ACHIEVING WORLD STANDARDS THROUGH QUALITY IN PROCESS

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Achieving excellence in manufacturing is the cherished goal pursued by any manufacturer. In pharmaceutical field, the responsibility on the manufacturer is tremendous as the end product directly deals with human health. Ayurvedic and herbal drug industry is gaining higher and higher significance and popularity day by day worldwide. However, due to the increased global presence of Ayurveda has also necessitated need of stringent norms for manufacturing and quality assurance of herbal dosage forms.

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In India, at present, Schedule T essentially describes the scope and statutory requirements under Drugs and Cosmetics Act for the manufacture of herbal medicinal products. This Schedule covers bare minimum requirements for herbal drug manufacturing & Quality Control.

We are all aware that the processes involved in manufacturing of Herbal formulation involves the basic steps of granulation, compression & coating in case of tablets, sugar syrup preparation, addition & dissolving actives, adjustment of pH & volume making in case of liquids etc.....

Manufacturing needs well designed qualified systems to be used in well designed & maintained facilities with the adoption of the latest technology to achieve consistency & repeatability of the finished products produced.

Implementation of Quality Systems through all stages of manufacturing & upgrading of technology for manufacturing in a controlled environment using HVAC system will ensure quality product, which enables us to face the global scenario.

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However, to meet the global standards of alternate medicines and to ensure export to regulated markets, we need to adopt Goods Manufacturing Practices of WHO standards (WHO supplementary guidelines for manufacture of herbal medicinal products – 1996).

For achieving international standing especially in the ever widening horizon of export market, schedule 'T' may not serve the ultimate purpose. The competition in the export market is going to be more and more stiff and accreditation of internationally accepted WHO-GMP will be very much essential in promoting of global business.

Let us view the requirements as perceived by WHO-GMP which will ultimately lead to manufacturing excellence and boost its standing worldwide, mainly with respect to personnel, premises & quality assurance.

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Although traditional systems of medicine have been recognized and accepted in most countries, efforts to provide validated techniques to ensure the quality, safety and efficacy of products are being developed.

Because herbal ingredients are of complex and variable nature, controls of starting material, storage and processing assume particular importance in the manufacturing process of herbal medicinal products.

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REQUIREMENTS AS PER GMP

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Therefore, in order to achieve the above goal, following measures should be stringently implemented in the herbal medicine manufacturing unit.

QUALITY MANAGEMENT SYSTEMS

documented in the Quality Manual.

- GMP Procedures
- Change Controls
- Failure Investigation
- Batch Deviation & Reprocessing
- Quality Complaints
- Product Recalls
- Vendor Development

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PERSONNEL

- Qualification of Personnel
- Gowning Requirements
- GMP training
- Responsibility of Quality Assurance / Control

PREMISES AND EQUIPMENT

- Cleaning and Sanitization Programme
- Pest Control
- Air Handling Unit Systems
- Equipment identification and status labelling
- Calibration and Maintenance

DOCUMENTATION

- Management of GMP Documentation
- Standard Operating Procedures
- Master Formula Cards
- Batch Manufacturing Records
- Material and Product Specifications
- Equipment, Instruments and Utility specifications
- Retention of Documents
- Prevention and Mix Up and Cross Contamination

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MANUFACTURING

- Technology Transfer
- Control of manufacturing operations
- Control of Packaging operations
- Control of artwork and printed packaging materials
- Environmental monitoring
- Water for Pharmaceutical Use
- Qualification and Validation
- Storage Condition and Holding Times for in process materials.
- Reconciliation
- Integrity of Containers and Closures
- Disposal of Pharmaceutical Waste
- Warehousing and Distribution
- Control of Quarantined and Rejected Material

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QUALITY CONTROL & ASSURANCE

- Control of laboratory operations
- Sampling procedures
- Analytical reference standards
- Retesting period and expiry dating
- Certificate of Analysis
- Product stability studies
- Release of product for sale
- Control of retention samples
- Out of specification results
- Out of trend results
- Annual product review

INSPECTION

- Regulatory inspections
- Self inspection

PREMISES AND EQUIPMENT REQUIREMENTS

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The location, layout and design of buildings should be suitable for the intended operations and should minimise the risk of cross contamination and errors during all aspects of manufacture, filling and packaging.

They should allow effective cleaning and maintenance in order to avoid build up of dust or dirt, and in general, any adverse effect on the product or the surrounding environment.

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DESIGN

1. Facilities should be designed for:
   - logical flow of materials and people
   - adequacy of working space and orderly and logical positioning of equipment
   - smooth/crack-free/easy to clean interior surfaces
2. Production of herbal products must be separated from the production of other products (eg. drugs, devices)
   - non-hazardous household products can share premises provided that care be applied to prevent cross contamination and risk of mix-up.
   - painted line, plastic curtain and flexible barrier may be used to segregate.

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DEDICATED AREAS

- Receiving of starting & packaging materials
- Sampling
- Weighing/dispensing
- Gowning/ change room
- Storage areas for approved raw material, packaging materials, and finished goods
- Quarantine & reject areas
- Processing
- QC laboratory
- Equipment washing
- Storage of idle, cleaned equipment
- Staging of bulk products
- Packaging/ labeling operations
- Storage of cleaning tools and supplies

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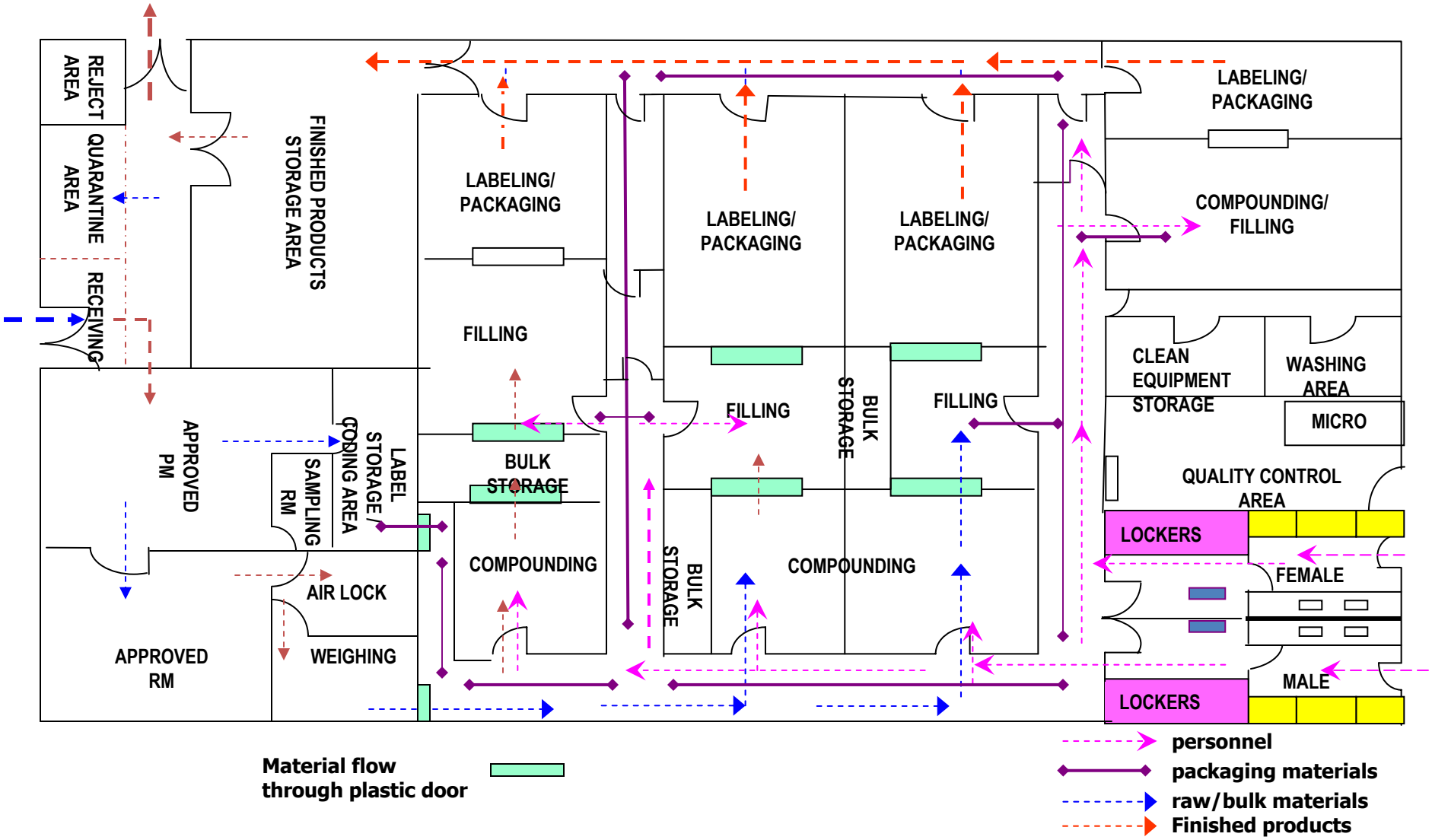
LAYOUT

SAMPLE OF FACTORY LAYOUT



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Premises is segregated into the following areas:

- Change rooms – Primary / Secondary
- Warehouse area
- Manufacturing area
- Quality assurance & control area

CHANGE ROOM IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

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CHANGE ROOM AS PER GMP

- Store working shoes separately.
- Keep gowns in cabinet to avoid dirt and dust.
- Soap for hand cleaning must be installed near the sink. Paper towels or hand drier should be provided whichever is suitable.

CHANGE ENTRY / EXIT FOR PRIMARY CHANGE ROOM AS PER GMP

ENTRY / EXIT FOR SECONDARY CHANGE ROOM AS PER GMP

Secondary change is mandatory before entry into the core areas such as sampling, dispensing & manufacturing area.

WAREHOUSE AS PER GMP NORMS

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Storage areas should be of sufficient capacity to allow orderly storage of various categories of materials and products with proper segregation. Status labeling of materials should be observed.

WAREHOUSE IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

RECEIVING OF RAW MATERIAL

LOADING & UNLOADING AS PER GMP

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Receiving and dispatch bays should be separated and materials and products should be protected from the weather.

WAREHOUSE IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

HERB'S STORE

WAREHOUSE IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

SUGAR STORE

WAREHOUSE IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

UNDER TEST AREA

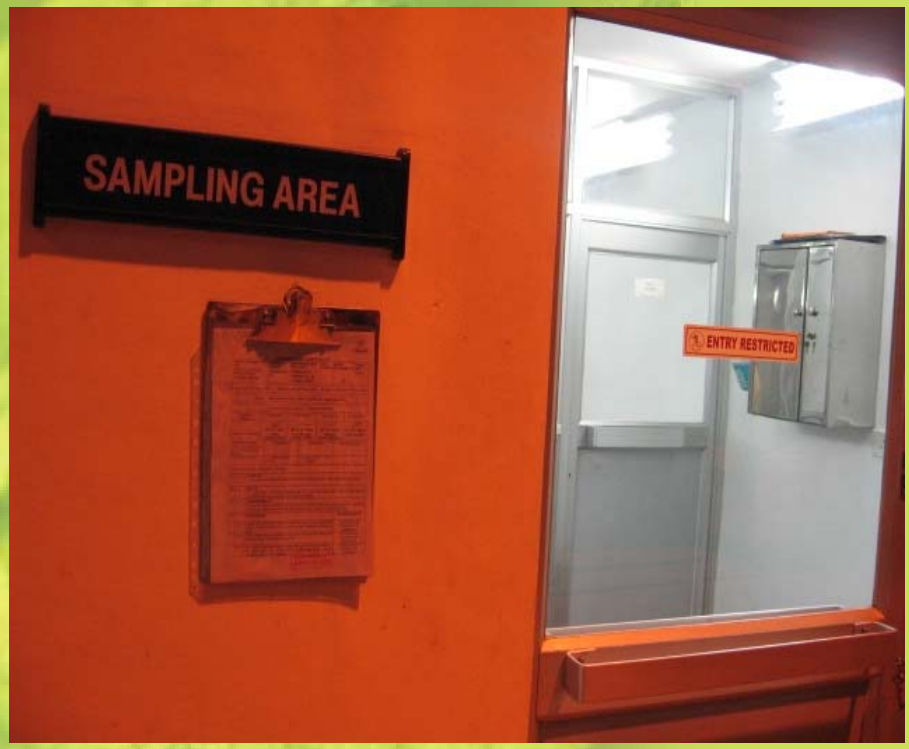
REJECTED AREA

RECEIPT OF
RAW & PACKING MATERIAL AS PER GMP

RECEIVING BAY RM & PM

All incoming materials should be checked for its label contents. Containers should be cleaned where necessary with a vacuum cleaner before its entry into the warehouse..

SAMPLING AREA AS PER GMP



SAMPLING AREA

MAN ENTRY

MATERIAL ENTRY

SAMPLING OF RAW MATERIALS AS PER GMP

SAMPLING BOOTH

Sampling should be conducted in such a way to prevent cross contamination. It is strongly recommended that the sampling booth shall be placed in a room provided with AHU. The sampling activity is done under the LAF.

CLEANED SAMPLING DEVICES

STORGE OF RAW MATERIALS AS PER GMP

A.C. STORAGE AREA AS PER GMP

QUARANTINE & REJECTED AREAS AS PER GMP

All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution

Reject area should be kept under lock and key. Rejected materials and products should be clearly marked as such and stored separately in restricted areas.

WEIGHING & DISPENSING

The weighing of starting materials should be carried out in a separate weighing area designed for that use, complete with provisions for AHU.

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DISPENSING OF RAW MATERIALS IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

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WEIGHING & DISPENSING AS PER GMP

The dispensing activity shall be carried out under the LAF.

The flooring in the area should be epoxy coated.

STORAGE OF PRIMARY PACKING MATERIALS IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

STORAGE OF PRINTED PACKING MATERIAL AS PER GMP

Printed packaging materials should be stored in secure conditions

A.C. STORAGE OF PRIMARY PACKING MATERIAL AS PER GMP

Aluminium Blister Foils should be stored under lock & key at a temperature not exceeding 25°

MANUFACTURING & PACKING AREAS

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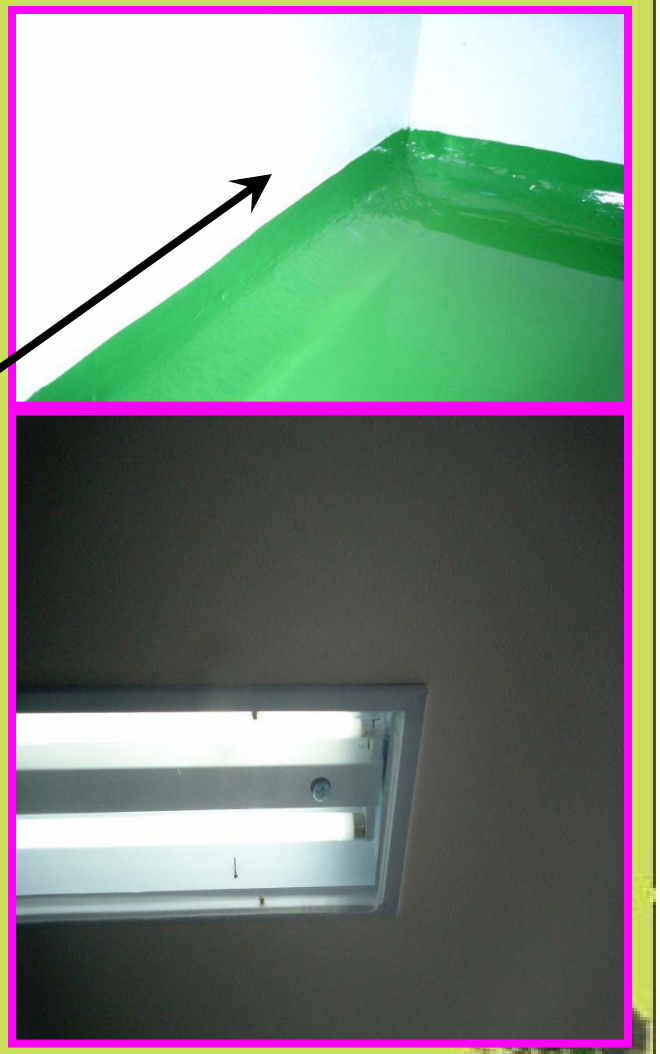
CONSTRUCTION AS PER GMP

FLOORS

- ✓ Solid concrete with epoxy or polyurethane resin finish is suitable for processing areas.
- ✓ Non skid
- ✓ Retard bacterial growth

- Smooth, cleanable, easy to maintain and impervious to chemicals or cleaning materials.
- Coverings where floor meets walls may be observed.
- Recessed light fittings where appropriate.



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WALLS & CEILINGS AS PER GMP

Block structural wall of high density, smoothly plastered, waterproofed by painting with acrylic or high polymer enamel

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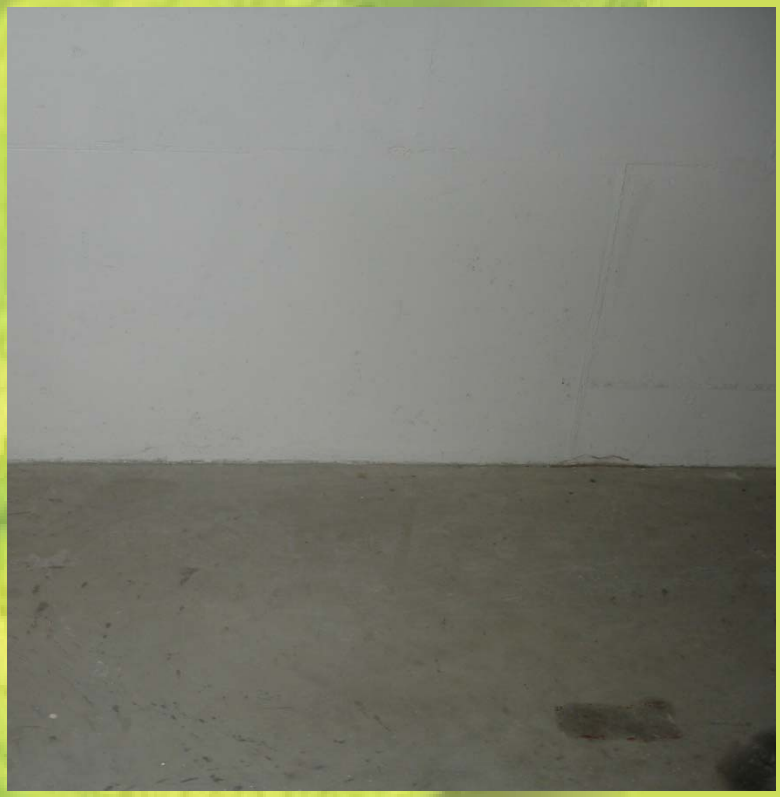
Cement boards :

- Weather resistant
- Termite & vermin resistant
- No formaldehyde content
- No asbestos content

WALLS & CEILINGS AS PER GMP



FLOOR

CEILING WITHOUT JOINT

CEILING WITH JOINT

JOINTS & FRAMES AS PER GMP

The design of joints and frames should be such that cleaning and sanitation can be done easier

THE JOINTS OF ALL SURFACES

THE DESIGNS OF WINDOWS AND THE WAY THEY FIT INTO THE FRAMES

Window ok

Window not ok

- What should be avoided:
- Windows opening to the outside
- Ledges and recesses

- Sliding doors must have proper cleaning procedure

VENTILATION AS PER GMP

1. Air should be appropriately filtered specifically in the processing and filling areas supported by a validated HVAC system.
2. Powdered and dry products should have a dust collection system installed.
3. For the rest of the areas where there is product exposure, suitable ventilation is required.
4. Dispensing and sampling areas where the product is exposed when handled should be provided with AHU's.

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MANUFACTURING AREA AS PER GMP

Adequate working space should :

- permit the orderly & logical positioning of equipment and materials to minimize the risk of confusion,

- avoid cross contamination and reduce the risk of omission or wrong application of any of the manufacturing or control steps.

EQUIPMENTS IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

DISTILLATION ASSEMBLY

EQUIPMENTS IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

LIQUID MANUFACTURING TANKS

EQUIPMENTS IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

MANUFACTURING TANK

TANK WITH STIRRER

EQUIPMENTS IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

EQUIPMENTS IN LIQUID MANUFACTURING AREA AS PER GMP

EQUIPMENTS IN LIQUID MANUFACTURING AREA AS PER GMP

LIQUID MANUFACTURING VESSELS

EQUIPMENTS IN CAPSULE MANUFACTURING AREA AS PER GMP

DOUBLE E CONBLENDER

EQUIPMENTS IN CAPSULE MANUFACTURING AREA AS PER GMP

CAPSULE FILLING MACHINE

EQUIPMENTS IN TABLET MANUFACTURING AREA AS PER GMP

RAPID MIXER GRANULATOR

EQUIPMENTS IN TABLET MANUFACTURING AREA AS PER GMP

FLUIDISED BED DRYER

FBD BOWL TRANSFER TO CONTA BIN

EQUIPMENTS IN TABLET MANUFACTURING AREA AS PER GMP

BLENDER WITH CONTA BIN

EQUIPMENTS IN TABLET MANUFACTURING AREA AS PER GMP

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EQUIPMENTS IN TABLET MANUFACTURING AREA AS PER GMP

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NEOCOTA – TABLET COATING SYSTEM

PACKAGING AREA IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

PACKAGING AREA IN A CONVENTIONAL HERBAL MANUFACTURING UNIT

PACKAGING AREA AS PER GMP

Premises for filling/ packaging should be designed and laid out to avoid mix-ups or cross contamination.

EQUIPMENTS IN LIQUID MANUFACTURING AREA AS PER GMP

BOTTLE WASHING MACHINE

EQUIPMENTS IN LIQUID MANUFACTURING AREA AS PER GMP

BOTTLE FILLING & SEALING MACHINE

EQUIPMENTS IN LIQUID MANUFACTURING AREA AS PER GMP

VISUAL INSPECTION

EQUIPMENTS IN CAPSULE MANUFACTURING AREA AS PER GMP

BLISTER PACKING MACHINE

EQUIPMENTS IN CAPSULE MANUFACTURING AREA AS PER GMP

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VISUAL INSPECTION AT CONVEYER BELT

QUALITY ASSURANCE & CONTROL AREA

REFERENCE STANDARD

LABORATORY APPARATUS

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RECORD CUPBOARD

QC lab should be designed to suit intended operations. There should be adequate storage space for samples, reference standards, solvents, reagents & records.

REAGENT & SOLVENT

CONCLUSION

We can easily draw conclusion that implementing defined Quality Systems & Latest Technology in manufacturing process supported by Process Validation, Cleaning Validation & Air Handling Units helps us to improve productivity with consistency & inbuilt Quality meeting Global standards.

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Thank You !

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