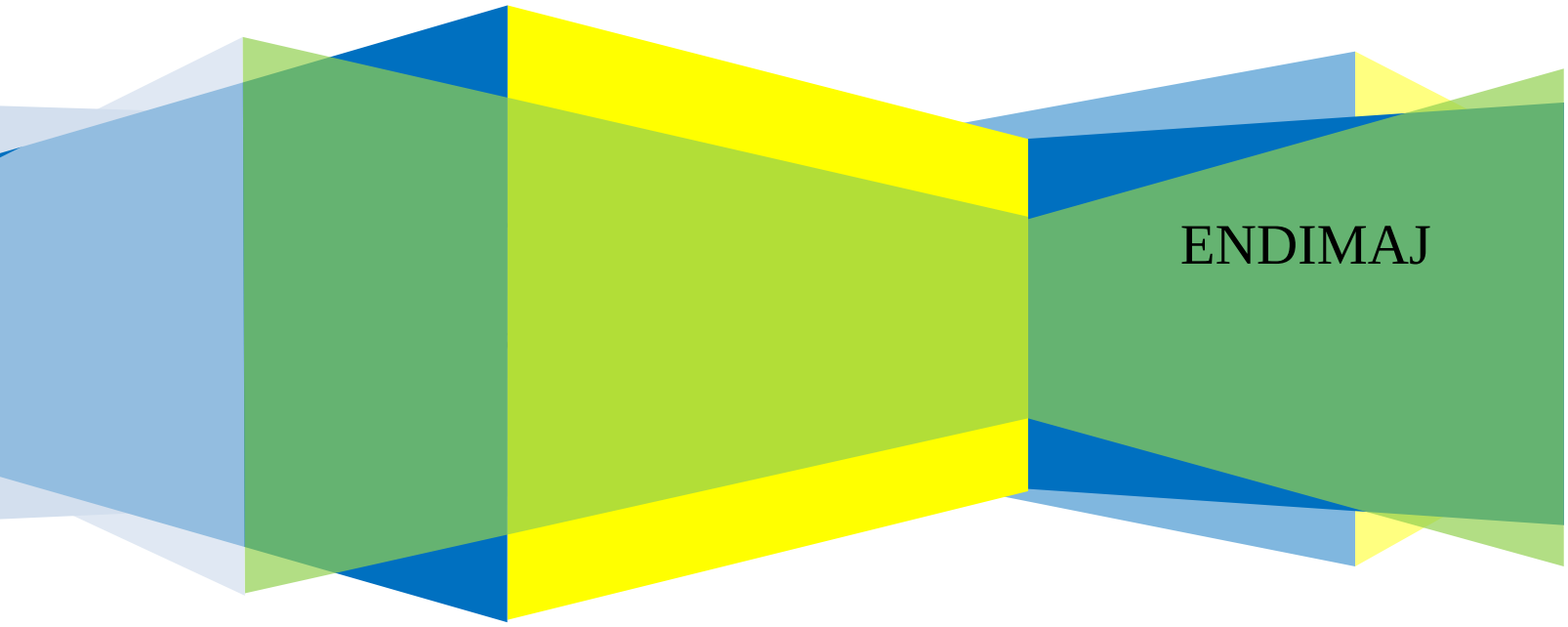
ENDIMAJ for specialized chemical & pharmaceutical industries Co.

Company profile



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Introduction

Brief Information:

Endimaj for specialized chemical & pharmaceutical industries Co. (ENDIMAJ) was established at Al-Hassan Industrial Estate in Irbid, Jordan.

The factory building is situated on a plot of 13,000 m² size and the construction area is 8,000 m².

The factory is divided into six different plants, each for a specific group of products:

1. Oral general production (OPA) plant with a design capacity of 500,000 liters per year for liquid and 500 tons per year for powder.
2. Oral Powder Penicillin production (OPB) plant with a design capacity of 500 tons per year.
3. General injectable production (IPB) plant with a design capacity of 3,500,000 unit (100ml) per year.
4. Penicillin injectable production (IPA) plant with a design capacity of 1,500,000 unit (100ml) per year.
5. Agrochemicals production plant (PPA) with a design capacity of 500,000 liters per year, powder production plant with a design capacity of 300 tons per year, granulation line with a design capacity of 300 tons per year.
6. Aerosol production plant (APA) with a design capacity of 1,500,000 can per year.

Endimaj for specialized chemical & pharmaceutical industries Co. (ENDIMAJ) consists of R&D, Quality control laboratories, Quality assurance, Maintenance, Utilities, and Warehouses departments, all these departments are working together to support manufacturing operations

A wide therapeutic range is covered by the company products, antibiotics, mixtures of antibiotics and vitamins, anticoccidials, anthelmintics, disinfectants, expectorants, ectoparasiticides, feed additives, mold inhibitors, vitamins, mixtures of vitamins and minerals and amino acids.

ENDIMAJ achieves through a process complying with the requirements of cGMPs.

This reflects on employees work practice and drives the staff towards a whole development process.

ENDIMAJ was aware of the importance of international certificates concerning quality and thus obtained ISO 9001:2015 Quality Management System Certificates and ISO 14001:2015 environmental management system certificate.

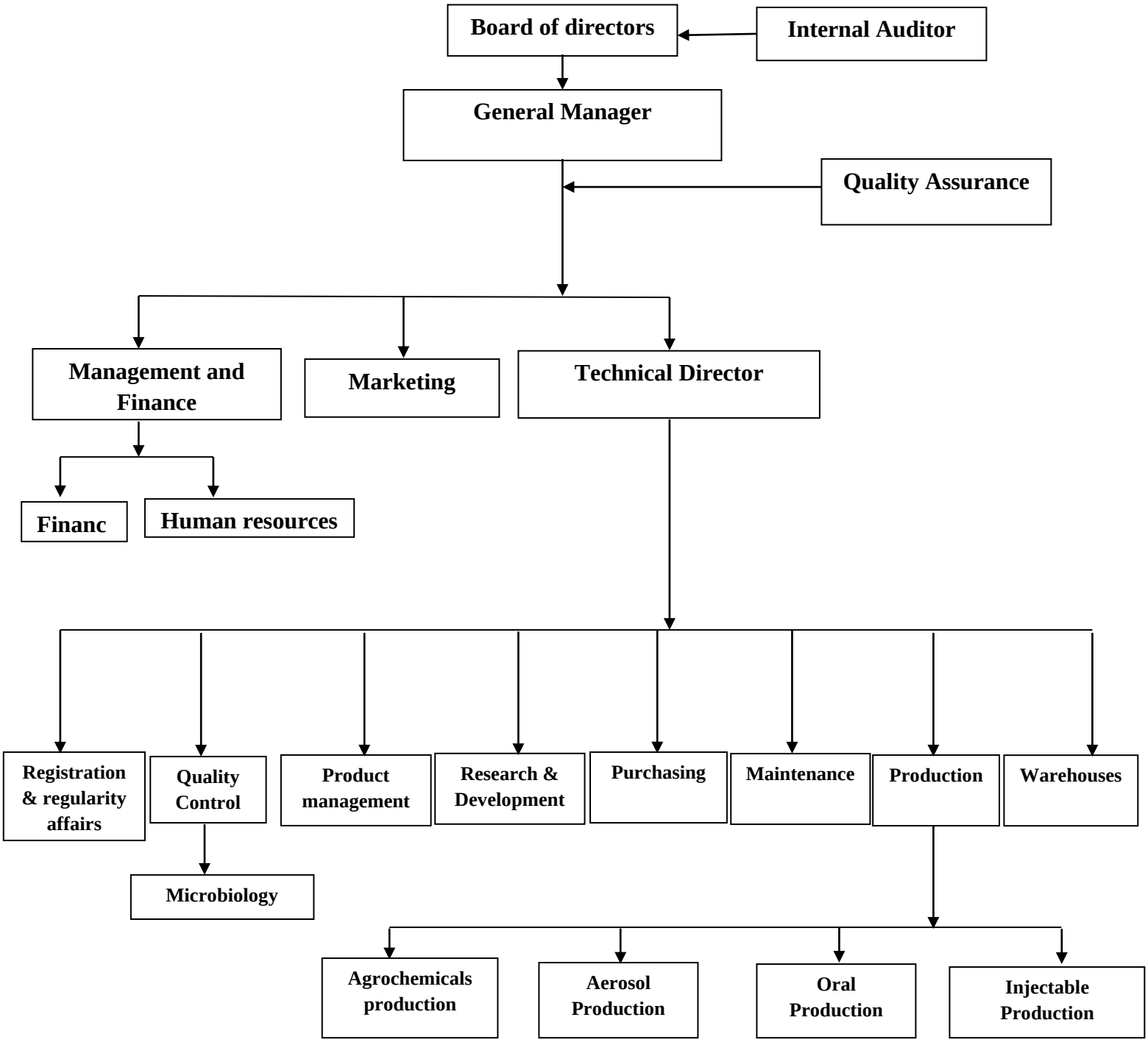


Fig. (1): (ENDIMAJ) Organizational Chart

Pharmaceutical manufacturing activities as licensed by the national Authority:
ENDIMAJ has a valid license document from the Ministry of Agriculture in Jordan, for manufacturing and marketing veterinary medicines. The validity of the license issued by the ministry of agriculture-Jordan is subject to auditing on annual basis or when introducing a new production line for **cGMP** guideline compliance.

Arrangements for basic and ongoing training:
Training requirements for each job position are identified; training programs are prepared by each department manager and approved by QA manager, training covers basic aspects of sanitation, personal hygiene, housekeeping, cross contamination, definition of **cGMPs** , elements of **cGMPs**, Gowning procedure, good documentation practice, levels of cleanness, line clearances, room fumigation, Aseptic discipline, basic microbiology plus the topics related to the employee's job description, all trainings are documented on employee's training record

Pre-employment medical examination:
Each new employee is sent to the clinic for pre-employment as well as routine annual medical examination, these tests include:
Fitness test, Chest X-Ray, Sight test for employees whose tasks include visual inspection and Lung performance test.

Reporting Sickness
Employees are to report illnesses or health problems that could affect product quality to their supervisors; the employee also has to report the nature of sickness if the period of absence is 3 or more days in continuation.
In such cases, the employee also has to produce medical fitness certificate.

Individuals with apparent illnesses or open lesions are to be excluded from direct contact with the product.

Human Resources department reviews medical forms and investigate the reason of any sick leave and inform QA department of any problem that could affect the products quality.

Personnel hygiene requirements including clothing, washing changing and rest areas:
The toilets are located away from the change rooms. Washing area consists of toilets, washbasins and bathrooms. Liquid soap dispensers, alcohol gel and hand driers have been provided. Personnel are required to clean hands with soap and water and sanitize them using alcohol gel after visiting the toilet.

Quality Assurance Responsibility:

In ENDIMAJ; Quality Assurance is a concept that represents a culture and a way of thinking, quality assurance department is the department which assists everyone else to produce quality products.

Its main goal is to ensure that production and control operations are clearly specified, c GMPs are adopted, and products are consistently produced and controlled to the quality standards appropriate to their intended use.

ENDIMAJ quality assurance system is comprehensively designed and correctly implemented.

It incorporates Good Manufacturing Practices and thus quality control.

Every attempt is made to provide for the discovery, reporting, correction and prevention of actions that could result on unsatisfactory conditions at the earliest possible point of detection. The system is fully documented and its effectiveness monitored.

Quality assurance department consists of the following units:

- Self inspection unit.
- Documentation Unit.
- GMP officers.
- Training and Awareness Unit
- Validation and Qualification Unit.

(ENDIMAJ) quality policy:

We, at ENDIMAJ are committed to produce products which meet standards of **cGMP** and national or international guidelines. Quality is the responsibility of each and every person working in the organization. We are serving animal producers by supplying the quality medicines through high standards of safety, efficiency and quality. We shall achieve through process of continuous improvement in all areas of operations giving emphasis on training and reducing manufacturing and operating cost without compromising quality. The policy shall be periodically reviewed and revised if needed.

Audit programs (Self inspection or audit by external organizations)

Self inspection is part of the our comprehensive quality assurance system, our Internal Audit team consist of five qualified and trained internal auditors, the internal audit covers the issues of GMP, this inspection is done by means of daily walk thorough unscheduled inspections.
The QA manager prepares the internal audit program that includes all departments.

The frequency of the audit takes into consideration the importance of the audited activity.

The QA manager should arrange for the planned audit to be carried out and may initiates additional audit as required.

The QA manager notifies the department / personnel to be audited at least one week prior the audit date and defines the audit scope. The audit date should be agreed by both, the auditor and the auditee. The auditor should prepare a checklist taking into account any nonconformity identified in previous audits or area highlighted for attention by the QA manager.

If any nonconformity is identified, the auditor will classify and record it on the internal audit report. Internal auditor's report is submitted to the QA manager to evaluate the audit and agree on the scheduled corrective action if applicable and sign the report.

Un-programmed inspection could be performed according to the need and treated like the scheduled audit. Also, the Un-programmed audits could be performed and recorded on walkthrough inspection form and maintained in walk through inspection file. At the end of each year, QA audit annual report is prepared to summarize all audits performed by the QA staff. External audits are carried out by the certification bodies for ISO14001 and ISO9001, external surveillance visits are performed by members of ministry of agriculture on semi-annual basis. Competent authorities in some countries do site inspection on regular basis

There are several kinds of documents including manuals, protocols, standard operating procedures, specifications, methods, posters, brochures, forms and lists are used in ENDIMAJ, Fig (2) shows how these documents are classified according to the documentation structure.

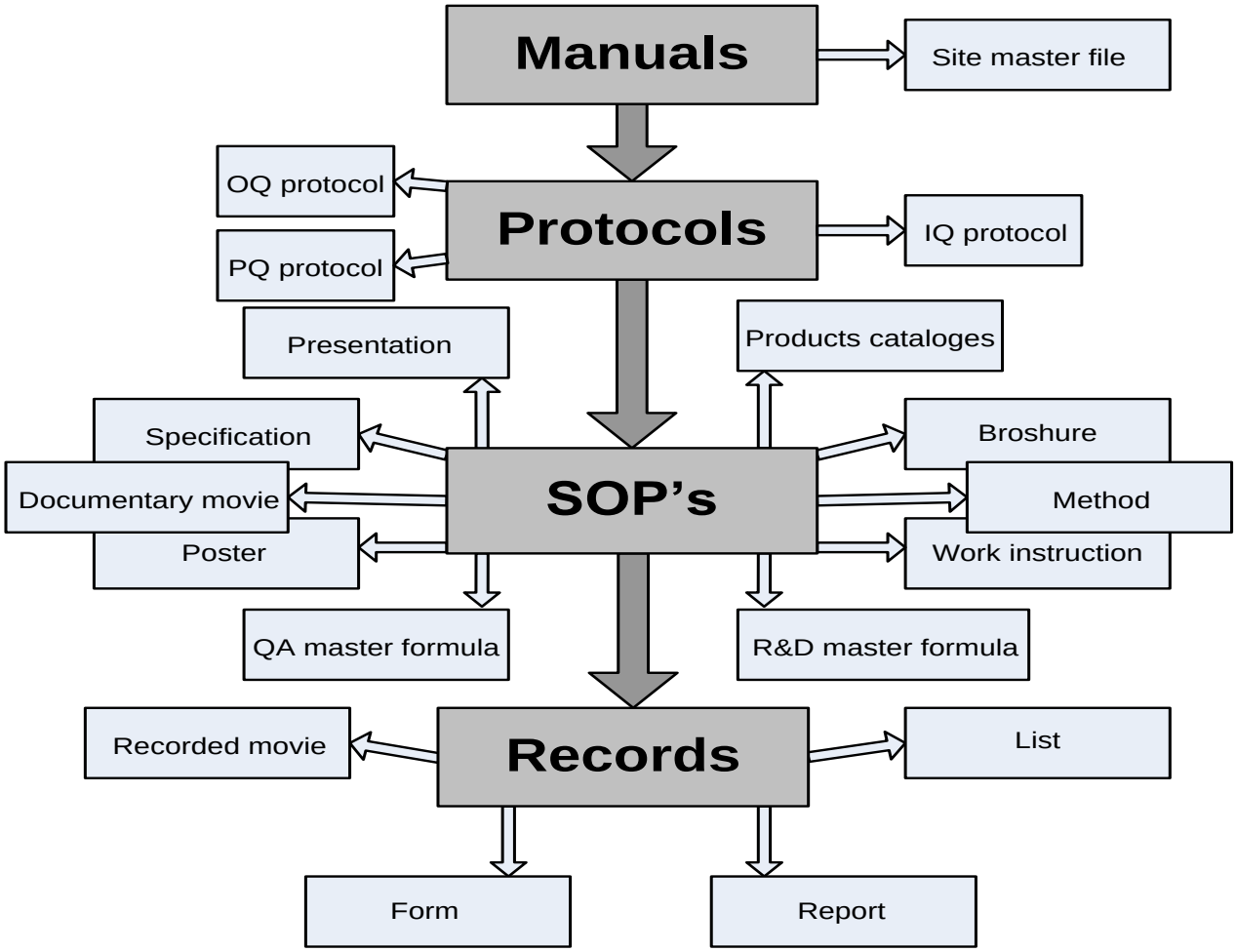


Fig. (2): Elements of the QA documentation system

Facility specifications:

General:

- Self leveling epoxy flooring with coving at wall-floor, wall-wall and wall-ceiling to avoid sharp corners.
- Walls are plastered to smoothness and painted with enamel paint for ease of cleaning.
- Concealed piping and electrical wiring in all areas.
- Provision of false ceiling to conceal HVAC ducting and utility pipelines.
- Entry points to production areas are provided with airlocks.
- The plant design allows linear material flow. The starting materials from the warehouses enter the plant from one side, are processed, quarantined and packed in a linear fashion. The finished goods leave the plant through the other end and are delivered to finished product store.
- Personnel entry is from the opposite side of the material entry thus allowing minimum possible cross flow of personnel and material.
- Kitchen and dining hall are away from production areas and QC laboratory.

Oral production (OPA),Ectoparacticides (PPA), oral powder penicillin (OPB), Penicillin injectable production (IPA) and aerosols production (APA) facilities:

The rooms were designed from concrete coated with epoxy resin, except for general oral production (OPA)which is fabricated from concrete covered with Alumetal ACP, which provides an impervious, smooth surface, resistance to mechanical damage and chemical attack. the floor is made of concrete coated with epoxy self leveling resin, which provides a smooth impervious, and durable finish. Windows are non-opening, flush fitting and sealed to prevent ingress of contamination there are no uncleanable recesses and minimum of projecting ledges (Coving wall to floor, wall to ceiling and wall to wall). Doors are made of stainless steel in (OPA) and (PPA) and from GRP material in (OPB) ceiling is made from gypsum board.

General injectable production facility (IPB):

The injectable production facility consists of clean rooms which were designed from Glass Reinforced Polyester (GRP) material; this includes the whole system of walls and ceilings. GRP material provides an impervious smooth surface resistant to mechanical damage and chemical attack. The floor is made from concrete, coated with epoxy self leveling resin, which provides a smooth, impervious, and durable finish. The panels are flame retardant quality rates as class "O". The standard panels are 961 mm wide and linked together with 231 mm service panels ,joints between panels are scaled flush with clear silicone sealant which provides a totally air tight room. Windows are non-opening, flush fitting and sealed to prevent ingress of contamination, production doors are equipped with interlocking system so that no door in the production area can be opened unless the adjacent door is closed.

False ceiling (GRP walk-on ceiling panels) are adequately sealed to prevent contamination from the space above them to reduce accumulation of dust and facilitate cleaning, there are no uncleanable recesses and minimum of projecting ledges (Coving wall to floor, wall to ceiling and wall to wall).the lightening and HEPA filters are recessed to the ceiling. Air is fed to the clean rooms via HEPA filters as terminal filters with over pressure against surrounding.

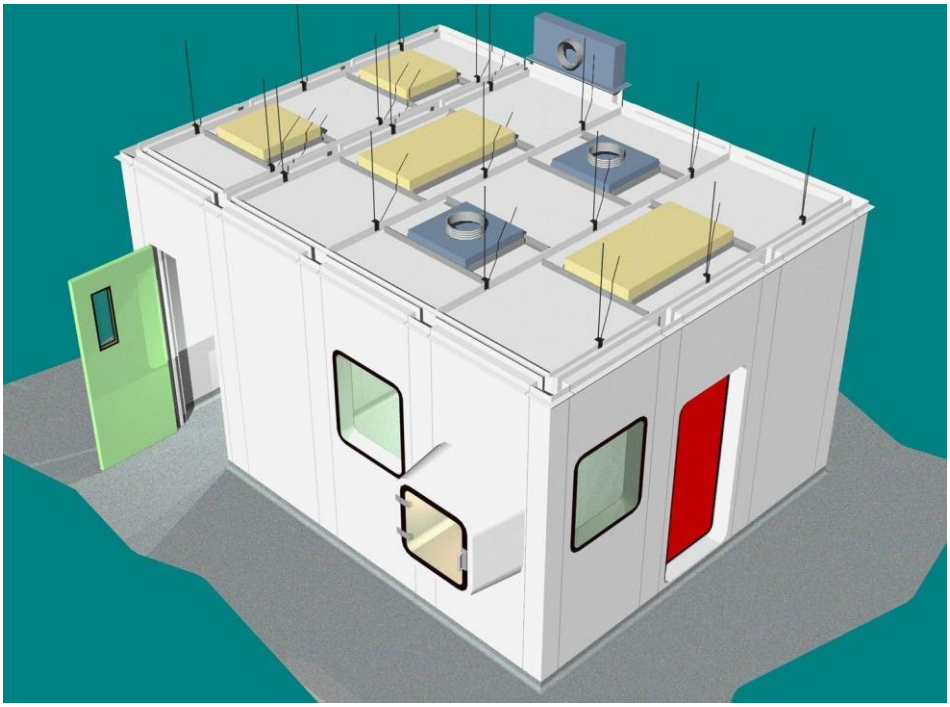


Photo (2): Standard clean room construction in (ENDIMAJ**)**

Equipment specifications:

General requirements:

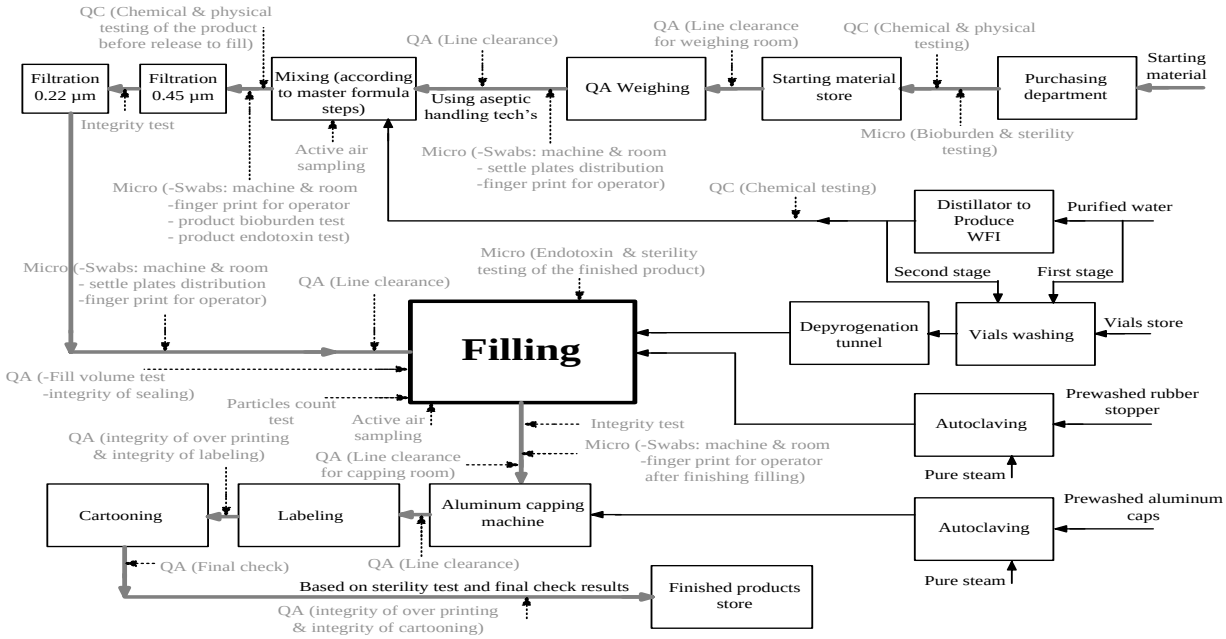
- All the internal parts coming in contact with vials or product/water/air are built of SS316 (L), max Ra-0.6m.
- External surface made of 304 SS .
- Material of construction for size parts, pipes, guides, etc. are made of no corroding material.
- Easy access for maintenance and cleaning.
- All welds are ground smooth and all internal corners are rounded.
- Automatic, orbital welds on piping.
- Control of working rate, WFI and compressed air pressures.
- The size parts are easily and quickly set up.
- Emergency breaker (s): automatic and manual.
- All operation is controlled by SIEMENS or Allen Bradley PLC's. Software complies with 21 CFR p.11.
- User-friendly HMI (Allen Bradley or SIEMENS): simple and friendly operating parameters display.
- Validation package to include: FAT, IQ, OQ products from the supplier.

Photo (3): Filling line in (ENDIMAJ)

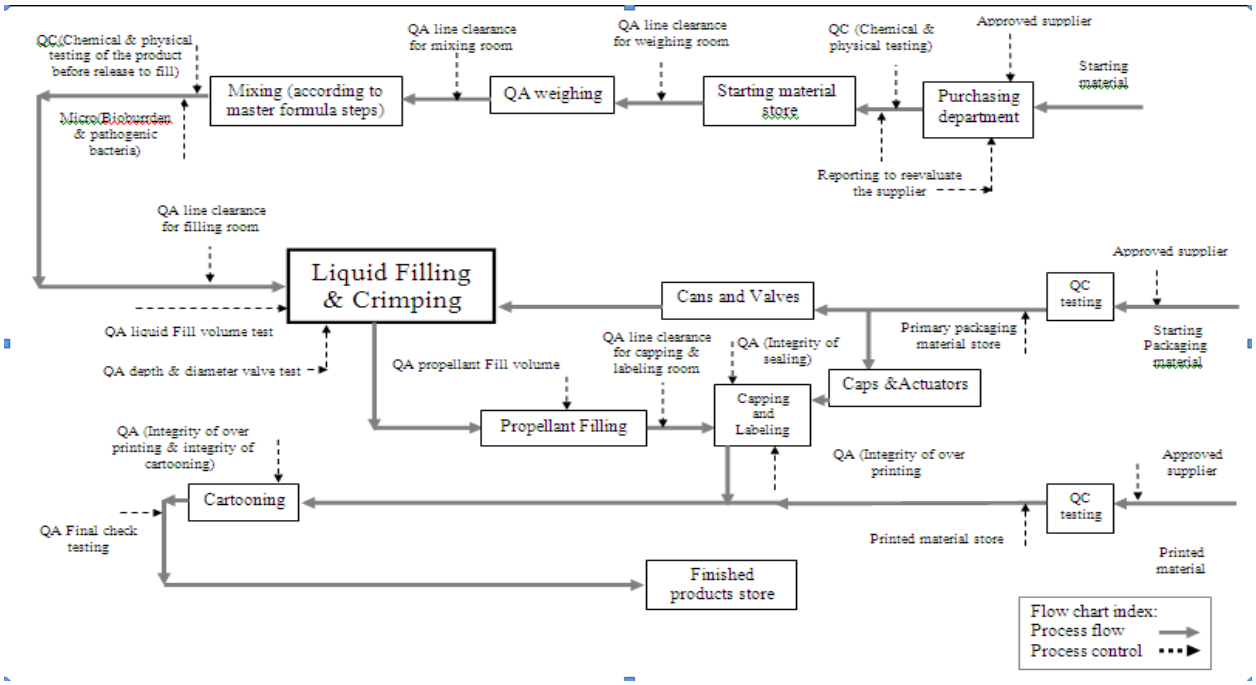
Photo (4): Product mixing in (ENDIMAJ)

Description of production process and the controls for each step in (ENDIMAJ):

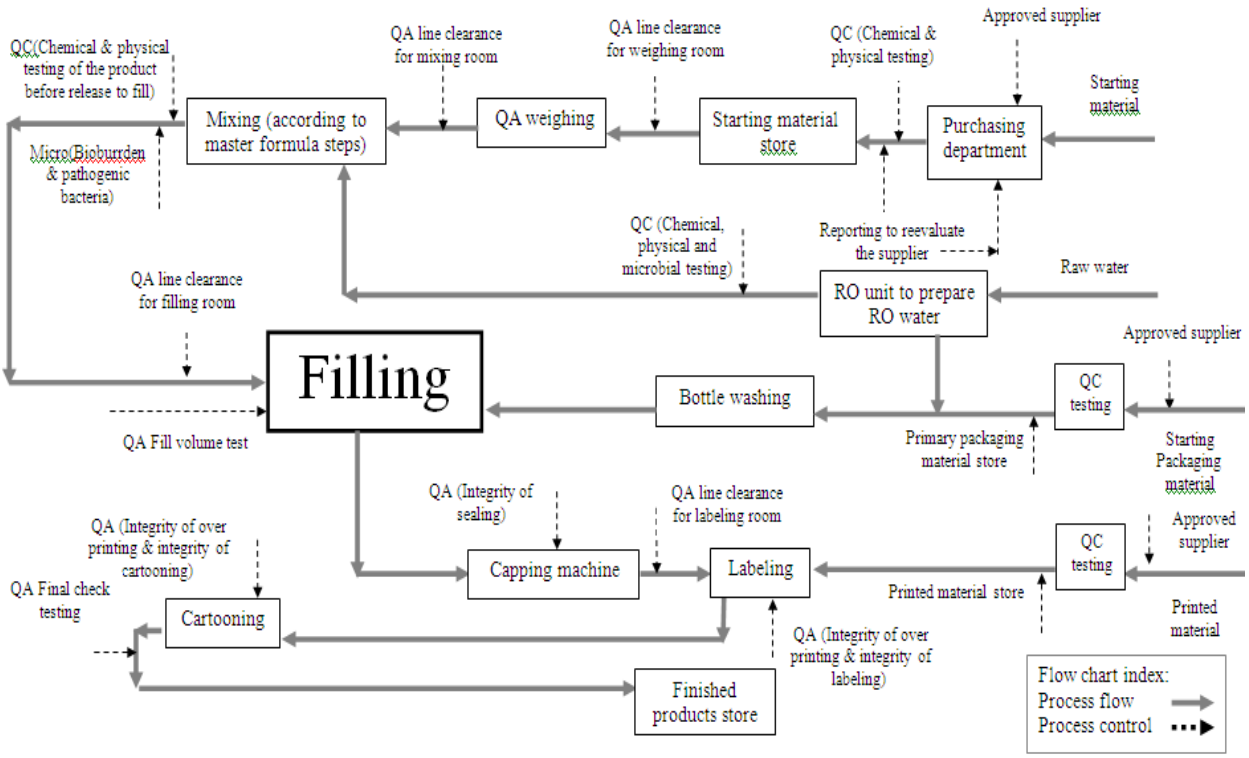
1- General Injectable (IPB) and penicillin injectable (IPA) production process control flow chart



2- Aerosols production (APA) process control flow chart



3- General Oral (OPA), Oral powder penicillin (OPB) and Agrochemicals (PPA) production process control flow chart



Quality control Department:

The quality control department in ENDIMAJ has the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products.

The quality control department is responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products are available the total area for QC laboratories is 800 square meter.

Each person engaged in the quality control department has education, training, and experience to enable that person to perform the assigned functions.

Photo (5): Quality control in (ENDIMAJ)

Training Topics for quality control employees:
A training record for each employee in ENDIMAJ is kept current showing the subjects of training, trainer and trainee signatures, and date of training.

Quality control employees are trained on the following topics:
Definition of cGMPs, elements of cGMPs, GMPs for aseptic process, GLPs, retest dating for raw materials, calibration policies for laboratory instruments, archiving laboratory documents, management of reference substance, laboratory workbooks, creation of certificate of analysis, managing analytical reagents, laboratory waste management, retention sample management in laboratory, laboratory supplier approval, laboratory results out of specification investigation, laboratory testing and documentation of raw materials, laboratory testing and documentation of finished products, laboratory testing and documentation of printed materials, entry procedure for production areas, sanitation and personnel hygiene, good documentation practices, status labels, aseptic discipline, aseptic handling techniques, document identification , establishment of standard operation procedure, change control procedure, QA weighing , basic microbiology, equipment and process qualification, process deviation procedure, safety in the laboratory, method development and validation procedure, sampling techniques, purchasing specifications, raw purified and WFI water sampling and testing, cleaning, calibration and operation of all laboratory instruments.

Microbiology staff is trained on the following topics:
Definition of cGMPs, elements of cGMPs, GMPs for aseptic process, GLPs, retest dating for raw materials, calibration policies for laboratory instruments, archiving laboratory documents, management of reference substance, laboratory workbooks, creation of certificate of analysis, managing analytical reagents, laboratory waste management, retention sample management in laboratory, laboratory supplier approval, laboratory results out of specification investigation, laboratory testing and documentation of raw materials, laboratory testing and documentation of finished products, entry procedure for production areas, sanitation and personnel hygiene, good documentation practices, status labels, aseptic discipline, aseptic handling techniques, document identification , establishment of standard operation procedure, change control procedure, equipment and process qualification, process deviation procedure, safety in the laboratory, raw purified and WFI water sampling and testing, cleaning calibration and operation of all laboratory instruments ,entry procedure for sterile filling areas, validation of aseptic gowning procedures, microbiological data recording procedure, destruction of Biological waste in micro lab, depyrogenation of glassware in micro lab, aseptic media filling and integrity leak testing procedure, environmental and plant hygiene monitoring procedure, sterility testing procedure, microorganisms to genus and species level, micro evaluation of bioburden, bacterial endotoxin testing, and sterile sampling procedure.

Major Production and quality control laboratory equipments

Equipments in production plants:

1- General oral production plant (OPA):

Ink jet printing machines, tapping machines with conveyers, seven balances with different ranges with printers, labeling machines with conveyers, eight nozzle liquid filling machine incorporating a capping machine, bottle induction sealing, two nozzle liquid filling machine with single head capper, 3000 liter RO storage tank, 1000 liter capacity double jacketed adjustable speed suspension mixer with CIP system, 2000 liter capacity double jacketed adjustable speed suspension mixer with CIP system, 150,1000 and 4000 liquid mixers adjustable speed, two diaphragm pumps, 2000 liter storage tank, two filter housings, two hummer mills, two 500 Kg ribbon powder mixer with vacuum feeding system, two 200 Kg ribbon powder mixers with vacuum feeding system, two powder filling machines with sealing machines and two manual sealing machines.

2- Oral powder penicillin plant (OPB) :

Powder filling machine, tapping machine, LINX 6200, three balances with different ranges ,vacuum suction device, fitz mill and ribbon mixer.

3- Penicillin injectable production plant (IPA):

Vial washing machine with two sanitary type pumps, 500 liter double jacketed adjustable speed mixer with CIP, SIP , auto vacuum feeding systems and sanitary type pumps, three pressurized vessels; two of 200 liter and one of 100 liter capacity, dry heat sterilizer, autoclave with vacuum pump, four head filling and rubber stoppering machine incorporating aluminum capping machine and vial inspection unit, laminar air flow unit, garment storage cabinet with UV lamp and LAF system, mobile trolley with UV lamp and LAF system, two UV pass boxes with LAF system and three balances with different ranges with printers.

4- General injectable production plant (IPB):

1000 liter variable speed jacketed mixer with vacuum feeding, CIP and SIP systems, three station laminar vial washing machine connected to decartooner unit with three pumps and pressure gauges, incorporating three 0.2 micron filter housings and 0.003 micron air filter housings, three chambers (neutralizing, sterilizing and cooling) sterilization tunnel with LAF system for each chamber, four pressure gauges between the chambers, three pressure gauges between HEPA filters with PLC control and alarm system, four head vial filling and stoppering machine with PLC system and safety devices with LAF system connected to aluminum

capping machine with PLC system and safety devices, labeling machine with LCD display controller, cartooning machine with LCD display controller, inkjet printing machine, tapping machine, autoclave with PLC and safety device connected to vacuum pump with de-vacuum system and fifteen channel temperature recorder, 100 liter sterile filling vessel, two pass boxes with UV lamp and LAF system, mobile trolley with UV lamp and LAF system, garment storage cabinet with UV and LAF system and two (120 cm) diameter turn tables.

5- Agrochemicals production plant (PPA):

Six balances with various ranges connected to printers, 2000, 3000 and 8000 liter capacity double jacketed mixers, two diaphragm pumps, two filter housings, 2000 liter storage tank, eight nozzle liquid filling and capping machine, induction sealing machine, two inkjet printers, labeling machine, cartooning machine, fitzz mill, 500 Kg capacity ribbon mixer with vacuum feeding system, two manual sealing machine and powder filling machine.

6- Aerosols production plant (APA):

Three balances with various ranges, 200 and 500 liter capacity mixers, 200 liter silverson homogenizer, can feeder with dump tray, single head 300 cc liquid filler, single head non vacuum crimper, propellant 200 cc two nozzle filling machine, propellant accumulator, carton taping machine and printing image 9020.

Quality control laboratories instruments:

Two Dionex HPLC with computer system, UV spectrophotometer with computer system, FTIR with computer system, Karl fisher moisture titrator, two analytical balances with different ranges, moisture analyzer , scientific melting point apparatus, pH meters, analytical digital polarimeter with computer system, refractometer, ultrasonic baths, chlorine meter, density meter, TDS meters, refrigerators , TOC instrument, Viscosity meter, test sieve shaker,
Mettler Toledo compact titrator and filtration unit..

Microbiology laboratory instruments:

Endotoxin tester (pyroskinetic flex),pH meter, thermoshaker, Microspin, PCR (Biometra),Two Laminar flow hood, five incubators @ (25°C, 25°C,37°C, 40°C and 50°C), plate mixer, two refrigerators, two autoclaves, balance, steritest vacuum filtration unit, microscope, colony counter, air Sampler, Tube shaker, ISO-GRID filtration unit, hotplate stirrer and water bath.

Validation strategy in (ENDIMAJ)

According to GMP definition Validation is "Establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."In (Mobedco- Vet), appropriate and complete documentation is recognised as being crucial to the validation effort. Standard operating procedures (SOPs), manufacturing formulae, detailed batch documentation, change control systems, investigational reporting systems, validation protocols and reports are integral components of the validation strategy. All validation documentation is prepared and maintained to be readily accessible to operations personnel. The validation documentation provides a source of information for the ongoing operation of the facility and is a resource that is used in subsequent process development or modification activities.

- All validation activities will incorporate a level of impact assessment to ensure that systems, services and products directly influenced by the testing have been identified.

- A revalidation programme will be implemented based on routine equipment revalidation requirements and on the change control policy.

Validation responsibilities of in (ENDIMAJ)

It is the responsibility of the general manager to source appropriate resources, assign responsibility and obtain agreement.

Validation teams are assembled for a limited or fix duration. Team members can be drawn from single departments or cross-functional divisional areas. Skills, which do not exist inside the organisation, or for which there is insufficient capacity, will need to be sourced externally.

All Validation Plan and Reports are reviewed, approved and accepted, as applicable by members of the review team identified below as a minimum. It is the responsibility of the individual project teams to identify appropriate and/or additional reviewers as identified in the individual Validation Plan for that project:

1- Quality Assurance Manager

2- Validation Manager

3- Operations Manager.

Specific test protocols are prepared and reviewed by identified technically competent persons, and authorized by members of the above validation review team as identified in the individual validation plan for that project.

Validation strategy

The validation strategy in (ENDIMAJ) progresses with the three types of validation: Prospective, Concurrent and Retrospective and includes the following categories:

1- Design qualification:

The intent of the DQ is met during the design and commissioning process by a number of mechanisms, which include:

- Generation of User Requirement Specifications

- Verification that design meets relevant user requirement specifications.

- Supplier Assessment /Audits

- Product Quality Impact Assessment

- Specifying Validation documentation requirements from equipment suppliers.

-Defining construction and installation documentation to assist with Installation Qualification (IQ).

2- Installation Qualification (IQ)

IQ ensures that a record of the principal features of the equipment or system, as installed, is available and that it is supported by sufficient adequate documentation to enable satisfactory operation, maintenance and change control to be implemented.

3- Operational Qualification (OQ)

All new equipment should be fully commissioned prior to commencing OQ to ensure that as a minimum the equipment is safe to operate, all mechanical assembly and pre-qualification checks have been completed, that the equipment is fully functional and that documentation is complete.

4- Performance Qualification (PQ)

The performance specification will reference process parameters, in-process and product specifications. PQ requires three product batches to meet all acceptance criteria for in-process and product testing. For utility systems, PQ requires the utility medium to meet all specifications over a prolonged sampling period.

The PQ documentation should reference standard manufacturing procedures and batch records and describe the methodology of sampling and testing to be used.

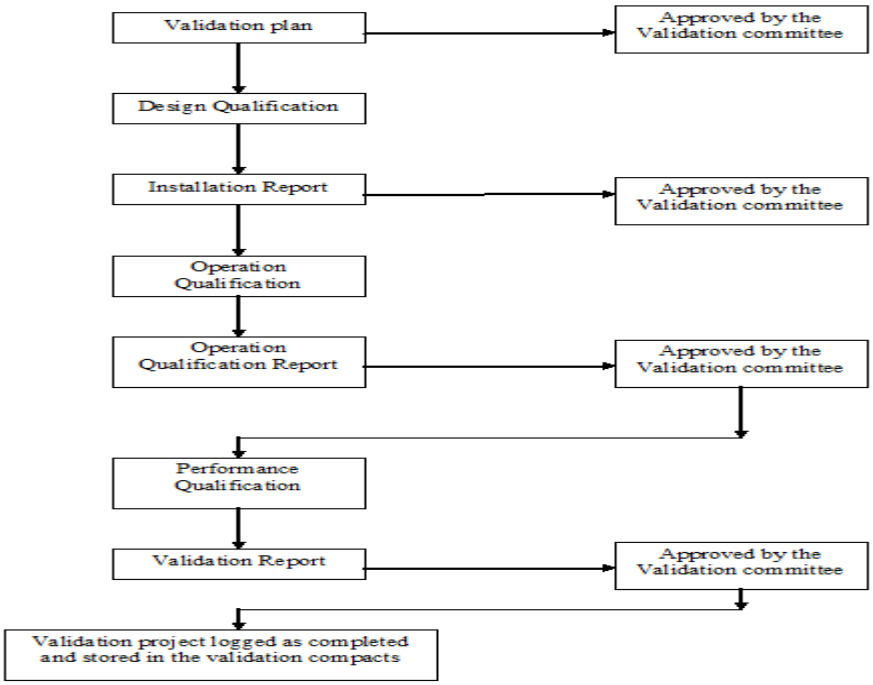


Fig (3): Validation strategy in (ENDIMAJ).

The validation strategy covers the following items:

-Facility

- Manufacturing area design.

- Personnel and material flow.

-Process and equipment design

-All process steps, production equipment, systems and environment, directly used for the manufacture of sterile and non-sterile products.

- Equipment washing and cleaning.

- Utility systems design

Raw/purified steam, Purified water, Compressed Air, Air conditioning system, Vacuum, Power supply, Lighting, Cooling water and Waste.

Validation Documentation

A typical documentation package relating to a validation project will consist of the following, as a minimum:

1- Validation plan.
2- Installation qualification report/s.
3- A series of operational qualification test protocols and raw data results (as defined in the validation plan).
4- An operational qualification report.
5- A series of performance qualification test protocols and raw data results (as defined in the validation plan and during the OQ phase).
6- A validation report.
7- System SOPs (a list of SOP's relating to the process).
8- System changes (change request forms).

All validation documents are to be clearly identified with numbered pages, with clear units of measure stated, results/signatures, and signatures of persons performing tests and dates conducted are all to be captured.

The original copies of approved validation documents are the responsibility of the validation manager. during the validation project they are to be kept in a secure place and copies issued to members of the validation team as required, in a controlled manner, by the project manger. The original approved copies are to be included in the validation file.

Raw data relating to the execution of operational and performance qualification tests can consist of result sheets, temperature recordings, etc. raw data is the real time recording of the results obtained and must always be signed and dated by the person performing the test and then included in the validation file. Operational and performance qualification protocols and the raw data relating to them are to be filed in a separate section or volume of the validation file.It is the responsibility of the person/s assigned responsibility for checking and approving the completed protocols to ensure that the data presented in the reports is factual and truly represents the validation effort. The reports are then presented to the validation committee for their approval.

The composite validation Files are to be appropriately numbered and indexed to allow for easy review of the validation effort and are to include a section to record any changes that are hence made to the validated equipment/process/system.

Revalidation

Based on the validation results and the type of subject a revalidation plan must be established. Revalidation is further required if the finding of the in-process and quality control results indicate the need.

For critical process, Revalidation is normally carried out on an annual basis or when significant changes are made to the equipment/process.

Changes that warrant revalidation are the changes that may impact safety, purity, identity, effectiveness or quality of the product, for example:

- Changes to master processing instruction
- Changes to raw material suppliers or components
- Changes to formulation or batch proportion
- Introduction of new equipment or utilities
- After extensive preventative maintenance work
- Replacement of spare parts (different make)

Main validation instrumnets: Thermal mapping**,** Temperature block (140 A)**,** Hydra data logger**,** RTD sensor (reference probe)**,** Airborne particles counter**,** Particles counter (0.1 cfm)**,** Iso-kinetic probe**,** AccuBalance**,** AC/DC adapter 6200**,** DOP integrity tester**,** VelociCale, Pressure regulator, Scanning probe