

Combino Pharm (Malta) Ltd. Non-Technical Summary

Combino Pharm is a finished dosage form pharmaceutical company set up in 2004-5. It started operations in 2005 and has been operating under an Environmental Permit issued by the Environment and Resources Authority (EP 0036/09) since 2009.

Raw materials

The raw materials used range from Active Pharmaceutical Ingredients (API's) to fillers (ingredients which help to bulk up the tablet to the desired size, usually the main ingredient in the tablet), binders to hold the ingredients in a tablet together, disintegrants and surfactants to help the tablet to break apart and be absorbed, lubricants, plasticizers and glidants to help the production process, and coating agents which are usually applied as a thin film on the tablet to protect tablet ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow.

From the environmental perspective, the API's constitute the main area of concern due to the nature of some of the substances. Hence, actions are taken to prevent the release of such substances into the environment.

Warehousing

The warehouse area has a loading and unloading area next to a material reception room. Typically, received raw materials are immediately sampled and remain in the quarantine status until approved and released by Quality Control. Released bulk product and packaging materials are issued to the Production Department by warehouse personnel.

Materials are stored on a pallet racking system within the warehouse. There is also a shelving system for small containers that are not usually stored on pallets. All printed packaging materials are stored in lockable areas of the warehouse.

Within the warehouse there are specific sampling and dispensing areas.

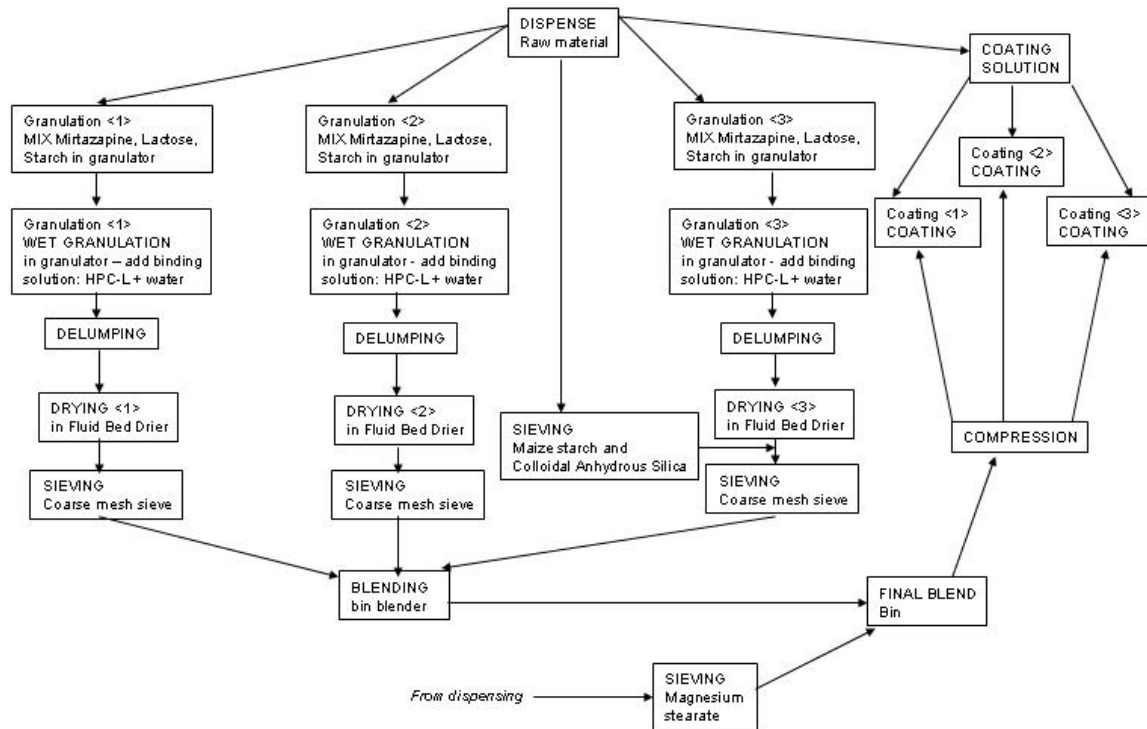
Finished goods are also stored in the warehouse until order allocation, transport packaging and shipment to customer.

Production Process

The production area comprises several rooms. The height of these rooms is determined by the dimensions of the production machinery, some of which are 4.00 m high. There is also a cleaning, drying and storing area for manufacturing equipment.

A technical area is located in the middle of the production area.

A typical manufacturing sequence is summarised on the next page. The diagram illustrates the production of Mirtazapine coated tablets from three sub-lots and employing the equipment train which is routinely used at Combino Pharm.



The process rooms are positioned in a manner to allow the most coherent flow from the reception of raw materials to packaging of finished product. The rooms for intermediate product processing are placed in a centralised area with appropriate adjacent support rooms, such as the weighing room and intermediate storage room.

Those process rooms which generate bulk products are positioned such that they connect with no cross flow to the warehouse. The cleaning area is designed to meet GMP requirements. The movement of equipment within the cleaning area is designed to ensure that equipment is protected from contamination at all times.

Once the manufacturing activities are carried out the Bulk Finished Products are received from Production and are placed in an area pending administrative closure. On completion of the necessary administrative updates, the batch is transferred to its designated location.

Quality Control

The Quality Control Laboratory is responsible for sampling, testing and assessing the quality of incoming raw materials, pharmaceutical products, components, labels and finished goods. The sampling of packaging material may be delegated to the warehouse personnel. The QC Manager supervises the laboratory activities and is responsible for the release of raw materials.

The labelling and packaging of sampled product is checked by QC for compliance with product specification and packing specification.

The stability chambers are the responsibility of the Quality Control Department and these are situated in the utilities building.

Utilities and Services

Utilities and services comprise a surface area of around 350 m². In these areas there are the necessary services to supply all process requirements, e.g. electricity, water treatment, compressed air, industrial steam, etc.

Electricity is supplied by Enemalta via a sub-station situated on the southern side. A diesel-powered generator is available for emergency situations.

Steam is generated by a LPG-fired boiler. LPG is stored on the eastern side of the site, under a licence issued by the Regulator for Energy and Water Services (REWS).

All areas of the building have their own HVAC system, except for the services area and technical areas, where there is natural ventilation. The air handlers controlling the pharmaceutical production area are designed to operate at an 80:20 recirculation where 80% of the extracted air is HEPA filtered at 99.99% efficiency and recirculated.

The installation utilises a 2-stage reverse osmosis system for the generation of purified water from treated mains water. Purified water is stored and pumped to the recirculating distribution loop by a pumping station.

Maintenance

A yearly schedule is generated for the preventive maintenance work necessary on the various production, QC and Utilities equipment. Dedicated SOPs give the details necessary for the maintenance works to be performed. The SOPs contain forms where the maintenance works and any necessary repairs and modifications are recorded.

Environmental Management System

The Environmental Management System of Combino Pharm is based on the ISO 14001 standard and is made up of the following components:

- Environmental Policy
- Roles and Responsibilities
- Objectives and Targets
- Competence and Awareness
- Operational Control
- Emergency Preparedness and Response
- Monitoring, Measurement, Analysis and Evaluation
- Management Review

Details of the EMS can be found in Annex B-5.

Waste Management

Various waste streams are produced on site. They are adequately segregated, awaiting on-site or off-site processing, including export where a local solution is not available. All wastes are handled according to current legislation (use of registered waste carriers for transfers within the country, together with the use of consignment notes and consignment permits). For exports, the Transfrontier System for the Movement of Waste is used through licenced waste brokers.

The table below lists the various waste streams generated or processed on site.

Type of Waste	Method of processing and/or disposal	Method of storage and containment
Pharmaceutical solid waste	Incineration	Tightly closed plastic bags stored in closed wheeled bins located outside
Contaminated Packaging	Incineration	Stored in plastic drums or else if bulky, packed on a pallet and stored inside metallic shed
Contaminated Absorbents and Clothing	Incineration	Stored in 1100ltr plastic bin with lid, lined with jumbo bag, located outside.
Contaminated filter materials	Incineration	Tightly closed double plastic bags stored in outdoor area
Waste oil	Recycling	Plastic jerrycans or metal drums on pallets with secondary containment
Solvent Lab Waste	Solvent recovery	200L plastic or metal drums on pallets with secondary containment
Acidic/Basic Lab Waste	Incineration	200L plastic drums on pallets with secondary containment
Aqueous waste	Incineration	1000L IBC or 200L metal drums on pallets with secondary containment
Paper/cardboard	Recycling	Closed metal skip located outdoors
Plastic	Recycling	Closed plastic wheeled bins located outdoors
Wood	Recycling / Reuse	Pallets piled in the outdoor waste storage area
Mixed Municipal waste	Landfill	Metal or plastic wheeled binf or skip.
Cytostatic solid waste	Exported for Incineration	Plastic UN approved drums with inner plastic bags. Drums are placed on wooden pallet and wrapped. They are stored in the outdoor storage area until disposal.

Cytostatic Liquid waste	Exported for Incineration	1000L IBC or 200L metal drums on pallets with secondary containment.
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