Pilot Plant Scale-up of Injectables and Liquid Orals

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Introduction

- In the pilot plant, a formulae is transformed into a viable, robust product by the development of a reliable and practical method of manufacture that effect the orderly transition from laboratory to routine processing in a full – scale production facility.
- So pilot plant is the miniature, intermediate plant between the laboratory scale and the production plant.

Why to build up a pilot-plant???

- To evaluate the effect on the process of a large change in the scale of operation and to gather other data so that a good design of a larger unit may be made with a high probability of commercial success.
- To produce trial lot quantities of the material in question so that its properties may be critically examined.
- To find and examine all by – products or waste. These may not be seen in laboratory scale. By the use of pilot plant, it is possible to minimize the waste, hence better yield of prescribed dosage form.

Scale-up for parenterals

Injectables

- The majority of the parenteral solutions are solutions requiring a variety of tankage, piping and ancillary equipment for liquid mixing, filteration, transfer and related activities.
- The majority of the equipments are composed of 300 series austenitic stainless steel, with tantalum or glass lined vessels employed for preparation of formulations sensitive to iron and other metal ions.
- The vessels can be equipped with external jackets for heating and/or cooling and various types of agitators, depending upon the mixing requirements of the individual formulation.

Working area of a parenteral pilot plant

- Incoming goods are stored in special areas for Quarantine, Released and Rejected status.
- A cold room is available for storage of temperature-sensitive products. Entrance into the warehouse and production areas is restricted to authorized personnel.
- Sampling and weighing of the raw material is performed in a dedicated sampling area and a central weighing suite, respectively.
- The route for final products is separated from the incoming goods; storage of final products is done in designated areas in the warehouse while they are awaiting shipment.
- Several clothing and cleaning procedures in the controlled transport zone and production area ensure full quality compliance.
- In addition, a technical area is located in between the production zone and the area for formulation development.
- Here, the water for injection equipment is located, as well as the technical installation of the lyophilizer.

Lay-out of the pilot-plant

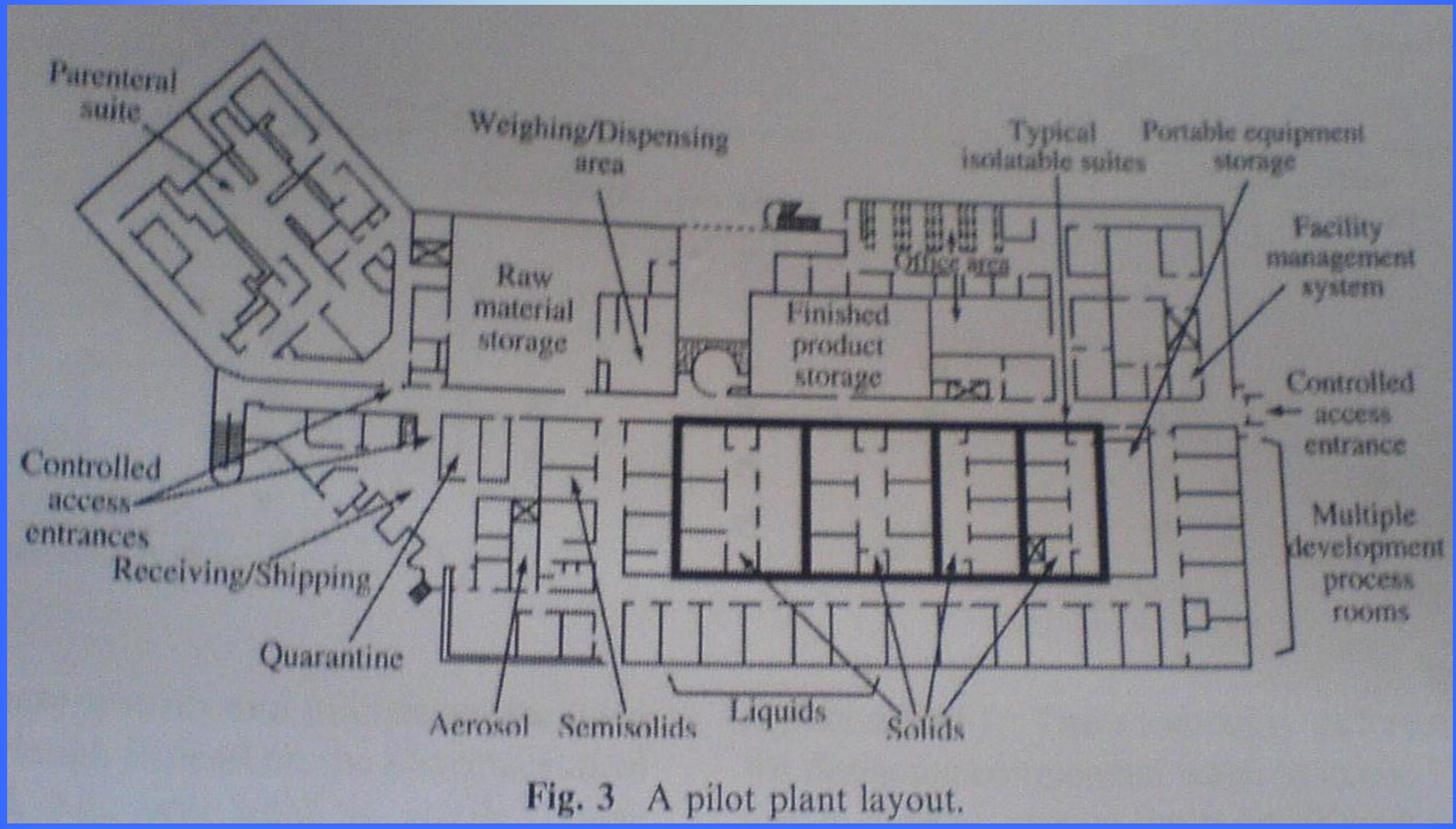

Fig. 3 A pilot plant layout.

Facility Design

To provide the control of microbial, pyrogen and particles controls over the production environment are essential.

- ***Warehousing:***

All samples should be aseptically taken, which mandates unidirectional airflow and full operator gowning.

These measures reduce the potential for contamination ingress into materials that are yet to receive any processing at any site.

➢ *Preparation Area:*

The materials utilized for the production of the sterile products move toward the preparation area through a series of progressively cleaner environments.

First the materials are passed through class 100,000 i.e. grade D environment for presterilization.

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Transfer of materials are carried out in air-locks to avoid cross contamination

↓

The preparation areas are supplied with HEPA filters.
There should be more than 20 air changes per hour

The preparation place is Class 100 area.

Production area

- ***Compounding area:***

  The manufacture of parenterals is carried out in class 10,000 (Grade C) controlled environments in which class 100 unidirectional flow hoods are utilized to provide greater environmental control during material addition.

  These areas are designed to minimize the microbial, pyrogen, and particulate contamination to the formulation prior to sterilization.

- ***Aseptic filling rooms:***

  The filling of the formulations is performed in an Class 100 environment.

- Capping and Crimp sealing areas:

  The air supply in the capping line should be of Class 100

- Corridors:

  They serve to interconnect the various rooms. Fill rooms, air locks and gowning rooms are assessed from the corridor.

- Aseptic storage rooms.

- Air-locks and pass-throughs:

  Air locks serve as a transition points between one environment and another.

  They are fitted with the UltraViolet lights, spray systems, or other devices that may be effectively utilized for decontamination of materials.

Formulation aspects

- ***Solvent:***

The most widely used solvent used for parenteral production is water for injection.

WFI is prepared by by distillation or reverse osmosis. Sterile water for injection is used as a vehicle for reconstitution of sterile solid products before administration and is terminally sterilized by autoclaving

- ***Solubilizers:***

They are used to enhance and maintain the aqueous solubility of poorly water-soluble drugs.

Solubilizing agents used in sterile products include:

1. co-solvents: glycerine, ethanol, sorbitol, etc.
2. Surface active agents: polysorbate 80, polysorbate 20, lecithin.
3. Complexing agents: cyclodextrins etc

They act by reducing the dielectric constant properties of the solvent system, thereby reducing the electrical, conductance capabilities of the solvent and thus increase the solubility.

- ***Antimicrobial preservative agents:***

- ***Buffers:***

They are used to maintain the pH level of a solution in the range that provides either maximum stability of the drug against hydrolytic degradation or maximum or optimal solubility of the drug in solution.

- ***Antioxidants:***

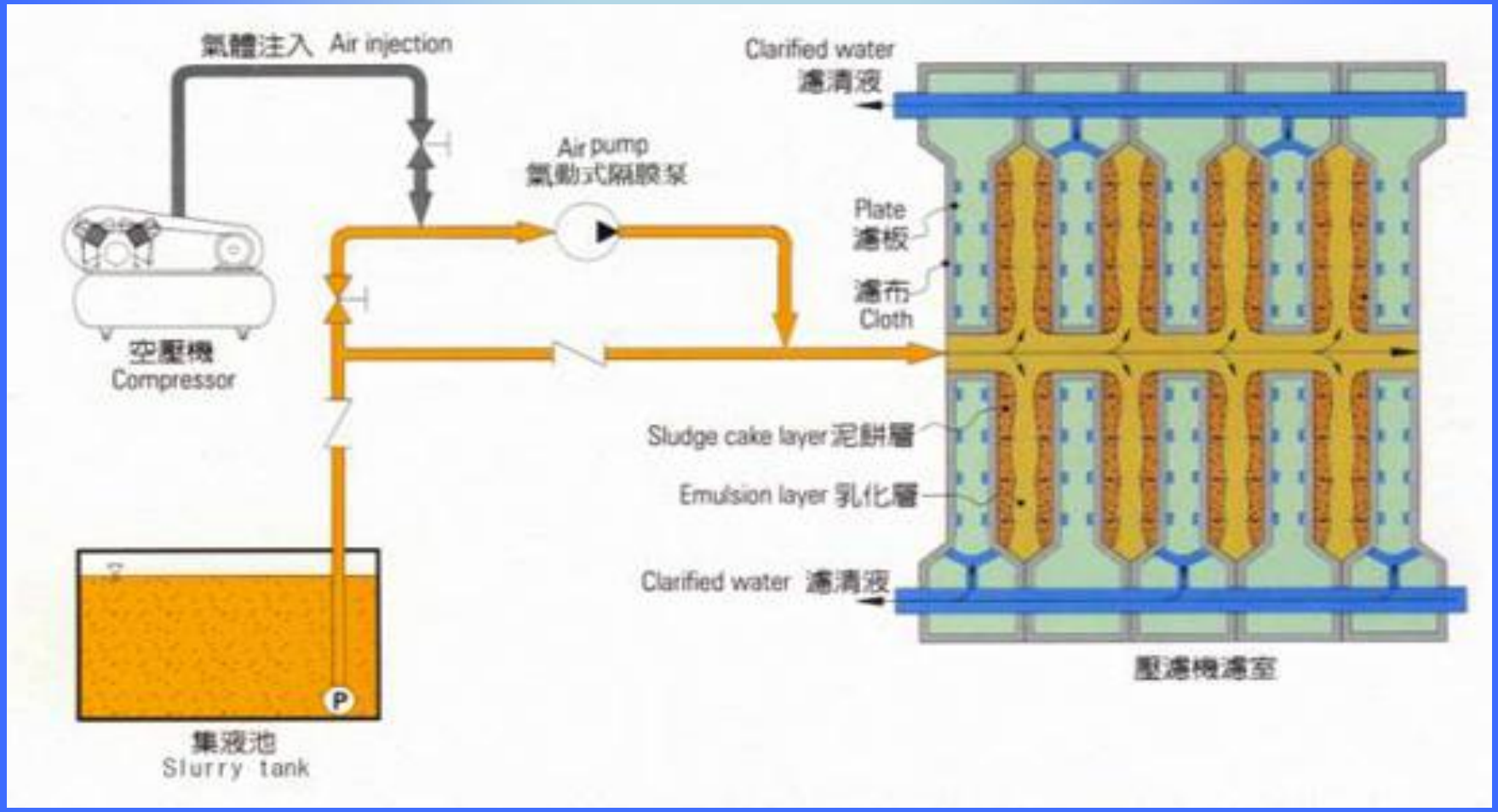
Antioxidants function by reacting prefentially with molecular oxygen and minimizing or terminating the free the free radical auto-oxidation reaction. Examples phenol (0.065-0.5%), m-cresol (0.16-0.3%) etc.

Instrumentation

- Mixer
- Homogenizer
- Filteration assembly
- Filling machinery

Mixer/Homogenizer

Filtration assembly



Bottling/Filling machinery

Sterilization and Depyrogenation

- Steam sterilization
- Dry-heat sterilization and depyrogenation
- Gas and vapour sterilization
- Radiation sterilization
- Sterilization by filteration

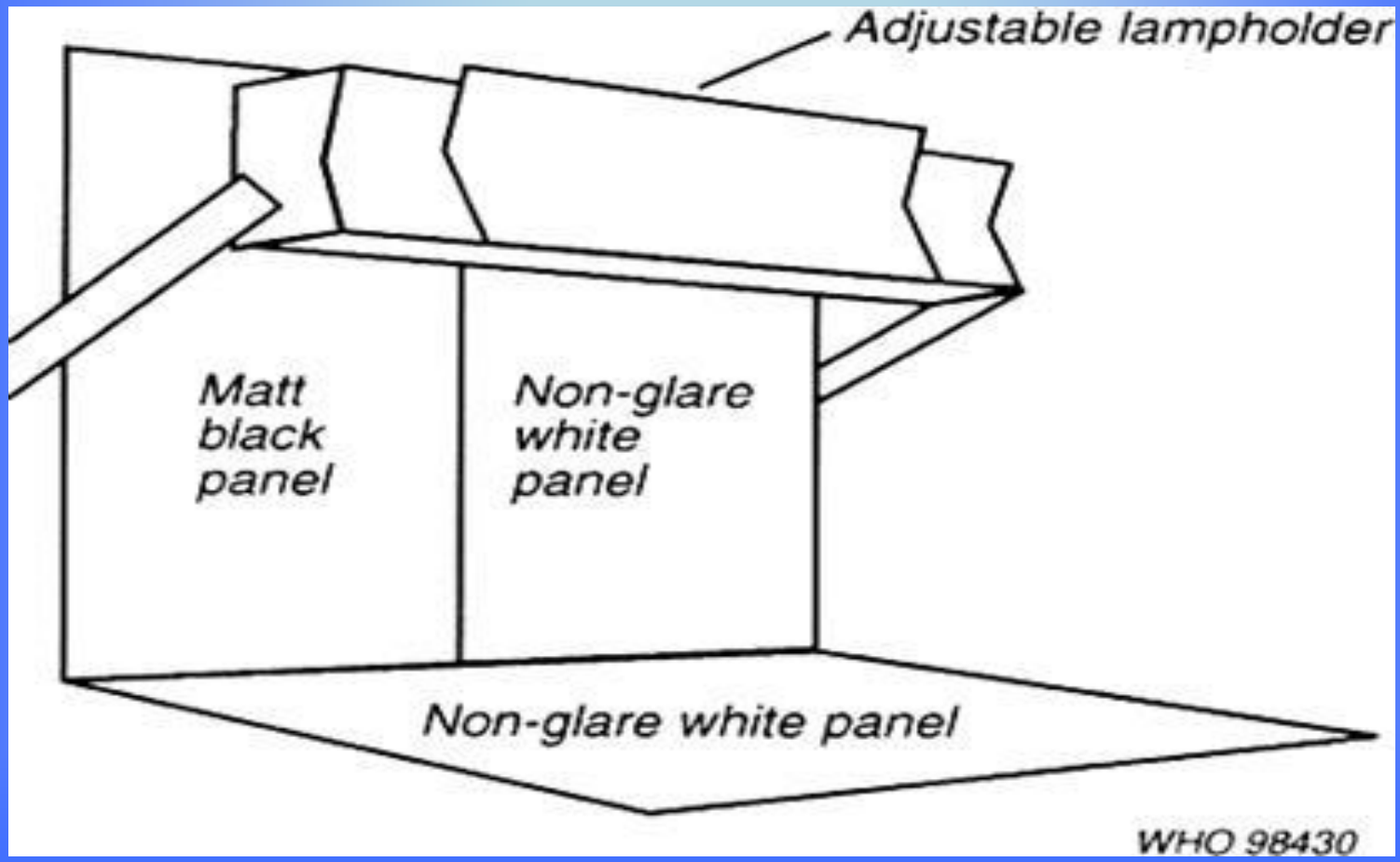
Aseptic processing control and evaluation

- In-process Testing:
- End-product Testing:
- Process simulations:

Quality Assurance

- Particulate matter
- Pyrogen test
- Stability test

Particulate matter detector



Liquid orals

- The physical form of a drug product that is pourable displays Newtonian or pseudoplastic flow behaviour and conforms to it’s container at room temperature.
- Liquid dosage forms may be dispersed systems or solutions.
- In dispersed systems there are two or more phases, where one phase is distributed in another.
- A solution refers two or more substances mixed homogeneously.

Steps of liquid manufacturing process

- Planning of material requirements:
- Liquid preparation:
- Filling and Packing:
- Quality assurance:

Critical aspects of liquid manufacturing

- Physical Plant:

- Heating, ventilation and air controlling system:

  the effect of long processing times at suboptimal temperatures should be considered in terms of consequences on the physical or chemical stability of ingredients as well as product.

Formulation aspects of oral liquids

- Suspensions:

Purpose	Agent
Facilitating the connection between API and vehicle	-wetting agents Salt formation ingredients
Protecting the API	- Buffering-systems, polymers, antioxidants
Maintaining the suspension appearance	Colorings, suspending agent, flocculating agent.
Masking the unpleasant taste/smell	Sweeteners, flavorings

- Emulsions:

Purpose	Agent
Particle Size	Solid particles, Droplet particles
Protecting the API	Buffering-systems, antioxidants, polymers
Maintaining the appearance	Colorings, Emulsifying agents, Penetration enhancers, gelling agents
Taste/smell masking	Sweetners, flavorings

- Solutions:

Protecting the API	Buffers, antioxidants, preservatives
Maintaining the appearance	Colorings, stabilizers, cosolvents, antimicrobial preservatives
Taste/smell masking	Sweetners, flavorings.

Layout of the pilot plant

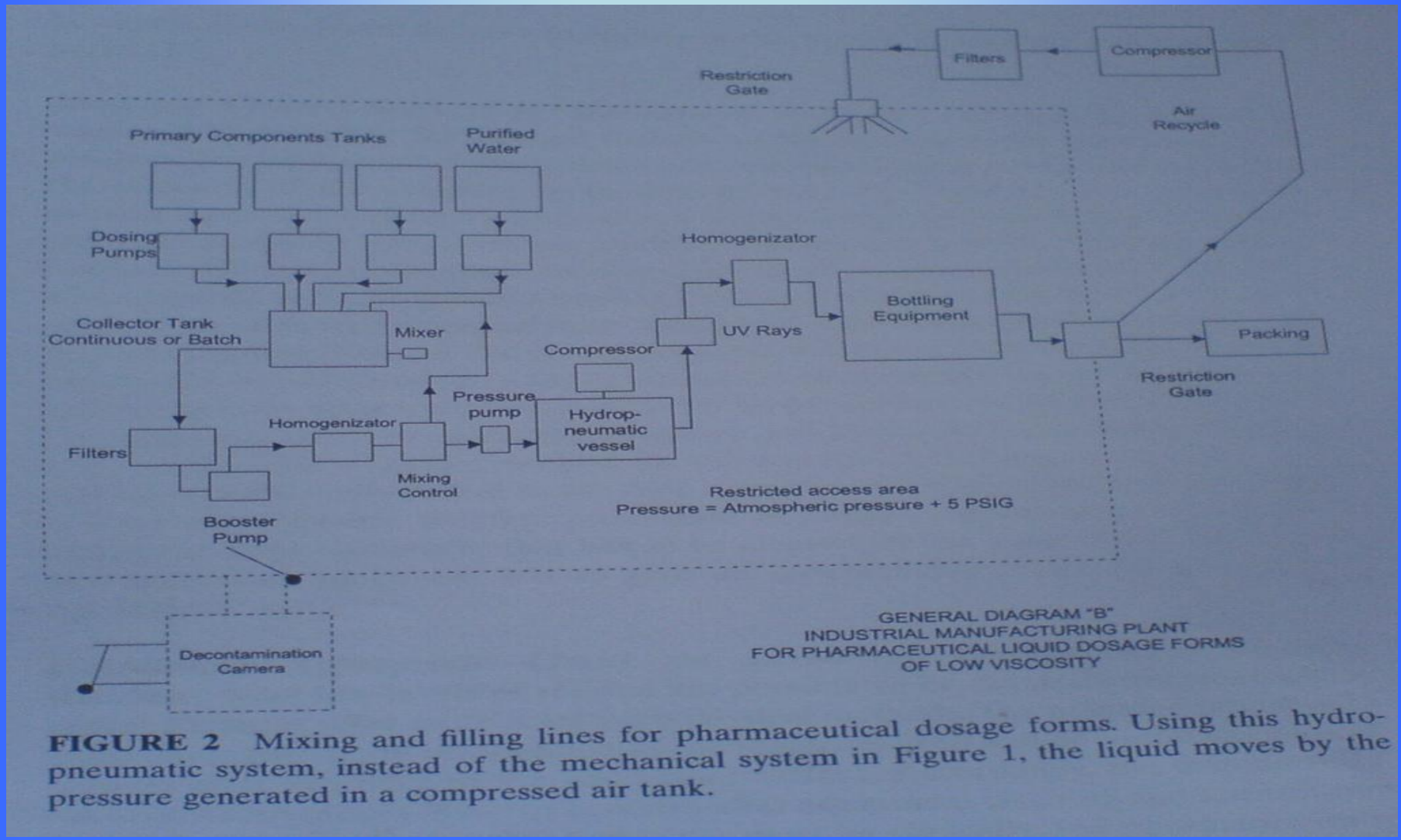
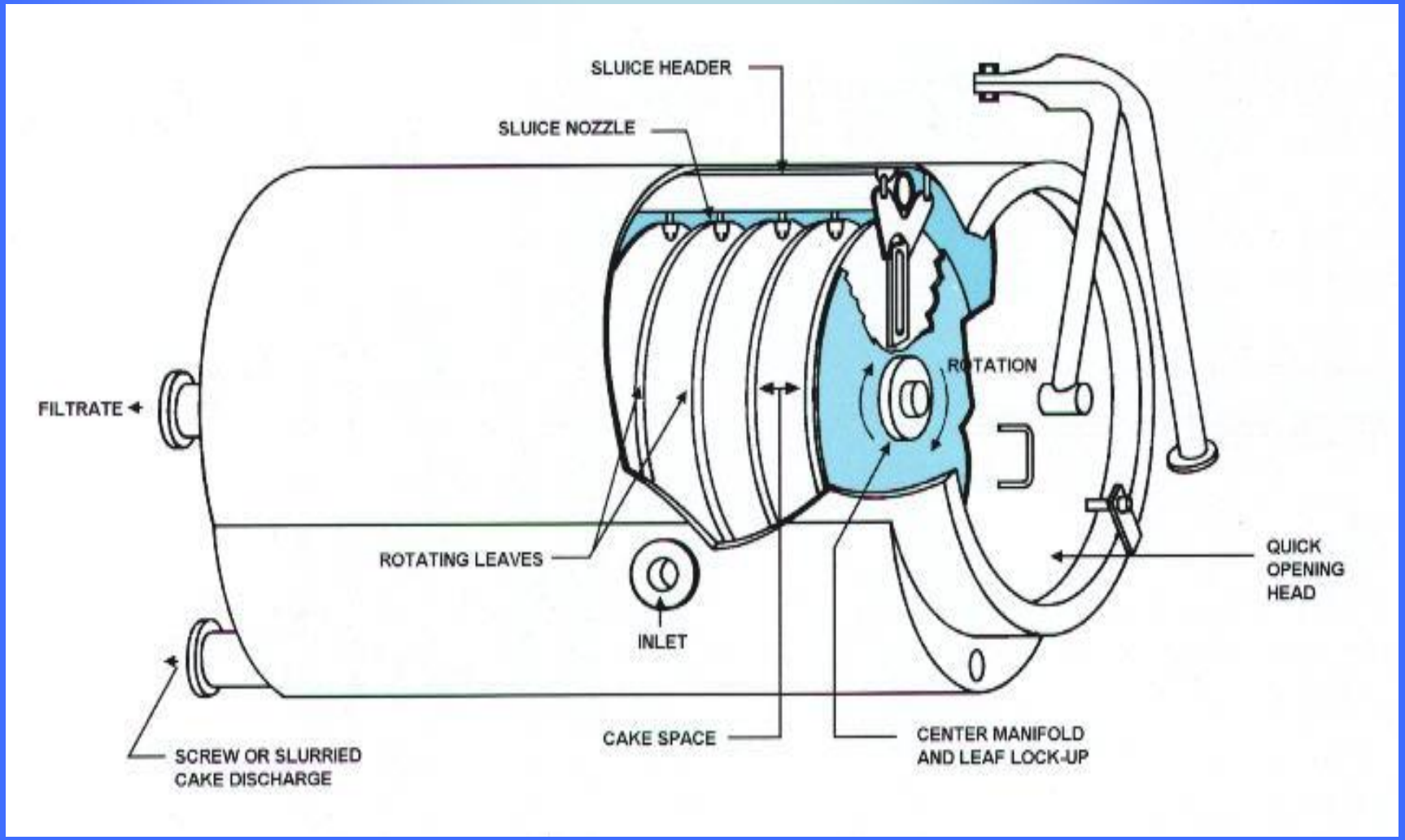


FIGURE 2 Mixing and filling lines for pharmaceutical dosage forms. Using this hydropneumatic system, instead of the mechanical system in Figure 1, the liquid moves by the pressure generated in a compressed air tank.

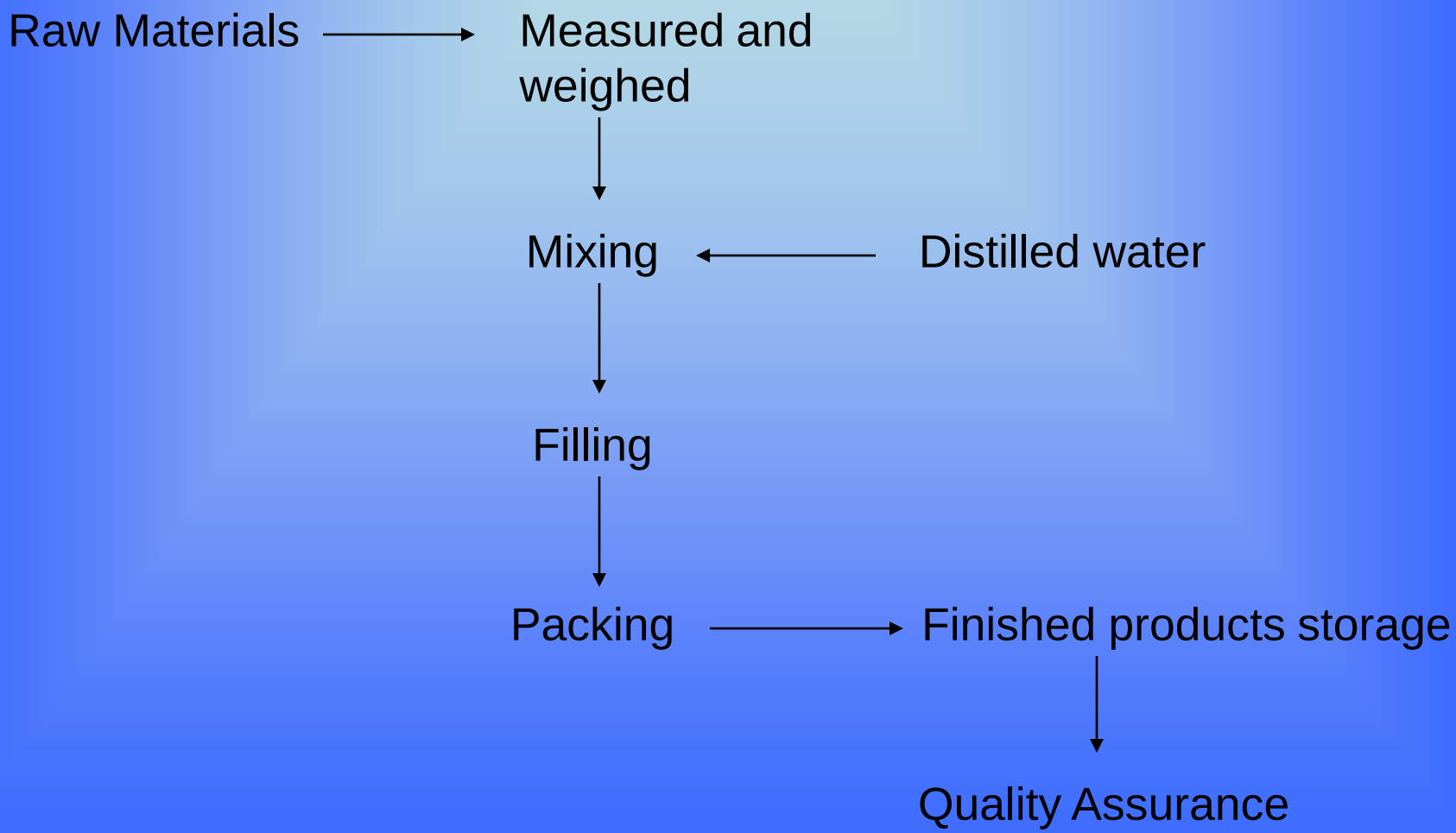
Equipments

- Mixer
- Homogenizer
- Filteration assembly
- Bottling assembly

Filtration assembly



General flow chart



Quality assurance

- Dissolution of drugs in solution
- Potency of drugs in suspension
- Temperature uniformity in emulsions
- Microbiological control
- Product uniformity
- Final volume
- Stability

References

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- www.google.com

Thank You