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1. Personnel Flow:

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1.1 Entry and Exit Procedure to Plant :

Do's	Don't
✓ Entry and exit change procedure should be through appropriate change rooms.	X Never take short cuts like Emergency exit area.
✓ Change the over gown twice in a week or during product change or if any visibly soiled and in case if spillage on uniform.	X Never carry valuables, Eatables, Personnel medication, Cosmetics, Ornaments and Mobile phones etc. in Manufacturing / Warehouse / Formulation Development area.
✓ Entry exit should be followed at the time of tea, lunch, biological breaks and at the end of the working hours.	X Avoid brisk movements.

1.2 Personnel Hygiene in Plant:

- Use appropriate PPE while handling products.
- Eating, Drinking, Chewing, Smoking, Storage of food, personnel medication are strictly prohibited in Manufacturing, Warehouse, Formulation Development.
- Hands should be disinfected with approved disinfectant prior to entry in manufacturing / process area.
- Impart proper training at appropriate intervals to every employee for following the necessary practices.
- All employees are trained and expected to report their illness to their immediate superior immediately, so that appropriate action can be taken. The supervisors check for such conditions in all personnel working in their area.
- Employees are trained to maintain their personal lockers in clean and tidy condition.
- Direct contact with unprotected hands with any material is avoided.
- Do not allow any persons to handle any starting material, packing materials, in process materials and drug products, showing open lesions, wounds, apparent illness which may affect adversely the quality of the product.
- Do not allow the person till the time his condition is ascertained to be no longer a risk to the product, by a registered medical practitioner.

2. Document Flow:

2.1 Document Receipt, Filling and Submission to QA:

- Request to QA from production.
- QA issues documents.
- On line completion of documents during process.
- Documents submitted to QA for review.
- Compliance done if required.
- Submit document to QA for release.

2.2 Good Documentation Practices:

- Overwriting should be avoided.
- Don't use gel pen or ink pen.
- Every cut/correction should have initiator sign with date. Draw a single line through the error. Make the correction next to the error. Write an explanation for the error
- Every document BMR/BPR entries should be done online.
- Ensure every document is signed by authorized person only.
- Do not leave empty lines or boxes, for e.g.
  1. Write "NA" (Not Applicable) in an unused area, initial and date your entry.
  2. Initial and date any comments added to the documentation.

3. Cleaning and Line Clearance:

Cleaning Concept:

A. Cleaning of area during batch changeover:

Changeover between two batches of same product, same coloured and having ascending or same strength.

- After completing the batch, transfer the material of previous batch to WIP storage area.
- Keep all the BMRs and BPRs in the manufacturing office and daily log books in the respective area.
- Clean the Equipment or Accessories for batch to batch change over as mentioned in the relevant operating and cleaning SOP of the equipment.
- If required clean the floor by vacuum cleaner and then sanitize the cubicle using sanitizing kit as per SOP.
- Get the area and equipment released as "CLEANED" and suitable for next batch by the Manufacturing and QA officer.
- Record the cleaning activity in the format.

B. Cleaning of area during product changeover:
Changeover between two different products or between same product having different colour or descending strength.

- Transfer the material of previous batch to WIP storage area.
- Keep all the BMRs and BPRs in the manufacturing office and daily log books in the respective area.
- Cover all the equipments, electrical and pneumatic panel boards with polythene bag to avoid the direct contact of water.
- Clean the area starting from top progressing to bottom of the cubicle.
- Clean the ceiling, AHU grills of supply and return with lint free duster by using ladder or mop.
- Clean the return air filters as per SOP.
- Clean the doors, windows, walls, tube light fixtures, AHU grills of supply and returns, pipelines (Water, compressed air etc.), switch boards, plug points, hygrometer, balance stand, manometer, tables (platforms if any), Pass box, PLCs, control panel, any attachments of machine, etc. with lint free cloth / duster.
- Clean the equipment for product to product change over as mentioned in the relevant operating and cleaning SOP of the equipment.
- Clean the floor using potable water and remove the water clogged on the floor using wet vacuum cleaner or mop or wiper.
- Sanitize the cubicle using sanitizing kit as per SOP and sanitize the drains as per SOP.
- Get the area certified as "CLEAND" and ready for use by the QA
- Record the cleaning activity in the format.

C. Cleaning of cubicles During Accidental spillages:

Note: Do not operate any electrical switches during solvent spillages

- During powder spillage, clean the floor by vacuum cleaner and then sanitize the cubicle using sanitizing kit as per SOP.
- If the solvent spillage occurs, remove all the solvent by dry mopping of the floor and then sanitize the cubicle using sanitizing kit as per SOP.
- Record the cleaning activity in the format.

Line Clearance Concept:

- For every batch to batch or product changeover line clearance must be performed.
- Do not initiate any new operation prior to line clearance.
- Check and ensure that, batch documents of the previous batch or product removed.
- Check and ensure that, all the log books in the area are updated up to last batch.
- Check visually area (floor, walls and ceiling) for cleanliness. Check the floor below equipment for cleanliness. Also check and ensure that RA filters in the area are clean.
- Check visually all contact parts of the equipment for cleanliness.
- Check for environmental conditions of cubicle viz. Temperature, Relative Humidity and Pressure Differential across the cubicles as per standard requirements and make entries of the same as per SOP.
- These all above mentioned checks is to be done by manufacturing Officer/ Executive first and then again verified by QA.
- Inspect the packaging & labeling facilities immediately prior start of any activity to assure that all materials have been removed from previous operation.
- Inspection shall also be made to assure that packaging & labeling materials not required for subsequent operation have been removed.
- Check stereos of previous batch, if any, have been removed.

supreme Health
Good Health, Globally.

4. Material Flow

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Do's	Don't
✓ Use only Material air lock for the movement. ✓ Dedust the material container before taking inside the plant. ✓ Use appropriate status label for each material. ✓ Maintain proper environmental & storage condition of materials. ✓ Use proper trolley for material movement. ✓ Segregate each batch. In case of product with multiple stages manufacturing. The dispensed material to be segregated using separate polybags with stage wise label.	X Never transfer the material through personnel change room. X Don't use rejects & quarantine material in manufacturing. X Don't open both the doors of room or airlock while transferring materials/ equipment.

- ❖ Equipments and Personnel movement in Manufacturing & Packaging area are designated to prevent contamination & Cross contamination.
- ❖ All materials must be stored, handled in order to maintain identification.
- ❖ Avoid accidental damage.
- ❖ Deterioration of products to be avoided.

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- Environmental conditions of area should comply with the materials specification or as per the BMR/ BPR.
- Appropriate handling system must be used while transferring API & excipients.
- Avoid degradation of photosensitive materials by appropriate storage condition.
- Comply the specifications at different conditions of temperature & humidity.
- Material containers should be cleaned externally prior transferring to another room for further processing.

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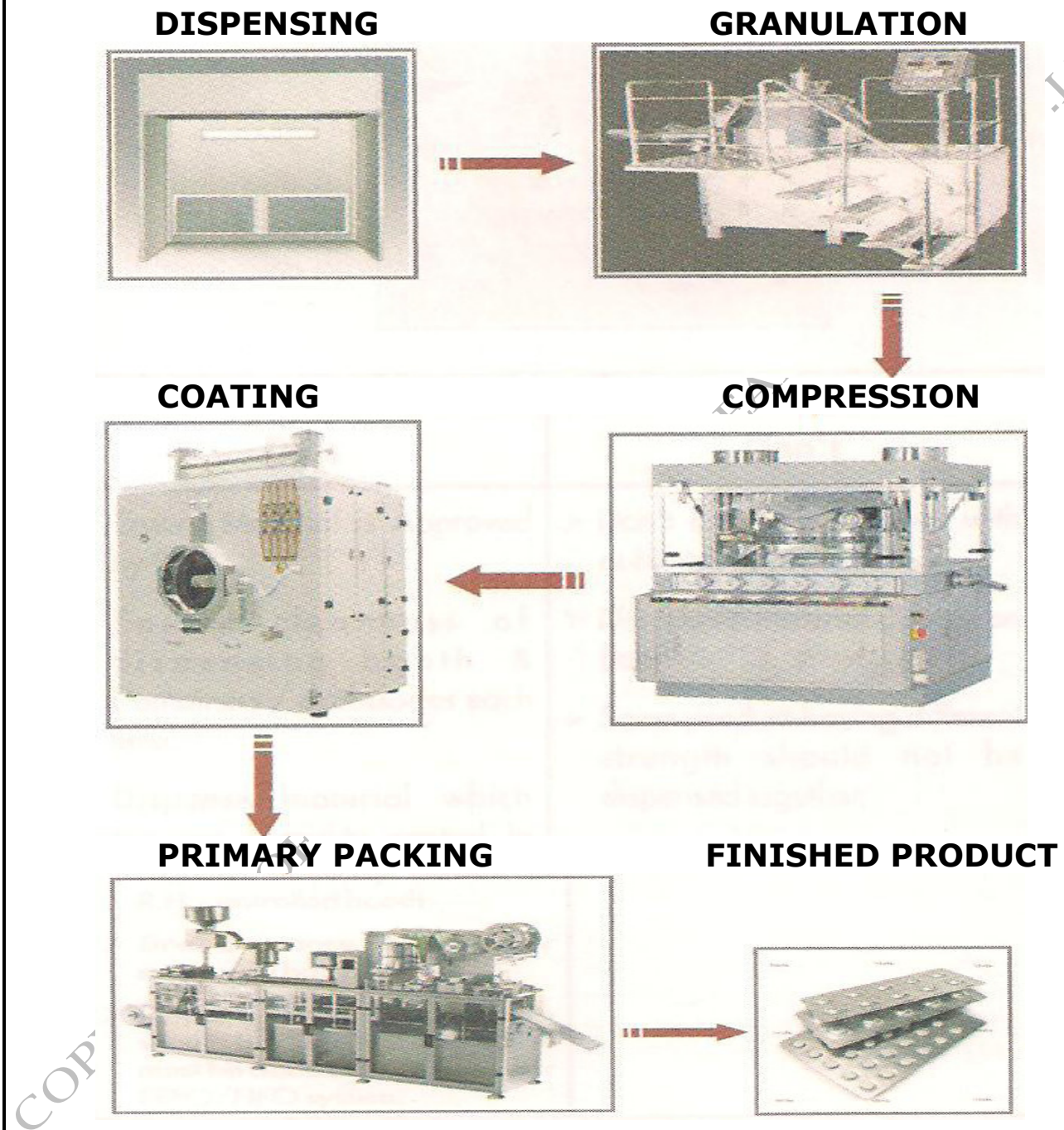
5. Process Flow:



5.1 Dispensing:

Do's	Don't
✓ Ensure cleanliness of dispensing booth & containers/ accessories each time.	X Don't keep material on floor.
✓ Ensure environmental condition.	X Don't dispense materials with out appropriate documents.
✓ Line clearance is must of every new batch activity.	X Same product having different strength should not be dispensed together.
✓ Dispensing of all excipients should be done first and API must be done at the end as per FEFO.	

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Do's	Don't
✓ Start the OFCB, AHU and Weighing balances for 30 minutes before start of Dispensing. ✓ Following points to be check at the time of Dispensing: a) Name of material. b) Pharmacopoeia grade of material. c) Item code d) QC Approved label e) Control No. f) Retest date g) Expiry date h)Vendor details ✓ While dispensing liquid material, calibrated measuring cylinder should be used. ✓ Use separate cleaned scoop for different materials. ✓ Weigh 100 empty capsules, calculate the average weight. Thus determine the weight for the required number of capsule and dispense the same. ✓ All dispensing operations must be carried out in safe working zone and in presence of Warehouse and Manufacturing Officer.	

5.2 Granulation:

Rapid mixer Granulator

Fluid Bed Processor

Do's	Don't
✓ Ensure & cross check all right materials are dispensed as per batch records.	X Never touch material with bare hands.
✓ Ensure cleanliness & status label of all equipments kept in specified area and also check equipments for swab if applicable.	X Never play with set parameters of equipments.
✓ Use hand gloves & masks for every operations.	X Do not enter the corridor with wearing hand gloves and mask.
✓ Ensure balance calibration prior to use.	X Do not overload Multimill and Comill to avoid machine jam and spillage.
✓ Check blank run and air purging before loading of material into RMG.	X Don't enter different cubicle having different products with same gowning.

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Do's	Don't
✓ Check amperage reading and end point in granulation stage. ✓ Check closing of discharge valve of RMG before loading material in RMG. ✓ Check Dew point in FBD as applicable. ✓ Check sieve, screen and finger bag integrity before fixing into the equipment & also at the end of operation. ✓ Check LOD as per BMR after drying. ✓ Check environmental condition in the area before starting operation. ✓ Check all in process test as per BMR and PVP. ✓ Label in process material for each and every step.	

5.3 Compression:

Compression Machine

Core Tablets

Do's	Don't
✓ Ensure right batch is taken for compression.	X Don't proceed without area clearance from QA.
✓ Ensure cleanliness & status label of all equipments kept in specified area and also check equipments for swab if applicable.	X Don't start the operation without closing machine door.
✓ Check environmental condition in the area before starting operation.	X Don't use spilled material or rejected material in the batch.
✓ Check all in process test as per BMR and PVP.	X Don't enter different cubicle having different products with same gowning.
✓ Ensure correctness and cleanliness of Punches and Dies before starting operation.	
✓ Ensure correct setting of machine to avoid rejects.	
✓ Ensure balance calibration prior to use.	

5.4 Coating:

Coating Machine

Coated Tablets

Do's	Don't
✓ Ensure & cross check all right materials are dispensed as per batch records.	X Never touch material with bare hands.
✓ Ensure cleanliness & status label of all equipments kept in specified area and also check equipments for swab if applicable.	X Never play with set parameters of equipments.
✓ Ensure the cleanliness and dry stage of the coating pan.	X Do not keep open the backside drain nozzle of the coating machine.
✓ Ensure balance calibration prior to use.	X Do not directly start with the higher spray rate or higher pan speed.
✓ Ensure correctness of the nozzles size and gun.	X Don't open door of the coating pan at the time of process.
✓ Ensure the proper working of peristaltic pump and water scrubber.	

5.5 Visual inspection:

- ❖ Ensure appropriate status label for each material.
- ❖ Maintain proper environmental & storage condition of materials.
- ❖ Inspect the capsules/ tablets using visual inspection machine.
- ❖ **Rejection of Capsules:**
  - Improperly locked capsules
  - Capsules with telescoped body and cap
  - Capsules with black, white or colored spots
  - Dented capsules
  - Missing logo or smudged product identification marks.
  - Mashed capsules
  - Capsules with cracks & hair-line cracks
  - Capsules with printing defects

❖ **Rejection of Compressed Tablets:**

- Tablet appearance, shape, color and finish.
- Embossing details and score line, if any.
- Defects like sticking, picking, chipping, layering, capping.
- Black, brown or colored sports or mottled appearance.
- Adherence/presence of any particle/foreign material.

❖ **Rejection of Coated Tablets:**

- Uniformity of color development and mottling
- Defects like 'Orange Peel' or 'Frosty' appearance
- Broken or damaged edges.
- Twin tablets and logo bridging
- Proper weight gain

❖ **Rejection of Blisters:**

- Unclear / Smudged / Missing Printed Text or Overprinted / Embossed information.
- Missing / Broken / Damaged tablets / capsules in the packed blister or strip.
- Cut Pockets or Open Ends / Sides.
- Improper Sealing of blisters (not knurled properly)
- Wavy slitting or blisters with frayed edges.
- Discolored or soiled product.

❖ **Rejection of Leaflets:**

- Correct Product Name and Strength
- Correct Item Code and/or Artwork Code
- Improper or Defective Text Printing
- Damages incurred during shipment.

❖ **Rejection of Cartons:**

1. Empty cartons:

- Correct product name and strength
- Correct item code and/or artwork code
- Overprinting errors (missing, smudged or unclear overprints)
- Improper or defective text printing
- Damages incurred during shipment or overprinting.
- Correct Stickers, if required by buyer, as specified in the EOPA.

2. Filled cartons:

- Fill Value i.e. Number of Blisters
- Fill Weight i.e. Weight of Filled Cartons checked to ensure that they are within predetermined tolerance limits in case of ALU-ALU packs.

❖ **Rejection of Shippers:**

1. Empty Shippers:

- Size, shape and general appearance.
- Absence of rusted Staple Pins
- Labels affixed on it for correctness of Product Information and Shipping Marks (As provided in the EOPA)

2. Filled Shippers:

- Fill Value i.e. Number of Cartons per Shipper.
- Fill Weight i.e. Weight of Filled Shipper checked to ensure that they are within predetermined tolerance limits.
- Proper taping and strapping
- Proper Labeling with Product Information
- Shipping Mark as required in the EOPA

5.6 Encapsulation:

Encapsulation Machine

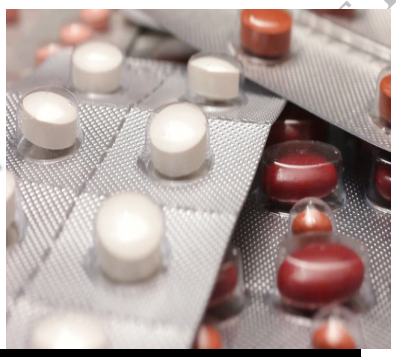
Hard Gelatin Capsules

Do's	Don't
✓ Ensure & cross check all right materials are dispensed as per batch records. ✓ Ensure cleanliness & status label of all equipments kept in specified area and also check equipments for swab if applicable. ✓ Check for quality of empty capsules. ✓ Ensure balance calibration prior to use. ✓ Ensure the correctness of the dosing disc and other change parts.	X Never touch material with bare hands. X Never play with set parameters of equipments. X Don't use spilled material or rejected material in the batch. X Do not start the operation without closing machine door.

5.7 Packing:

Blister Pack Machine

Blisters



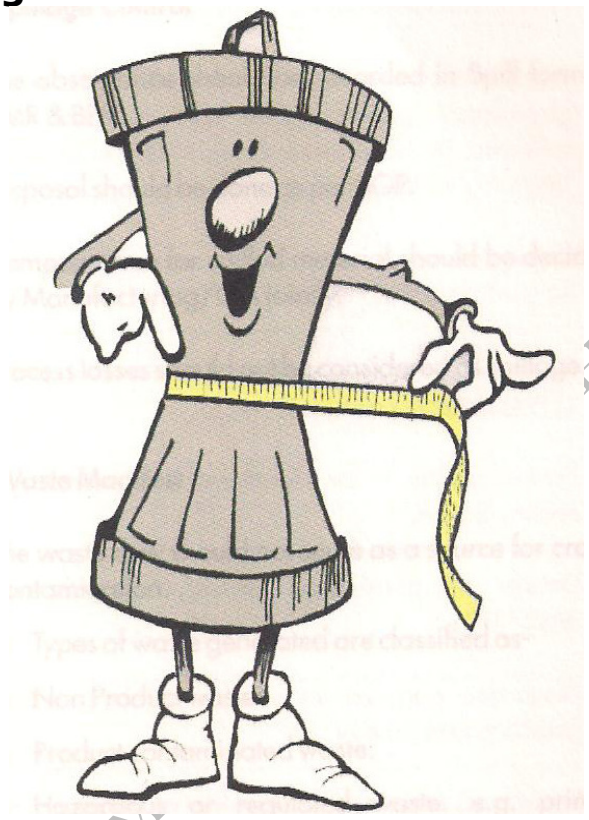
Do's	Don't
✓ Ensure & cross check all right materials are dispensed as per batch records. ✓ Labeling to be done properly in case of partial dispensing. ✓ Ensure cleanliness & status label of all equipments kept in specified area and also check equipments for swab if applicable. ✓ Check environmental condition before line clearance. ✓ Stereos have to be stored properly in lock & key. ✓ Printed packing material has to be controlled. ✓ Online rejected material segregation has to be done separately with proper labeling.	X Never touch primary packing material with bare hands. X Never play with set parameters of equipments. X Don't use spilled material or rejected material in the batch. X Don't Returned EMRM/ EMCM to Warehouse without approval from QA.

5.8 Environmental Monitoring:

Thermo-Hygrometer

- Ensure that the Air Handling Units (AHU) in the area is started and in operation at least 30 minutes before recording the room conditions.
- Ensure all doors are properly closed during checking of differential pressure.
- If in any area, pressure differential is out of limit do not undertake any operation where product is exposed to environment
- For manufacturing area the acceptance criteria for temperature and relative humidity should be within limits as per SOP or product specific.
- Record Temperature, % RH and Pressure difference of the area/ cubicle three times in a shift. Record Minimum/ maximum temperature of storage areas.
- During pressure differential recording ensure that pressure gauge of area shows zero reading. If not, inform engineering and QA department.
- All areas requiring controlled temperature and humidity conditions for 24 hours a day must have a calibrated min-max thermometer as well as a dry –wet thermometer or a hygrometer placed in them.

6. Waste Management:



Spillage Control

- The observance should be recorded in spill format, BMR and BPR.
- Disposal should be done as per SOP.
- Compensation for spilled material should be decided by Manufacturing/ QA jointly.
- Process losses should not be considered as spillage.

Waste Manifest:

- The waste flow should not serve as a source for cross-contamination.
- Rejected material and product should be clearly marked and stored separately in the storage area. They should be destroyed, after approval from Head-QA, along with proper recording & in presence of QA person.
- Waste generated in the manufacturing of investigational medicinal products should be destroyed with prior written authorization after satisfactory recording of destruction /disposal in presence of QA.
- Waste generated from manufacturing in solid/liquid form should be disposed in a safe, timely and sanitary manner, with clear identification of containers meant for it (waste).
- Ensure that, if waste is not destroyed immediately, it should be kept in clearly separate area, so as to avoid any type of contamination.
- During disposal operation transfer the rejected material (transferred in the HDPE container lined with double polybag) to the wash area, add water just to wet the material and loose the identity in front of QA person. Tie the polybags and transfer the HDPE containers to the scrap room on platform trolley.
- Carry the containers to the ETP plant and hand over to the respective ETP person.
- Disposal of material note is not required for disposing the material viz. nylon thread, nylon fastener, poly bags, gloves and nose masks. Dispose them directly by cutting them into pieces using scissor, put then in poly bag affixed with "Material for disposal" label and transfer them to scrap room. Inform to respective ETP person for further disposal.