priced but not so long lasting
- welded PVC - excellent chemical resistance but costly. If heavy traffic is anticipated, it is not a good choice
- self levelling (epoxy, polyurethane).
- epoxy terrazzo - most expensive and longest lasting. Inclusion of granite chips for best chemical resistance, good in high traffic areas.

WALLS

Walls must be air tight (sealed) with no recess or grooves.

- Epoxy coating - low cost, durable and impact resistant, best in high traffic areas. Because of the hardness of the material, the 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 not installed expertly, can create headaches.
- Welded sheet - same as seamless but thicker, most durable but most expensive.
- Prefabricated wall panels (see cleanroom section).

CEILINGS

- Class 100,000 - non shedding tiles with hand drawn clips is sufficient. Simple ceilings may be painted over structural concrete, painted or vinyl covered gypsum plaster or modular.

- Class 10,000 should have a cleaner epoxy painted finish.

- Class 100 environment filters and lighting fixtures usually occupy the entire ceiling grid work.

The intersections of walls, floors and ceilings should be coved, so that no cracks or grooves are available for accumulation of particles or microorganisms. These intersections must be resistant to thermal expansion and contraction. Note the quality of ceiling material must reflect pressurization within the room.

WINDOWS & DOORS

Windows and frames should be metal or constructed with materials that are smooth and impervious to corrosion.

HVAC

The success of HVAC design depends on paying attention to detail such as:

- the design of doors and windows as these are sources of leakages
- service penetrations
- special fittings
- corners and joints
- ventilation duct

HVAC Construction details must be defined in order to achieve the following:

- keep particulate counts and microbial counts low
- be non-dusting and non-shedding but easily cleanable
- be chemical resistant non-degrading after sustained contact with product
- process chemicals or cleaning agents
- be physically durable (resistant to steam, moisture)
- be easily maintained

The most fundamental qualities required of an environmental air system are:

- Quality of air; number of air changes per hour

The correct quantity of air necessary to displace from the environment, pressurize the space and control the temperature and humidity

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,

In AHU panel filters	unclassified environment
In AHU bag filters	class 300,000
Terminal HEPA filters	class 10,000

- Flow pattern of air

Symmetrical supply and exhaust configuration is needed. As classification decreases, low level exhausts become much more important.

Pressurization of enclosed space; always move from cleanest to dirty.

- air leaks
- containment
- temperature and humidity

Temperature and Relative Humidity Considerations in HVAC Design

Process equipment can give off heat and product quality can get affected by severe temperature and humidity. Heavily gowned production personnel may find it difficult to operate if the temperature and humidity is not adequately controlled.

Thus, ventilation with respect to temperature and relative humidity should be designed to balance the need for personnel and product. Additionally, in tropical countries where the humidity is greater than 90% and the temperature is over 90°F, it is prohibitively expensive to operate at 20°C ± 2°C and RH of 40 ± 5 %.

In general, temperature of 20 ± 2 and relative humidity of 50 ± 5% is normal.

UTILITY SYSTEMS AND THEIR IMPORTANCE IN DESIGN

Process utility systems are designed to satisfy the requirements of the facility and are based on the operational philosophy - single shift, double shift or 24 hour working. The capacity requirements of the various utility processes and process equipment are estimated by using existing in-house data and data from vendors, and allowing for expansion in future.

Water Systems

- Identify the quality of water for each part of the process
- Daily and peak usage rates
- Quality of incoming municipal water
- Pipe, storage tank and treatment plant sizes required are then calculated
- Future needs (expansion capacity)

STEAM

- One of the most expensive utilities
- Boiler house should be at the centre of gravity of steam usage, normally adjacent to sterilization for economic reasons.
- Condensate (containment considerations)

COMPRESSED AIR

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) 5 mg/L
Particles, NMT 100/m^3 of 5 micron 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 pneumatic equipment.
- Breathing air - as process air but HEPA filtered.
- Instrument air - as breathing air.

EXHAUST AIR FROM EQUIPMENT IF CONTAMINATED, MUST BE CORRECTLY HANDLED TO AVOID ENVIRONMENTAL CONTAMINATION.

Electrical Equipment

Equipment connections - are individual cables, conduit or trunking acceptable , or are service drop points necessary?

- Is equipment hardwired or are re-socket disconnects needed?
- What are the special clean area or wet environmental requirements?
- Location of control panels.
- Lighting must be safe, waterproof, sealed.
- Any areas required to be explosion proof, if so, needs to have special electrical systems:

Effluent and Efficient Handling Systems

- Drains must be capable of receiving effluent at a wide range of temperature with a variety of chemicals, pollutants and other undesirable materials.
- They must be easily accessible for repair and replacement. Drains are a source for contamination; and care must be taken during design, such as use of backflows.
- It is very common in pharmaceutical industry to have stainless steel drains as these can be sanitized without corrosion problems.

NO CRITICAL SYSTEM SHOULD EVER BE DIRECTLY CONNECTED INTO A DRAINAGE SYSTEM!

Effluent Handling Systems

These must be instituted to protect the environment from the process.

The most common types are:

Lagoons

- Trickle tanks to avoid problems with peak discharge conditions.
- Neutralization tanks to get back the chemical imbalance
- Holding tanks for emergency discharge or materials to be disposed of by other means.

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 _____ Roomnumber _____
Room name _____ Area _____

Specifications and locations of required services

Electricity
Voltage & number of outlets _____
_____
Horse power _____
Phase _____
Resistance _____

Air-conditioning
Temperature _____
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 Heights _____
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 sheets became an integral part of the facility design and is an invaluable source of information for Architect and Process Engineers.

Following these detailed requirements, the next question is the building itself. How and where to design the building? This brings us to site selection.

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.

SITE SURVEY CHECK LIST

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 Municipal authorities Should be consulted	_____ ltr _____ PSIG _____ C _____ cents/m _____ ltr	_____ ltr _____ PSIG _____ C _____ cents/m _____ ltr
B. Well what has been the experience in the area	_____ ltr _____ PSIG _____ C _____	_____ ltr _____ PSIG _____ C _____
C. Tower, Pond or River	_____ ltr _____ PSIG _____ C _____	_____ ltr _____ PSIG _____ C _____

V. Telephone Service

Describe current or future status.

VI. Power

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

A.	Natural or manufactured	_____	_____
B.	Heating value	_____ Btu/cu	_____ Btu/cu
C.	Volume	_____ cu.Ft.	_____ cu.Ft.
D.	Cost	_____ $/M cu. Ft.	_____ $/M cu Ft.

VIII. Sewage

		Requirements	Availability
A.	Flow	_____ GPD	_____ GPD
B.	Type	_____	_____
C.	B.O.D.	_____ ppm	_____ ppm

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

IX. Building site

A. Topography of land _____
B. Fill or cut required _____ Cu.Yd.
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:

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 _____ Ft
E. Prevailing Wind _____ mph

XII. Neighbourhood

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

XIII. Transportation Facilities

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

XIV. Eating facilities

A. Are restaurants or cafeterias near
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
B. Availability of skilled labour
C. General education level in neighbourhood
D. Can good supervisors be obtained
E. What is the experience with trade unions in the area

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 Requirements 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 PHARMACEUTICAL 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

CLEAN ROOM

WHAT IS 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 to type and count of microbial contamination.

PRIMARY CONSIDERATIONS IN CLEANROOM DESIGN AND CONSTRUCTION

- Room size & layout
- Gown-up and entry areas
- Procedures for operations
- Utility penetrations
- Spill containment
- Door, windows, pass-thrus
- Interior surface
- Temperature, humidity, pressurization
- Air flow and direction
- Cleanliness level
- Future expansion or relocation

WHAT ARE THE MAIN CRITERIA FOR CLEAN ROOM DESIGN

- effectiveness
- functional/reliability
- cost efficiency

CLEAN ROOM AIR FLOW CHARACTERISTICS:

Three most common types of clean room air flow designs are:

- Random flow - in this design the HEPA filters are located randomly throughout the room to provide clean air. This results in zone of cleanliness. Random flow rooms are usually greater than Class 1000

- 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.

- Laminar flow, vertical - vertical laminar air flow from HEPA filters provide an even continuous unidirectional flow of clean air from the ceiling toward the flow (air usually returns through baseboard vents). A vertical flow of clean air keep activities, occurring on the horizontal plan within the room separate.

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. This is typically 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 600 air changes/hour at 90 feet/min ± 20%. Microbial count must be less than 10 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 30-40 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. Purification is typically carried out in Class 10,000 room.

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 a minimum of 3 pressurization levels are required for cleanrooms; required in aseptic processing facilities.

WHAT IS THE BASIS FOR DESIGN

- cleanliness
- containment
- prevention of cross contamination

ROOM AIR CLEANLINESS IS AFFECTED BY

- amount of contamination released in the room
- quality of air supplied to the room
- quality and method of supply of room air
- 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

HOW DOES ONE DESIGN FOR CONTAINMENT?

- negative pressurization
- entrance and exit air locks
- filtration
- glove box technology

HOW CAN CROSS CONTAMINATION BE PREVENTED?

- no air recirculation between areas
- filters in room exhaust registers
- positive pressurization
- locate AHU intake upstream of building exhaust

FINISHES

- smooth crevices free, non-flaking
- no ledges
- minimum exposed piping

LAYOUT

- air locks
- unidirectional flows

CONTAMINATION SOURCES IN CLEAN ROOMS

- people (skin, clothes, breathing, talking)
- material brought into the facility
- shedding, shipping, breaking of building surface finishes
- abrasion, chipping breaking or shedding of metal or non metal containers, machinery and tools e.g. centrifuge
- opening and closing of internal and external doors
- make up of air and air leaks
- all types of operations; eg. equipment operation, granulator, lyophilizer etc.

LOCATION OF AIR RETURNS

- Near doors and pass thrus
- Not directly below diffusers
- Near particulate generating operations

SPECIFICATIONS AND CONTROL IN CLEAN ROOMS

Class 100,000

- no more than 100,000 particles greater than 0.5 micron or larger per cubic foot of air
- air circulation rate - 20 room volumes/hour minimum
- air supplied by HEPA filter
- temperature 72 ± 5F
- relative humidity 30 to 50%
- differential pressure of 0.05" of water
- bioburden < 25 CFU/10 cubic feet

CLASS 100

- no more than 100 particles of 0.5 microns or larger per cubic foot of air
- air velocities of 90 cfm +/- 15 cfm, corresponding to air circulation rate of 600 volume changes per hour for a 9 foot ceiling
- terminal HEPA
- laminar flow
- temperature 72 ± 5 F
- relative humidity 30 to 50%
- differential pressure
- bioburden < 1 CFU/10 cubic feet.

WHEN DESIGNING A CLEAN ROOM, WHAT SORT OF SPECIFICATIONS ARE REQUIRED ?

- air quality - particulate count/microbial count
- temperature
- humidity
- room pressurization
- air velocity or changes
- directional flow pattern

- room finishes
- lighting

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

DIFFUSERS USED SHOULD BE :

- stainless steel
- non aspirating
- flush with ceiling and sealing

RETURN AIR INTAKES SHOULD BE :

- stainless steel
- 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 very high

HOW MANY DIFFERENT CLASSIFICATIONS OF CLEAN ROOM EXIST?

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:

- pressurized room
- pressurized corridor
- pressurized room and airlock

AIR HANDLING UNIT (AHU) CONSTRUCTION

Prefilters

- 30% ASHRAE dust spot efficiency
- 85% ASHRAE efficiency

Coils

- no more than 8 fins per inch
- no more than 6 rows of coils

Insulation

- External insulation such as fiberglass is generally used . Internal duct insulation is not recommended since it can not be cleaned, and will harbour microbes and will shed particles in to the air stream.

AIR SUPPLY

The first three areas of the cleanroom definition, air supply, air distribution and filtration are very closely interrelated, 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? This will influence the size of the air handling plant, size of utilities such as power, steam and chilled water, ductwork, etc.

Therefore, it is essential to consider at the outset HVAC design how much air, what is the heat load, 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, 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 cleanrooms 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 cleanroom.

- Turbulent flow - conventional design approach where terminal outlets represent only a proportion of the total ceiling area located to suit the individual process requirements. Extracts may be located within the ceiling or at low levels within the walls. It is possible to reach Class 1000.

For facilities requiring Class 100 and better, 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, 90ft/min. (0.45 m/s) from a fully filtered ceiling, particle travel is easy to predict, there being no dead areas for contamination build up. Air changes of 600/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 lends levels increase so does the importance of air exhaust location. Cleanliness of Class 100,000 can be maintained efficiently with exhaust air grille in the ceiling or at a high level in the walls. With higher cleanliness levels, low level extraction 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.

FILTRATION OF AIR SUPPLY

Cleanroom technology is dependent on the use of High Efficiency Particle Arrester (HEPA) filters comprising of pleated packs of high density glass fibre paper with aluminum or craft paper, revealed into a timber or metal frame with. The newer design has better advantages such as:

- lower pressure drop, producing reduced system resistance
- higher CFM capacity
- greater loading capacity, resulting in larger service life
- reduced risk of pinhole leaks, etc

The relative efficiency of HEPA filters is extremely important and all filters will be tested at least once during the manufacturing installation process. While this provides an overall indication that a specified efficiency has been achieved, they can give 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 cleanrooms may require HEPA filtration on exhaust air system also. To be effective, filters should be located as close as practicable to the point of extract from the room, reducing the

ductwork susceptible to contamination to a minimum. Filters must be capable of being charged without breaching the integrity of the ductwork system.

HUMIDITY CONTROL

- desiccant humidifiers are required for humidity control in cold room or low RH environmental rooms
- when required, should be specified as a maximum annual humidity variation of either 5 % RH or 2 % RH
- 2 % RH humidity control uses the same equipment, but measurement & control systems are different add 10 % cost
- dehumidifiers and controls add 25 % to costs
- humidifiers and controls add 15% to costs

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

Parenteral Contaminants

For parenteral products, contamination in the form of particulate matter is defined as unwanted mobile insoluble matter. Particulate matter may come from a number of sources and may be loosely defined into:

- intrusive
- extrusive

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 its real that were not removed by the wasting process.

Extrusive contamination is material from the environment falling into the product and its container during the filling operation.

Example of mean particle sizes generated by various activities (encyclopedia of cleanrooms, bio-cleanrooms, and aseptic areas by Philip R. Austin)

Note: The eye can see particles as small as 25 microns

Activity	Mean Particle Size
Rubbing latex painted surface	90
Rubbing epoxy painted surface	40
Rubbing Formica surface	10
Rubbing stainless surface	2
Manipulating standard paper	65
Manipulating plasticized cleanroom paper	10
Manipulating Tyvek cleanroom 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

Detection of Contaminants

A UV light of specially selected frequency, will increase detection. Capability by a factor of x 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
	SCALP	approx. 1 million/cm^2
	ARMPITS	approx. 1-10 million/ cm^2
	NASAL/SECRETION	approx. 10 million/g
	SALIVA	approx. 100 million/g
	FECES	> 100 million/g
PARTICLES	SKIN SURFACE	approx. 1.75m^2
	REPLACEMENT OF SKIN	approx. every 5 days
	SHEDDING OF PARTICLES	> 10 million/day

TRAINING FOR CLEANROOM

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 cleanroom to minimize the potential for contamination.

When personnel are being trained in the cleanroom, 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 easiest training programme to make is a booklet training programme. In this booklet, list the rules that you wish the cleanroom personnel to obey. The next step is to explain each rule.

If a booklet training programme is prepared, prepare 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.

Pre-test question:

When doing cleanroom garments, the first item to put on is the:

a) head cover
b) coverall
c) shoe cover
d) gloves
e) face mask

Post-test question:

When doing cleanroom 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 question:

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 question:

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) gloves
d) moved quickly
e) fingers touching the bench top when resting

Psychological points to consider:

Some differences between men and women are applicable to cleanroom operations include:

a) women in general, have better control of their hands than men. For example application of cosmetics is an exacting application.

b) women tend to be more conscious of their physical appearance than men and take care to see that clothing is worn properly.

c) women generally prefer a warmer environment then men. The reason is physiology and clothing. The weight of women's clothes is tighter and the amount of surface area of body covered is different between men and women. Thus women tend to cool better that men and prefer a higher room temperature.

d) men generally have "less cleaner" hands and nails than women. Women generally on the other hand touch their hair and face more often than men. Each touch results in contamination.

e) in terms of personal habits, women tend to touch themselves when referring to themselves. This may automatically happen in a conversation when she says "I" or "one."

Both men and women must be made aware of the appropriate actions to be taken if such a contamination of the gloves takes place.

Training must also be a repetition and reinforcement of ideas. Check lists provide necessary reinforcements to employees of cleanrooms and bio cleanrooms. Check list 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 and understands. 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 cleanroom:

- keeps hands, fingernails, and face clean
- never touch, adjust or comb your hair in the cleanroom
- do not wear jewellery on wrists or hands
- valuable items such as wallets may be moved into the cleanroom provided they are not removed inside the cleanroom

- personal items such as keys, coins, cigarettes, matches, pencils, handkerchiefs, tissues, combs, etc. should not be carried into the cleanroom
- no eating, chewing gum or tobacco or smoking in the cleanroom
- 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 cleanroom
- never apply or wear cosmetics in the cleanroom
- wear cleanroom 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 cleanroom
- 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 Cleanroom

"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 secure 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 cleanrooms, an Austin Contamination Index was created. Personnel emissions are stated for different types of garments as shown in the table below. In every use but 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 date 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 of 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 producting the contamination at a steady rate.

Conditions	Quality of Bacterial
Surgical teams	**Aerosols**
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 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 contaminants levels in the bio-cleanroom.

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 and the downstream side. If no garment is the exterior 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.

Cleanroom Construction; recent additions:

In addition to clinical wall panels, glazing is becoming an increasingly popular choice in cleanrooms.

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 cleanroom through a complex changing process
- improved work environment for production operations.
- glass is actually an extremely suitable material for cleanroom use as it readily satisfies the principle requirements:

  hard
  smooth
  impervious
  easily cleanable

Disadvantages include contaminated air can leak 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 cleanrooms adjoin one another. Glass should be located into tailor made frames in stainless steel or equivalent using silicone sealant.

OTHER MISCELLANEOUS ITEMS USED IN CLEANROOMS

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 thru's
- piped 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 cleanroom 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 practicable.

Long horizontal service runs should be avoided whenever practicable. The zone above the suspended ceiling provides an ideal area for installing 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 matte 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 invention being allowed to contact 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 room fabric.

CLEANROOM CLOTHING

The single biggest source of contamination in the cleanroom is the people who work there. Cleanroom 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 INTO CLEANROOM

- A key item of importance in cleanroom design is access into the cleanroom. 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 cleanroom, close to the employee's entrance to the building, or it may form part of a double change procedure the grey area in where the coveralls, etc are held.

- Facilities should be available in the grey area for staff to scrub-up and dependency of the cleanroom garments. Flooring should be contamination controlled and lead to the white area.

- The "white" area is where staff change into their cleanroom footwear and step over into the cleanroom via a bench. Ideally, the air must flow from white to grey to black zones.

- Materials movements throughout the pharmaceutical process are important, but their introduction to and removal from the cleanrooms 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 paper 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

	IQ	OQ	PQ
DEHUMIDIFIERS	X	X	
HVAC AHU	X	X	
CENTRAL HEPA FILTERS	X	X	
FANS	X	X	X
DUCTWORK	X	X	
COILS	X	X	X
CONTROLS	X	X	
TERMINAL HEPA FILTERS	X	X	X

Validation of Clean Room

a) 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 declared.
- Finishes used for walls, floor and ceiling should be declared.

b) Operational Qualification (OQ)

This section is mostly concerned with calibration of temperature, humidity sensor, air velocity recorders, leak testing photometers, particulate monitoring equipment.

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 ± 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.

c) 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 & CEILING SYSTEMS

- Chemically inert
- Impermeable to moisture
- Cleanable & sterilizable
- Non-shedding
- Non-dust shelving
- Fully insulated for noise & thermal attenuation
- Non-combustible & fire retardant
- Non-outgassing
- "Monolithic" - smooth, crack free, homogenous
- Monoblock, non-progressive, de-mountable
- Integrated fittings, utility & HVAC chases

BENEFITS OF MODULAR DESIGN & CONSTRUCTION

- Lower start-up costs
- Earlier production & market entry
- Reduced interruption to existing operations (especially in expansions & modifications)
- Reduced congestion, construction infrastructure and outside labour on the plant side - higher labour productivity
- Improved site safety
- Improved quality control
- Advance planning & Firm Scope Definition eliminate "Cost Creep"

HUMIDITY CONTROLS IN PHARMACEUTICALS

- Personnel Comfort & adherence to aseptic techniques
- Electrical/Mechanical/Chemical processing stability
- Corrosion & 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.

CLEANROOM MECHANICAL SYSTEMS
THE KEY TO CONTROLLING CLEANLINESS

eg. Parenteral facility:

- Pressurization

Typically ± 0.25 inches w.g.

- Temperature

Typically range 65 - 75 degrees Fahrenheit
Constant temperature setting more important than the setting
Normal tolerance ± 2 degrees F
Where thermal stability critical ± 0.1 degree F

- Humidity

Without control can vary between 30 and 60% RH
Typically 40 ± 5 % RH
For critical applications , ± 0.5

- Air flow

Typical laminar flow room changes 50 - 110 fpm
Average for class 100 is 70 fpm, with normal 9 ft high ceiling expect 480 air changes per hour

SECTION 3

HISTORY OF VALIDATION

In the early 1970's 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 sterilization and radiation sterilization became mandatory.

By late 1970's, sanitization, water systems, media fills and environmental control was 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.

GMP's 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 for example, pure steam generator, filling machines, test equipment, filter integrity test and 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.

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 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 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.

- During validation, the process is challenged.

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.

- Demonstrates that the process meets an established range of operations for the chosen parameter's consistency.

- Demonstrates the ruggedness of equipment or process performance by challenging equipment or process at the limits of established operating conditions.

- Demonstrates accuracy, precision, reliability of analytical test method used to assess the performance, identity, strength and potency of chemical substances, components, equipment and product.

HOW TO IMPLEMENT A VALIDATION

- 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.

  For example: (This is not a complete list)

  Utility System

  - clean steam
  - compressed air
  - purified water system
  - chiller

  Production Equipment

  - granulator
  - dryer
  - lyophilizer
  - autoclave
  - vial washer
  - filling machine

Support Equipment

- depyrogenation oven
- pumps
- processing holding vessels

VALIDATION STRATEGIES

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:

Installation Qualification (IQ)
Operational Qualification (OQ)
Performance Qualification (PQ)

Each apply where appropriate.

Definitions

Validation

Validation is an activity which assures that facilities, systems, procedures, processes and products are maintained in accordance with cGMP compliance.

Installation Qualification (IQ)

Documented verification indicates that all key aspects of the installation will be in accordance with design specification and applicable regulatory codes and guidelines.

Operational Qualification (OF)

Documented verification that the systems and/or subsystems perform as intended throughout the all anticipated operating ranges.

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 will 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. This event must be demonstrated repeatedly which usually translates into a minimum of three consecutive successful runs.

Consistency and reliability at the limits of acceptable operating conditions are a fundamental for performance qualification, e.g., when validating a heat sealing unit the most important parameters are temperature, pressure and elapsed time.

It is not necessary to show:

> *Highest temperature, lowest temperature, lowest time, lowest temperature, highest pressure, lowest time etc.*
>
> 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. Categorize the items in the list according to level of concern.

Level 1

Lowest level of concern. Reliability of the item can be assured by PM and calibration programme; these include 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.

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 Biotechnology Facility Producing Parenteral Product

Facility Suites	IQ
Receiving, Quarantine & Released Storage of Materials	✓
Media preparation Suite	✓
Inoculum Preparation Suite	✓
Fermentation Suite	✓
Downstream Processing Suite	✓
Purification Suite	✓
In-Process laboratory	✓
Quality Control Laboratory	✓
Product Filling	✓
Product Quarantine	✓
Gowning Suite and Corridor System	✓

Process Equipment

	IQ	OQ	PQ
Sterilization Autoclave	✓	✓	✓
Decontamination Autoclave	✓	✓	✓
Biohazard Hood/Laminar Flowhood	✓	✓	✓
Glassware Washer/Dryer	✓	✓	✓
Inoculum Fermenter	✓	✓	✓
Production Fermenter	✓	✓	✓
Holding Vessels *	✓	✓	
Acid, Base & Antifoam Holding Tanks	✓	✓	✓
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	✓	✓	✓
Dust Collection System	✓	✓	✓
Facility Access System	✓	✓	✓
Electrical System	✓	✓	
Utility Station Panels	✓	✓	
Instrument Air	✓	✓	
Process Air	✓	✓	✓
Purified Water System	✓	✓	✓
Plant Steam System	✓	✓	✓
Steam /Condensate Distribution System	✓	✓	
Chilled Water System	✓	✓	
Pure Steam Generator	✓	✓	✓
Domestic Hot and Cold Water	✓	✓	
Filter Integrity Test System	✓	✓	✓

What kind of validation can be performed?

- prospective
- concurrent
- retrospective

Most widely accepted and practiced is prospective validation.

(a) **Prospective**

This is the simplest and most common approach. The product is developed and the manufacturing process is validated before introducing the product into the market.

(b) **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.

(c) **Retrospective**

This type is much more difficult and intensive. 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.

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, 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.

PREVENTIVE MAINTENANCE, 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 PM, routine calibration and change control.
PM and calibration are 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.

PROCESS VALIDATION

Candidates for Process Validation

A Examples of Manufacturing Processes:

Fermentation	Formulation
Primary Recovery	Decontamination
Purification	Cleaning
Depyrogenation	Sterilization

B 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- an example of process validation

The cleaning process is 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:

Firstly identify the raw materials that are used in the cleaning process: i.e. chemicals, water, buckets, sponges, mops, etc.

Secondly define how people are trained in cleaning techniques.

Thirdly define the cleaning techniques that are appropriate for specific areas, equipment, etc.

Fourthly, 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.

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, some

exceptions are like virus removal validation. The testing, inspection etc which occurs during this stage is called design verification and not validation.

LEVELS OF 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:

1. Sterilization, depyrogenation, aseptic processing, etc.

2. A diagnostic product which is a sole source of information to a critical treatment decision.

Level II

This requires qualification and components interacting in the process must be identified and controlled that the process itself must be established.

Example:

> Automated packaging process for a non sterile product requires qualification but not validation. In this case, it is demonstrated that the process can be performed effectively but there is no demonstration of process consistency under ideal and challenged conditions as it is not necessary.

Level I

This process can be assured with controlled documentation, training of personnel, simple equipment calibration and PM procedures.

Example:

> Mixing.

WHEN TO REVALIDATE/CHANGE CONTROL?

The time element, once a year, it is a good idea 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 4

INTRODUCTION TO DOCUMENTATION SYSTEM

DOCUMENTATION AND DOCUMENTATION CONTROL FOR cGMP COMPLIANCE

A. 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 (examples include: Master Batch Protocol, Product and In-Process Specifications, Standard Operating 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, LUMAC, etc.).

- Traceability documents: these documents allows 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 control to seek assurance that:

- The facility, utilities, equipment and instruments are 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 for the production are fully validated.

- Personnel are adequately trained to perform their required duties.

- A traceability system exists in the event 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.

B. POINTS TO CONSIDER WHEN CREATING A DOCUMENTATION SYSTEM

a) Language

The language and choice of words used when preparing documents should be such that it is:

- Instructive to the technician (ie. 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 a # 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 optimally 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 below:

> *"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 above 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 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 filler 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.

b) Change Control

Change Control is an option to use only when absolutely necessary. There are cases where SOP's have several revision numbers (for example TM 1081.27 - Method for Measuring Protein Concentration).

This SOP was two years old but revised 27 times! When an inspector sees this kind of information it does not create confidence in the credibility of an organization.

Issues to consider when implementing change control:

All changes must be reviewed by Departments affected by a change, thus for example, a QC document change must be circulated through QC, QA and production. (Since the change was in QC, the technician performing that task must be retrained).

- If the change is dramatic ie. it can affect the identity, strength, safety or efficacy of the drug, then the Senior Management must be advised. It may also be necessary to contact the Inspecting Agency before the change is implemented.
- One copy of the previous revision must always be kept on file and archived. Outdated versions 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.

c) Documentation Control Design

Before implementing a documentation system, the QA Department must prepare an SOP on how to write SOP's. The information in such an SOP describes:

- How to write the different 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 or different documents.
- How will the documents be controlled and distributed in the facility, and the number of controlled copies.
- How will they be numbered and identified.

d) 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, 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 the SOP for nature environmental monitoring for Class 10,000 Purification Suite and say for example 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 delay the planned environmental monitoring a few days to take care of this emergency, in this case the QC department must send out a memo to Production and QA stating something like:

> *"Due to urgent and heavy work load in the QC Department the environmental monitoring in the production area 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 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 files.

A good system to implement is CNN - Change Control Number. For example, for Measles Vaccine production, one can implement a Change Control System 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 CNN-MV log book for Measles.

For example, when a deviation occurs, it would be recorded:

"CCN-MV-91-01-14, Sodium Phosphate, ACS grade was changed to Sodium Phosphate, USP grade." 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.

- Who writes the documents?
- Who controls?
- Who approves?
- Who describes and archives?

C. 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 drug. There are different kinds of numbers for different types of documents as described below:

a) Master Document Index (MDI)

MDI is an index of all documents (Document Number and title of each document) currently in place, and, those which have been retired at the facility. 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 & Engineering

For example:

SOP-001.0 Operating 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

b) Production Batch Numbers (PBN) or Final Product Lot Numbers (FPLN)

A batch 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 determined. The 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.

c) 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 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.*

i) 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, eg. 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

ii) 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 GMP environment but **NEVER** reassigned to another item.

iii) 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 recorded and on the quarantine label 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 eg. 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) isoenzymes analysis, phenotype and genotype characteristics, MSDS, storage, expiry date, etc.*

> *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, expiry date, etc.*

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 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 the purification process Class 10,000 clean room to produce a drug will need to be tested fully; 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 vendors 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, handwipes, measuring cylinders, etc.

All Specification Forms must indicate an expiration date, to assure that the item maintains its original quality until its last day of use. A vendor assigned expiration date must be honoured unless the 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.

iv) Receiving Codes

The only way to completely identify an item used in the 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 normal 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.

v) Labelling Part Numbered Items:

Each item received from the vendor is labelled with its Part Number and Receiving Code and placed into a locked quarantine area; Quarantine label is usually orange in colour. 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 flourescent green in colour:

RELEASED
Lot # _____
Release Date: _____ By: _____
Expiry Date: _____

The REJECTED label is yellow in colour:

REJECTED
Lot # _____

Date: _____ By: _____

D. 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 colour with green lettering:

SOLUTION Name: _____
Lot # _____ P/N: _____
Conc.: _____ pH: _____
Amt: _____
Prep By: _____ Date _____
Store @: _____ Exp _____

E. INTERMEDIATE PART NUMBERS

There are several examples of Intermediate Part Numbers.

1) 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, aliquot into small containers and store frozen. The containers are labelled as 1 of 20, 2 of 20, etc.

2) 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 this 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.

Sometimes an intermediate is stored for reasons other than awaiting results of tests; for example:

Since the storage period may be quite long, the Part Numbered Intermediates must be tested to make sure that it meets acceptance prior to further processing. Thus an in-process test must be designed to check whether storage has had any deletion effects. In case of a validated process, this test may not be necessary as during validation, the impact of storage must have been evaluated. Since an item stored at 2-8°C for prolonged periods of time may get contaminated, storing the in-process intermediate in a sterile container after sterile filtration shows good manufacturing practices.

F. STANDARD OPERATING PROCEDURES (SOP'S)

SOP's 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:

1. Title: This should be brief and direct.

eg. Operation of Chemap FZ 2000 Fermenter
Calibration of Accumet 20 pH Meter

The SOP may be about:

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 a user friendly system.

2. Purpose: usually restates a well written SOP title. It allows the writer to expand the procedure further which was not possible in the title.

3. Scope: this is very important section, as it informs the person what this particular SOP does and does not apply to.

For example:

> SOP on Measurement of Absorbance of Protein using a colorimetric assay at 590 nm. This SOP might apply to the double beam spectrophotometer, or to the spectrophotometer in GMP area but not the spectrophotometer in the QC laboratory.

4. Responsibility: this section declares who is responsible for training and maintaining the SOP.

5. Safety: it is advisable that this section should appear in all SOP's. For eg. if dealing with BL2 or BL3 level of organism or product; safety precautions must be listed. If dealing with harsh chemicals such as phenol crystals, for example, precautions on how to avoid contact with skin and what to do if contact is made with skin. This section may also include what to do in the event of a biological or chemical spill.

6. 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 in place. Another example would be in the sanitization of biohazard hood before starting a procedure.

7. Procedure: This is the heart of the SOP; simple and short step by step instructions:

a. Add this to ...
b. Pour ...
c. Label the flask ...
d. Observe colour ...
e. Record

8. 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.

9. Documentation Requirements: this section 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 SOP's are usually more than one page long, the title, SOP #, pagination, name of the Company must appear on all pages. Approvals and dates of Approval are only necessary on the front 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 & 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 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 colour, 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 F&E (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.

G. 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.
- "Completeness" of information - by simple fill in the blanks, etc. all information required can be recorded.
- 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.

Use of laboratory notebook should be discouraged as entries are quite informal and usually incomplete.

Best way to ensure "user friendly" forms is to avoid asking for detailed comments, sections or use of questions which are vague and require input of a large amount of information. 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 (eg. 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 SOP's, the original Form must be of a different colour stored in a locked, secure, place and copies may be filed in an appropriate location where easy access is possible.

H. 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 is called the Production Batch Protocol. This copy of the PBP, when fully completed during the course of manufacturing becomes the official record of the product manufacture and is then called Production Batch Record or PBR. A record of all PBR's must be available at the facility during an inspection.

The PBP is used as a training guide to ensure all personnel involved in the 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 Bulk Drug Substance
- Assembly and processing of raw materials to make the final product.
- In-process testing and schedule.
- Final product packaging and labelling.
- 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 results (00S).
- 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 Biologics 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 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 the final purification step. In such an event, QA may design the five or six PBP for production of the material from fermentation to the end of concentration step only and one PBP 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 PBP into production
10 Date of release PBP into production

Items 1-6 must appear on every page. Items 7-10 on the first page only.

Example of MBPP for a Lyophilized Product:

Key Unit Operations involved in lyophilization involve:

- component preparation which includes - cleaning and sterilization of vials, stoppers, seals and appropriate equipment
- formulation and filtration includes: weighing, mixing and sterile filtration of the product
- filling - aseptic fill of vials
- lyophilization - freeze drying of the vials
- sealing - crimping of the vials and application of aluminum over seals
- inspection - labelling, packaging, and final inspection

The above are the key unit operations in the lyophilization of the drug product. Each unit operation may be carried out in the same general area or perhaps in a different area. It is quite likely that operation a, b & c would be performed in the same area. d is most likely to be carried out in the lyophilizer room, e in another area and f in yet another area. In such a case, it is important to provide instructions in the PBP on movement and storage of the product as it moves through the manufacturing event.

a) Points to consider with MBPP:

- When to Write One?

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.

Who Should Write It?

- Production and QC should write the MBPP.

How Should It Be Written?

- It should be written in a manner which achieves 2 objectives:
    - provides a convenient, practical and efficient set of instructions for the line worker
    - ensure that fundamental principles of cGMP compliance are met

Who should keep the completed BPR?

- It should be kept within QA 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 eg. 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 SOP's
- change of shifts
- completion of Batch Protocol
- importance of following the Batch Protocol

Generally on the first page of the PBP, it is recommended to have a section where the technician can verify his/her understanding of the contents and requirements of the PBP as exemplified below:

I have read and understand the content of this PBP

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 PBP, processing (wherever possible) must be stated, with limits of acceptance.

For example:

Adjust the conductivity of the supernatent with WFI (P/N 2182) to 5.0 ± 0.2 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 BR.

Best Company in the World
PRODUCTION BATCH PROTOCOL

Date Effective:	**Production Batch Protocol for Tetracycline**	**Confidential Information**
Supersedes Date:	**PBP 9071.0**	**Page 1 of**

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	RC #	Quantity Received	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/Logs
4111					
4261					
4814					

Calculation: A/B + C + D = % gain or loss _____/_____ = _____%
Acceptance Criteria = ± 5%
Calculated By: _____ Verified By: _____
Date: _____ Date _____

When the PBR is issued, the Lot Number of the Batch is filled in by QA. Each page of the PBP must be stamped by QA to indicate it is an official copy of the MBPP.

I. 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:

- Production Batch Protocol
- QC Records
- Sterilization Charts
- Move Tickets
- 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 for approval for release or rejection with respect to analysis. QA approves the Product Record with respect to documentation.

J. 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; 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 GMP. However, when such as document is written, it **must** be followed. The inspector who reads such a narrative will expect to find it is being implemented fully.

Typical contents of a Master Facility Plan are comprised of 7 major sections:

The first section is rather short it describes the following: Company description, ie. whether it is a Biologics, New Chemical Entities, Generics, 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 various 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 the senior management and their proposals are usually implemented. If such a MRB exists, it should also report to the same hierarchy as production.

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 flow from raw material to finished product. Separation of finished and in-process materials is important, so must untested product 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 retrofit 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 about it." 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.

The fourth section must address all the major utilities and processing equipment, key specifications of these equipment, their capabilities and intended use.

The fifth section should describe 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 SOP, a Validation Protocol, QA document, Test Method, etc. are an example and 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 so as 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, a Preventative Maintenance (PM) Programme, Calibration, Material Control, Cleaning Validation, Environmental and water monitoring, data trending and cGMP training.

K. DOCUMENTATION RELATED EQUIPMENT

a) Documenting Equipment Monitoring and Maintenance

Once validated, the validated state must be maintained 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:

- LUMAC
- Work Orders for Preventative Maintenance and Calibration
- PM Schedule

b) 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 cleanrooms, all utilities and major equipment used in processing.

A LUMAC for a cleanroom will contain information on why was the room used, for how long, how and when was it cleaned, etc.

For equipment, similar information would be recorded. For example:

> If temperature monitoring of the cold cabinet (2-8°C) is required on a daily basis, an entry is made in the LUMAC to show the temperature readings.

Typical LUMAC log book has the following sections:

Date	Client	Product Used	Activity Performed on Equipment	Performed By

The log book must be a bound book with numbered pages and located in plastic folders very close to the equipment in question.

c) Work Orders

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 Preventative Maintenance. This period of time is also used for recalibration once the maintenance work is completed.

In addition to routine Preventative Maintenance, stays 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 on the mechanical seal, 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:

Maintenance Work Order

Date Effective:	**FE - 001.0**	**Confidential Information**
Supersedes Date:	**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 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 not 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.

Example of calibration sticker will be scanned to appear in the next edition.

L. 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, IQOQ or IQ OQ & PQ) have been performed and all acceptable criteria have been met.

General Acceptance Criteria

i) 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:

  a. Process and Utility Schematic Diagrams
  b. Engineering Schematic Diagrams
  c. Piping and Instrumentation Drawings
  d. Equipment Specifications
  e. Vendor Supplied Documentation
  f. 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.

ii) 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 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.

iii) 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 individuals 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.

iv) 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:

a) **Method Principles:**
this section describes the general principles at work and assay sensitivity.

b) **Method Suitability:**
describe how the assay will be used and when appropriate and why it is preferred or superior to other methods.

c) **Method Categorization:**
most analyses are performed in the QC laboratory. All assays need to be controlled 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 considerate 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.

d) **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 the 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 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 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 accessory requirements. Reference Standards must all be described and discussed and explained to the technician before validation is started.

When evaluating a method the following must be considered (ICH guidelines)

- 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. 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, greater than 100 ppb, recovery of 60-110% is acceptable while for more concentrated samples recovery of 80-100% 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.

- LOQ:
  the lowest concentration of a sample that can be quantified with an acceptable degree of precision.

- Selectivity, Specificity and Interference:
  this is to measure of the assays sensitivity to impurities, related chemical compounds and degradation products. This is usually achieved by spiking a known concentration of sample with known concentration of potential cost 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, the Y-intercept is a measure of potential assay elicit been.

- 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 (eg. 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.

v) Process Validation Protocols

"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 processes that cannot be adequately tested in the final product.

Biologics production in particular, requires rigorous process validation on these molecules as these are highly susceptible to processing conditions.

Key Sections of a Process Validation Protocol

1) Introduction

- Reason for validation, for example, it could be because it can:

  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.

- Preliminary Operation

  This section should list activities that must be completed satisfactorily before the validation can begin. Examples include: raw materials, equipment, environmental processing, personnel equipments, etc.

- Process Qualification

  Process Qualification demonstrates that the process can proceed as described and meet equipment and process dependent quality criteria. For example, aseptic processing.

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 this 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 parts of the process operations for example: 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.

M. 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 cautions 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's 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 labelling claims.

Choice of worse case scenario is not always 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 # 1of 3 is complete, the document is reviewed for compliance. Deviation from failure to follow PBR and must be investigated and failure identified and restored before Validation cycle #2 starts. Once all three runs are complete, a Validation Certificate is issued to the process. It may be necessary at this point to review all relevant SOP's and other supporting documents to ensure that they are still valid as changes may occur to procedures during validation.

N. REFERENCE STANDARDS

Reference Standards must be characterized according to written procedures and stored under known conditions to preserve their integrity. In order to prove the authenticity of a Reference Standard, 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.

O. MISCELLANEOUS STANDARDS

a) Calibration Records

No matter which country's regulations are followed, it is clearly stated that equipment and instruments used in the GMP production or testing must be calibrated, inspected, and checked according to a written programme which is designed to assure proper performance. It is also required that a record of the work be maintained ie. calibrations 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. Further, calibration should measure the accuracy of 1°C changes in the range of the experiences in production.*

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 for example: 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 production on equipment, other agencies may have similar requirements, this information must be checked by QA prior to destroying calibration records.

i) 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 2nd person in QC dated and signed or critical the log is documentation of the work performed. Entries must be made in chronological order.

ii) Sanitization Record

In aseptic operations, not only must the equipment be sanitized but the facility surfaces (walls, floor and ceiling) must also be disinfected. Therefore, the requirements for sanitization and documentation of such work are virtually identical to those described above for equipment.

iii) Distribution Record

Records of distribution of drug products must accurately reflect who received each batch of drugs so that in the event of product recall, all units comprising of the batch can be located in the market place.

Such records must contain:

- Name and strength of the product
- 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

FIFO: First in; First out must be strictly adhered.

Returned Goods Documentation:

These records should indicate the:

- Identity (name and strength) of materia 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 drug is destroyed immediately, this should be noted on the record of returned together with the date of disposition.

Training Records

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 performance of a job, one can define the training requirement. To document that training has been received, a record for each employee should be prepared 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.

Drug Manufacturing Audit Program 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 drugs or drug components that will react, add to, be absorptive, or adversely affect the identity, strength, quality, or purity of the drug.

____ 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 Program*.

____ Management supports the *cGMP Program*.

____ A documented *Training Program* 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 labelled.

____ 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 labelled, 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 compound prior to further processing.

___ There is adequate documentation to show that in-process samples were collected and tested as per the 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 labelled 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 labelled 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 drug 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 Labelling 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 labelling 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 labelled.

____ There is adequate physical separation of the packaging lines.

____ All packaged and unlabelled 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 labelling 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 program 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 labelling.

____ 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 program 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 tested 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 labelling 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 program 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 when:

A. Finished product meets predetermined specifications

B. The documentation to support the production and testing of the product is accurate, complete and retrievable.

Thus there are two products of the factory for every batch produced:

product
documents

Neither can be sold without the other.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 002.0 CURRENT GOOD MANUFACTURING PRACTICES	Confidential Information
Supersedes Date:		Page 1 of 3

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.

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:

Date Effective:	QA 002.0 CURRENT GOOD MANUFACTURING PRACTICES	Confidential Information
Supersedes Date:		Page 2 of 3

5.0 PROCEDURE:

5.1 Written procedures shall exist for all production, quality control, packaging and labelling 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.

5.5 Packaging and labelling 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 003.0**	**Confidential Information**
Supersedes Date:	**GENERAL HOUSEKEEPING AND SANITATION**	**Page X of X**

1.0 PURPOSE:

To provide a system for the complete and timely cleaning, sanitizing, packaging, labelling and shipping departments.

2.0 SCOPE:

Applies to all parts of the facility, involved in the packaging, labelling and shipping of any drug product.

3.0 PROCEDURE:

3.1 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.

3.2 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.

3.3 An approved cleaning product list and inventory will be keep, no substitutions to this list can be made without approval from Quality Assurance.

3.4 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.

Housekeeping Log

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: _____

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QUALITY ASSURANCE

Date Effective:	**QA 004.0**	**Confidential Information**
Supersedes Date:	**MASTER AND WORKING BATCH RECORDS**	**Page 1 of 3**

1.0 PURPOSE:

To provide a system for the control and use of Batch Records.

2.0 APPLICATION:

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 PBP record.

Best Company in the World
QUALITY ASSURANCE

Date Effective:	QA 004.0	Confidential Information
Supersedes Date:	MASTER AND WORKING BATCH RECORDS	Page 2 of 3

4.0 THE 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 of the raw materials, designated by names or codes, that sufficiently indicate any specific quality characteristics.

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 PRODUCTION BATCH 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 Production Batch Protocol.

5.2 The Production Batch Protocol is retained for at least one year after the expiration date.

5.3 Each Production Batch 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 005.0**	**Confidential Information**
Supersedes Date:	**TRAINING PROGRAM AND DOCUMENTATION**	**Page 1 of 3**

1.0 PURPOSE:

To provide guidelines for the implementation and documentation of an internal Training Program, for all employees involved in the manufacture, testing, packaging, and shipment of final product.

2.0 APPLICATION:

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 Program will consist of three separate and distinct sections:

3.1.1 The 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 Program will be developed from the regulations promulgated in 21 CFR parts 211.1-211.208.

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.

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 SOP's for the Production Department serve as the primary documents for the SOP Training Program.

3.4.1 The SOP's which are used on a daily basis for the operation of all of the equipment and instrumentation, are also 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.

Date Effective:	**QA 005.0** **TRAINING PROGRAM AND DOCUMENTATION**	**Confidential Information**
Supersedes Date:		**Page 3 of 3**

3.5 For each different type of Training Program 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 Program file for each individual. A copy of the Training Documentation Sheet will be keep by the Production Director.

Best Company in the World.
QUALITY ASSURANCE

Date Effective:	QA 006.0 TRAINING PROGRAM FOR THE PRODUCTION FACILITY	Confidential Information
Supersedes Date:		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 APPLICATION:

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 SOP's 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.

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QUALITY ASSURANCE

Date Effective:	QA 006.0 TRAINING PROGRAM FOR THE PRODUCTION FACILITY	Confidential Information
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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 agree have been mastered by the employee.

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 current 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

cGMPTraining 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 5

UTILITY SYSTEMS FOR THE PHARMACEUTICAL INDUSTRY

cGMP Utilities

- High Purity Water (WFI, Purified, DI)
- Clean Steam
- Process Air
- Clean-In-Place (CIP)
- Product Contact Water
- Product Contact Steam
- Product Contact Air
- Product Contact Cleaning Solutions

PHARMACEUTICAL WATER SYSTEMS

Water is the most difficult product to maintain to the standard requirements especially as the quality increases. For example 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 used at fermentation and primary recovery steps and as a final rinse when cleaning fermentation and primary recovery equipment.

Design Approaches:

- Analyze 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

FEED WATER QUALITY

3 Major Areas Where Feed Water is Obtained Include :

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 & River Water	Seasonal Variation High Turbidity High Silica High Molecular Weight Organics

(Low Molecular Weight Organics can be Present in all Waters)

WATER SYSTEM COMPONENTS

- Feedwater Pretreatments
- Production
- Storage and Distribution
- Cooling for Use

CARBON ADSORPTION

- Removes Chlorine and Low Molecular Weight Organics
- Should be Heat Sanitizable

PRODUCT WATER SPECIFICATION

	Purified Water	WFI
pH	5-7	5-7
TDS	< 10 ppm	< 10 ppm
Resistivity	< 3 Megohms	< 1 Megohms
Heavy Metals	< 0.1 ppm	< 0.1 ppm
Bacteria	< 100 cfu/mL	< 0.1 cfu/mL
Pyrogens	Not Applicable	<0.25 EU/mL

USP Purified Water Generation

- Dual Bed Ion Exchange
- Reverse Osmosis

R.O. Membrane Materials

- Cellulose Acetate
- Cellulose Triacetate
- Polyamide Thin Film Composites
- Polysulfone

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

WFI Generation Systems

- Single Effect Stills
- Multiple Effect Evaporation (usually 3 are sufficient)
- Vapour Compression Stills
- Reverse Osmosis

Storage Vessel Requirements

- Stainless Steel vessel rated for minimum 15 psig and full vacuum
- Non-rusting 316L 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.

STORAGE & DISTRIBUTION SYSTEM MATERIALS

DI Water	•	Unpigmented Polypropylene
	•	PVDF
	•	Stainless steel
WFI	•	Stainless Steel

DISTRIBUTION SYSTEM MATERIALS

DI Water	•	Unpigmented polypropylene
	•	PVDF
	•	Stainless Steel
WFI	•	Stainless Steel

PROCESSED COMPRESSED AIR

Compressed air that directly contacts the product or directly contacts material that come into product contact.

DESIGN CRITERIA FOR PROCESS AIR

Item	Process
Temperature	Less than 100° F
Dew Point	Less than -40° F (100 psig)
Hydrocarbons	Less than 1ppm
Particles	99.9% removal @ 1 micron

PROCESS AIR SYSTEM COMPONENTS

- 'Oil Free' Compressor
- Receiver
- Filtration
- Air Dryer
- Distribution Piping System

CLEAN STEAM cGMP REQUIREMENTS

Proposed LVP GMP Requirements CFR 21 Sections (FDA Regulations) 212.227

- Free of boiler additives
- Free of volatile amines or hydrazine
- Steam, if considered, should meet WFI specification for constituents such as pyrogens, bacteria & dissolved solids

Applications where clean steam is used:

- Autoclave Operations
- Lyophilizer Sterilization
- Humidification for HVAC Systems
- Equipment Sterilization

CLEAN STEAM PIPING

- Conventional Stainless Steel Piping (schedule 10, 304 L, 316 L)
- Sanitary Tubing not Required
- Butt Welded Joints
- Pitched to drain with Adequate steam Traps
- Sample Cooler to test Quality

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 - CLEAN IN PLACE ; DEFINITION OF CIP

A Technique for Cleaning Process Systems and Equipment Without Dismantling

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 SYSTEMS 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?
- Investigating 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

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 Cycle parameters
- Design Equipment to Facilitate Cleaning
- Arrange Equipment to Facilitate Cleaning
- Design Piping to Facilitate Cleaning
- Design CIP Fluid Circulation System

SECTION 6

PROCUREMENT

Procurement will be defined as the action of obtaining materials or equipment to meet with standards set out for pharmacological production or usage.

1.0 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)
- Federal Drug Administration (FDA)
- Health Canada (HC)
- Local Governing Agencies, etc.

1.3 The Process:

- Written specifications drawn up to determine what is required.
- Inclusive and clear

The following examples are of two completely different materials that your company could order for use in the pharmaceutical industry in your country.

(these examples are not complete and will be used through out this section for demonstration purposes only)

Example #1 - Purchase of Water for Injection

- 5,000 units at 0.5 Litre per bottle
- containers to comply with Type I glass containers
- product to comply with USP XXIII Water for Injection
- produced under current Good Manufacturing Practices (cGMP) of country
- produced in an accredited facility inspected by such as FDA (USA), HPB (Canada) agencies
- product to be sterile filled and packaged in accordance with USP XXIII, unless otherwise specified
- labelling to comply with USP XXIII specifications

Example #2 - Purchase of Pure Steam Generator

- 400 kg/hr at 60 psig, to meet USP specification for WFI water
- ASME Section VIII Division I Specifications
- CRN approved (Canadian Registration Number)
- CSA approved (Canadian Standards Association) for all electrical and electronic components
- all stainless steel to meet ASTM Specifications for either 304 L or 316 L (for all wetted parts)
- surface finish shall be average 15 to 20 Ra and be treated by electro polishing
- welding procedures and documentation to comply with ASME Section IX for gas tungsten arc welding (GTAW) procedures
- testing procedures and documentation to comply with ASME Section V

2.0 Vendor Qualifications

2.1 Why is it required

To ensure that you are dealing with reputable companies in the field of manufacturing of products that are in compliance with the standards that your company requires to be able to market its products

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.

2.2 Who to Qualify

Qualifications should be conducted on all companies you intend to do business with:

ie. contractors and/or equipment suppliers
material and product supply companies
testing facilities
shipping and freight companies

2.3 What to Investigate

Expertise in the field

ie. does the company have the proper trained personnel on staff, professional (doctors, engineers, etc.) and technical members (with supporting certifications)

what standards does the company comply with (GMP's, USP, FDA, BP, IP, etc.)

2.4 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

2.5 References of Recent Sales or Completed Projects

when dealing with both new and established companies ask for their listing of recent customers

any company that is unwilling to supply a listing should be removed from your qualified vendors list as suspect to it's ability to do business in a professional manner

2.6 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 - Purchase of Water for Injection

- manufacturing experience in the field
- documentation programs QA and QC
- testing practices to USP XXIII or BP, etc.
- FDA or equivalent approved facilities (last inspection report)
- inspection of the manufacturing site (very good to do for your own comfort level, but unfortunately not always very practical)

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 programs (videoscope of welds, x-ray and hydrostatic testing)
- electro polishing capabilities
- inspection of the fabrication site (as noted before, may not be very practical, but if you are using a local shop, it will be well worth the effort)

3.0 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 supplies. At this stage your company can either be in a position to take advantage of impending purchases, due to their scale (capital value) or be at a disadvantage if the value is generally low and location may be remote or other financial considerations may come into play.

In any of these cases it is imperative that you have specified the product fully before negotiations start. As these negotiations maybe out of your direct control through purchasing departments or purchasing agencies.

ie. 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, your company has an advantage in writing the purchasing agreement and 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 suppliers, the contractors were aware of or were informed of through various means. To these people this is a golden opportunity to make real money that is guaranteed, as they know you are serious and the project is 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

Example #1 - Purchase of Water for Injection

- payments will be FOB to the suppliers warehouse
- usually net 30 days upon receipt of the materials (provided you are a established client with adequate financing)
- if not, by 100% payment before shipment of materials is likely
- 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 reliable 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
- 50% upon receipt of the equipment
- 10% hold back, for QC inspection of equipment, documentation before release of funds

4.0 Quality Control & Quality Assurance

Your company must have an established set of procedures (SOP's) for the receipt of all incoming materials and equipment to your facility.

All documentation is to be inspected, reviewed by the appropriate groups, and approved as received in the specified conditions for the original 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 (ie. 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 7

ROLES, RESPONSIBILITIES, AUTHORITY AND ACCOUNTABILITY OF PERSONNEL WORKING IN GMP ENVIRONMENTS

An example of an organigram of a typical biologics production facility is shown on the next page.

- Note this is one way to organize personnel in a company, different company culture and philosophy may dictate a different kind of organization

Department of Facilities and Engineering

The primary function of Facilities and Engineering is to provide support to 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 which:

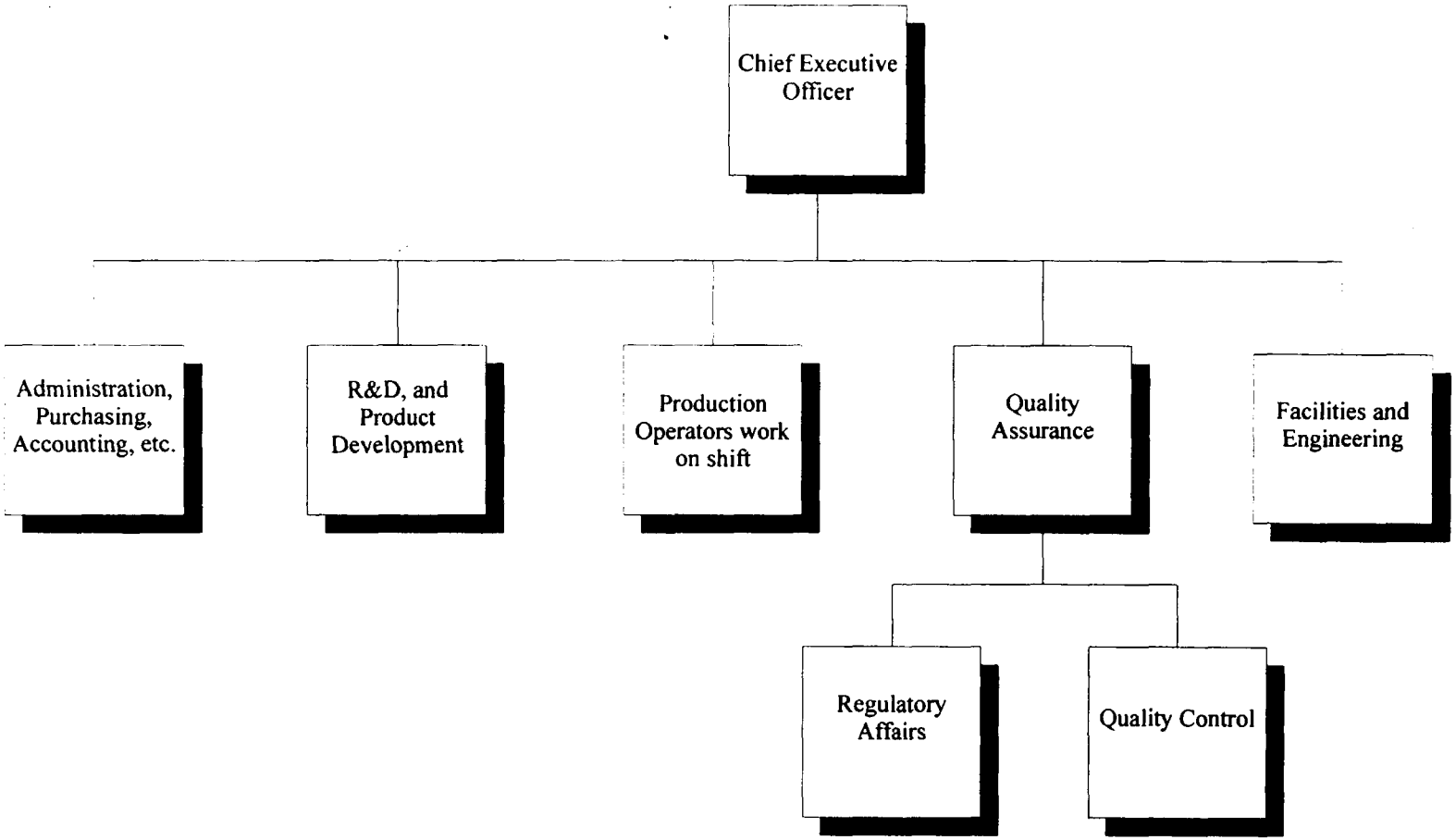
  the identity, strength, purity, performance, safety or effectiveness of the drug is not compromised

  it must not adversely affect the critical operating parameter 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 there must be written procedures which are followed for equipment construction, cleaning, calibration, preventative maintenance and written procedures to document the same.

  all equipment and utility system operations as well as repair/maintenance activities


Chief Executive Officer
Administration, Purchasing, Accounting, etc.
R&D, and Product Development
Production Operators work on shift
Quality Assurance
Facilities and Engineering
Regulatory Affairs
Quality Control

- 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 builts

  Company SOP's

  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 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 or earthquakes. An emergency response manual must be created by Facilities and Engineering Department; all personnel must be trained in the event of emergency.

Facilities and Engineering must work hand in hand with QC to review results of environmental and water monitoring so as to service areas falling within alert limits, as is QA to ensure all equipment, utilities and facilities, remain in a validated state and with Production to ensure that all equipment is functionally as per specifications.

Department of Research and Development

R & D department has several roles to play:

- It can trouble shoot a process problem in the production area or analytical or QC test. For example if a test reproducibility is a problem in QC, personnel R & D department who developed the test can be an excellent resource.

- Keep excellent records with the help of QA for inspection purposes for new product, this inspectors like to see R & D data from research to the final production process.

- Work with Production Department to perform technology transfer of the process and scale-up.

- Work with QC department to check specification of materials used in GMP production. Approve break points in the process and assist in preliminary write-up of Batch Protocol (QC and Production are responsible for preparing the Batch Protocol).

- Train production and QC staff to perform 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

Department of Production

The major functions of the Production Department are to: manufacture, formulate, fill, package and label the final product under the following constraints of cGMP;

- all above operations must be performed by trained personnel
- using equipment and personnel who are validated
- operating variables must be controlled within acceptable limits
- all events are fully documented
- any deviations or variances are investigated and reported

The environment set-up required to fullfil these criteria by cGMP's means that QC and Production must work hand in hand to create this environment.

Production operations must assure control of all process operating variables so that the final product which is produced by an acceptable 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 help from facilities and engineering.

- 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 so as to ensure there is no quality problem. Traceability practices ensure that the testing, approval, use and effectiveness or suitability of specific critical components and must be documented.

- Production Department controls processing by following established SOP's and then documenting that these procedures have been followed routinely. Always, a Batch Record accompanies a processing event. Verifying signatures at critical steps are compulsory 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)

- Quantity of materials - ie. lot size.

  The lot size is determined by validation. The upper and lower limit should not be surpassed. Eg. if the operating volume of the fermenter is set at 900 L ± 50 L for a 1500 L name plate fermenter, the volume should not exceed 950 L even though the fermenter has the capability to go to 1100 L of operating volume.

- Time limits for processing should be set within acceptable limits. If an ultra filtration step takes 3 hours to complete, and ends up taking 5 hours, this should be investigated.

- Limits should be established for the number of processing events. For example: *"concentrated supernatents from up to 4 batches may be loaded into the DEAE Flow column."* This means no more than 4 as the process is validated for 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.

Department of Quality Control

1. Material Control

Material Control can be a separate department known as Material Handling Department, if the organization is very big, this is a QC function and however, this function must evolve as a QC function which is then transferred into a Material Handling Department. 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 product, intermediate and final products within the facility. There must be areas within material handling to ensure adequate and appropriate space for:

- Quarantine of raw materials, components, closures and labels
- Release/Approved 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 (eg. use of move tickets). Materials must be stored in a manner to accommodate FIFO - First In/First Out.

2. Microbial Monitoring and Testing

This is required in several areas by monitoring and testing

- water and condensate every point of use
- air and moisture
- environmental - particulate and bioburden
- personnel - cleanliness, contaminants
- surfaces - cleanliness, bioburden and particulates
- equipment - cleanliness
- incoming materials, raw materials containers and closures

3. Master Cell Bank/Working Cell Bank MCB/WCB

Preparation and maintenance of Cell Banks so that they are contaminant free

4. Testing intermediates and final product for Endotoxin, Sterility, and General Safety in addition to other tests.

Physical and chemical testing which includes:

- identification, 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

5. 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 cleanroom, etc.

6. Other Duties

Establish a particular library of known contaminants, known slides of pathology studies to compare as Reference in the future for trouble shooting, etc.

Maintain retain samples appropriately.

Appropriate calibration standards for laboratory instrumentation.

Department for Quality Assurance

Key function of the QA Department are:

- Documentation
- Compliance Auditing
- Validation
- External Inspection
- Training

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 Programs should be scheduled periodically throughout the year and must be documented.
- generally, 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.

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. Training personnel for task specific duties is not sufficient. There must be a thorough understanding of product similarities, product hazards and product characteristics.

An example of training program 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.

- cGMP's

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, SOP's, 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 conclude at a minimum, the basic principles of aseptic technique, such as proper use of biohazard laminar flow hoods, clean room gowning, etiquette, etc.

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