GMP for Pharmaceutical Products containing Hazardous API

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Hazardous Pharmaceutical Products

- In pharmacology, **hazardous drugs** are drugs that are known to cause harm, which may or may not include *genotoxicity* (the ability to cause a change or mutation in genetic material). Genotoxicity might involve *carcinogenicity*, the ability to cause cancer in animal models, humans or both; *teratogenicity*, which is the ability to cause defects on fetal development or fetal malformation; and lastly hazardous drugs are known to have the potential to cause fertility impairment, which is a major concern for most clinicians.[1] These drugs can be classified as *antineoplastics*, cytotoxic agents, biologic agents, antiviral agents and immunosuppressive agents.

NIOSH (National Institute for Occupational Safety & Health)

- Healthcare workers may be occupationally exposed to drugs and may experience adverse health effects as a result.
- ***The NIOSH Alert***: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs
- NIOSH published updated Lists in 2010, 2012, 2014, 2016, 2022 and now this in **2024**.

1. Carcinogenicity,
2. Developmental toxicity(teratogenicity)
3. Reproductive toxicity,
4. Organ toxicity at low doses,
5. Genotoxicity,
6. Structure and toxicity profile that mimics existing drugs determined hazardous by exhibiting any one of the previous five toxicity types

Other Ref

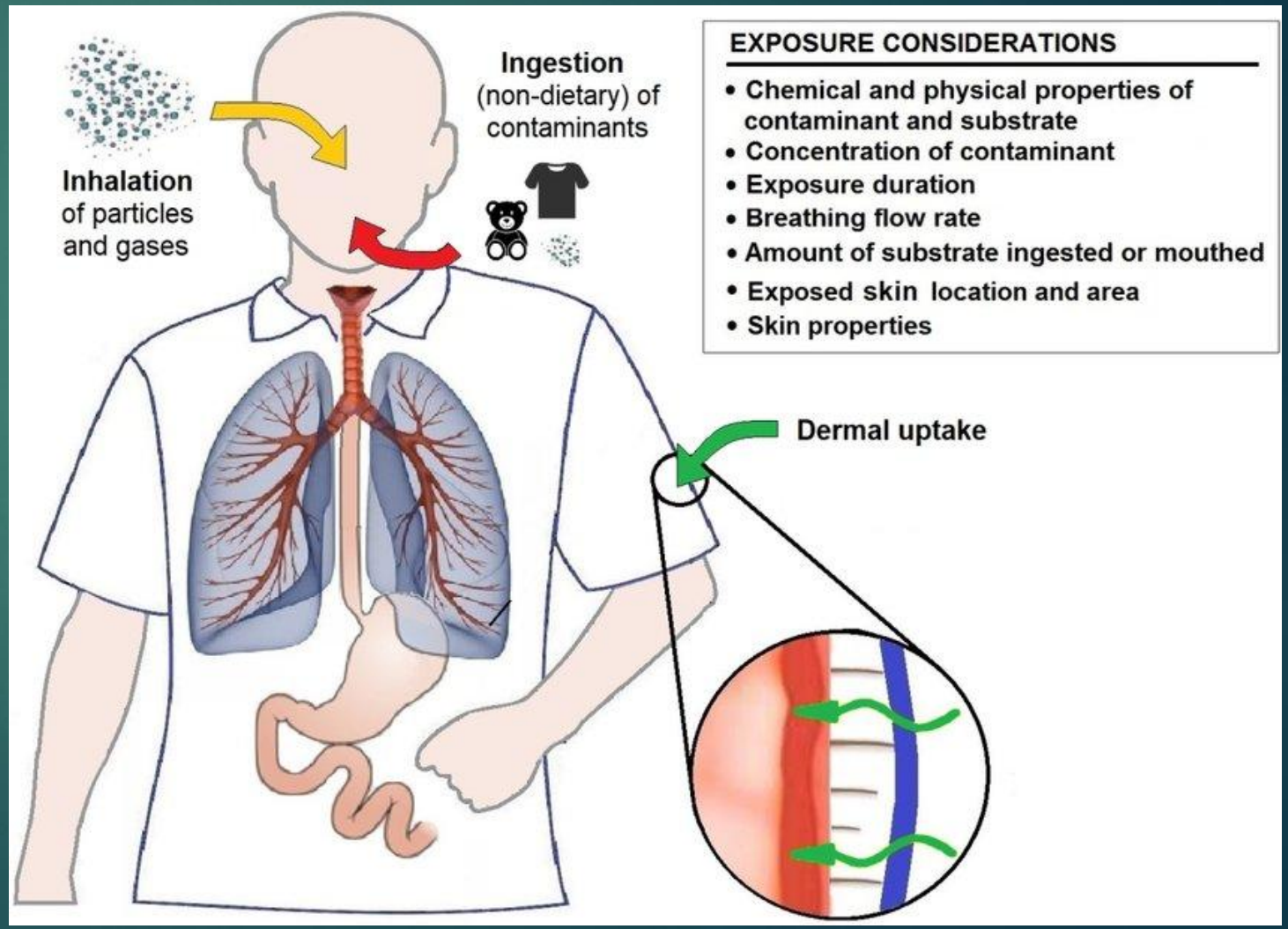
- *OSHA* (Occupational Safety + Health Administration)
- *CEN* (European Committee for Standardization)
- ***DIN*** (Deutsch's Institute for Normung)

Who is at risk of Exposure

- Workers at the Line
- Maintenance personnel
- IPQC personnel
- QA personnel
- General personnel in the area

What is the pathway for exposure

- Inhalation
- Skin
- Ingestion

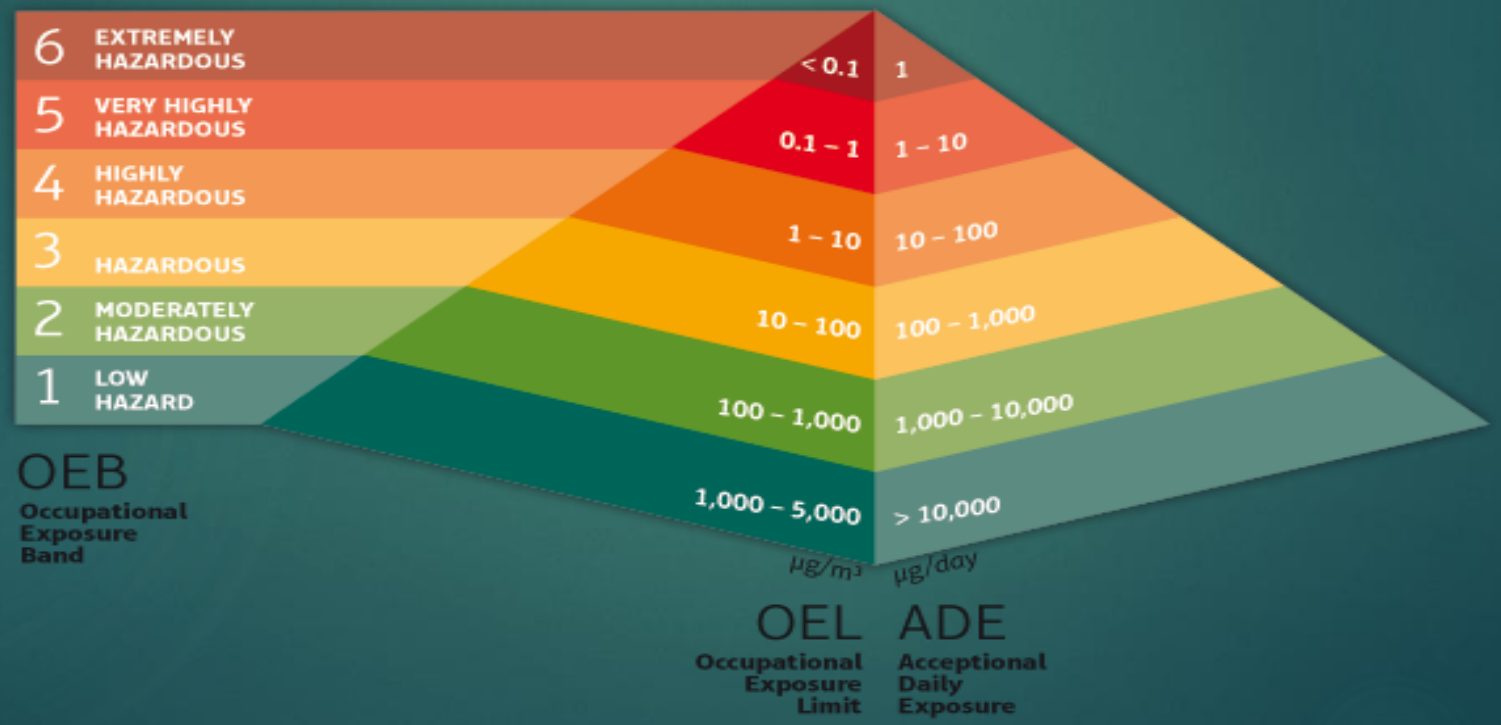


OEL
(Occupational Exposure Limit)

- Airborne concentration of substances that will not result in adverse effects to most healthy workers, exposed for **8 hours/day**, **40 hours/week**

OEB
(Occupational Exposure Band)

- **Occupational Exposure Band** ia a mechanism used to precisely assign chemicals into “categories” or “bands” based on their adverse health outcomes and potency considerations.



World Health Organization (WHO)

- These guidelines set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs) that contain hazardous substances such as certain hormones, steroids or cytotoxins

1. The primary focus of these guidelines is on the air-conditioning and ventilation systems of the facility; however, the document also provides some guidance on personnel protection.
2. Where possible products should be manufactured in closed systems.

GMP Principles

- to ensure quality of product
- to protect the operators from possible harmful effects of products containing hazardous substances

And

- to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing **hazardous substances**

- The production of certain products containing hazardous substances should generally be ***conducted in separate, dedicated, self-contained facilities.***

- These self-contained facilities may be in the same building as another facility but should be separated by a physical barrier and have, e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessment.

The effective operation of a facility may require the combination of some or all of the following aspects:

- appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using ***closed systems*** or ***barrier technology*** enhance operator and product protection
- manufacturing process controls including adherence to standard operating procedures (**SOP**s)
- appropriately designed environmental control systems (ECS) or heating, ventilation and air-conditioning (**HVAC**)
- personal protective equipment (**PPE**)

Barrier Technology

- A system designed to segregate people from the product, contain contaminants or segregate two areas, which could be a :
- Barrier Isolator (**BI**)

OR

- Restricted Access Barrier System (**RABS**)

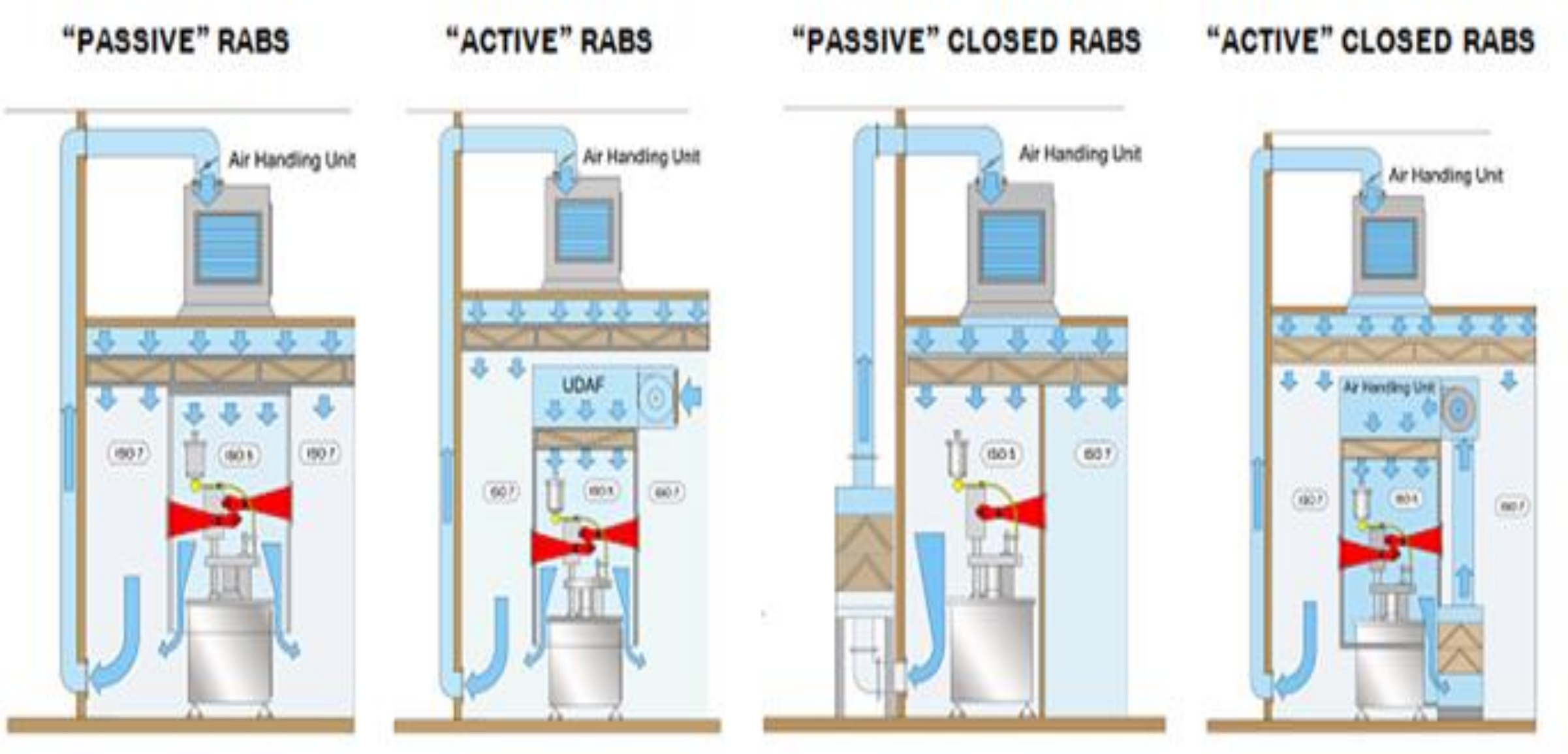
A RABS is a type of barrier system that reduces or eliminates interventions into the critical zone. In practice, its level of contamination control is less than that of a barrier isolator.


3
4


BOSCH

RABS is more than just a barrier around a machine – it is a system. RABS barriers can be arranged in a variety of ***different configurations***

C_RABS / O_RABS



Open passive RABS utilise existing clean room overhead air supply systems to deliver HEPA filtered air over the particle process before returning air back into the clean room. In an open active RABS on board fan/filtration units supply HEPA filtered air over the critical process before returning air back to the clean room. In open RABS, the enclosure is not sealed to the equipment.

Closed RABS is a positive pressure system with on board fan/filtration units to supply HEPA filtered air over the critical process before being recirculated. All RABs can include glove ports, RTP systems, access door with interlocks and EM systems.

IBC

- An **Intermediate Bulk Container** ***(IBC)*** is defined as a container used for transport and storage of fluids and bulk materials.
- IBC systems are widely used in pharmaceutical manufacturing as storage, transport and, with the increasing use of in-container applications, blending vessels
- An important feature of any containment system is preventing operator intervention.


AGIERRE
AGIERRE


MCG 300-2

IBC BIN

- These are special containers that are made from stainless steel type of AISI, either **304** or **316**

- Bins and bin systems are the accepted industry standard for powder handling applications where close containment is essential. Custom Powder Systems bins and bin systems are used in virtually all powder handling and processing applications, and will be custom designed to meet your specific requirements


SERVOLIFT
SERVOLIFT
SERVOLIFT
SERVOLIFT

ptk High Containment Line

All in one granulation line.

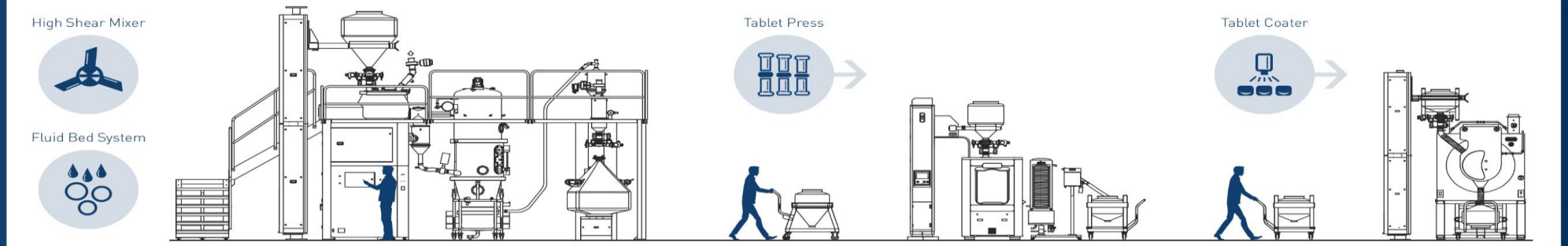
HSM, Fluid bed dryer/granulator, blender, and material transfer system are all united in a single work platform.
Every connection is efficiently contained by means of PTK's own solution.
Raw material is fed and processed by the means of an IBC to IBC system.

Integrated computer control of the entire granulation line.

Closed material transfer.

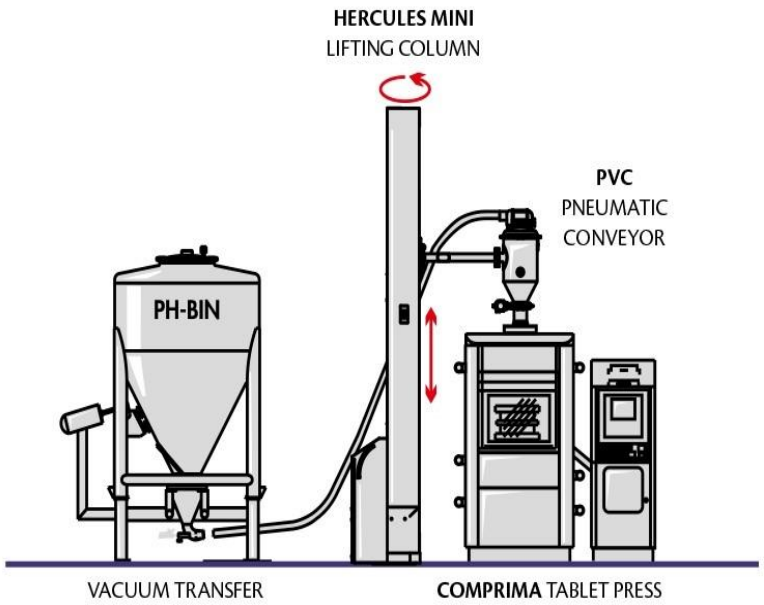
Air purge activated product filter.

Containment Process Flow

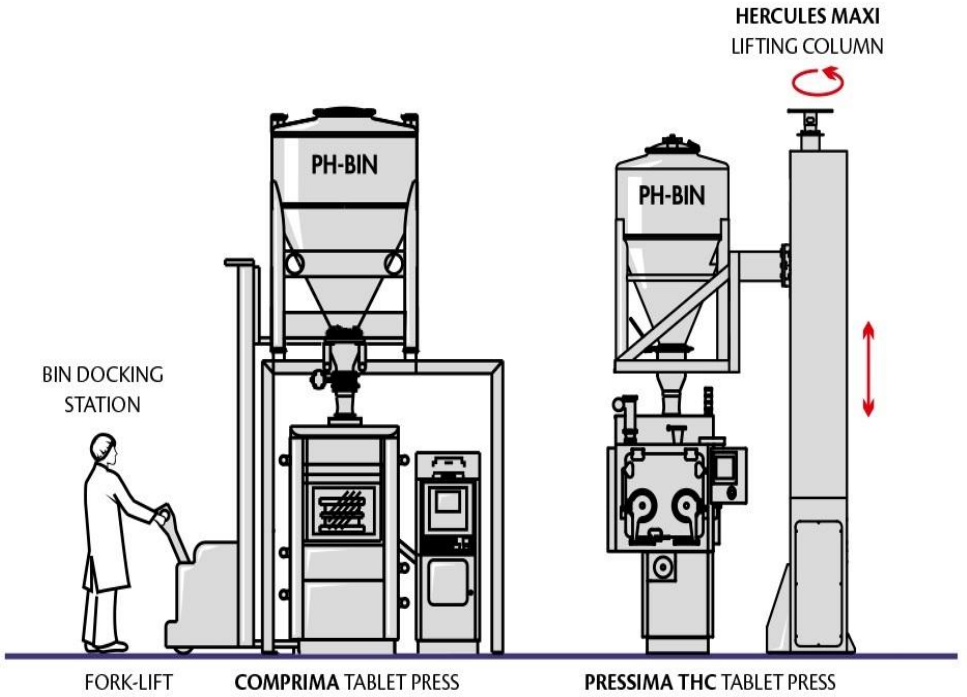


Closed system process & packaging

VACUUM FEEDING



GRAVITY FEEDING



Bin System Benefits

- Close containment
- Ease of cleaning
- Off-line storage and testing
- Quick batch changeover
- Repeatable, homogenous blending
- Modular design for ease of transport and versatility

IBCs are designed to be CIP-compatible with Wash Station


ProSys


FETTE
2000i WIP

Personal protection equipment and breathing air systems

- Where breathing air systems are used, these should be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility. Personnel should be appropriately trained and assessed in the use of these systems before they can enter the area. The breathing air systems should comprise a protective face mask, which should form an integral part of a protective suit

- for zones with lower contamination levels, a half-mask high efficiency particulate air filter (HEPA) cartridge respirator of N95-type paper filter mask may be acceptable.

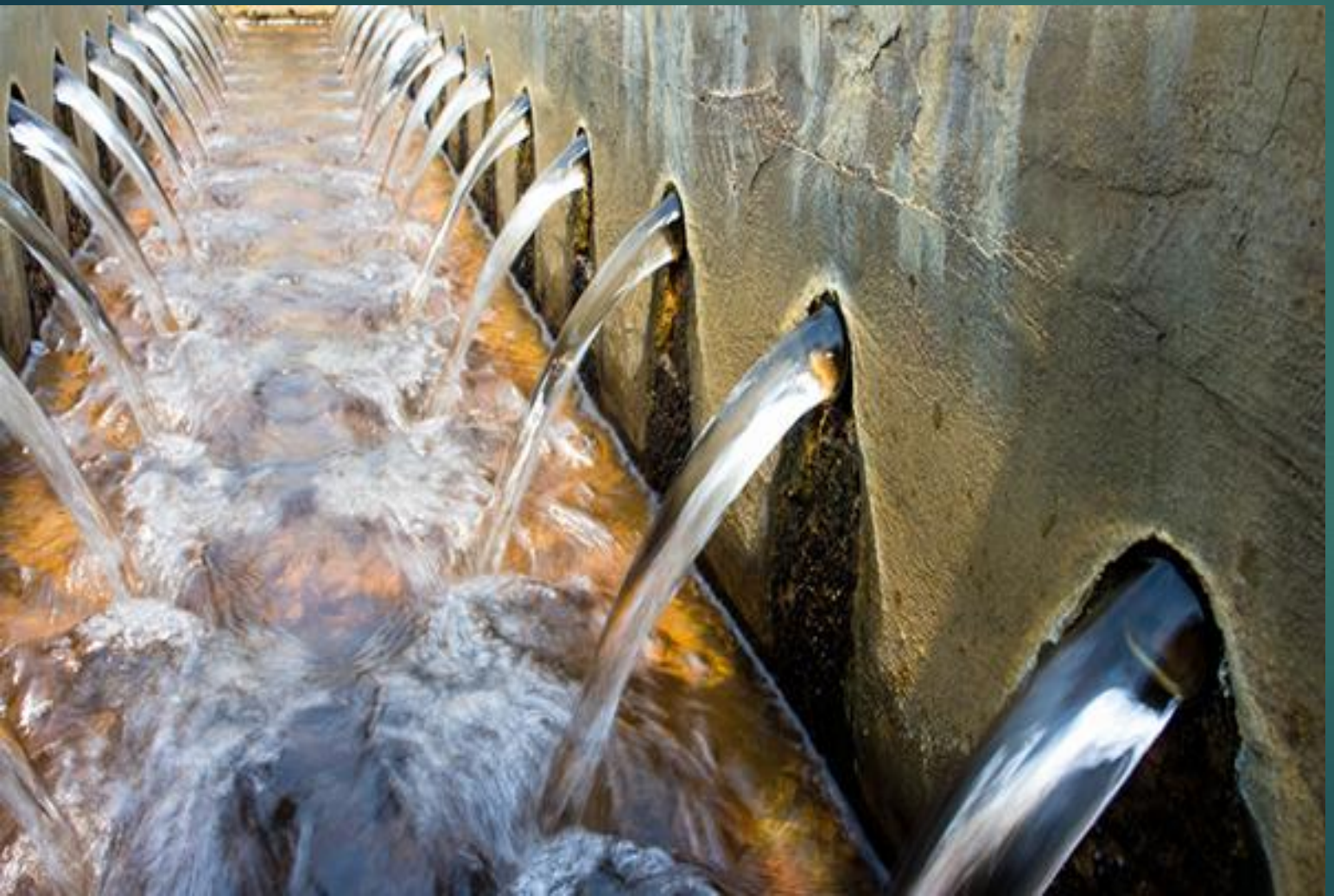
The breathing air systems could be any of the systems described below:

- a central air supply system which connects to the operator's face mask by means of flexible hoses and quick coupling sockets, also called an airline respirator (AR). The air connection should incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure a temperature and level of humidity that are comfortable for the operator. ***The air source could be a high pressure fan or an air compressor. If an air compressor is used, it should be of the oil-free type or have suitable oil removal filters fitted***

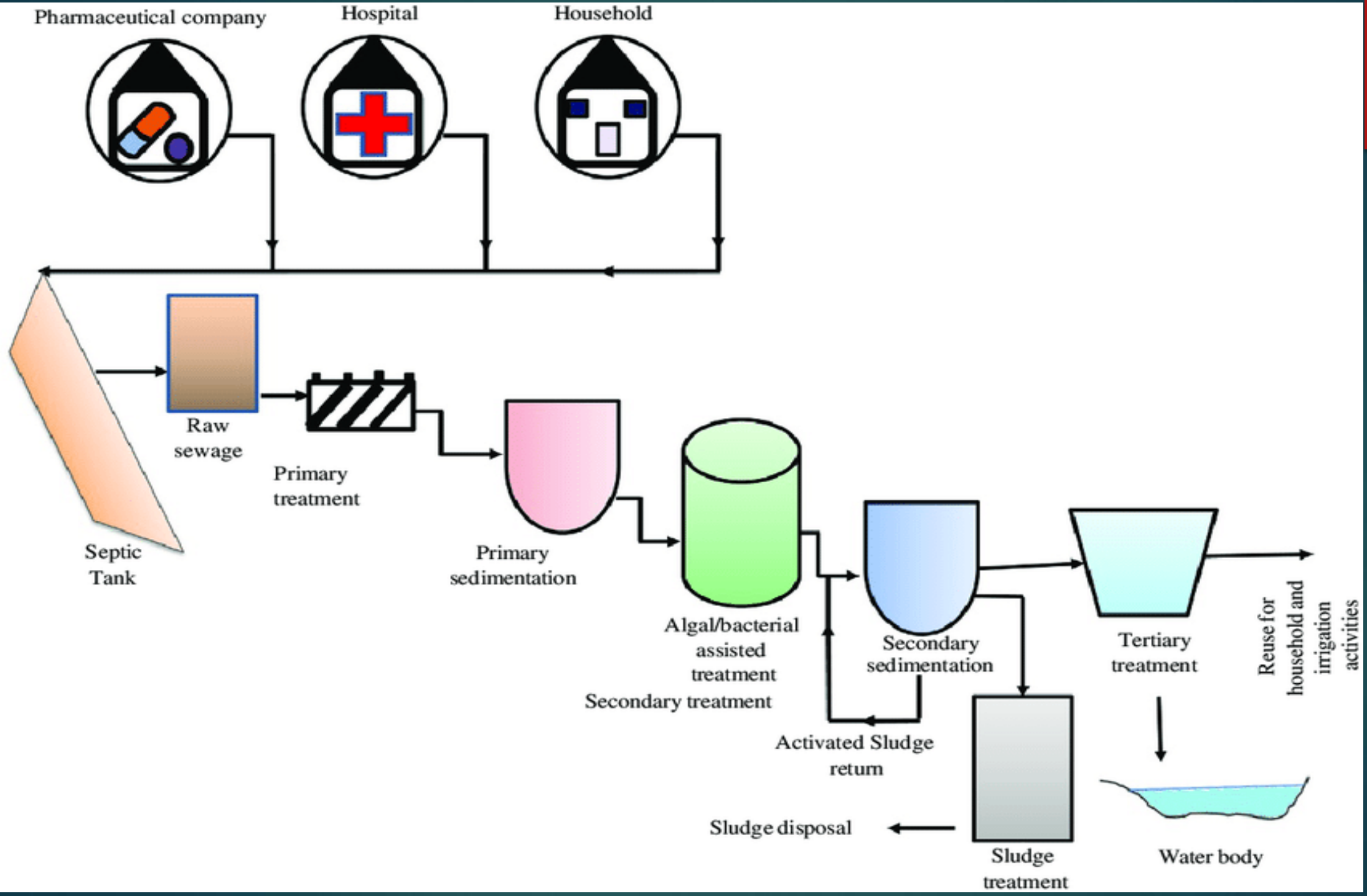
Environmental protection

- If liquid effluent poses a safety or contamination risk, the effluent ***should be treated*** before being discharged to a municipal drain

Effluent treatment



- Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.
- All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products


Pharmaceutical company
Hospital
Household
Raw sewage
Primary treatment
Septic Tank
Primary sedimentation
Algal/bacterial assisted treatment
Secondary treatment
Secondary sedimentation
Tertiary treatment
Reuse for household and irrigation activities
Activated Sludge return
Sludge disposal
Sludge treatment
Water body

Environmental protection

- Exhaust air filtration to ensure environmental protection
- BIBO System (**B**ag **I**n **B**ag **O**ut)

HVAC

- The Best Type to supply : **Fresh Air**
- For prevention of particle stickness : **V = 15 – 20 m/s**
- Pressure gauge must be exist for knowing when we should change the filter
- EXP : **2 years**
- Type of HVAC : **Stainless steel 304**
- Air Change for Class D : **10 – 25 Time/h**

For the pharmaceutical industry to do this, there must be an :

- **Efficient HVAC system** that controls and monitors elements like temperature, humidity, and pressure of various areas of pharmaceutical facilities
- **Efficient P.W system** that provide the qualified water for every process in pharmaceutical company

including production areas, laboratories, and storage areas.

HVAC = Heat Ventilation Air Conditioning
PW = Purified Water

HVAC (Heat Ventilation Air Conditioning)

HVAC (Heat Ventilation Air Conditioning)

- HVAC systems play an important role in keeping workers safe and products high in quality
- Heat or cool the air to maintain a desired temperature range
- Humidify or dehumidify the air, and maintain the moisture in the air.
- Filter the air to remove dust, microbes, and other contaminants
- Appropriate number of air changes to remove dust, microbes, and other contaminants
- Ventilate the air to ensure adequate air exchange and prevent stagnation
- Control the pressure to create positive or negative pressure zones for different areas

HVAC Systems Separated on 2 systems as below :

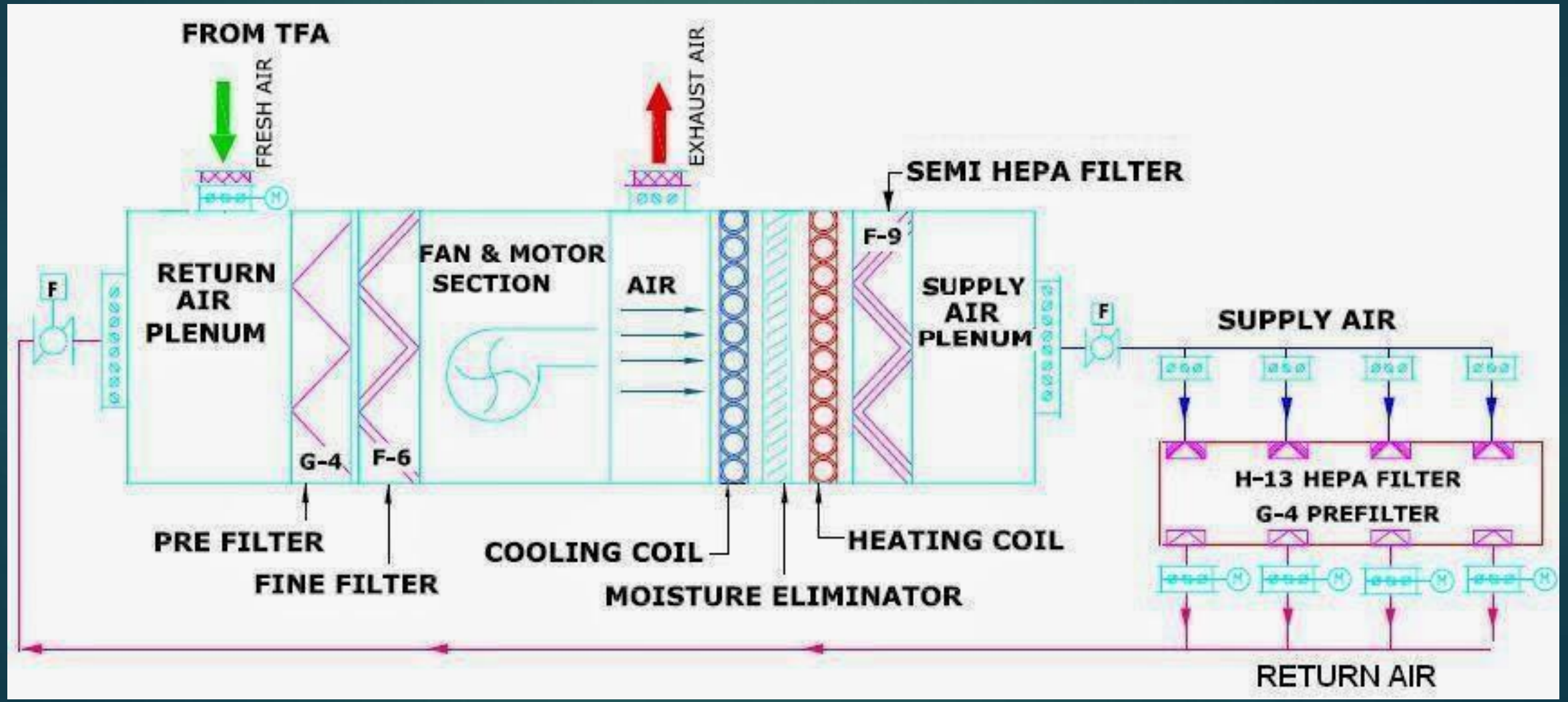
AHU (Air Handling Unit)

Exhaust System

AHU (Air Handling Unit)

Filters	Panel filters	Fans
Cooling Coils	Heater	Mixing Box
Dampers	Air intake	Humidifiers
Dehumidifiers	Control Gauge	Silencer
Blower	Ducts	Diffusers

AHU (Air Handling Unit)



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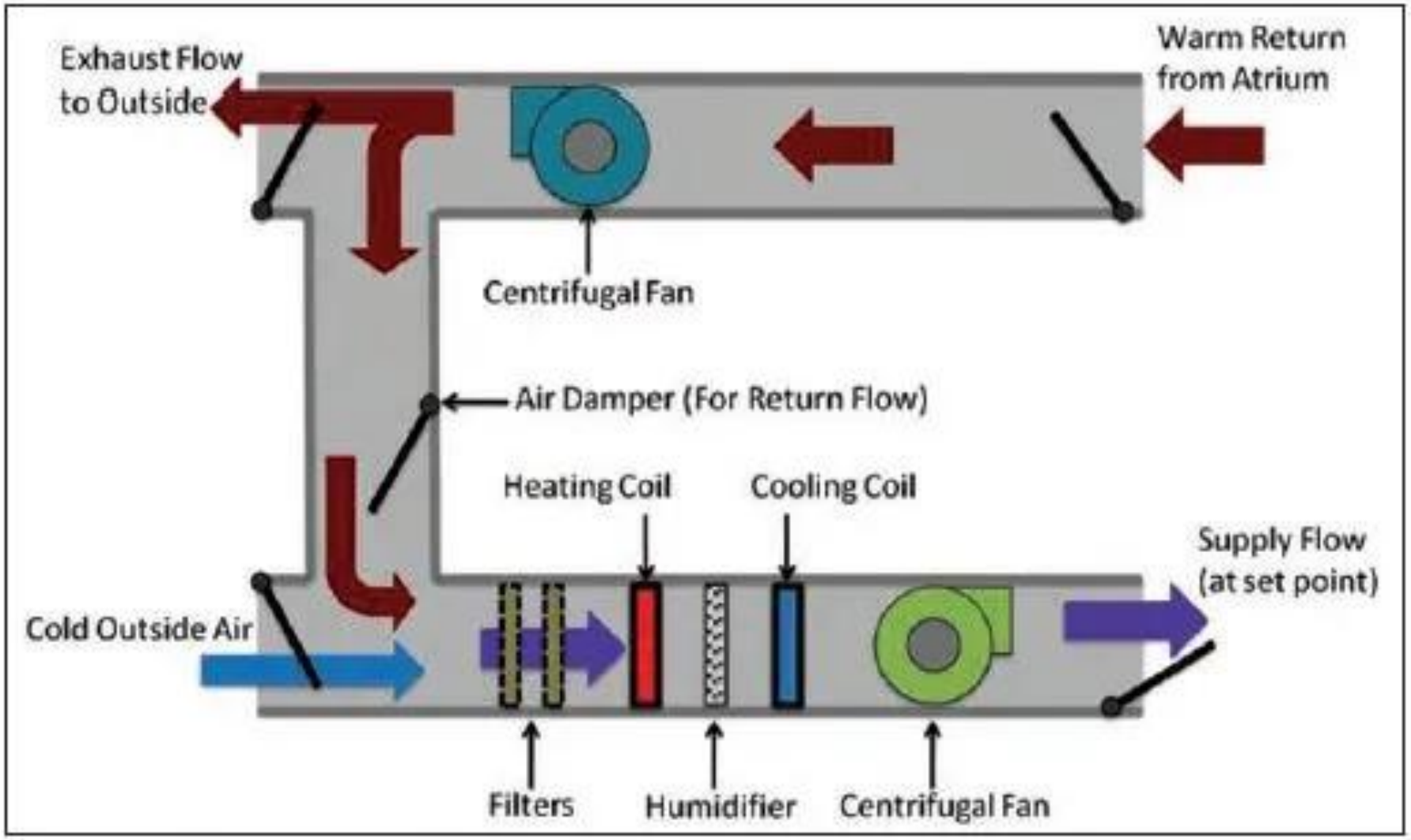
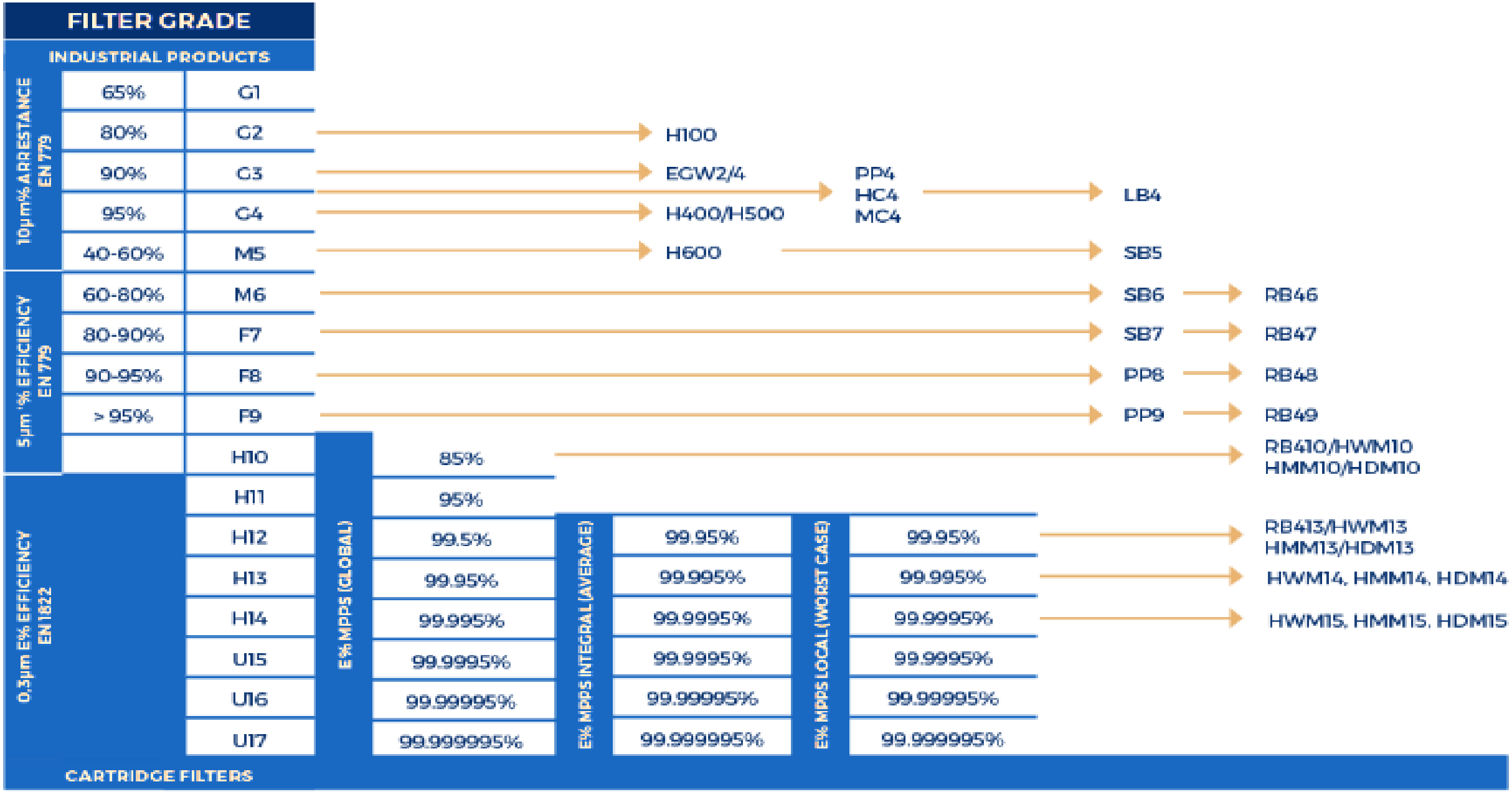


Fig. 1: Typical AHU layout...

Type of Filters



Classification (Clean Room)

- In pharmaceutical industries, two ranges of particle size are considered for classification of clean rooms :
- one is ≥0.5 micron
- other is ≥5.0 micron.

Grade	Maximum Allowable Particles/m^3			
	During Rest		During Operation	
	≥ 0.5µm	≥ 5µm	≥ 0.5µm	≥ 5µm
A	3500	0	3500	0
B	35,000	0	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	Not Defined	Not Defined

HVAC

- Air should be exhausted to the outside through HEPA filters and **not be recirculated except to the same area**, and provided that a further HEPA filtration stage is applied to the return air.

Diffuser

Swirl

Induction

Integrity Test

- 1. poly-alpha olefin (PAO)
- 2. shell ondina (EL) food quality mineral oil
- 3. dioctyl sebacate (DOS)
- 4. **di-2-ethyl hexyl sebacate (DEHS)**
- 5. dioctyl (2-ethyl hexyl) phthalate (DOP)

Thanks for your attention