The manufacture of medicines: product contamination and preservation

Chapter 17

Key facts:

2.mixing individually sterilized ingredients under sterile conditions
Why? To avoid high endotoxin levels from dead bacteria

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

ممنوع يكون non sterile ophthalmic and oral ولكن لازم يكونو
Controlحتى ما يعمل مشاكل صحيه و اقلل من degradationللماده الفعاله
مثلا suspentsionممكن تعمل emulsifying

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

- Sterile medicines can be made in two ways:

1. Terminal sterilization: امثله عليه
)outoclav;dry,radiation,microbiosidalgas,filtration)

- Make sure to minimize contamination during manufacture, why?

عندي اشي لسمه toxen load ,biogen loadهدول بقايا البكتيريا
الي تعمل immune responseوطبعا هدول لازم يكون بعدد معين
ممنوع يزيدو ولكن اذا كان endotoxinاعلى من المسموح هون
ممنوع ينزل على السوق

2. Aseptic manufacture

هون زي ما نعرف واكيد حفظناه قد ما نكرر انو كل اشي لازم يكون معقم

Key facts:

الشغل باللاب/وضع لازم يكون الجو فيه خالي من M.Oبكل اشي وبوخذ عينه من كل اشي حتلى من الهواء ()routinely monitoring

- 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

ومسوؤلClear room ;level M.O in atmosphere control عنه qualityولازم نكون محافظين على shelf lifeطول ما انو مسكر

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

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

اذا بدي اضل اوخذ جرعه من الشراب او المعلق وحتى امنع تكون contamination لازم احط preservative وهاد لازم يكون بقيم معينه وما يتفاعل مع مكونات active ingrediant

- Knowledge of the concentration exponent of the biocide is important to appreciate the consequences of any loss of preservative

مهم يكون exponent عالي لذلك اي زياده فيه رح يزيد الفعاليه واذا كان قليل رح ياثر على preservative بشكل كبير


أحضري أيتها الطاقه الدراسيه
يخرب بيتك هسقط

The bioburden of medicine must be controlled, why?

- Look for pg 162

حتى ما يؤذي ويشكل مشاكل وحتى ما يعمل لمستحضري degradation

Microbiological standards of medicines

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

- Injections
- Those applied to eye
- 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

The regulatory authorities do not condone a strategy whereby poor manufacturing practices are covered up by terminal sterilization or the use of preservative chemicals

Methods of making sterile products

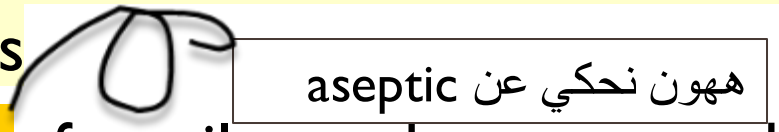
1. Terminal sterilization: the product is made completely packed into its final container and then sterilized

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

Pyrogen ; تسبب مشاكل بالمناعه
Endotoxin; تسب ارتفاع الحراره

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)

Strategies to assure appropriate standards:

- Cleaning and sanitization with validation

في اشياء محدده الي مسموح نستخدمها بالتنظيف وبعد ما نخلص تنظيف بوخذ عينه من اي مكان وبعمل testوبعيدين واو الطريقه الي استخدمناها بالتنظيف طلعت perfect

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

وظيفه المسؤول بتاصيدليه انو يدور على raw materialمنيح ويكون عندي regular environmentطبعا في اكثر من قصه وفي من هيئه الغذاء والدواء يجو يعملو تفتيش ويشوفو

- Avoidance of conditions suitable for microbial growth:
  - Storage of aqueous solutions at neutral pH in warm conditions (particular if contains prtn or CHO)

المي الي بالمصانع بتكون على درجه حراره 80 وهاي لا تسمح لنمو M.Oويكون يعبر بسرعه من الانابيب من مكان المعالجه لتصنيع ;لمنع تكون نقاط راده من الماء وتسمح بنمو M.O

- 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

Raw material specification both chemical and minimum levels of microbial contamination
- Precisely written procedure together with validation to confirm that the procedures effectively control levels of microbial contamination

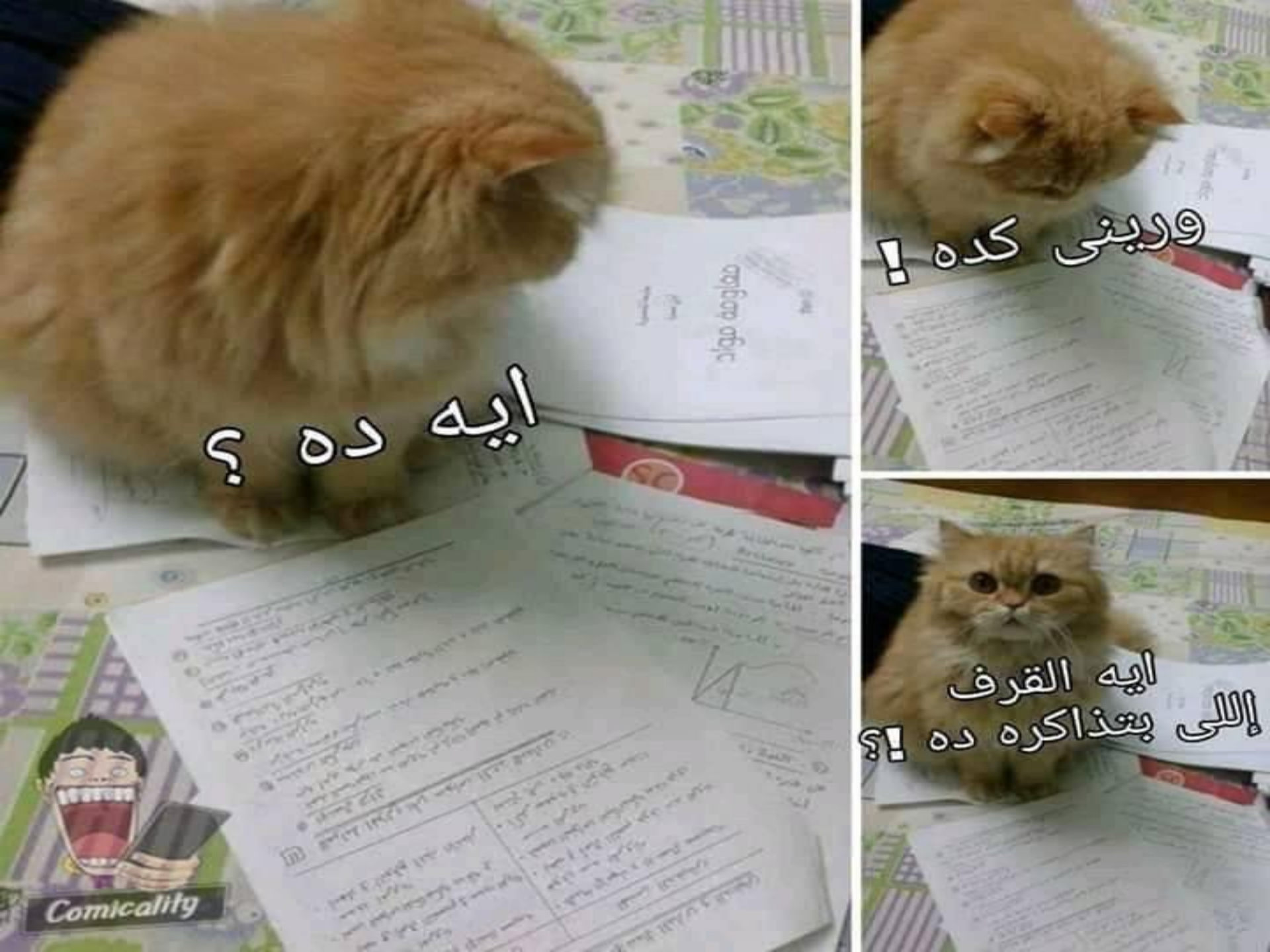
Strategies to assure appropriate standards:

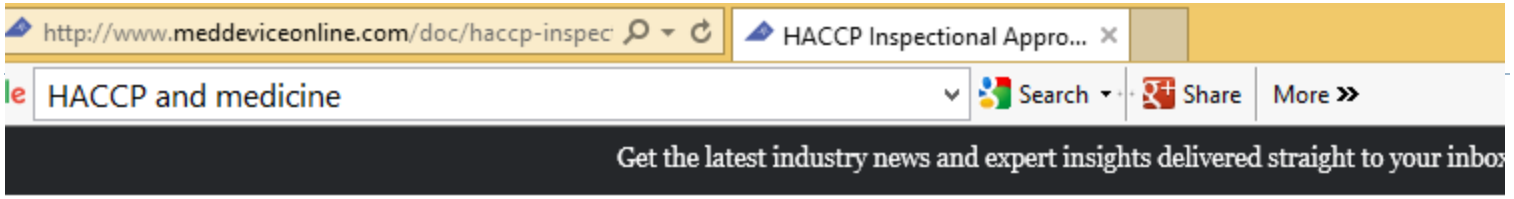
- Increasing use of policies designed to identify and protects stages in the manufacturing process where problem might arise:

Hazard Analysis of Critical Control Points (HACCP)

هدول بيشيكو على كل المصنع شبر شبر وكل زاويا حتى يتاكدو اصحاب المصانع انو مصانعهم معقمه بشكل ممتاز وطبعاااا يدفعو مصاري الهم حتى يجو

HACCP would identify the final stage in which aseptically manufactured medicine is filled into open vials or ampoules as one of the most vulnerable points bec the liquid is no longer enclosed in a pipe but exposed to possible contamination from atmosphere


ايه ده ؟
وريني كده !
ايه القرف
إللى بتذاكره ده !؟
Comicality



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.

ما يفضل استخدام jarولكن tubeاحسن عشان اقلل من contamination

هسا singleما فيها preservativeعلى عكس multi

The Packaging Problem:

Jars or Tubes?

Sources of microbial contamination, and environmental monitoring

Each represents a potential source of contamination

Atmosphere

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
- لان استخدامهم ضروري ما بقدر امنع الهواء من المصانع نموت
- - and serve as a medium in which MO can grow to high concentrations

Solid surface

Equipment

Personnel

Raw materials(الي ندخل لتصنيع)

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:

كل ما زاد operator كل ما زاد contamination

- 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

على الرغم من انو يتخلص من 9.99 الميه من particle الي اني ما بقدر احكي انو الهواء steril

Bacteria, protozoa and viruses do not normally exist in the air as individual cells or clumps of cells. Fungal spores are often released into the air from the fruiting body of the a mould.

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Microorganism do not grow –reproduce- in air bec it is too dry. Indeed many organisms die on prolonged suspension in the atmosphere as a result of drying, oxygen toxicity (in case of anaerobes) or even photosensitivity

Generally it is gram positive bacteria and spore forming organism (of both bacteria and fungi) that survive drying best. Gram negative bacteria normally arise in aqeous environment and are much more sensitive to desication

Despite filtration, clean-room air is not sterile

There is usually a low level of microbial contamination validation refers to establishing documented evidence that a process or system, when operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its pre-determined specifications and quality attributes


اجمد كدا..لا بص متعيطش!

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:

- 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)

- Active air sampling:

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

Settle plates: are simply petri dishes exposed to the atmosphere in prescribed locations for a fixed time typically four hours so that orgabisms can settle under gravity onto the moist surface of the agar and develop into visible countable colonies after incubation.
The

Passive

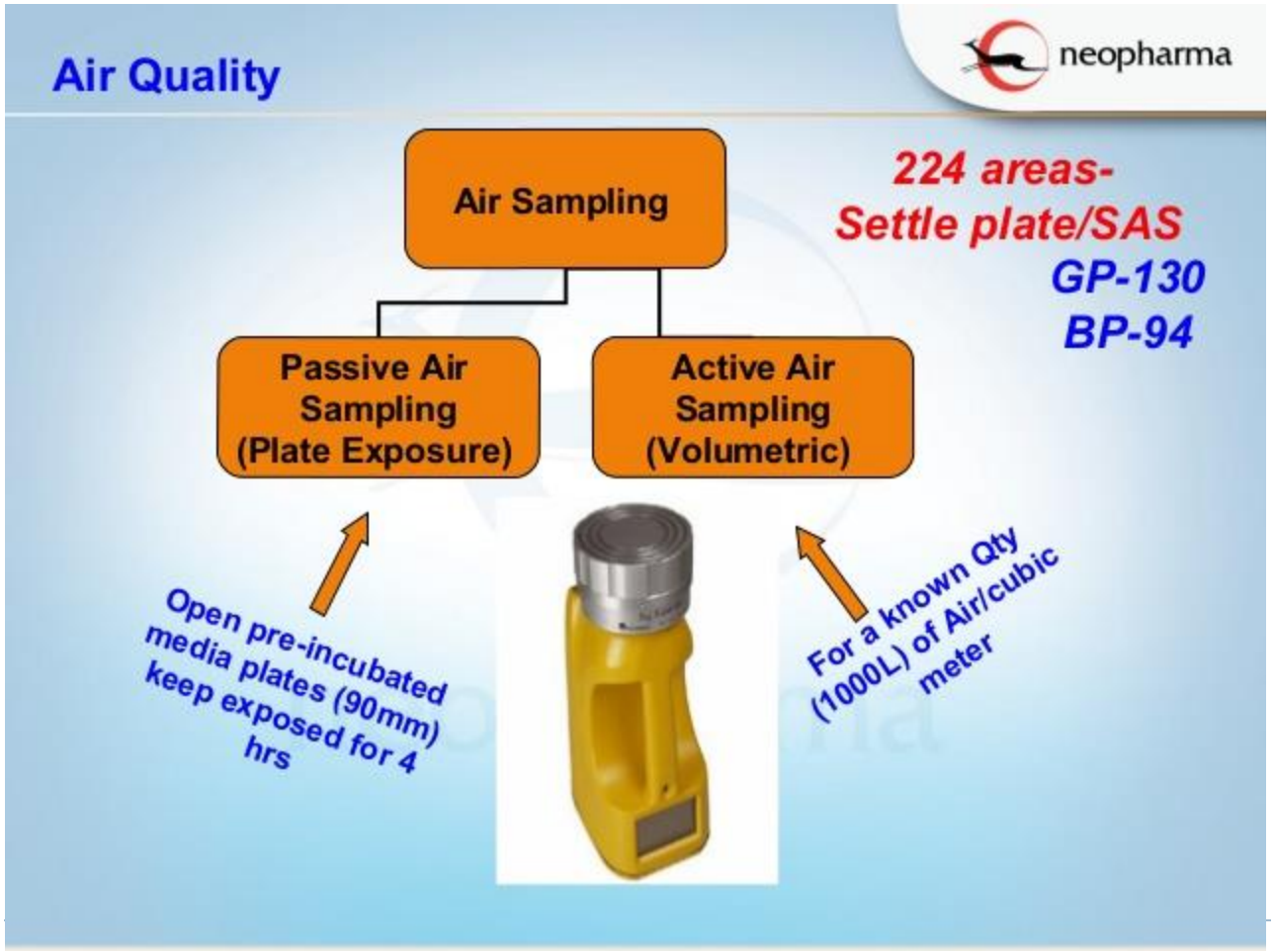
بغرفه الخلايا نجيب petri يكون steril وبفتحه وحطه ب
certain location ل 4 ساعات وبعدين اسكره واحطه
incubation ب وبشوف في M.O ولا لا

Active

جهاز يشفط volumej معين الهواء وبعدين بعرضه ل ال petri dish
وبتركه لمده معينه واخر اشي بحطه ب incupation
والحلو فيه بقدر اربط ال volume مع M.O

Sources of microbial contamination, and environmental monitoring: The atmosphere

- Colony count is plotted on a graph



Passive monitoring: settle plate→ the volume of air passing over the plate will influence the count so high air turbulence location as doors give high cout…in a sterile manufacturing area there would be normally no colonies arising at all following a four hour exposure
Active air sampling: measure the concentration of mo in the atmosphere in terms of numbers per liter→ have pump that passes air through a slit and causes the suspended particles to impinge onto the surface of the agar in an open petri dish or plastic strip→ more reproducible and reliable results bec a known volume of air is sampled→ expensive ,bulky instrument, difficult to disinfect.