Design and construction of Pharmaceutical plant GMP

Preparation / Planning / Requirements / Resources

- What we want to do
- Where we want to make it
- How we want to make it
- What we want to use
- What we want to make of
- Who we want to do with

Guidelines to follow

- **GMP (Good Manufacturing Practice)**
  - Applies to manufacture
  - It is of a technical nature
- **GLP (Good Laboratory Practice)**
  - Applies to tests
  - Toxicological elements
- **GCP (Good Clinical Practice)**
  - Ethical elements

Additional guidelines (GXP)

GMP: Good Pharmaceutical Practice

GLP: Good Laboratory Practice

GCP: Good Clinical Practice

GDP: Good Documentation Practice

GVP: Good Validation Practice

GEP: Good Engineering Practice

GWP: Good Storage Practice

GAP: Good Audit Practice

Good Manufactoring Practice (GMP) guidelines

Part I - Basic Requirements for Medicinal Products

- Chapter 1 - Pharmaceutical Quality System
- Chapter 2 - Personnel
- Chapter 3 - Premise and Equipment
- Chapter 4 - Documentation
- Chapter 5 - Production
- Chapter 6 - Quality Control
- Chapter 7 - Outsourced activities
- Chapter 8 - Complaints and Product Recall
- Chapter 9 - Self Inspection

Part II - Basic Requirements for Active Substances used as Starting Materials

Part III - GMP related documents

What is GMP?

- Quality system for pharmaceuticals
- It also specifies technical requirements
- In some chapters it refers to ISO standards

Quality Management

The holder of a manufacturing authorization must ensure that the products manufactured by him are fit for the purpose for which they were intended and that the requirements of the marketing authorization were satisfied.

In addition, these products should not endanger patients by their inadequate safety, quality or efficacy.

The quality management tasks are the responsibility of the top management of the pharmaceutical company, but there is a need for staff at different levels and in different departments, as well as for the manufacturers of starting materials and

and the involvement and commitment of wholesalers.

Quality Assurance

The broad concept of quality assurance includes everything that, alone or in combination with other factors, can influence the quality of a product.

Quality assurance is the set of planned and organized works that can be followed to ensure that the quality of medicines is appropriate for their intended use.

Therefore, quality assurance includes GMP (that is, the rules of good pharmaceutical manufacturing) and other aspects that go beyond those rules.

Basic requirements of GMP (1)

I. All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
II. Critical steps of manufacturing processes and significant changes to the process are validated;
III. All necessary facilities for GMP are provided including:
    a) Appropriately **qualified and trained personnel**;
    b) Adequate premises and **space**;
    c) Suitable **equipment and services**;
    d) Correct **materials**, containers and labels;
    e) Approved **procedures and instructions**, in accordance with the Pharmaceutical Quality System;
    f) Suitable **storage and transport**;

Basic requirements of GMP (2)

IV. Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
V. Procedures are carried out correctly and operators are trained to do so;
VI. Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected.
VII. Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;

Basic requirements of GMP (3)

VIII. Records of manufacture including distribution which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;
IX. The distribution of the products minimises any risk to their quality and takes account of Good Distribution Practice;
X. A system is available to recall any batch of product, from sale or supply;
XI. Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Personnel - Principle

The correct manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

Personnel – General

The manufacturer should have an **adequate number** of personnel with the **necessary qualifications** and **practical experience**.

Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the quality management system and continually improve its effectiveness.

The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

Key Personnel

Senior Management should appoint Key Management Personnel including the

- **head of Production,**

- the head of **Quality Control**, and if at least

- one of these persons is not responsible for the duties described in Article 51 of Directive 2001/83/EC1, an adequate number, but at least one, Qualified Person(s) designated for the purpose.

A factory has a minimum of 3 employees:

- Production Manager
- Quality control leader
- Top manager (bosses of the previous two)

Personnel - Training

- The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.
- Besides the basic training on the theory and practice of the quality management system and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

Personnel - Hygiene

- The staff must show good hygiene and health behavior.
- Persons manufacturing pharmaceutical products should have no infectious disease and no open wounds on their exposed skin.
- Personnel must wear clean clothing appropriate to the manufacturing activities they carry out and be changed at the appropriate time.
- If necessary, additional protective clothing, such as head, face, hands, arms, should be worn to protect the intermediates and active ingredients from contamination.

Premises and Equipment

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.

Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

Areas

- **Production areas**
- **Storage areas**
- **Quality control areas**

- Related areas
  - *Lounge and dining areas*
  - *Change of clothes and bathrooms*
  - *Toilet*
  - *Maintenance workshops*
  - *Animal Houses*

Production areas

Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities.

The measures to prevent cross-contamination should be commensurate with the risks.

Quality Risk Management principles should be used to assess and control the risks.

Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products.

Storage areas

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

Storage areas should be designed or adapted to ensure good storage conditions.

In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

Quality Control Areas

Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.

Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Equipment

- Manufacturing equipment
- Washing and cleaning equipment
- Production equipment
- Balances and measuring equipment
- etc….

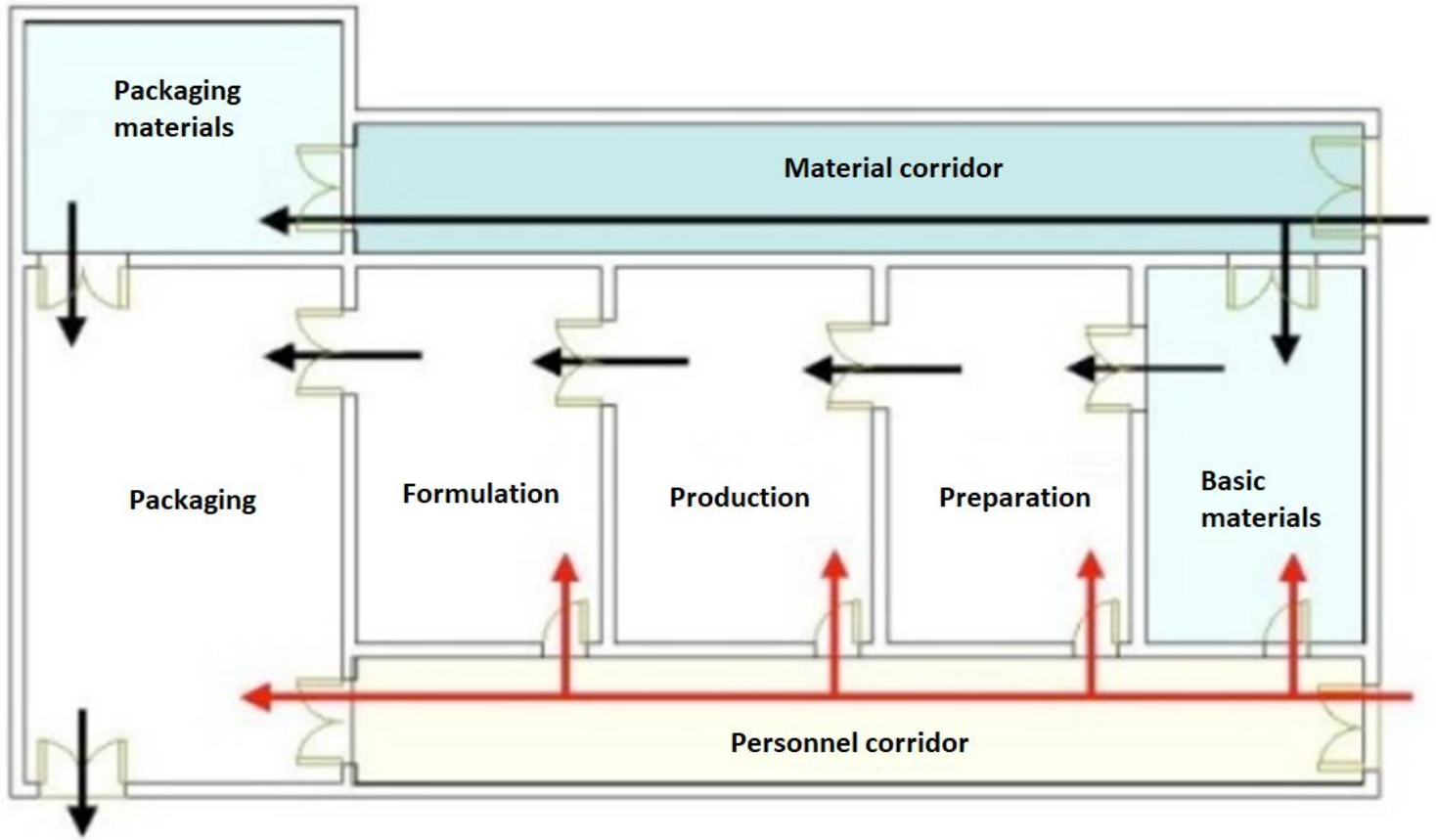
Manufacturing process

Person and material traffic

Principles:

- the need for airlock systems required by the dosage form,
- storage of materials used for manufacturing and packaging,
- the possibility of moving materials safely.

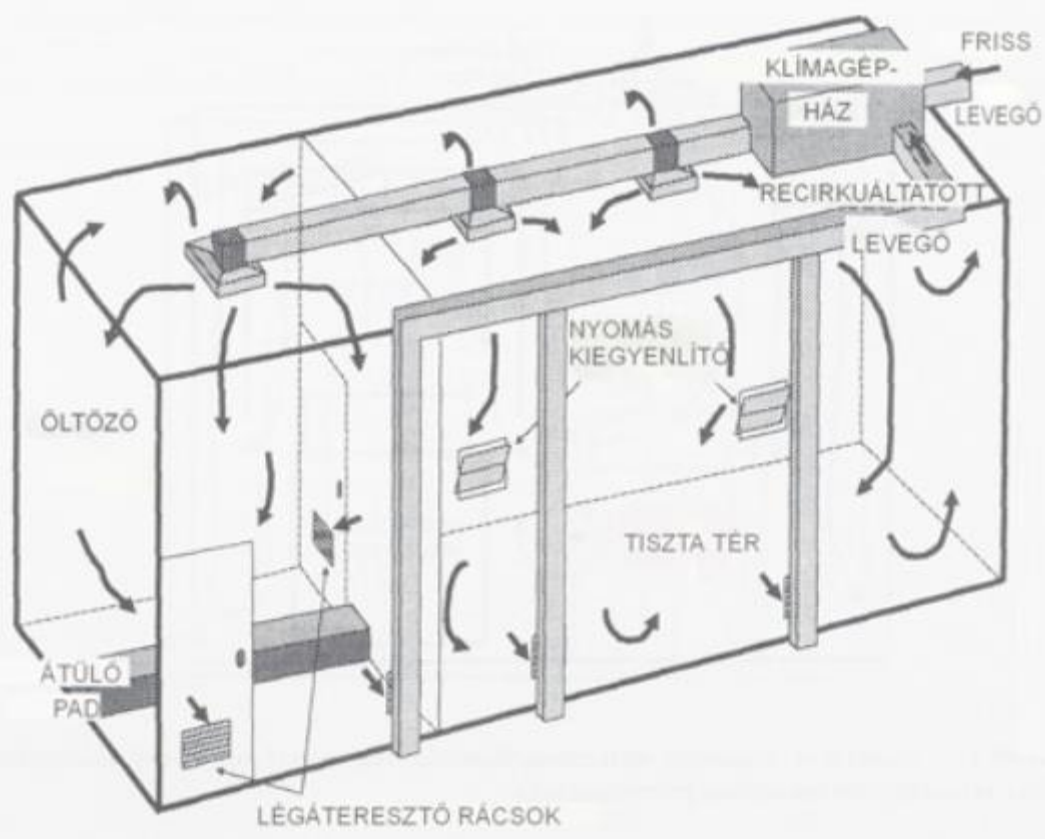
Personal traffic should always be **strictly regulated** for **drug safety** and **occupational safety** reasons.



Air supply

When planning an air supply, the following factors should be considered:

- the **purity criteria** for the pharmaceutical form to be manufactured,
- critical **room parameters** which influence product quality (temperature, humidity, pressure differential),
- location of **rooms, sluices, air volume**,
- potential **sources of contamination** of premises.



Utility systems

Utility systems are those that **do not come into contact with the product or materials** that will eventually become part of the product. (Eg: fresh air, air heating, steam, cooling water, sewage, etc.).

Utility systems are not considered as critical as technological and technological auxiliary systems.

However, the risk of indirect pollution needs to be carefully analyzed and the systems must be designed, built and installed in accordance with the principles of Good Engineering Practice.

The drainage openings shall be adequately insulated from the technological systems and shall be organically connected to the cleaning system.

Signs and labels

In accordance with GMP regulations, a sign and a label shall be affixed to:

- technology rooms,
- technological equipment,
- service piping systems (vacuum, steam, nitrogen, etc.),
- process pipelines (material lines),
- other means of formulation.

Material of the labels and signs:
It shall be made of materials which:

- easy to clean,
- does not release particles (clean spaces),
- good resistance to the drug or ingredients to be formulated and to other external influences.

Signs and labels

Designation of technological rooms:

Outside the room, usually **non-changeable** signs containing the room name and other information are placed on the door.

The tables must bear:

- the name of the room,
- the number of the room,
- room cleanliness class,
- the fire classification of the room.

Signs and labels

Technological rooms shall be provided with **up-to-date labels** indicating the product being manufactured, packaged or packaged (eg. product name, serial number, date of manufacture, expiry date).

Designation of technological equipment:
Equipment must bear details of the product being manufactured at that time.
If there is no production, it must be marked with the status of the equipment (eg during cleaning, waiting to be cleaned, cleaned).

Marking of server wiring systems, process lines, and other devices:
The service wires should be marked in a prominent position, which has not only technological but also security reasons.
The status of the technology lines and devices that are not in use should be indicated.

Walls and ceiling

The most important requirements for walls are:

- be firm and of sufficient capacity,

- their surface must be perfectly flat, free from gaps, do not give off particles,

- can be washed with suitable cleaning and disinfecting agents,

- their color suggests and allows the desired purity to be controlled,

- have sufficient heat and noise insulation, and must not contain thermal bridges.

The walls of the production and service spaces must be treated separately.

Production area

They use almost exclusively assembled sandwich panels with a sintered steel plate.

When designing, care must be taken to design suitable hollows for floor and ceiling connections. (Easy to clean!)

The color is usually white or very pale pastel.

Surfaces are excellent for cleaning and can be disinfected with standard disinfectants (sodium hypochlorite, invert soaps, peroxide and per-acetic acid).

Where there is a need for interchangeable material conduits, it is advisable to install a specially designed pipe in the wall.

Unused transfer openings shall be properly closed.

Service and other spaces, ceilings

Suitable waterproof, multilayer resin paint, usually applied to smooth cement plaster.

Beware of tiled surfaces, if possible only in toilets.

In this case too, waterproof, flexible grouting should be required.

Ceiling

Due to the lowering of ventilation and lighting fittings, there is now only a sintered steel sheet or plastic, mounted and sealed panel ceiling.

Floor

A good floor meets the following conditions:

- be solid and have a load capacity greater than the right one (tools, fittings fall!),
- its surface must be perfectly flat, free from gaps, permanently waterproof,
- have a slope to the drain (and only that!), not have puddles, stagnant water,
- be completely resistant to the materials used for the manufacture and cleaning, and must not be colored or etched,
- washable and disinfectant suitable for the purpose for which it is intended,
- their color suggests and makes the required cleanliness controllable, corresponding to the cleanliness of the room,
- be non-slip, prevent an accident,
- cleaning should be easy and efficient.

Stone coverings

The floor of the areas most exposed to physical forces is almost exclusively techno-granite (or other high-strength artificial stone) slabs with anhydrous grouting.

The advantages are high strength and durability.

Its disadvantages are that it is almost impossible to lay it flat, and that it has little resistance to acidic cleaners and disinfectants.

Another major disadvantage is that the hollow sections of the walls are not adequately resolved, causing deposits and strong corrosion, which makes the room unclean.

In practice, it is recommended to cover only service areas where heavy machinery traffic or metal equipment slides (barrels, crates) are expected.

Synthetic resin floors

In other areas, self-leveling synthetic resins based on polyurethane or polyacrylate are preferred.

They generally have excellent cleanliness and cleanliness requirements, are easy to form and have smooth, flat surfaces, but are not durable and have very low physical resistance. They have the advantage of being lubricated, so that the right wall-to-floor connection is inexpensive and well designed.

The color of the resin topcoat should be chosen to indicate the boundaries of spaces of various purity or function.

Windows

Key requirements:

- they cannot be opened, as this results in poorly-tuned aeronautical parameters and irreversible contamination of the production site,
- their surface must be completely flush with the wall and must not have a ledge or gap,
- be properly insulated,
- allow only enough light of such wavelengths that does not damage the manufacturing or its materials.

If required by technology, they can be covered with a light filter or a foil on the inside. Windows, especially those used for inspection in sterile spaces, are often built into traditional wall structures. The construction here must be the same as the sandwich panel.

In many places there used to be a traditional metal frame window structure embedded in a metal panel in the production areas.

Unfortunately, this solution is not durable, because the expansion of the metal and the resonance of the machines cause the joints, which at first appear to be perfect, to loosen, creating gaps.

Doors

Key requirements:

- they must be airtight and secure when closed,
- their opening must be in the correct direction according to the technology and must be open for alarm purposes (light or sound),
- doors that cannot be opened from a technologically incorrect direction shall be equipped with a panic lock to allow escape in the event of an emergency,
- their opening, rotation must be secure and can be locked even when open,
- their locks and frames shall be well cleaned and shall be free of dead space.

Installing foreign doors into panels is a very difficult and insecure undertaking. The panel contains the locking-transmission elements that hold and stabilize the system door. If the transmission points do not fit, the door and panel may be damaged or torn.

It is advisable to install the panel door surface with a steel cover - a protective rail for truck traffic - to protect the door leaf from impact.

There is an eternal debate between designers and pharmaceutical technologists to make the door sliding or opening.

Air supply connectors

Today, the pharmaceutical industry is united in its efforts to introduce the concept of "upper airflow and lower airflow" in air technology. This technology is implemented through the following connectors:

Supply air diffuser: Ceiling-mounted junction boxes made of sintered steel, including the final filter. The grille on the work area is removable, washable, and the filter insert is replaced here.

Exhaust diffuser: side and wall mounting boxes with sintered surface with mechanical and dust filters. Work area grille removable, washable inside, can be disinfected, the filter is replaceable.

Overpressure vents: mechanical socket, wall-mounted junction box. They are identical in design, but the blades only open when there is excess pressure or a sudden increase in pressure in the working space. The excess air can then escape. In normal operation, the blades are closed.

Air supply connectors

The fittings must always be flush with the wall or ceiling and sealed with elastic sealant. Leakage or defects, depending on overpressure, in the form of whistling, will cause extremely unpleasant noise.

If, for example, the filter housings will be monitored later (clogging, pressure differential, air velocity, etc.), so the necessary connections to the clean room must be made at the same time as the installation, since later this can only be done by violating the integrity of the space.

Lighting

The required fixtures must be sealed, and **household lighting fixtures must not be used** in pharmaceuticals.

The degree of leakage is primarily a matter of the technology used.

If workflow involving dust formation or the introduction of flammable or explosive material into the area to be exposed occurs, only fittings with IP54 tightness are acceptable.

If such workflows are not to be counted on, IP34 fittings are also suitable.

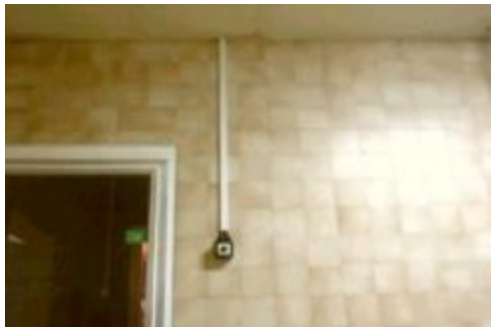
Lighting

Lighting fixtures and switches can only be installed in the clean room if they can be mounted in the plane of the wall or ceiling, and can be mounted on the wall or ceiling. they can also be cleaned together with the ceiling.

Older fittings (fittings mounted, suspended, etc.) cannot be used.

The reason for this is that on their surface material particles, dust can be deposited, which can constantly contaminate the clean room.

Consumables and fittings which, as prescribed, must be placed outside the wall shall be placed in a closed box, which may be washed and disinfected under the same conditions as the masonry, or in a protective cover.



Utility connections

In older plants, we often meet so-called. connector panels, which cover conventional soluble connectors assembled on a practically separate metal board, with appropriate markings. This solution has many drawbacks.

On the one hand, they can be extremely poorly cleaned because there is a lot of dead space in the fittings.

On the other hand, traditional bolt structures can leak or drip even with minimal wear, contaminating the production space and the product.

For new plants, the entire wiring system is in the background, usually in the sandwich panel wall structure or behind the wall cladding.
Only the end connectors are placed in the production space, aesthetically removed from the wall and labeled accordingly.

Production area

It is important in the production area:

- Preventing cross-contamination (due to multifunctional plants).
- Minimize dust formation.
- Minimizing contamination hazards.
- Ensure cleanliness.
- The status of equipment must be marked on the status plate as well as the state of clean rooms.
- Lighting, temperature, humidity, air exchange should be adequate.
- Prevent insects and rodents from entering.
- Everyone can only go where they have permission to enter.

Manufacturing process

- It must be done in accordance with regulations.
- Qualified personnel may be involved in the production.
- Devices and containers are marked with the product name and serial number.
- Daily records must be available.
- Simultaneous documentation is required.

What to do in case of rejected materials?

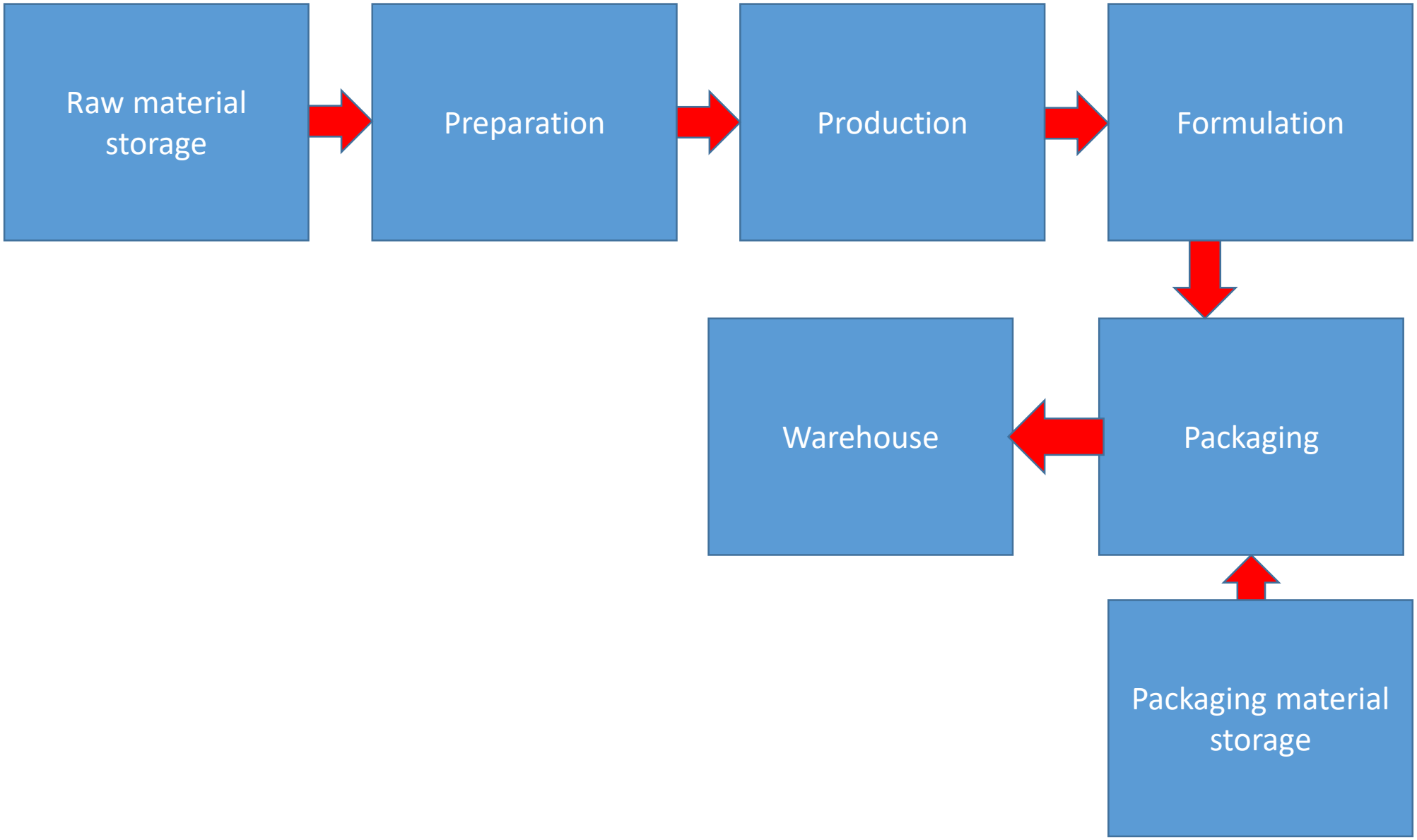
- Marking, separation is required
- Repair method: reprocessing, recasting, destruction

Warehouse

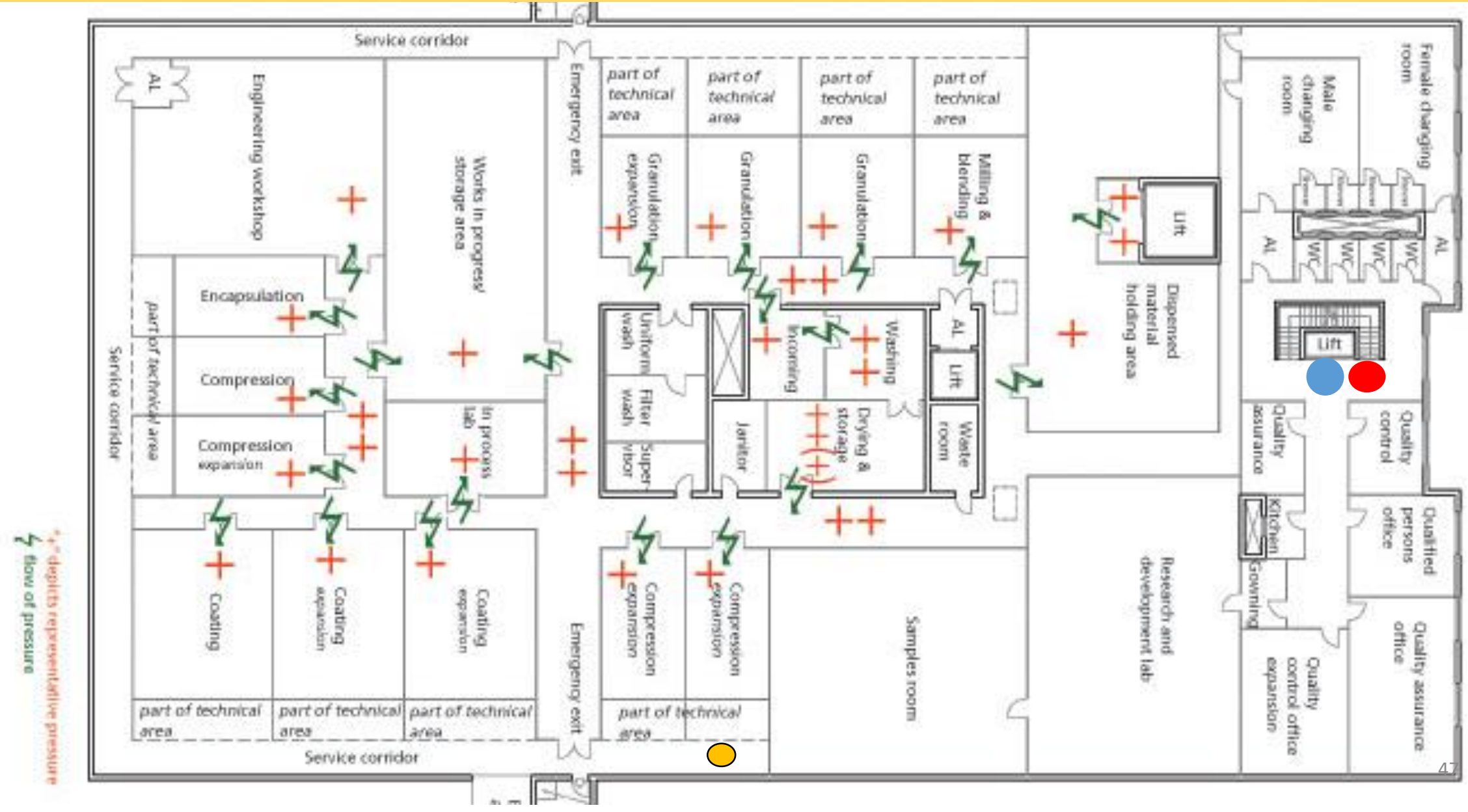
Basic requirements for warehouse:

- Different materials need to be stored neatly and cleanly.
- Quarantine is required for materials that cannot be used in production.
- Control of sampling.

Planning


Raw material storage
Preparation
Production
Formulation
Packaging
Warehouse
Packaging material storage

Factory plan



Thank you
for your attention!