تفريغ تعقيم

محاضرة: _____

الصيدلاني\ة: غروب طرابشة

The manufacture of medicines: product contamination and preservation

Chapter 17

Key facts:

يتم التحكم فيهم لـ:-

- The numbers and types of MOs present in nonsterile medicine are controlled both:

لحتى مايصير الدواء مصدر عدوى للمريض

1. to avoid the product becoming an infection hazard
2. and to minimize degradation of the active drug or the excipients

لتقليل تدهور المادة الفعالة او المادة المضافة

مثل قطرات العين

- Sterile medicines can be made in two ways:

1. Terminal sterilization: →

تعقيم الدواء بعد التعبئة

- Make sure to minimize contamination during manufacture, why?

2. Aseptic manufacture →

تعقيم لما يكون لحاله
لعدم بنجهم في بيئة معقمة

Key facts:

مراقبة روتينية لوجود البكتيريا والفطريات في :-(١-٦)

- pharmaceutical industry are routinely monitoring for levels of bacteria and fungi in the atmosphere and on working surfaces, equipment, personnel, and their protective clothing as well as in water and raw materials.

- Medicines and medical devices are made in "clean rooms" where the levels of MOs in the atmosphere are carefully controlled

هاي الغرف بيهارتها بارمه على عدد MO اللي بوجد بالهواء حتى نقلل خطر التلوث

- The manufacturer of a medicinal product is responsible for the quality of that product throughout its user life

الشركة المصنعة هي المسؤولة عن جودة المواد طول فترة استخدامه

Key facts

- Multiple use products must be formulated to prevent the growth of MOs that arise as contaminants during use
- The preservative should not interact with the formulation's components
- Knowledge of the concentration exponent of the biocide is important to appreciate the consequences of any loss of preservative

The bioburden of medicine must be controlled, why?

- Look for pg 162

Microbiological standards of medicines

1. Sterile medicine: those containing no living organisms at all

a. Injections

b. Those applied to eye

c. Irrigation solutions and those introduced into the ear may also be sterile

1. Nonsterile medicines:

- There is a control on the number and types of MOs that may be present

فيها حدد محدود من MO

Methods of making sterile products

1. Terminal sterilization: the product is made completely packed into its final container and then sterilized

- The preferred
- Safe → آمنة
- Reliable → موثوقة
- Cheaper → رخيصة
- Steam is the most commonly used method
- GMP to prevent introduction of bacteria during manufacture → dead bacteria are still pyrogenic → fail endotoxin test

مثل ما حكينا من قبل (تعقيم الدواء بعد التعبئة)
وصار الطريقة هي المفضلة

هتا لو ماتتا
تسبب الحمّى
معايير التصنيع الجيد

Methods of making sterile products

1. Aseptic manufacture: ingredients are individually sterilized and then mixed together using sterile equipment under conditions that do not allow the entry of MOs

- Majority of sterile products are made by this
- For heat sensitive medicines (ingredients or product as a whole , i.e. ophthalmic cream)

لضمان المعايير المناسبة في التصنيع

Strategies to assure appropriate standards:

- The use of high quality raw materials
- Environmental monitoring: sampling of air, equipment, work surfaces, water, personnel….results recorded and made available for inspectors

  اخذ عينات من:-

  تسجيل النتائج وتوفيرها للتفتيش
- Cleaning and sanitization with validation → منتظم ومثبت علمياً
- Avoidance of conditions suitable for microbial growth:
  - Storage of aqueous solutions at neutral pH in warm conditions (particular if contains prtn or CHO)
  - Water to be used for manufacturing is maintained at 80C and is passed through the pipes of distribution system at a flow rate of 1-2m/s to avoid formation of bacterial biofilms

    درجة حرارة المي لازم تكون

    لتجنب تكوين الاغشية الحيوية البكتيرية

Strategies to assure appropriate standards:

- Increasing use of policies designed to identify and protects stages in the manufacturing process where problem might arise:

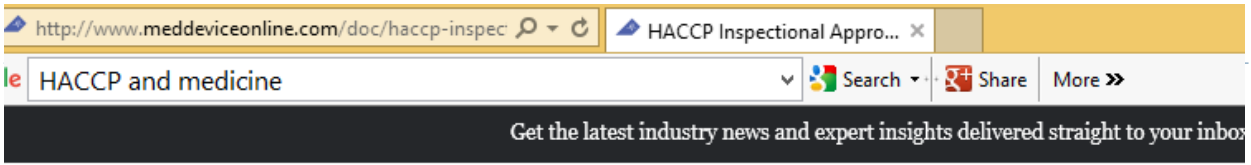
Hazard Analysis of Critical Control Points (HACCP)

استخدام سياسات خاصه لحمايه مراحل التصنيع اللي ممكن يصير فيها مشاكل

هاي السياسه اسمها وتعني:- تحليل المخاطر و نقاط التحكم الحرجه

فكرتها:- نحدد وين ممكن يصير تلوث او خطأ، ونراقب هاي النقاط بحذر

* تم استخدامه اولاً في الصناعات الغذائيه تكمله الان ممكن بدء في الصناعات الدوائيه



Before going into the reasons behind FDA's evaluation of this inspectional approach, having an understanding of HACCP would be appropriate.

What is HACCP?

HACCP is an acronym for Hazard Analysis and Critical Control Points. When used properly, the HACCP approach of evaluating your medical products and the production processes could provide you some assurance that you have determined the hazards associated with the device and its processes. It also shows that you have determined the critical control points and that you are able to control them.

HACCP is a preventive, not a reactive, management tool used to assure that the manufacturing process addresses all potential hazards of the device. HACCP is not a zero-risk system but is designed to minimize the risk of potential hazards.

There are seven principles to HACCP:

1. Identify critical control points (CCP) in the process.
2. Establish critical limits for preventive measures associated with each CCP identified.
3. Monitor each CCP. (Establish procedures for using monitoring results to adjust the process and maintain control.)
4. Establish corrective actions to be taken when a critical limit deviation occurs.
5. Establish a record-keeping system.
6. Establish verification procedures that the HACCP system is working correctly.

Strategies to assure appropriate standards:

- Appropriate use of chemical preservatives in medicines that are vulnerable to microbial spoilage
- Design of containers to avoid in-use product contamination
- Cream and ointment tubes rather than the wide-mouted jars that are vulnerable to contamination from the patient's fingers
- Single-dose eye drops to eliminate contamination from multi-dose eye drops
- Individual dose packing-blister packs- for tablets, capsules.

The Packaging Problem:

Jars or Tubes?

Sources of microbial contamination, and environmental monitoring

1. Atmosphere
2. water

- Of particular importance because:
- -Vectors which facilitate movement of MO from one place to another
- - Widespread use: serve as a cleaning agent, raw material
- - and serve as a medium in which MO can grow to high concentrations

3. Solid surface
4. Equipment
5. Personnel
6. Raw materials

Sources of microbial contamination, and environmental monitoring: The atmosphere

- MO in the air attached to dust particles
- Dust particles in pharmaceutical factory consist largely of skin flakes shed from personnel:
- Conc. is influenced by: no of operators and extent of movement around (100,000 particles/min for a motionless person to 10 million per minute for a vigorously active one
- Suitable clothing (gowns) that covers as much skin surface as possible
- High efficiency particulate air (HEPA) filters capable of removing 99.99% of 0.3 μm diameter particles

- Despite filtration, clean-room air is not sterile

حتى بوجود HEPA الا ان هواء الغرفه النظيفه مش معقم كما مر

FINE FILTER

PRE FILTER

HEPA FILTER

Industrial Filters For Pharmaceutical Industries


Clean Rooms
HEPA Filtration
Surgerical Suites
Pharmaceutical
Research
Biological

Sources of microbial contamination, and environmental monitoring: The atmosphere

- How to monitor levels of MOs in atmosphere:

1. Passive monitoring: uses settle plates- Petri dishes exposed to atmosphere in prescribed locations for a fixed time (4 hrs) → MO settles under gravity onto the agar surface → incubation & counting (using one for bacteria – Tryptone soya agar and one for fungi- Sabouraud dextrose agar)

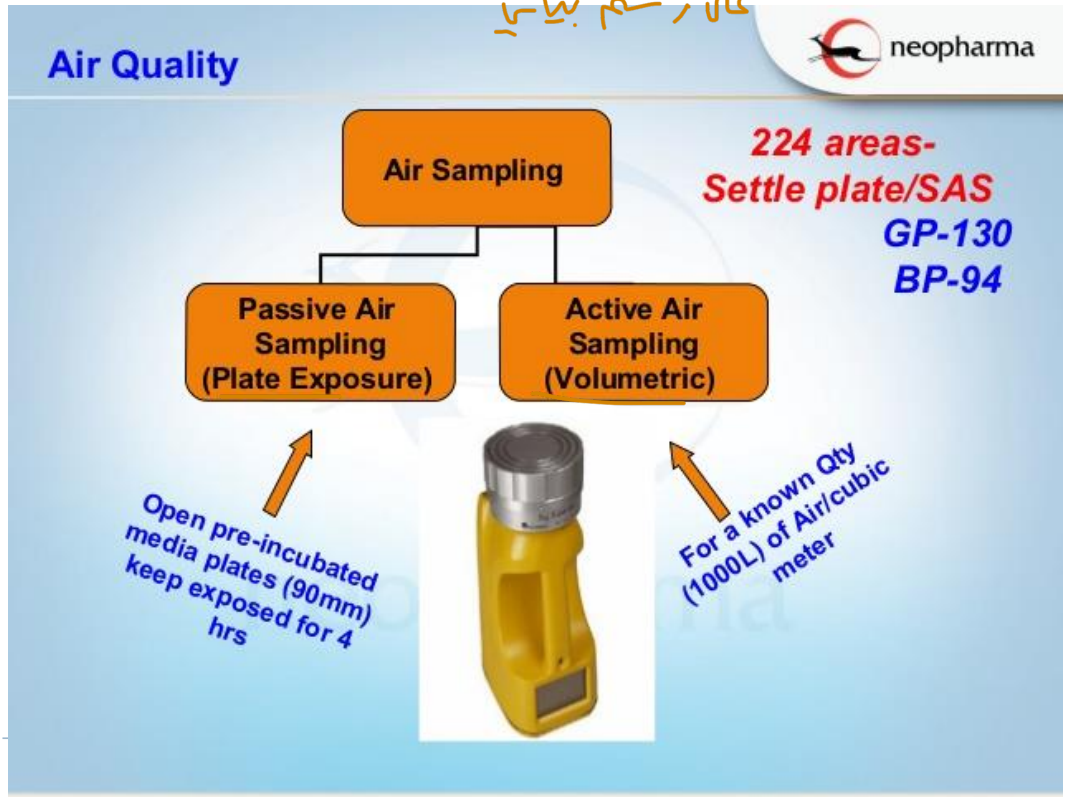
2. Active air sampling:

- Measure the concentration of organisms in the atmosphere in terms of number per liter

Sources of microbial contamination, and environmental monitoring: The atmosphere

- Colony count is plotted on a graph

بعد عد المستعمرات يتم رسم النتائج على رسم بياني



Sources of microbial contamination, and environmental monitoring:
Solid surfaces:

- Monitored by :

1. Sterile Swabs → نفس اللي استخدمناه بلاب اما يكرر
2. Contact plates (replicate organism detection and counting plates –Rodac) with small plates with convex surface that extends above the plate → for flat surfaces, pressure applied affect number, much easier than swab.

Sources of microbial contamination, and environmental monitoring:

Water

- Most commonly used raw material
- Extensively used for cleaning
- Most commonly found MOs in water are Gram-negative bacteria
- Chlorine in water limits CFU→ once removed by heating or deionization→ water become vulnerable to bacterial growth
- Stored water is likely to have a higher count than water that has recently been purified
- Pharmacopoeia specifications for purified water limit is 100 CFU/ml (membrane filtration)
- Water piping with sufficient access points for hypochlorite
- Flow rate within the pipe

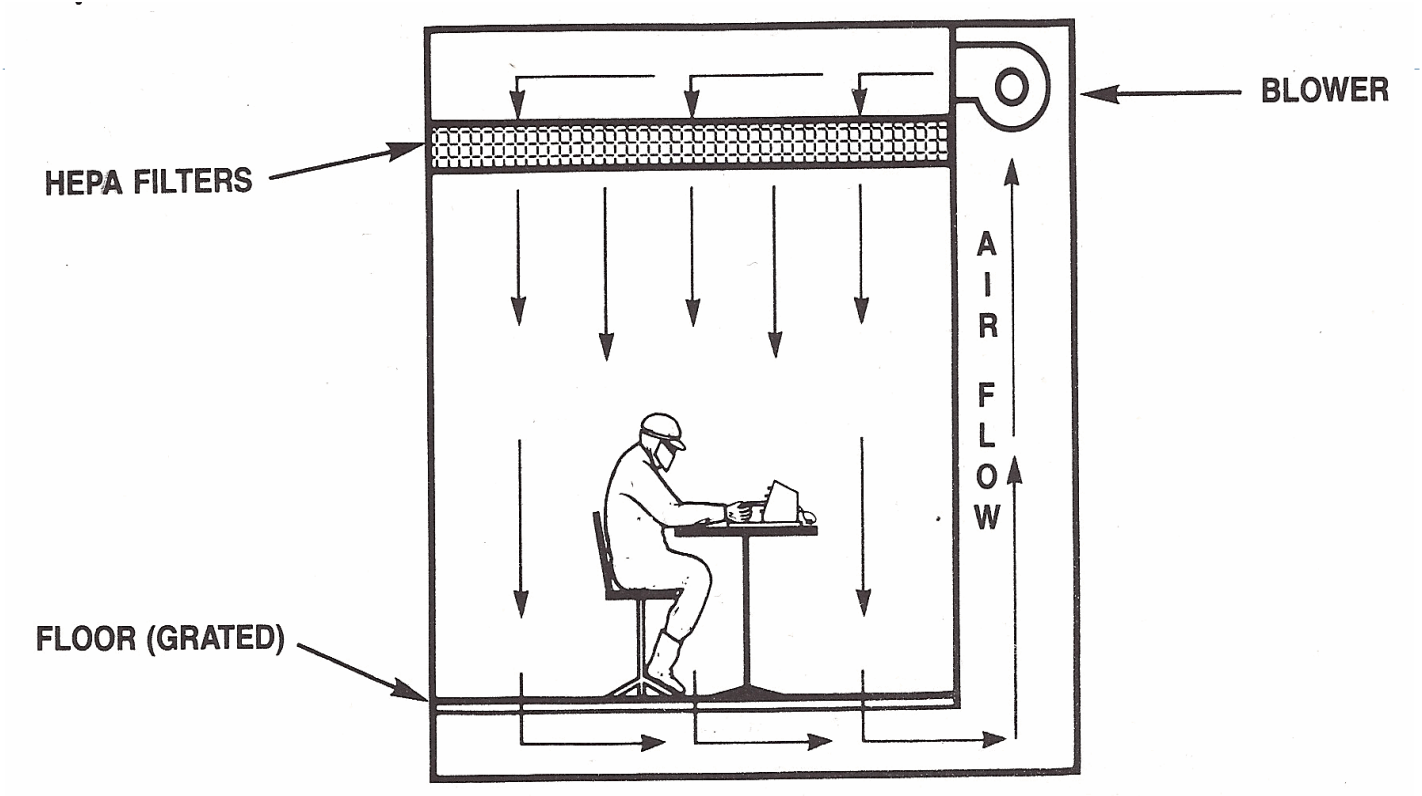
عند ازالة الكلور من الماء بعيرالماء معرضالنمو البكتيريا

لازم يكون فيه اماكن سهلة الوصول داخل انابيب الماء عشان نقدر نضيف مواد معقمه مثل hypochlorite

لازم ننتبه لسرعة تدفق الماء

Clean-room design and operation:

- Medicines and medical devices are manufactured in a "clean room"
- Clean room: an environment with a controlled low level of atmospheric contamination (dust, MOs or chemical vapors) احادة تلوثه
- Air is recirculated through HEPA filters which are located in the ceiling to give a vertical laminar (unidirectional) air flow through the room بشكل عامودي وصنعظم


HEPA FILTERS
BLOWER
AIR FLOW
FLOOR (GRATED)

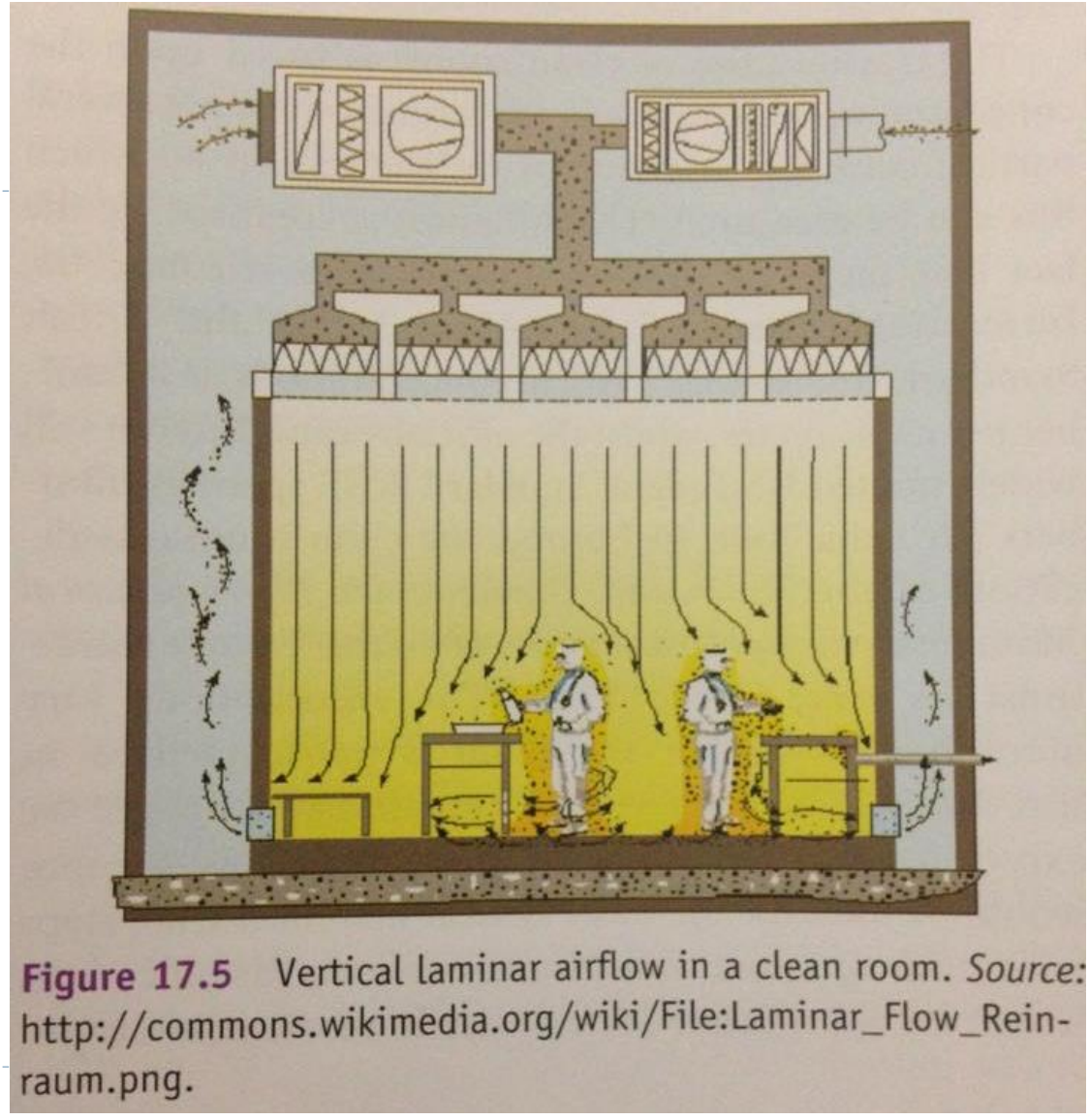
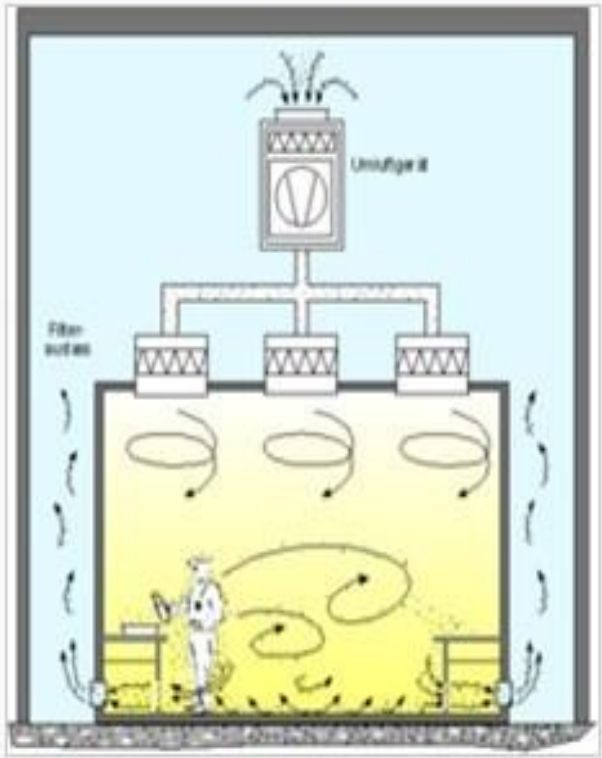
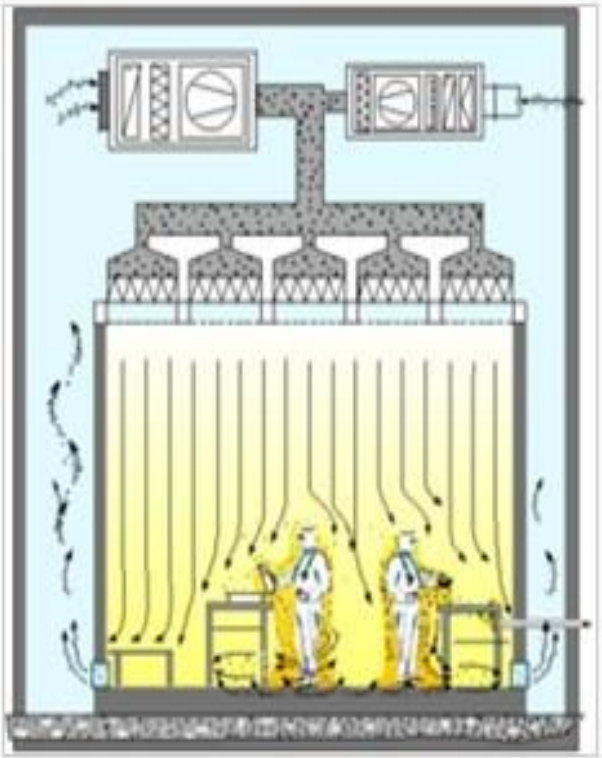


Figure 17.5 Vertical laminar airflow in a clean room. *Source:* http://commons.wikimedia.org/wiki/File:Laminar_Flow_Reinraum.png.

Air flow principles



Air flow pattern for "Turbulent Cleanroom"



Air flow pattern for "Laminar Flow Cleanroom"

Clean-room design and operation:

- Rooms dedicated to the most critical manufacturing steps like filling of sterile liquid into ampoules only accessible to operators who have gowned-up in outer rooms of low air quality and enter the critical areas through air locks
- Clean rooms operate at a slight positive pressure relative to surroundings→ contaminated air does not enter the clean room when the door is opened
- Also Temp & RH are controlled
- Surfaces are smooth, nonabsorbent, free of cracks and ledges and made up of material that could be disinfected (stainless steel)
- Clean rooms are expensive to build and operate→ use of isolators as an alternative

العوازل

- Isolators:

توفير حاجز يفصل بين العامل والجهاز

- Provide physical barrier between the operators and work place
- Capable of being gassed with hydrogen peroxide

يتم تعقيمها بواسطه غاز

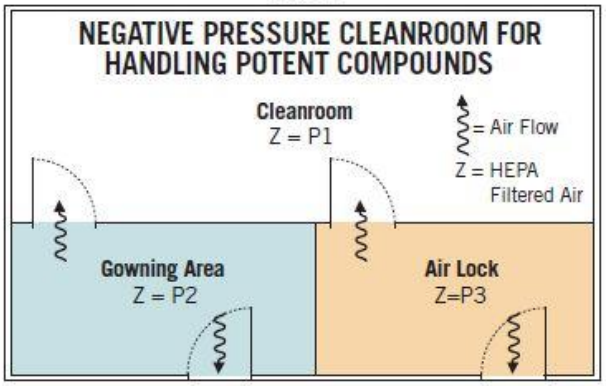
غرفة العزل الهوائي

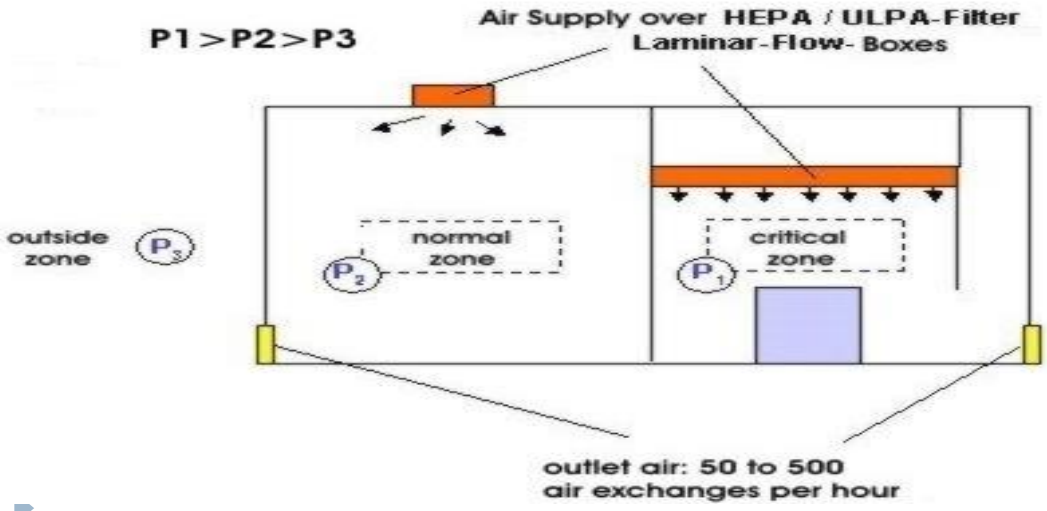
تستخدم كطبقة حماية عند الدخول والخروج لمنع دخول الملوثات

- Airlocks are used for cleanrooms as an additional line of defense against foreign particles.
- An **airlock** is a device which permits the passage of people and objects between a pressure vessel and its surroundings while minimizing the change of pressure in the vessel and loss of air from it. The lock consists of a small chamber with two airtight doors in series which do not open simultaneously.
- An airlock may be used for passage between environments of different gases rather than different pressures, to minimize or prevent the gases from mixing.

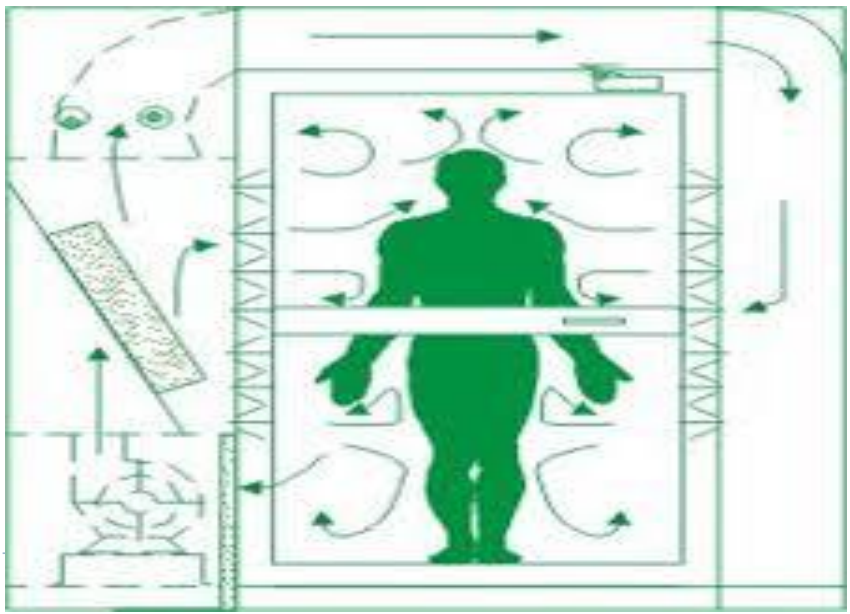
بين منطقتين بضغط مختلف

Figure 1


NEGATIVE PRESSURE CLEANROOM FOR HANDLING POTENT COMPOUNDS
Cleanroom
Z = P1
= Air Flow
Z = HEPA Filtered Air
Gowning Area
Z = P2
Air Lock
Z=P3
Particle Sciences


P1>P2>P3
Air Supply over HEPA / ULPA-Filter
Laminar-Flow- Boxes
outside zone
P3
normal zone
P2
critical zone
P1
outlet air: 50 to 500
air exchanges per hour


THINK
MAKE EVERY
MOVE A
SAFE ONE



Clean-room design and operation:

- Clean rooms classified according to their air quality (table 17.1)
- Different classification systems
- In Europe, the clean-room classification of the Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007-the "Orange Guide' must be used
- Based upon the concentration of particles in the air (particles counting instruments)
- Class A room for the most critical manufacturing steps for sterile products
- Rooms of lower classification for nonsterile medicines

Classification

- WHO Technical Report Series, No. 902, 2002 Annex 6

Comparison of different airborne particulate classification systems for clean areas[a]

WHO (GMP)	United States (209E)	United States (customary)	ISO/TC (209)	EEC (GMP)
Grade A	M 3.5	Class 100	ISO 5	Grade A
Grade B	M 3.5	Class 100	ISO 5	Grade B
Grade C	M 5.5	Class 10000	ISO 7	Grade C
Grade D	M 6.5	Class 100000	ISO 8	Grade D

EEC: European Commission; ISO/TC: International Organization for Standardization Technical Committee.

This comparison is defined based on at-rest limitations.

Class	maximum particles/m^3			
	At Rest	At Rest	In Operation	In Operation
	0.5 µm	5 µm	0.5 µm	5 µm
Class A	3,520	20	3,500	20
Class B	3,520	29	352,000	2,900
Class C	352,000	2,900	3,520,000	29,000
Class D	3,520,000	29,000	n/a	n/a

Grade	Activity
A	High Risk - filling, open vials, stopper bowls
B	Aseptic preparations
C	Clean area of rless critical operations
D	Clean area of rless critical operations

	Recommended limits for microbial contamination (a)			
GRADE	air sample cfu/m3	settle plates (diam. 90 mm), cfu/4 hours(b)	contact plates (diam.55 mm), cfu/plate	glove print. 5 fingers.cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

The protection of pharmaceutical products from microbial contamination:

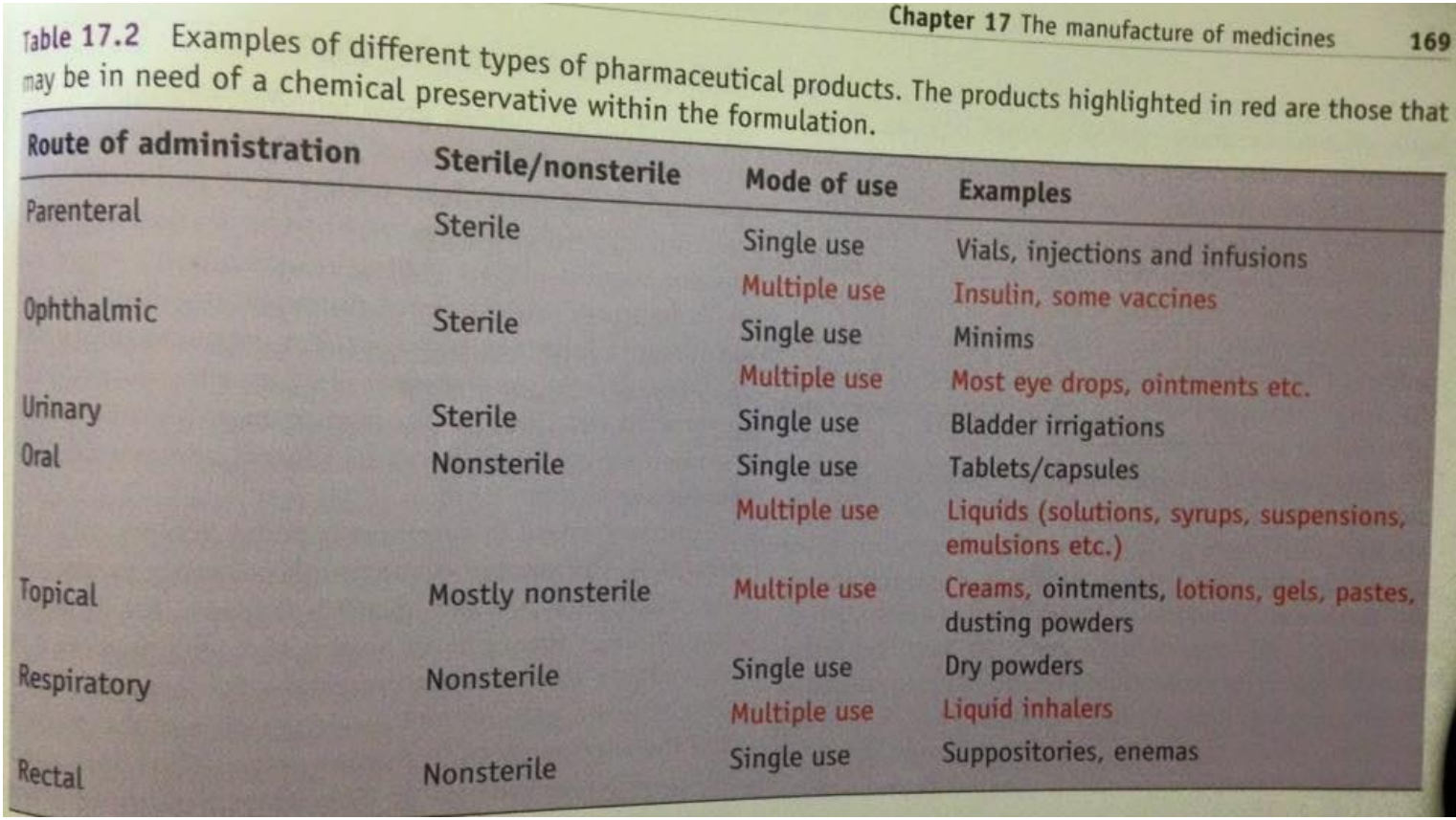


Table 17.2 Examples of different types of pharmaceutical products. The products highlighted in red are those that may be in need of a chemical preservative within the formulation.

Route of administration	Sterile/nonsterile	Mode of use	Examples
Parenteral	Sterile	Single use	Vials, injections and infusions
		Multiple use	Insulin, some vaccines
Ophthalmic	Sterile	Single use	Minims
		Multiple use	Most eye drops, ointments etc.
Urinary	Sterile	Single use	Bladder irrigations
Oral	Nonsterile	Single use	Tablets/capsules
		Multiple use	Liquids (solutions, syrups, suspensions, emulsions etc.)
Topical	Mostly nonsterile	Multiple use	Creams, ointments, lotions, gels, pastes, dusting powders
Respiratory	Nonsterile	Single use	Dry powders
		Multiple use	Liquid inhalers
Rectal	Nonsterile	Single use	Suppositories, enemas

The protection of pharmaceutical products from microbial contamination:

- Factors associated with the risk to the product during its use:

Refer to pg 169

The consequences of microbial contamination:

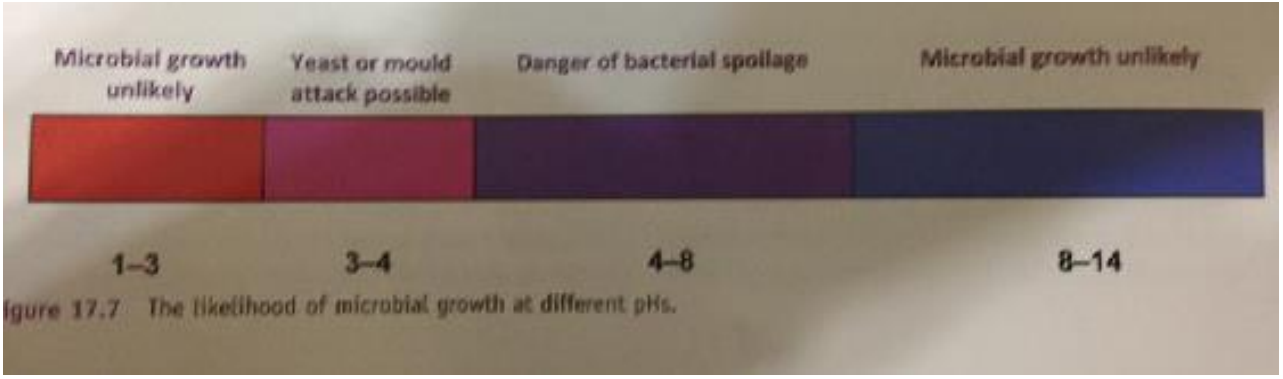
- Refer to pg 169-170

Fig. 1. Moisturizing cream contaminated with mold.
Credit: Kevin Roden, Thor Specialties

Methods for the protection of products from microbial spoilage

طرق حماية المنتجات من التلف الميكروبي

1. pH:



igure 17.7 The likelihood of microbial growth at different pHs.

- Extremes pH of values in food industry: pickles → مخلل
- With some household cleaning products
- Not useful in pharmaceuticals

high pH → Food industry
→ cleaning product

Methods for the protection of products from microbial spoilage

2. Water activity (Aw): the amount of un-complexed water available to MO for growth

- Aw= the ratio of the vapour pressure of the product/ vapour pressure of pure water
- Pure water Aw= 1

- Syrups contain high amount of water but most of it unavailable to the MO for growth
- Tablets tend to be safe from contamination → dry
- Non aqueous products: oils and ointments → no worry but be-carful storage in high humidity negate this protective effect

Water activity of some pharmaceutical products

product	Aw
Most creams	0.8-0.98
Syrup BP	0.86
Jam	0.7

Limits of water activity below which MO will not grow:

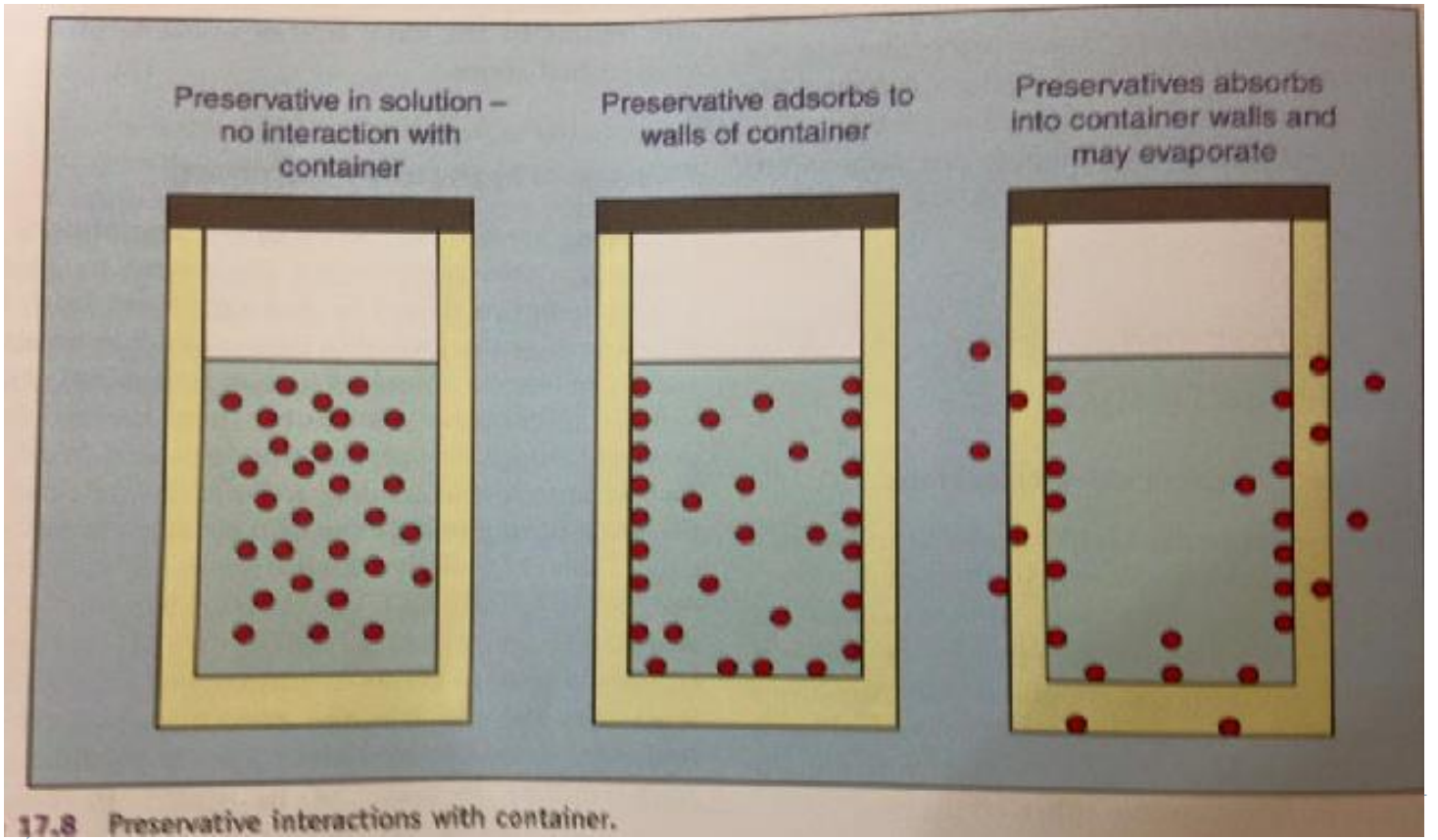
MO	Aw
Gram-negative bacteria	0.95
Gram-positive bacteria	0.90
yeasts	0.88
Some fungi	0.61

Methods for the protection of products from microbial spoilage

- The use of specific chemical preservatives:
- Multiple-use pharmaceutical products
- Should be part of the original design process
- Should not be included to mask poor manufacturing process or a deficient formulation
- Pay attention to:

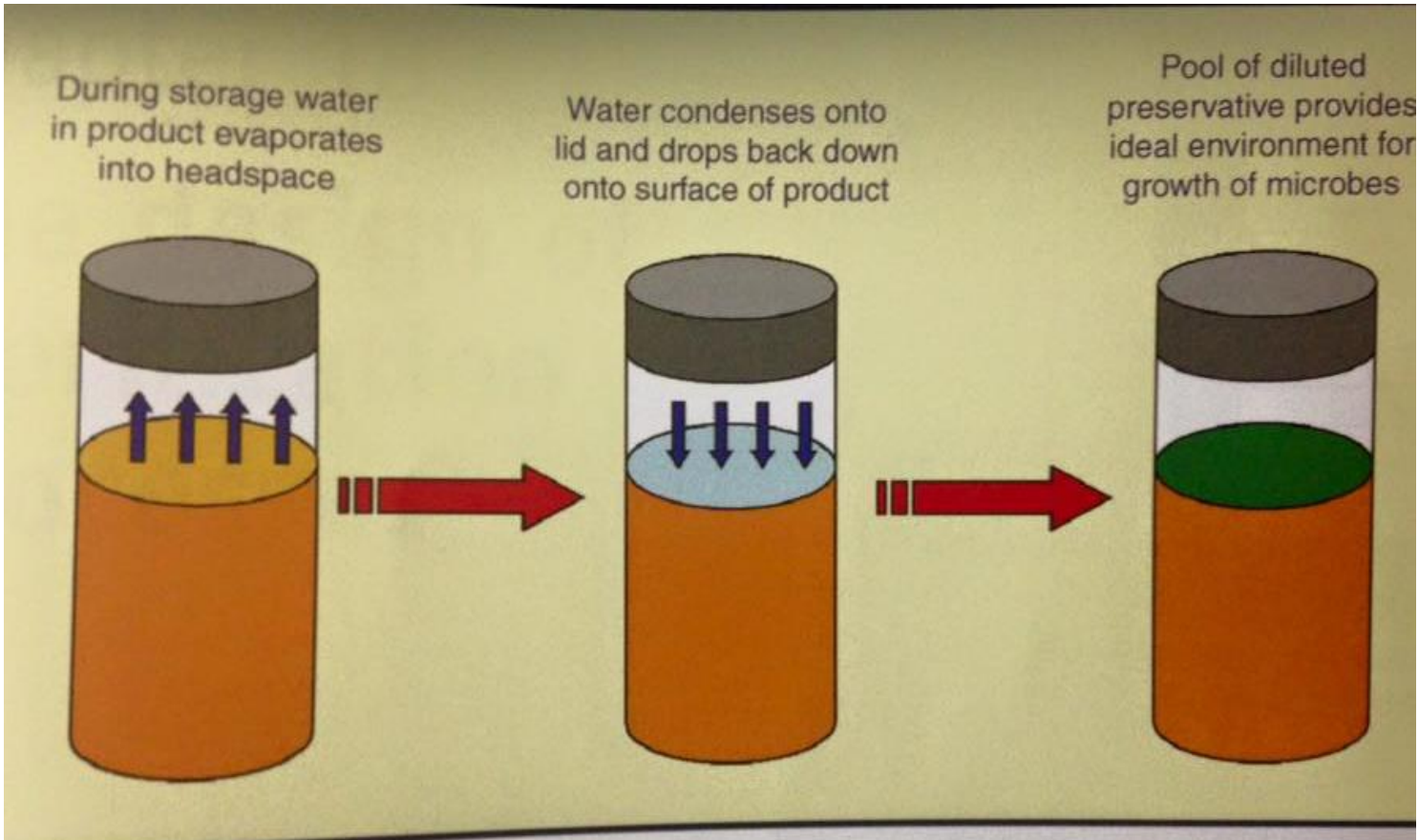
1. Interaction with specific chemicals: bronopol can complex with aluminum present in collapsible tubes (pg171)
2. Partitioning
3. Adsorption to suspended solids: paraben adsorb to calcium carbonate. Chlorhexidine to calamine.

Reasons for product failure
Loss of preservative: case study



17.8 Preservative interactions with container.

Loss of preservative: case study



7.9 The effect of fluctuating temperatures on the storage of a preserved product.

- Does this really matter?
- Concentration exponent vs biocidal activity

بعض المواد اذا قل تركيزها بنسبة بسيطة مجلن
فعاليتها تقل بنسبة عالية جدًا