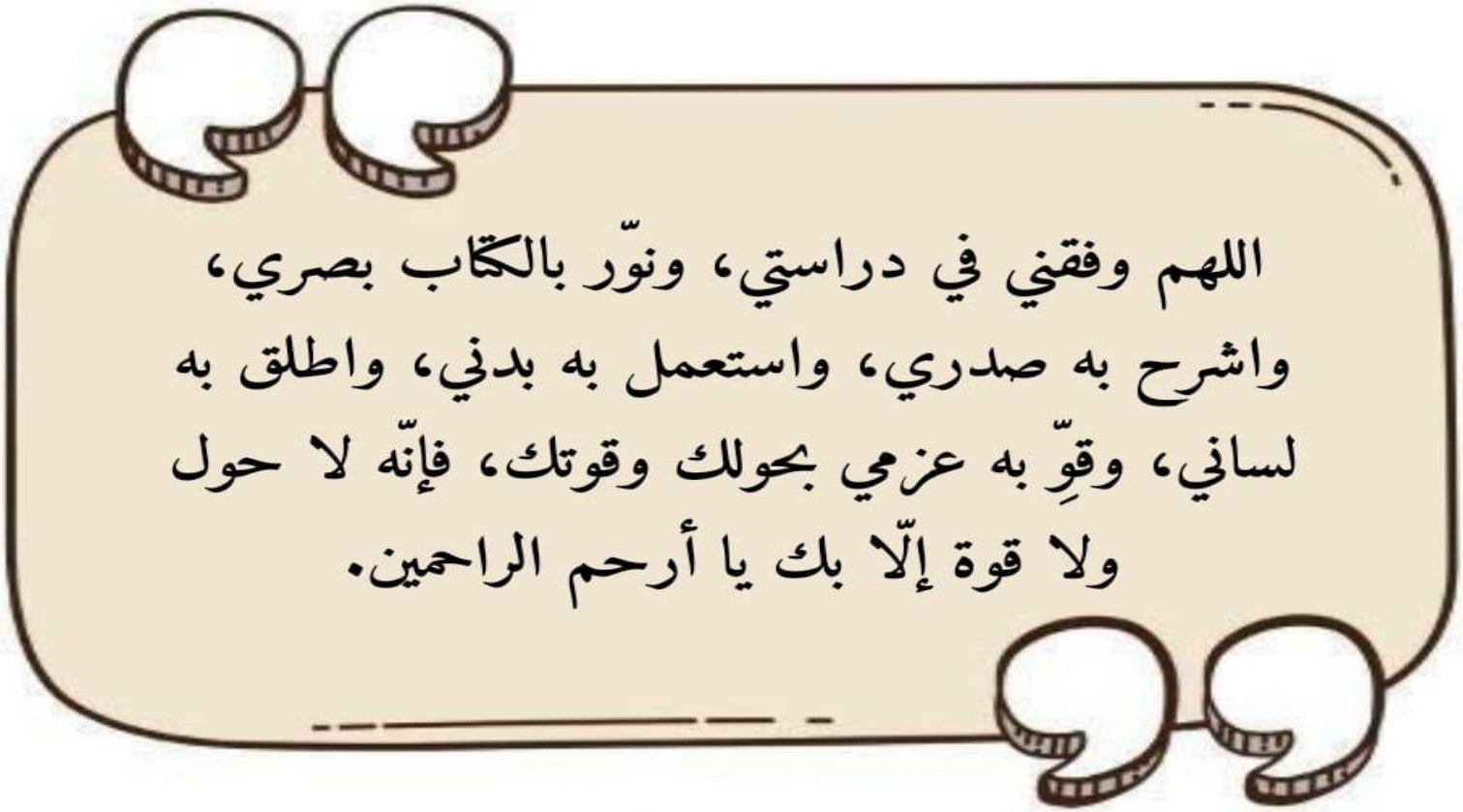
MIRACLE Academy

التعقيم والتصنيع المعقم

لجان الدُّفعات


اللهم وفقني في دراستي، ونوّر بالكتاب بصري،
واشرح به صدري، واستعمل به بدني، واطلق به
لساني، وقوِّ به عزمي بحولك وقوتك، فإنّه لا حول
ولا قوة إلّا بك يا أرحم الراحمين.

وفقكم الله...

Filtration sterilization and aseptic manufacture

- Many drugs and pharmaceutical materials are damaged both by heat and radiation and are not suitable for gaseous sterilization either
- drugs containing proteins (for example, monoclonal antibodies, interferons) and other biological polymers (such as polysaccharide- or DNA-vaccines→ the only sterilization option is to use filtration to physically remove the contaminating microorganisms and then manufacture the product aseptically using sterile ingredients

- ال filtration هي بتعمل physically removal يعني لا تقتل ، بتعمل فقط removing حيث مثلا ال gaseous sterilization بتعمل alkylation ف طبعا بحالة لما يكون عنا بروتين مستحيل يزبط ال gaseous sterilization لانه رح يصير carcinogenic

- هسا شغلة ثانية انه ال Filtration يقتل ال MO العايش و الميت لكن ال Radiation يقتل ال Cell اللي عايشة و ال Dead cell بتضل بال Product

Filtration sterilization and aseptic manufacture

- filters are available for the removal of:

- bacteria
- yeasts and mould spores
- viruses
- and they can even remove pyrogens (endotoxins),

- An advantage afforded by filtration is that the method physically removes both living and dead cells from solution and in this respect it differs from heat and radiation methods where the dead cells remain in the product and possibly contribute to the pyrogen load.

so filtration is a common means of sterilizing injections and eye drops as well as air and other gases.

تستخدم ال Filtration method لإزالة :

1) Bacteria
2) Yeast and mould spores
3) Viruses

و أهم نقطة انه بتزيل ال Pyrogens اللي هي ال Endotoxins حيث ان ال radiation بخلي الخلايا الميتة و هاد بزيد من احتمالية ال Pyrogen load
فالحلو بال filtration انه بشيل ال pyrogens
وكمان بنستخدمه لتعقيم الهوا بالمصانع اللي هو ال HEPA filter

Pyrogen load:

ال pyrogen مادة موجودة بال bacterium مسموح بعدد معين فيها لو تم تجاوزه رح يصير المنتج غير صالح للإستخدام و رح يعطي الجسم immunological response

Filtration sterilization and aseptic manufacture

- **Filtration is not a terminal sterilization process,**
- **Solutions that are filter sterilized still have to be dispensed into their containers and the operation being undertaken in a class A atmosphere**
- **Media fill test for the same factory filling line that would be used to fill the product**

Slide note:

there is the opportunity for contamination to arise during this process. To confirm the suitability of the environment for the purpose, sterile products' manufacturers are required to undertake process simulations (commonly known as 'media fills') in which the same factory filling line that would be used to fill the product in question is first tested by dispensing sterile culture medium into, typically, 5000–10 000 sterile containers. These are sealed and incubated, and should, ideally, yield none showing growth; one positive container would be deemed by the regulatory authorities to be sufficient to justify an investigation and two would require the whole process to be repeated. Because filtration is inherently less reliable than terminal sterilization processes, products sterilized in this way must be subjected to a test for sterility.

- ال filtration ليس Terminal sterilization يعني بس بتعمل removing .

- المحلول اللي بنفلتره لازم لسا ضل Process نحطه بال container فلازم يكون sterilized فعملية وضعه داخل ال container لازم تكون هي العملية تحت class A atm

بالمصانع بكون في Classes لل atm عشان نحقق اعلى sterility بدنا ياها

Media fill test:

- اختبار التعبئة للمستحضر ، هو انه بنجيب media معقمة و بنعمللها incubation اذا في نمو لل MO يعني بكون في خلل بالهوا او ال Instrument فهدفنا نتأكد ان الجهاز بعمل تعبئة لل Sterile product صح و تمام فبنروح بنعمل ال test

- ال media عائدة على ال MO

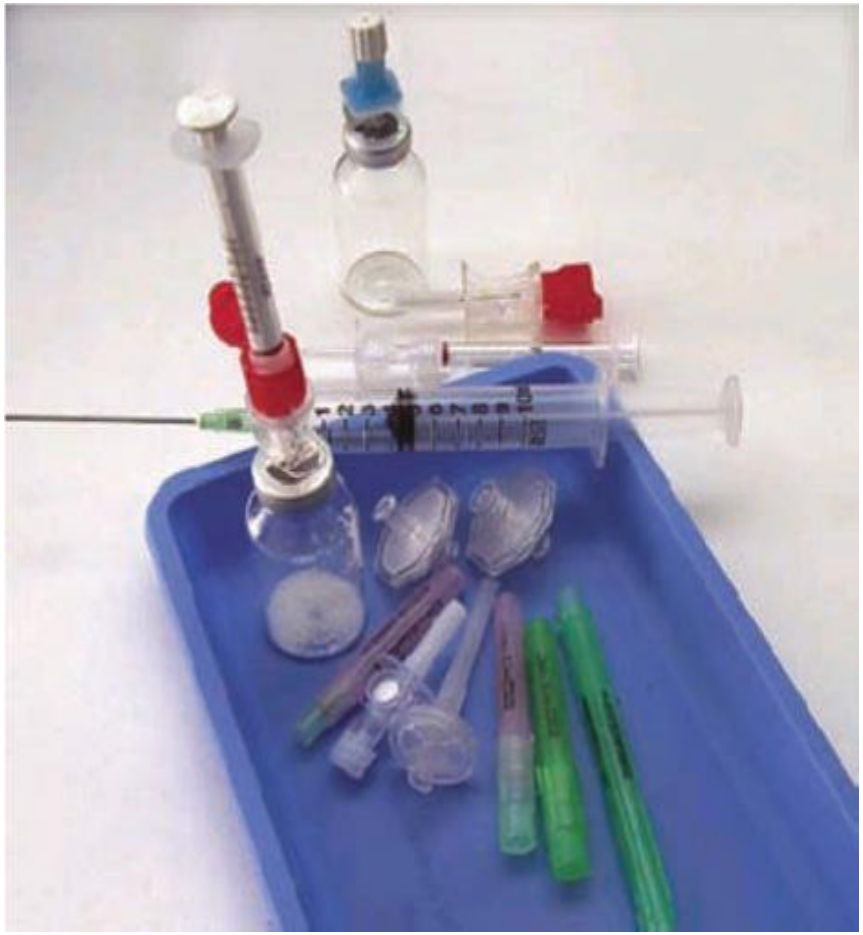
Filtration sterilization and aseptic manufacture

- Sterilization-grade filters are made of cellulose derivatives and polymers like PTFE, polycarbonate and polyethersulfone

هي شكل ال filters و بكون حجمها صغير

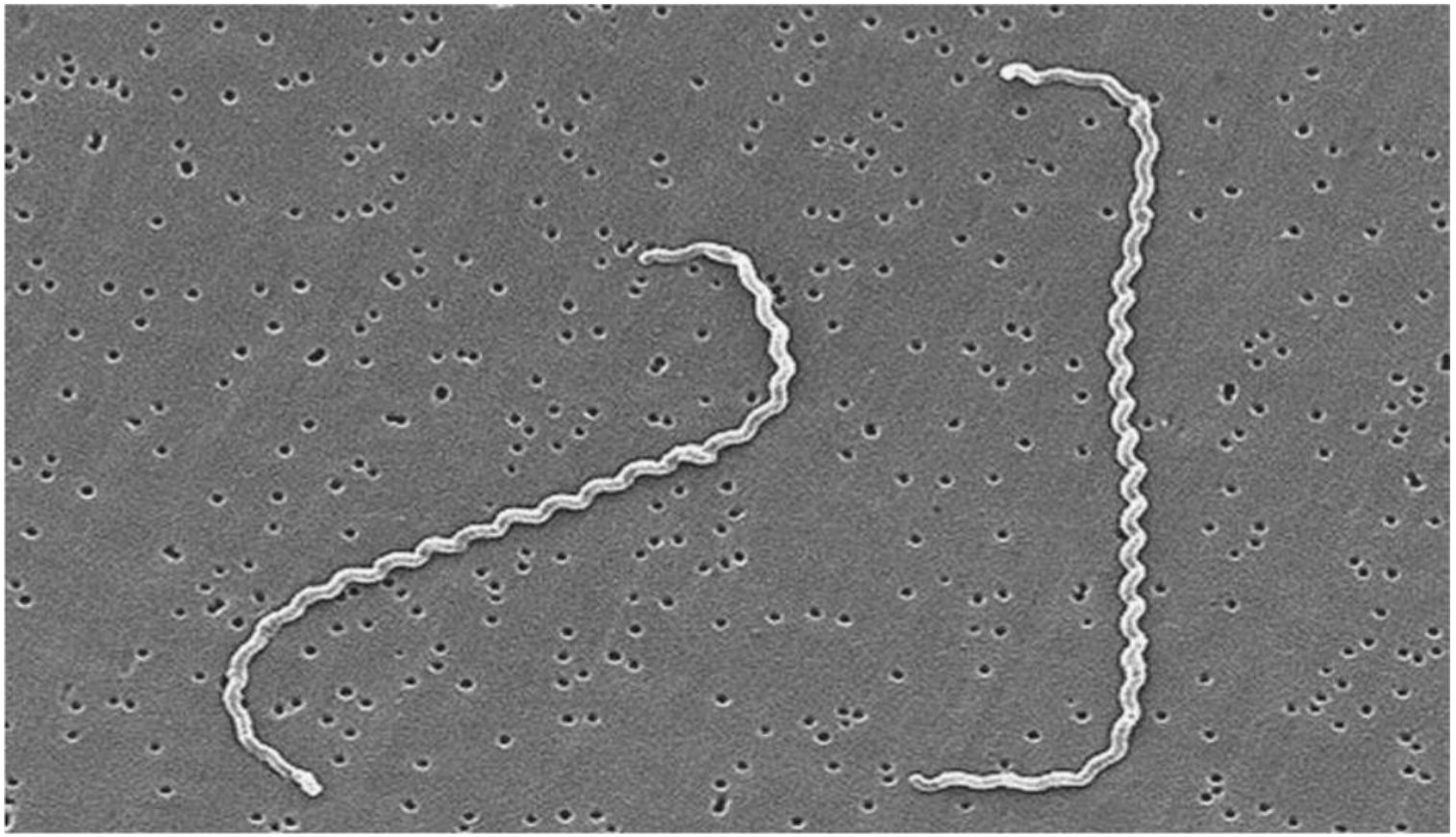
A selection of disposable units that fit onto syringes for sterilizing small volumes of liquid

- **Filters are available having a wide variety of pore sizes, and for sterilizing purposes 0.2 μm or 0.22 μm diameter pores are recommended**
- **but 0.1 μm membranes are becoming more popular.**



متذكرين زمان لما حكينا انه pore size المستخدم
للـ filtration اكم ؟ 0.22 μm

Leptospira bacteria attached to the surface of a 0.2 μm pore size filter membrane



هي بهي الصورة شايفين بس دخل ال oil او ال water اللي بالدوا لكن ال MO ما بتدخل و بتضل معلقة عال Filter زي هون البكتيريا ما دخلت

Membrane filters

شو صفات هاد ال membrane ؟

- good particle removal (sterilizing efficiency)
- good mechanical strength

هدول ال Filters لازم يكون عندهم strength منيحة و كبيرة مش زي filter المختبر

- they are easily sterilized in situ by steam,

هسا ال filter ممكن يكون disposable يعني بنتخلص منه اول ما نخلص فلترة ، أو بكون non disposable يعني ما بنتخلص منه و انما بنعيد تعقيمه بال steam

- of low fluid retention,

- ما يخلي ال fluid تتجمع وانما يكون عنده نفاذية منيحة الهم

- low solute absorption

لو بسمح بال adsorption of the drug هاد معناه رح نخسر جزء من الدوا

- no grow-through of microorganisms
-
- no shedding of fibers into the filtrate.

Filtration sterilization and aseptic manufacture

- **Filtration is the most convenient method of sterilizing air and other gases and it is used to supply air to pharmaceutical manufacturing suites ('clean rooms') and isolators, surgery rooms and microbiological safety cabinets**

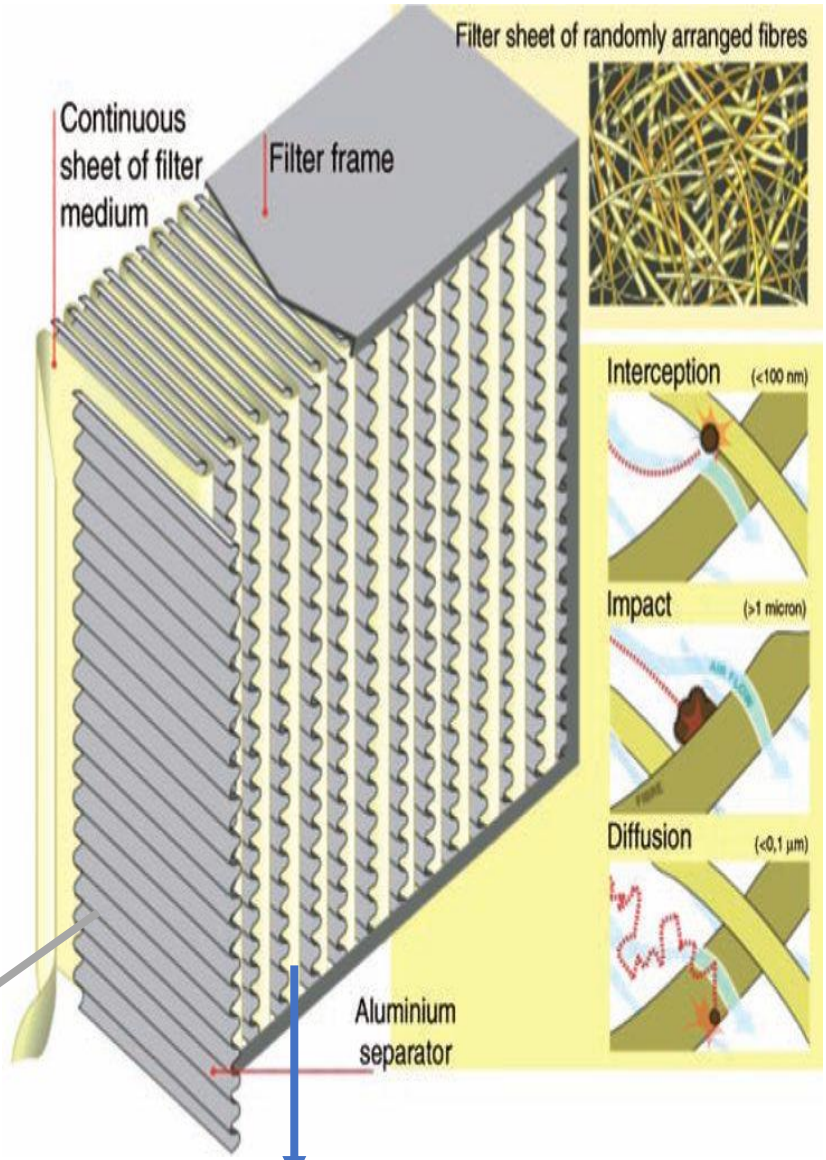
ال filtration method يستخدم بغرف العمليات لانه لازم لازم لازم
يدخل غرفة العمليات هواء معقم فقط مش هوا الشباك و ل clean
rooms و ل isolators هي بتكون مش غرفة لا هي للتعقيم بس
مش غرفة و انما شي اصغر بكون من stainless steel و لل
safety cabinets

مهم جدا نعرف ان ال filtration مش بس لل solution و انما بنعمله كمان لل gases مثل ال clean room

http://www.asbestosguru-oberta.com/hepa.htm

- **Depth filters, typically made of glass microfibres separated by aluminium sheets, are normally used for gas filtration**

- **High efficiency particulate air (HEPA) filters typically remove 99.97% of airborne particles of 0.3 μm in diameter, although some with higher specifications exist.**



لأنه شوفوا شكلهم Depth filter
وليس depth thin

الاصفر هو ال microfiber

Capture mechanism of HEPA filter

- The filter media is made up of densely packed fibers.
- Each fiber traps particles in the airstream passing through the filter by the three physical mechanisms.

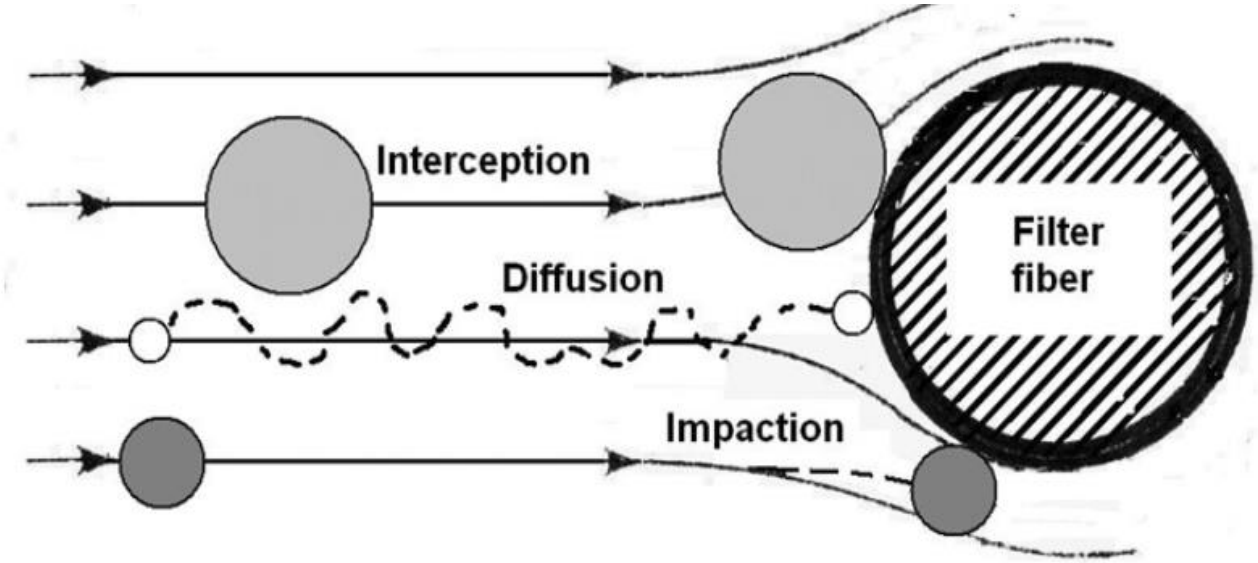


Figure 4. Capture mechanisms for a depth filter

إذا ال particle صغيرة بتكون العملية اسمها: **Interception**

اذا اصغر : **Impaction**

اذا كان حجمهم اصغر شي بكون اسم العملية: **Diffusion**

http://www.asbestosguru-oberta.com/hepa.htm

Capture mechanisms of HEPA filter

الثلاث تقسيمات هي حسب ال size

- *Watch:* **3D filtration principles**
  https://www.youtube.com/watch?v=AuVbcvPcjAw

- ***Interception*** **– A particle following an imaginary airflow streamline is intercepted by the fiber because the diameter of the particle is more than twice the distance from the fiber surface to the streamline that passes through the center of the particle.**

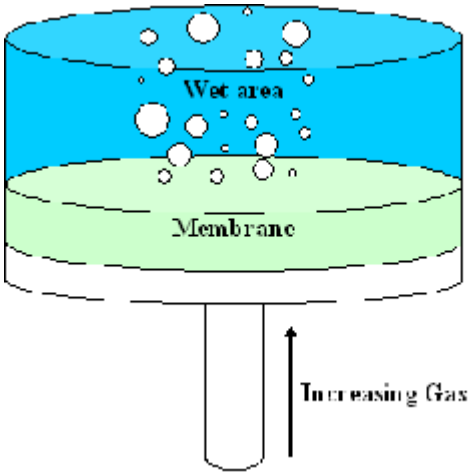
- ***Impaction*** **– The trajectory of the particle departs from the imaginary airflow streamline due to its inertia, which is a function of the particle's mass and velocity, and the particle impacts the fiber.**

- ***Diffusion*** **– The particle's trajectory oscillates about the imaginary airflow streamline in a random manner known as Brownian motion, which can cause the particle to impact the fiber.**

Slide note:

- The larger the particle, the greater the role of interception and impaction in capturing particles, which is a way of saying that these mechanisms are more efficient in capturing larger particles than smaller ones. Diffusion works in the opposite direction: smaller particles act more like the gas molecules we associate with Brownian motion, so it is a more efficient particle capture mechanism for smaller particles.

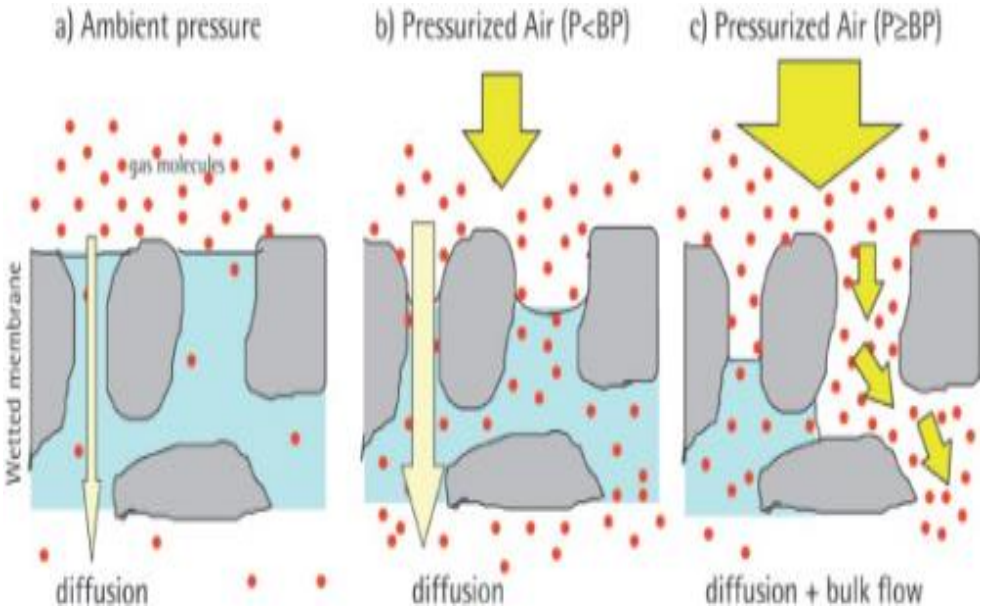
bubble point test



- **Filter integrity**
- A procedure which measures the pressure needed to be applied to the upstream side of a filter causing bulk or open pore flow through the largest pores of a wetted filter.
- **Watch:**

Bubble Point Filter Test

https://www.youtube.com/watch?v=RDjSCb4sC2c&t=24s



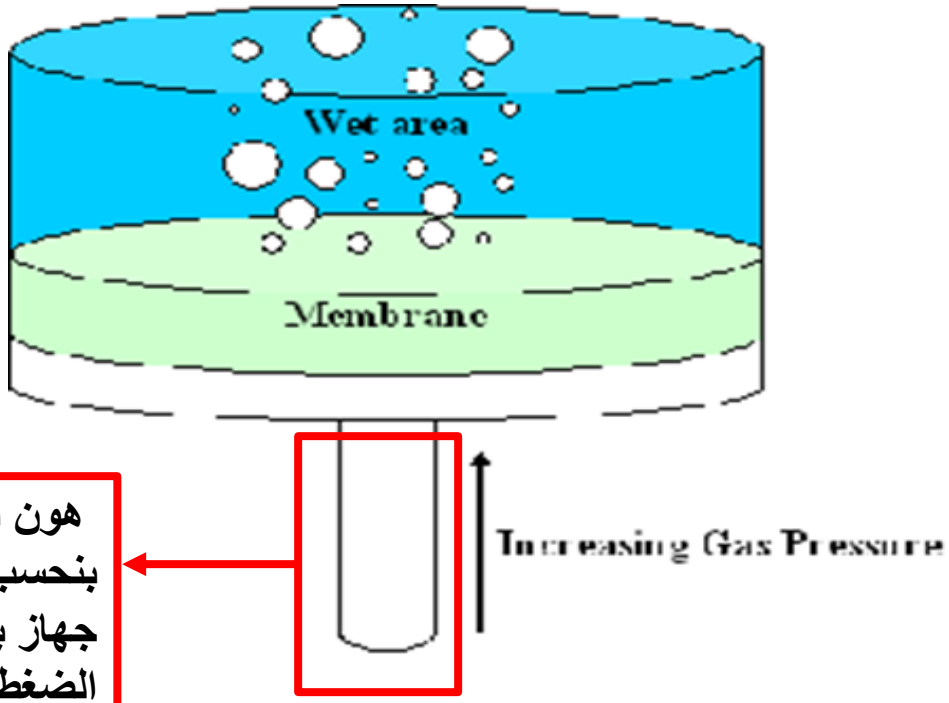
طبعا لازم نتأكد من ال integrity ال membrane اي سلامة ال membrane ف لو كنت بستخدم membrane و عقمته و بدي ارجع استخدمه لازم اتأكد انه سليم و انمزع و انه ضل معقم و بنقدر نستخدمه

Note of the previous slide:

There is no simple method of monitoring the operation of a filtration sterilizing process as there is with heat and radiation, although a sudden fall in pressure on the upstream side of the filter might indicate a fracture of the filter itself.

All three tests are based on the same physics, the flow of a gas through a liquid-wetted membrane under applied gas pressures.

If the recorded pressure is greater than or equal to the minimum expected bubble point listed above, the filter is integral. If the recorded pressure is lower than the minimum bubble point listed above, the filter has failed the integrity test.



هون بنأثر بقوة ضغط و بنحسب الضغط من هون في جهاز بكون مربوط بقيس اكم الضغط اللي اثرنا فيه عالسائل

هسا فكرة ال bubble point test هي انه بنجيب ال membrane و بنحط Water و بنبلش نضغط (يعني بنبلش نسلط ضغط داخل السائل مثل ما شفنا بالفيديو اللي ورجتنا ياه الدكتورة بالمحاضرة) و بنضل نضغط لكن متى ما صار في air bubbles يعني هون بنكون فتحنا ال pores و هاد ال testهدفه نفيس ال integrity تاعت ال membrane

كلما زاد الضغط اللازم لفتح ال pores و تكوين ال air bubble
كلما كان ال filter ممتاز و مش مخزوق

Test for sterility

- the item to be tested is placed into liquid culture medium and if, after incubation, there are no signs of growth (turbidity) the item is deemed to have passed the test.
- Tests for sterility have been internationally harmonized
- False positive result→ many companies, even quite large ones, do not conduct their own sterility testing but engage specialist contract laboratories to undertake it on their behalf.

Slide note:

From a financial perspective, sterility tests and endotoxin tests could be considered to be more important than many of the other quality-control tests to which a medicine is subjected because they are undertaken at the very end of the manufacturing process when all the added value has been built into the product. If a product were to fail a sterility test it is likely that the batch would be discarded, so it is particularly important that a sterility test is conducted with all possible care in order to maximize the chances of it giving the correct answer. Failing and scrapping a batch that is really sterile costs the money that has been invested in its manufacture, whilst passing a batch that is really contaminated risks initiating infections in patients who receive the medicine. Contaminated batches are likely to lead to product recalls, damage to the company reputation, major scrutiny from regulators and possibly even litigation.

Test for sterility

هسا هاد ال test هدفنا فيه نشوف ال sterility
فبنروح بناخد عدد من المنتجات النهائية يعني مثلا ابرة
فبنروح بناخد ابرة و بنحطها ب liquid culture
media و بعدها بنشوف هل طلع MO وهيك وقتها
بكون المنتج Fail فيعني بهمنا نشوف في turbidity
او لا

- **Positive** means there is turbidity
- * **Negative** means it is clear and sterile

نتائج ال test :

False positive
يعني المستحضر sterile
يعني negative و ال test
اعطى positive

False negative
يعني المستحضر فيه MO
يعني positive لكن اعطانا
انه Negative وانه sterile

Sterility tests and endotoxin tests could be considered to be more important than many of the other quality-control tests, Why?

False positive

- Failing and scrapping a batch that is really sterile costs the money that has been invested in its manufacture, whilst passing a batch that is really contaminated risks initiating infections in patients who receive the medicine.
- Contaminated batches are likely to lead to product recalls, damage to the company reputation, major scrutiny from regulators and possibly even litigation

False negative

يعني لما المصنع يصنع عينات contaminated رح تدهور سمعة المصنع و يكون في مقاضاة