MIRACLE Academy

التعقيم والتصنيع المعقم

لجان الرفعات

هالتفريغ شوي طويل ، لكن جددوا النية و شدوا العزم و بلشوا ولا تنسوا تقسيم دراستكم لعدة بارتات بينهم بريكات صغيرة رح تفيدكم ان شاء الله

بعون الله و قدرته سيمضي كل ما هو صعب

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...

PARENTERALS

Chapter 15 from Ansels, 9th Ed

Introduction:

- pharmaceutical dosage forms with the common characteristic of sterility:

1. Small and large-volume injectable preparations,

1. irrigation fluids intended to bathe body wounds or surgical openings, and dialysis solutions.
2. Biologic preparations, including vaccines, toxoids, and antitoxins,
3. Ophthalmic preparations

- Sterility in these preparations is essential because they are placed in direct contact with the internal body fluids or tissues, where infection can easily arise.

هاي السلايدة بتحكيلنا شو ال Dosage form اللي Sterility هي احدى خصائصها يعني مثل:

1) السوائل والادية اللي بنحقنها الصغيرة و كبيرة الحجم مثل : Normal saline IV injection وهو مثال عالسوائل كبيرة الحجم

2) ال Irrigation fluid اللي يستخدموا لـ:
Bathe body wounds or surgical opening and dialysis solution

3) ال biological preperations مثل ال :
Vaccines & toxoids & antitoxins

4) ال Ophthalmic preperations

- **Why sterility in these preparation is essential ????**

because they are placed in direct contact with the internal body fluids or tissues, where infection can easily arise.

parenteral preparations are sterile, pyrogen-free liquids (solutions, emulsions, or suspensions) or solid dosage forms containing one or more active ingredients, packaged in either single-dose or multi-dose containers.

They are intended for administration by injection, infusion, or implementation into the body. Parenteral drugs are administrated directly into veins, muscles or under the skin or more specialized tissues such as the spinal cord.

مثل ابرة الظهر لازم نعمللها injection the needle in directly to spinal cord

- **Parenteral should be :**

1) Sterile 2) Pyrogen free Pyrogen limitted لكن الاصح نحكي

- هسا ال Injection preparation **ممكن يكون شكلها الصيدلاني:**
solid or liquid (solution or emulsion or suspension)

- وايضا ممكن تكون Single dose or multiple dose

هاي التحضيرات يتم اما استخدامها لل infusion بحيث اعطي جرعة بمقدار ثابت كل مدة لنحافظ عالدوا بتركيز معين بالجسم او ل injection يعني بعطي جرعتي مرة وحدة او ل implementation يعني ندلخهم هي ال Preperation داخل الجسم ونزرعهم

Injections

- **Injections:**

- are sterile,

- pyrogen limited, that is, bacterial endotoxin units limit, preparations

- intended to be administered parenterally

- The term ***parenteral*** refers to the injectable routes of administration:

- It derives from the Greek words *para* (outside) and *enteron* (intestine) and denotes routes of administration other than the oral route.

- حكينا فوق الاصح نحكي pyrogen limitted not pyrogen free!
  لأنه ما في شي اسمه Pyrogen free %100

هسا اصلا شو هي ال pyrogen ، هي عبارة عن bacterial endotoxins وهي طبعا نستطيع قياسها يعني في الها limit معين و رقم مهين ممنوع تجاوزه

- البارت الثاني من السلايد بحكيلك شو يعني parenteral ؟؟ عارفين انها طبعا يعني عن طريق ال injection ولازم نعرف تعريف اشمل الا وهو :

Any administration route that is outside the GI route

- **بال Pharmacopeia مقسمين ال GI tract لـ:**

1) Parenteral 2) Enteral (through GI tract)

Injections

- The parenteral routes are used when:
- rapid drug action is desired, as in emergencies
- when the patient is uncooperative,
- Unconscious
- or unable to accept or tolerate oral medication
- or when the drug itself is ineffective by other routes.

- most injections are administered by the physician, physician's assistant, or nurse in the course of medical treatment (With the exception of insulin injections, which are commonly *self*- administered by diabetics)

- **هدف استخدام ال injection:** هو انه لحتى يوصل الدوا بشكل سريع او ممكن المريض يكون غير واعي او ما بقدر ياخد الدوا orally او اصلا الدوا بصير غير فعال بس نعطيه orally مثل ال insulin

الانسولين هو بروتن فبالتالي رح يتحطم بإنزيمات المعدة و اصلا الحموضة كفيلة تقضي عليه

- آخر شي ناقشلنا مين بعطي هي ال injections ؟؟
في شي by patient itself مثل الانسولين و في شي by physician or nurse

- The earliest injectable drug to receive official recognition was the hypodermic morphine solution, which appeared first in the 1874

يعطى تحت الجلد: Hypodermic

تطلعوا كيف كانت الابرة !!!
الحمد لله هسا الإبر صارت تتصنع بطريقة بتعطي الم اخف

PARENTERAL ROUTES OF ADMINISTRATION

حفظ

- Drugs may be injected into almost any organ or area of the body:
- including the joints (*intraarticular*),
- joint fluid area (*intrasynovial*),
- spinal column (*intraspinal*),
- spinal fluid (*intrathecal*),
- arteries (*intra-arterial*),
- and in an emergency, even the heart (*intracardiac*).
- However, most injections go into a vein (*intravenous, IV*), into a muscle (*intramuscular, IM*), into the skin (*intradermal*, *ID*; *intracutaneous*), or under the skin (*subcutaneous, SC*; *sub-Q*, *SQ*; *hypodermic*, *hypo*)

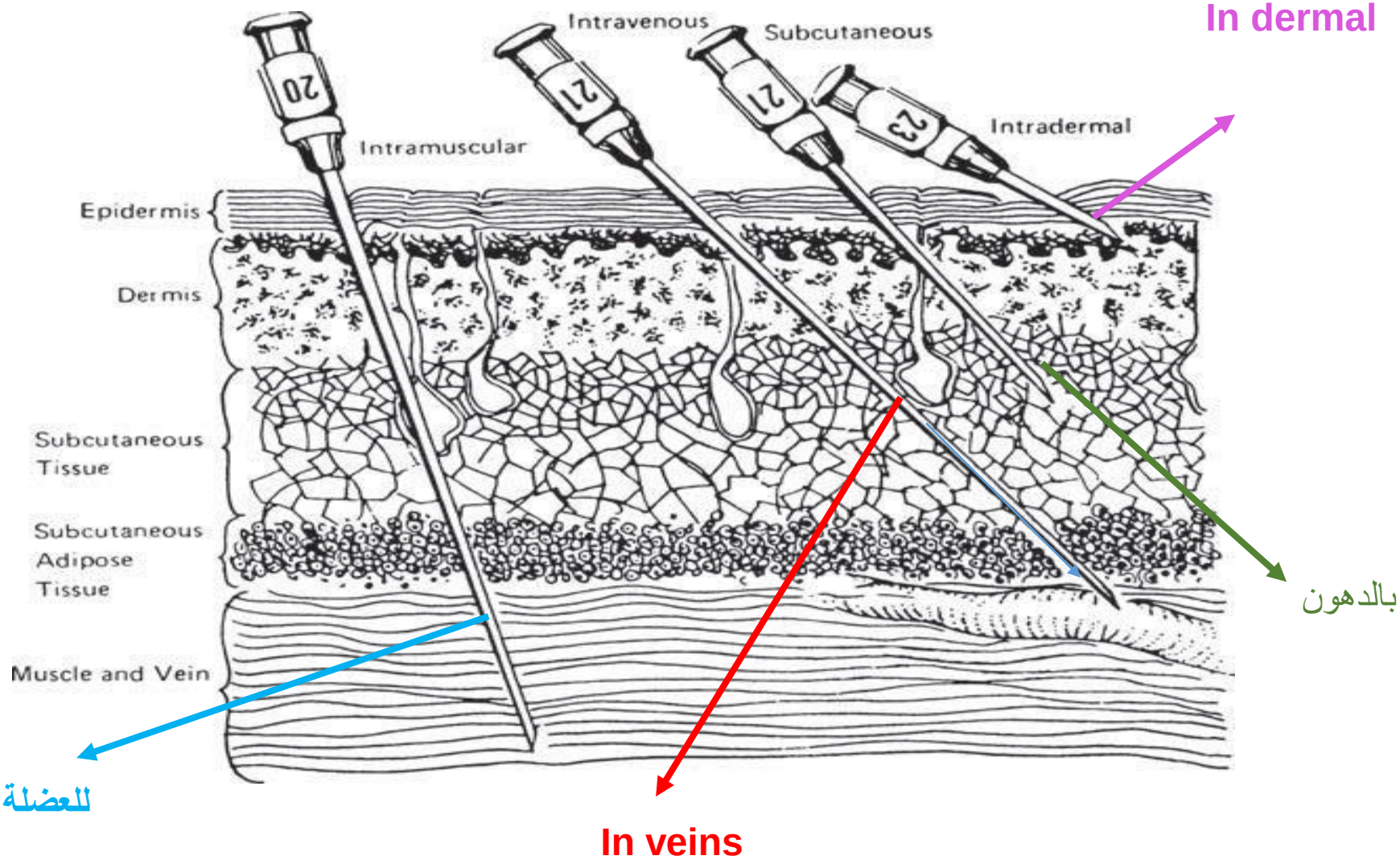


FIGURE 15.1 Routes of parenteral administration. Numbers on needles indicate gauge of the needles (outside diameter of shaft).

Intravenous Route

- IV injection of drugs had its scientific origin in 1656 in the experiments of Sir Christopher Wren, architect of St Paul's Cathedral and Using a bladder and quill for a syringe and needle, he injected wine, ale, opium, and other substances into the veins of dogs and studied their effects.

في عام 1656 بلش ال IV ، هاد واحد اسمه Sir Christopher Wren راح جاب bladder الحيوانات وال quill اللي هو ريش الطيور وهيك يعني صنع syringe and needle وعمل injection for dogs

North African Arabs, and formed from an animal's bladder and bamboo. (Wellcome Collection).

Diagram 3: An artist's rendering of Dr. Alexander Wood's syringe. The original is now in the Royal

Pig bladders and feather quills: a history of vascular access devices.

Source: British Journal of Nursing . 2014 IV Therapy Supplement, Vol. 23, pS21-S25. 5p. 3 Black and White Photographs.

Author(s): Kelly, Linda J.

Abstract:

Vascular access is a requirement for many hospitalised patients. Over the years there have been many technological refinements and advances in the Renaissance period, the discovery of the circulatory system in the 15th century, to the present day, and will give the reader a notion of the origins and

Intravenous Route

IV drugs provide:

- rapid action compared with other routes of administration
- Drug absorption is not a factor, optimum blood levels may be achieved with accuracy and immediacy
- In emergencies, IV administration of a drug may be lifesaving because of the placement of the drug directly into the circulation

سريع وما في absorption اللي يعمللنا مشكلة لكمية الدوا اللي حتوصل و ممتاز بحالة ال Emergency

On the negative side:

- once a drug is administered intravenously, it cannot be retrieved.
- In the case of an adverse reaction to the drug the drug cannot be easily removed from the circulation, as it could, by induction of vomiting after oral administration of the same drug.
- The IV dose may differ greatly from the oral dose. Thus, great care must be taken to prevent overdosing or under-dosing.

يعني مشكلته لو المريض تحسس ما بقدر اسحب الجرعة من جسمه, ولكن فقط وقتها رح نعالج ال symptoms، زكمان بحكيلنا انه جرعة ال oral دايما اكبر لانه محسوب حساب مش كل الجرعة رح توصل

Intravenous Route

- Both small and large volumes of drug solutions may be administered intravenously.
- The use of 1,000-mL containers of solutions for IV infusion is common-place in the hospital:

- solutions, containing such agents as nutrients
- plasma volume expanders,
- electrolytes,
- amino acids,

The infusion or flow rate may be adjusted according to the needs of the patient.

هون بحكيلك عن الادوية اللي حجمها كبير و بنعطيها Parenterally وهمه اللي مكتوبين بالاحمر ، حيث بنعمل adjusting for drug infusion

Intravenous Route

- flow rates for IV fluids range from 42 to 150 mL per hour.
- Lower rates are used for keep-open (KO, KVO) lines.
- The main hazard of IV infusion:

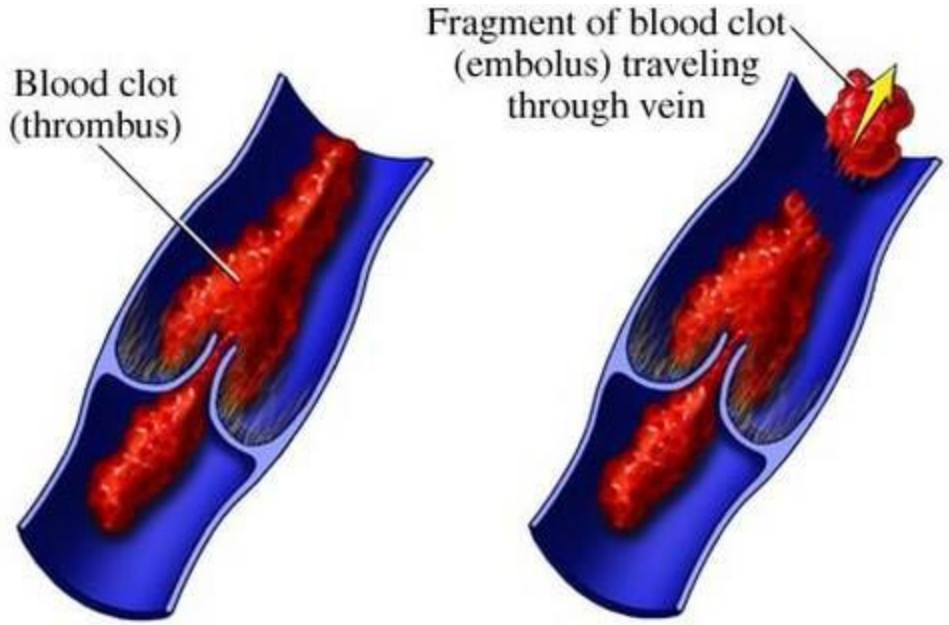
- thrombus formation induced by the catheter or needle touching the wall of the vein.

- A *thrombus* is a blood clot formed within the blood vessel (or heart), usually because of slowing of the circulation or an alteration of the blood or vessel wall.

- Once such a clot circulates, it becomes an *embolus*, carried by the blood stream until it lodges in a blood vessel, obstructing it and resulting in a block or occlusion referred to as an *embolism*.

Thrombus: هي clot غير متحركة
Embolus: clot لما تتحرك

هي اللي مكتوبة بالاحمر و اللي IV route من احد مشاكل ال
بالاخضر هو تعريفها


Blood clot
(thrombus)
Fragment of blood clot
(embolus) traveling
through vein

Intravenous Route

اللي بالاحمر حكت الدكتورة مش حفظ

مستحيل تذوبه بـ oil لانه
مش رح يعمل mix مع
الدم و رح يعمل تسكير للدم

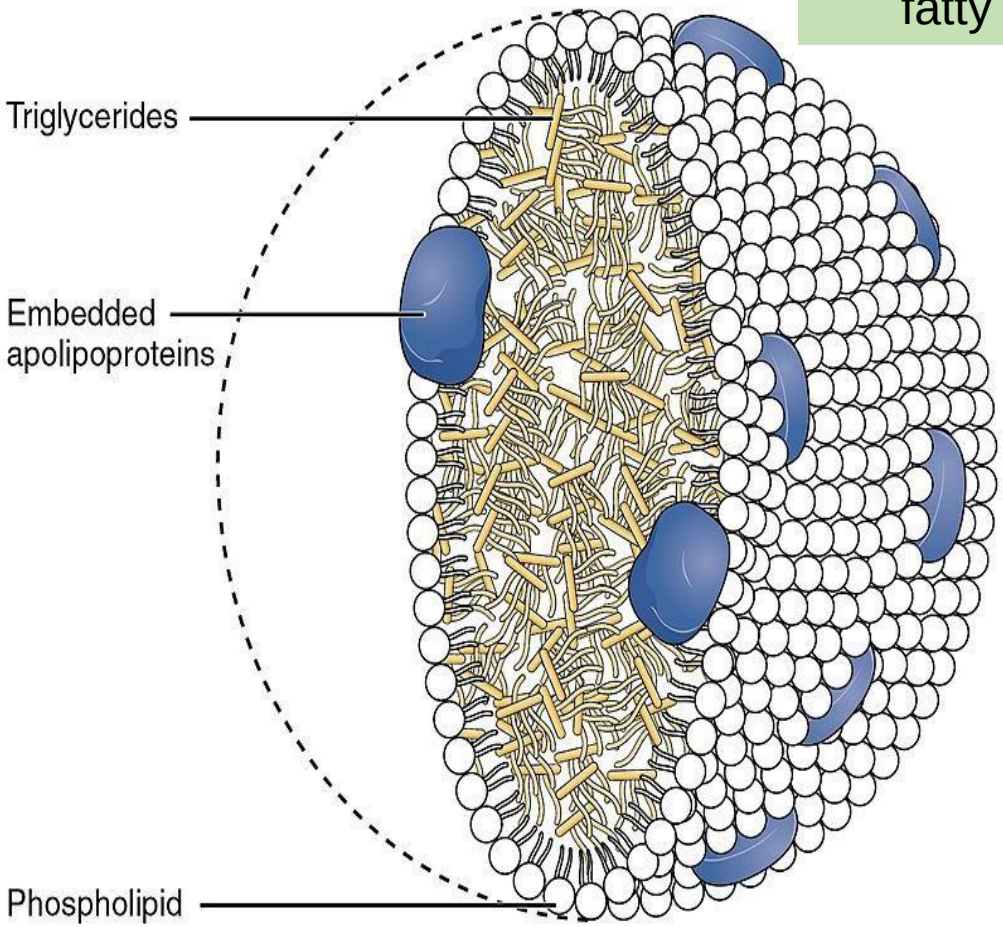
- IV drugs ordinarily must be in aqueous solution:
- they must mix with the circulating blood
- and not precipitate from solution → Such an event can lead to pulmonary microcapillary occlusion and blockage of blood flow.
- IV fat emulsions (e.g., Intralipid, 20%, 30%, Baxter; Liposyn II, 10%, 20%, Hospira; Liposyn III, 10% to 30%, Hospira) have gained acceptance for use as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods, usually more than 5 days.

تستخدم ل(TBN) total body nutrient يعني للناس اللي ممكن تقعد 5 ايام ما تقدر تاكل

- The product contains up to 30% soybean oil emulsified with egg yolk phospholipids in a vehicle of glycerin in water for injection.

عاملينها نفس مبدأ نقل ال Fatty acid بالدم

هون تذكير كيف درسنا بتم حمل ال fatty acids



اوقات اذا ما كنت عامل حساب ال solubility of drug in blood بصيرله precepitation حيث ان امتصاص ال fat يكون triglyseride من جوا و phospholipids من برا اللي بتسمح بإنتقال ال chylomicron بالدم

Intralipd is the trade name

Intralipid® 20% *10 x 100 ml*

Fat emulsion for intravenous use

400266 / 01
83 18 00-220

100 ml contains: Purified soybean oil 20 g
Excipients: Purified egg phospholipids 1.2 g, Glycerol anhydrous 2.2 g, may contain Sodium hydroxide, Water for injection to 100 ml. & glycerin

Energy content: 0.84 MJ (200 kcal)/100 ml.

The contents of this bag are for a single infusion only. Any remaining emulsion must be discarded.
Electrolyte solutions should not be added to this bag.
Read the package leaflet before use.

Store at or below 25°C. Do not freeze.

PL 8828/0110
MA 134-00101

POM

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Expiry date: 01/2012
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- Automated IV delivery systems for intermittent self administration of analgesics became commercially available.
- Patient-controlled analgesia (PCA)
- PCA devices can be used for IV, SC, or epidural administration.
-

هي وسيلة لتعطي intermittent self administration of analgesics
يعني للناس اللي بحاجة لل morphine اول بأول بدون انقطاع حيث لو انقطع برجع الم شديد جدا جدا ...اللي همه مرضى الكانسر وال terminally ill اللي هي مرض ما اله علاج

Intramuscular Route

- IM injections of drugs:
- provide effects that are less rapid but generally longer lasting than those obtained from IV administration
- Aqueous or oleaginous solutions or suspensions of drug substances may be administered intramuscularly.
- Depending on the type of preparation, absorption rates vary widely, explain? Soln. vs susp. and aq. vs oil

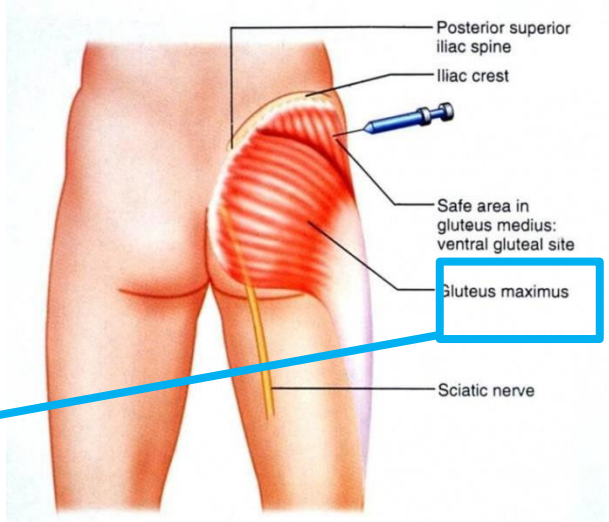
هسا هون بنحقن العضلة مباشرة ، شو الفرق عن ال IV ؟؟
انه هون less rapid effect و لكنه long lasting لانه بكون زي Depot
وكمان شغلة انه هون بنقدر نستخدم aqueous or oil solution لانه الابرة موجهة للعضلة فعادي

- **Solution has rapid absorption rate than suspension**
- **Aqueous has rapid absorption rate than oil**

- What determine the physical type of preparation?

1. properties of the drug itself **(if it is soln or susp & if it is aq or oil)**
2. and the therapeutic goals.**(Depot or sustained & susp or oily يعني هل بدنا ياه)**

- The point of injection should be as far as possible from major nerves and blood vessels.
- paralysis resulting from neural damage, hematoma, and scarring.
- The volume of medication that may be conveniently administered by the IM route is limited, generally to a maximum of 5 mL in the gluteal region and 2 mL in the deltoid of the arm.



هي منطقة مش مزحة لأنه فيها nerve لانه ممكن يصير paralysis لو انعمل nerve damage او hematoma او scarring

Subcutaneous Route

- The SC route may be used for injection of small amounts
- of medication.
- The site of injection is usually rotated when injections are frequently given→ daily insulin injections.
- The maximum amount of medication that can be comfortably injected subcutaneously is about 1.3 mL, and amounts greater than 2 mL will most likely cause painful pressure.
- Syringes with up to 3-mL capacities and 24- to 26-gauge needles are used.

هون بنعطي الجرعة بالدهون مثل الانسولين ، الجرعة اللي معنا ما نتجاوزها عشان ما نسبب الم للمريض هي 1.3 ml ولكن فوق ال 2ml بتكون مؤلمة !!

لازم نغير مكان الجرعة مش كل مرة نعطي بنفس منطقة الدهن عشان ما تتورم وتؤلمه و تدايقه للمريض

Subcutaneous Route

- Irritating drugs and those in thick suspension may produce induration, sloughing, or abscess and may be painful.
- Such preparations are not suitable for SC injection.

اللي بالاحمر هي ادوية لا يفضل انه نعطيهم SC

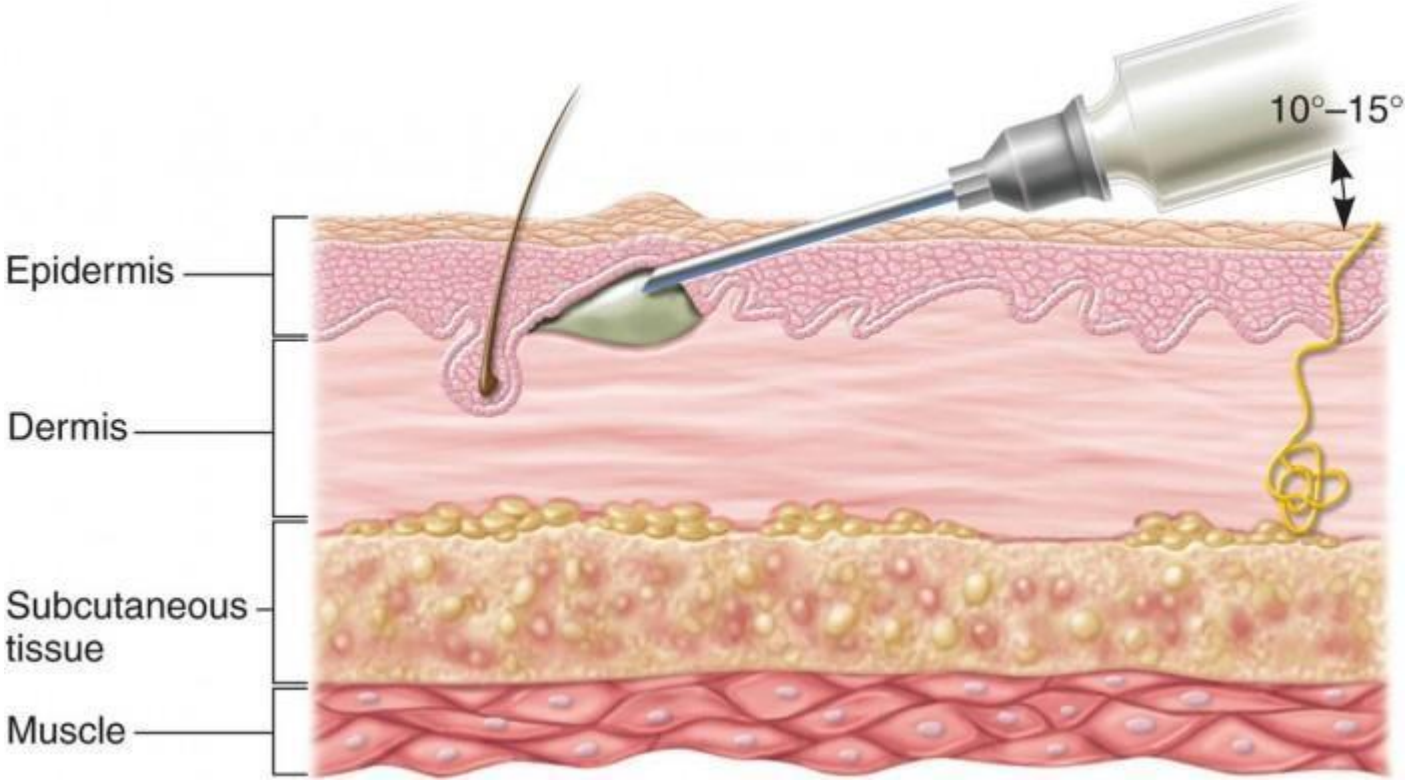
Intradermal Route

هدول بنعطيهم تحت الجلد عند ال Dermis يعني بعد ال epidermis

- A number of substances may be effectively injected into the corium (dermis), the more vascular layer of the skin just beneath the epidermis.
- These substances include various agents for diagnostic determinations, desensitization, or immunization.
- The usual site for ID injection is the anterior forearm.
- A short and narrow needle is usually employed.
- Usually, only about 0.1 mL may be administered in this manner.

INTRADERMAL TECHNIQUE

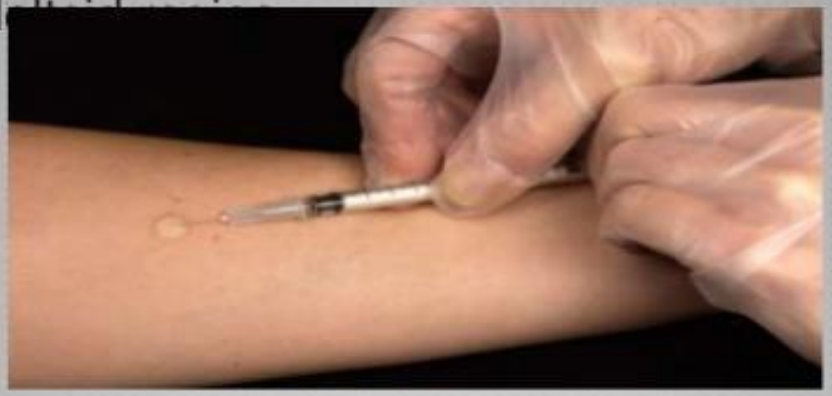
- **26 TO 27 GAUGE NEEDLE**
- **SYRINGE: 1 ML (CALIBRATED IN 0.01 ML INCREMENTS)**



هو المكان المفضل

INTRADERMAL INJECTION

- **Most commonly used site**: Inner surface of the forearm
- Subscapular region of the back can be used as well as the d



OFFICIAL TYPES OF INJECTIONS:

According to the USP, injectable materials are separated into:

1. *Injection*: Liquid preparations that are drug substances or solutions thereof (e.g., Insulin Injection, USP).
2. *For injection*: Dry solids that, upon addition of suitable vehicles, yield solutions conforming in all respects to the requirements for injections (e.g., Cefuroxime for injection, USP).
3. *Injectable emulsion*: Liquid preparation of drug substance dissolved or dispersed in a suitable emulsion medium (e.g., Propofol, USP).
4. *Injectable suspension*: Liquid preparation of solid suspended in a suitable liquid medium (e.g., Methylprednisolone Acetate Suspension, USP).
5. *For injectable suspension*: Dry solid that, upon addition of suitable vehicle, yields preparation conforming in all respects to the requirements for *injectable suspensions* (e.g., Imipenem and Cilastatin for injectable suspension, USP).

1)Injection:

هي لما يكون التحضيرة المراد حقنها اصلا سائلة ، مثل :Insulin

2)For injection :

هون يعني التحضيرة المراد حقنها هي solid ولازم نحلها بـ sterile water تعطى مع التحضيرة عشان نحلها وقت الحقن مثل:

Cefuroxime

3) Injectable emulsion :

نفس تعريفنا لل Emulsion انه عبارة عن dispersed phase and dispersed medium لغرض الحقن مثل : propofol

4) Injectable suspension:

هون بتكون تحضيرة ال suspension جاهزة عبارة عن solid تم حلّه بـliquid فمباشرة بس نحقن مثل : Methylpredisolone

5) For injectable suspension :

هون بكون solid و بنحلّه بـ suitable vehicle مثل:

Imipenem and cilastatin

اذا كان ال vehichle مخلي الدوا Blood immiscible مثل حالة انه مش stable بالمي او بال solution بالتالي فما رح نستخدمهم IV لانه they can interrupt the normal flow of blood

- if a drug is unstable in solution?? بنحضره على شكل emulsion or suspension
- If the drug is unstable in water
- If an aqueous solution is desired???, a water-soluble salt form of the insoluble drug is frequently prepared.
- Aqueous or blood-miscible solutions may be injected directly into the blood stream. Blood-immiscible liquids, such as oleaginous injections and suspensions, can interrupt the normal flow of blood, and their use is **generally** restricted to other than IV administration.

او ممكن نعمله كـ salt اذا بدنا نستخدمه parenterally

- بهي الحالة نستخدن vehicle او suspension او نحضر منه form يذوب بالماء او نحضره على شكل Dry poewder و وقت بدنا نستخدمه نحلّه

- The onset and duration of action of a drug may be somewhat controlled:

1. by its chemical form,
2. the physical state of the injection (solution or suspension),
3. and the vehicle.

- Drugs in aqueous suspension are ???????? rapid acting than drugs in oleaginous suspension.
- If long action is desired to reduce the frequency of injections. These long-acting injections are called repository or depot preparations.

- The solutions and suspensions of drugs intended for injection are prepared taking the following considerations:

look for pg 437

1. Solvents or vehicles must meet special purity and other standards ensuring their safety by injection.
2. The use of added substances, such as buffers, stabilizers, and antimicrobial preservatives, fall under specific guidelines of use and are restricted in certain parenteral products. The use of coloring agents is strictly prohibited.
3. Parenteral products are always sterilized, meet sterility standards, and must be pyrogen limited.

1) هسا في Standard ل ال solvent اللي بدنا نستخدمه ، ففرضا بدنا نحط ال glycerin كـ cosolvent فما بنقدر نستخدم تاع الصيدلية ولا حتى ال oil ما بزبط تاع البيت

2) هسا مستحيل نلاقي coloring agent فلو كانت الابرة ملونة بتكون المادة الفعالة ملونة ولكن مستحيل نضيف لون من عنا

3) اكيد لازم تكون التحضيرة sterile & pyrogen limitted

4. Parenteral solutions must meet compendial standards for particulate matter.
5. Parenteral products must be prepared in environmentally controlled areas, under strict sanitation standards, and by personnel specially trained and clothed to maintain the sanitation standards.
6. Parenteral products are packaged in special hermetic containers of specific and high quality. Special quality control procedures are used to ensure hermetic seal and sterile condition.
7. Each container of an injection is filled to a volume in slight excess of the labeled volume to be withdrawn. This overfilling permits ease of withdrawal and administration of the labeled volumes.
8. The volume of injection permitted in multiple-dose containers is restricted, as are the types of containers (single-dose or multiple-dose) that may be used for certain injections.
9. Specific labeling regulations apply to injections.
10. Sterile powders intended for solution or suspension immediately prior to injection are frequently packaged as lyophilized or freeze-dried powders to permit ease of solution or suspension upon the addition of the solvent or vehicle.

Notes:

*Particulate matter:

يعني هو موجود كـ un adsorbed particle

*Enviromentally controlled areas :

يعني داخل clean room

*Hermetic container:

يعني عبوات محكمة الاغلاق

*اذا الابرة فيها 3 ml لكن هي بتكون اكثر من هيك عشان لما نيجي نسحبها بكون في فقاعات بالتالي بكون في excessعن ال 3ml حساب اللي رح يروح فقاعات

* في volume محدد بال pharmacopeia لل multiple و لل single حيث وحدة بدنا ع قد استخدام واحد و وحدة معنا حجم اكبر لانه اكثر من مرة

SOLVENTS AND VEHICLES FOR INJECTIONS

- **The most frequently used solvent for injections is *water for injection*, *USP*:**
- This water is purified by **distillation** or by **reverse osmosis**
- and meets the same standards for the presence of total solids as does ***Purified Water*, *USP***—that is, not more than 1 mg/100 mL water for injection, USP
- and may **not contain added** substances.
- water for injection is **not** required to be **sterile**
- it must be **pyrogen free**.
- The water is intended to be used in the manufacture of injectable products to **be sterilized after preparation**.
- Water for injection should be stored in tight containers at temperatures below or above the range in which microbial growth occurs.
- Water for injection is intended to be used **within 24 hours** after collection.
- the water should be collected in sterile and **pyrogen-free containers**. The containers are **usually glass or glass lined**.

ببساطة المي اللي لل injection مش لازم يكون في اضافات و مش لازم تكون بتحتوي على solids اكثر من 1 mg/100 ml و مش نفس المي اللي مصنعة لتنزل عالسوق لا هي لازم تكون مصنعة خصيصا للحقن فلازم تكون terminally sterilized وتكون pyrogen free ولازم تتخزن على درجة حرارة تحت او فوق الحرارة اللي بصير فيها نمو بكتيري و طبعا بعد تصنيعه معي بس 24 ساعة ليتم تعبئته!

SOLVENTS AND VEHICLES FOR INJECTIONS

- ***Sterile water for injection, USP***:

- is packaged in single-dose containers not larger than 1 L.
- it must be pyrogen free or pyrogen limitted
- have an allowable endotoxin level, not more than 0.25 USP endotoxin units per milliliter.(endotoxin free)

- it may not contain any antimicrobial agent or other added substance..
- This water is intended to be used as a solvent, vehicle, or diluent for already sterilized and packaged injectable medications.

هداك ال **injection** اللي بنعمله **terminally sterilized** لكن هون بدنا نفهم واحنا بنصنع لازم نستخدم كلشي **sterilized** يكون

- The 1-L bottles cannot be administered intravenously because they have no tonicity. Thus, they are used for reconstitution of multiple antibiotics.

يعني لو عنا **1L** بدنا نحقنه من ال **sterile water** وما عنا **normal saline** فما رح يزبط نحقنه بال **blood** لانه ما حيكون في **tonocity (osmotic balance)** فبالتالي رح يصير **blood damage**

SOLVENTS AND VEHICLES FOR INJECTIONS

هاد النوع بنضيف عليه
antibacterial agent

- ***Bacteriostatic water for injection, USP***:
- Is sterile water for injection containing one or more suitable antimicrobial agents.
- It is packaged in prefilled syringes or in vials containing not more than 30 mL of the water.
- The water is employed as a sterile vehicle in the preparation of small volumes of injectable preparations.
- the water must be used only in parenterals that are administered in small volumes (toxic amounts of the antimicrobial agents that would be injected along with the medication).
- if more than 5 mL of solvent is required, sterile water for injection rather than bacteriostatic water for injection is preferred.

بهي الحالة ما بزبط نستخدم هي المي لانه 5ml معناها ف كمية antibacterial كبيرة يعني جرعة عالية
فبهي الحالة نستخدم sterile water for injection

- chemical compatibility of the bacteriostatic agent or agents with the particular medicinal agent being dissolved or suspended.

يعني بنستخدم هي المي لما بدنا نحل ال vials و نستخدمهم اكثر من مرة فهاي المي تستخدم لحمايتهم من ال MO

- USP labeling requirements demand that the label state Not for use in neonates

ال label مهم لانه الاطفال حديثي الولادة ال liver تاعهم ما بكون بتحمل ال antibacterial agent

SOLVENTS AND VEHICLES FOR INJECTIONS

- ***Sodium chloride injection, USP*:**

- is a **sterile isotonic** solution of sodium chloride in water for injection.
- It contains no antimicrobial agents
- has approximately 154 mEq each of sodium and chloride ions per liter.
- It may be used as a sterile vehicle in solutions or suspensions of drugs for parenteral administration.

- is frequently used as a catheter or IV line flush to maintain patency.

- No preservative needed for this prepration
- *there is needdinf for water for injection

SODIUM CHLORIDE
INJECTION, USP
0.9%

NDC 0517-2810-25
25 x 10 mL
SINGLE DOSE VIALS

FOR DRUG DILUENT USE
PRESERVATIVE FREE

Rx Only

Each mL contains: Sodium Chloride 9 mg, Water for Injection q.s. pH adjusted with Hydrochloric Acid and/or Sodium Hydroxide.
0.3 mOsmol/mL. Sterile, nonpyrogenic.
WARNING: DISCARD UNUSED PORTION.
Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F)
(See USP Controlled Room Temperature)
Directions for Use: See Package Insert.

Lot / Exp.

Rev. 11/05

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

SOLVENTS AND VEHICLES FOR INJECTIONS

- ***Bacteriostatic sodium chloride injection, USP:***

- is a sterile isotonic solution of sodium chloride in water for injection.
- It contains one or more suitable antimicrobial agents, which must be specified on the labeling.

لازم على الليبل نكون كاتبين شو ال **antimicrobial agent**

- Sodium chloride 0.9% renders the solution isotonic.
- This solution may not be packaged in containers larger than 30 mL.
- When this solution is used as a vehicle, care must be exercised to ensure compatibility of the added medicinal agent with the preservative or preservatives and with the sodium chloride لازم نوضح و نكتبه عشان في ناس ممكن تكون بتتحسس
- also used to flush a catheter or IV line to maintain its patency

SOLVENTS AND VEHICLES FOR INJECTIONS

- bacteriostatic sodium chloride injection also carries the warning Not for use in neonates.

معنا بس 30 ml عشان اكثر من هيك بندخل المريض بـ toxicity من المادة الحافظة

SOLVENTS AND VEHICLES FOR INJECTIONS

- ***Ringer's injection, USP***: There is 3 types of salt:

- is a sterile solution of sodium chloride, potassium chloride, and calcium chloride in water for injection.
- The three agents are present in concentrations similar to those of physiologic fluids.
- Ringer's is employed as a vehicle for other drugs or alone as an electrolyte replenisher and plasma volume expander.

1000 mL

NDC 0409-7982-09

RINGER'S INJECTION, USP

EACH 100 mL CONTAINS SODIUM CHLORIDE 860 mg; POTASSIUM CHLORIDE 30 mg; CALCIUM CHLORIDE, DIHYDRATE 33 mg IN WATER FOR INJECTION. MAY CONTAIN HCl OR NaOH FOR pH ADJUSTMENT. ELECTROLYTES PER 1000 mL: SODIUM 147 mEq; POTASSIUM 4 mEq; CALCIUM 4 mEq; CHLORIDE 155 mEq.
309 mOsmol/LITER (CALC.). pH 5.4 (5.0 TO 7.5).
DO NOT ADMINISTER CALCIUM CONTAINING SOLUTIONS CONCURRENTLY WITH STORED BLOOD. ADDITIVES MAY BE INCOMPATIBLE. CONSULT WITH PHARMACIST, IF AVAILABLE. WHEN INTRODUCING ADDITIVES, USE ASEPTIC TECHNIQUE, MIX THOROUGHLY AND DO NOT STORE. SINGLE-DOSE CONTAINER. FOR INTRAVENOUS OR SUBCUTANEOUS USE. USUAL DOSAGE: SEE INSERT. STERILE, NONPYROGENIC. USE ONLY IF SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED. MUST NOT BE USED IN SERIES CONNECTIONS.

(01) 0 30409 79820 9 7

Rx ONLY

3 V
CONTAINS DEHP

LATEX

PRINTED IN USA

IM-0051 (4/04)

HOSPIRA, INC., LAKE FOREST, IL 60045 USA

Hospira

1 2 3 4 5 6 7 8 9

SOLVENTS AND VEHICLES FOR INJECTIONS

- ***Lactated Ringer's Injection, USP***:

- has different quantities of the three salts in Ringer's injection
- and it contains sodium lactate.
- This injection is a fluid and electrolyte replenisher and a systemic alkalizer.

نستخدمه نفس مبدأ ال Ringer ولكن هاد نزيد فيه ال pH لـ certain fluid in our body

LOT EXP

250 mL **6E2322**

NDC 0338-6307-02

Lactated Ringer's Injection USP

50

100

150

200

EACH 100 mL CONTAINS 600 mg SODIUM CHLORIDE USP 310 mg SODIUM LACTATE 30 mg POTASSIUM CHLORIDE USP 20 mg CALCIUM CHLORIDE USP pH 6,5 (6,0 TO 7.5) mEq/L SODIUM 130 POTASSIUM 4 CALCIUM 2,7 CHLORIDE 109 LACTATE 28 OSMOLARITY 273 mOsmol/L (CALC) STERILE NONPYROGENIC SINGLE DOSE CONTAINER **NOT FOR USE IN THE TREATMENT OF LACTIC ACIDOSIS** ADDITIVES MAY BE INCOMPATIBLE CONSULT WITH PHARMACIST IF AVAILABLE WHEN INTRODUCING ADDITIVES USE ASEPTIC TECHNIQUE MIX THOROUGHLY DO NOT STORE DOSAGE INTRAVENOUSLY AS DIRECTED BY A PHYSICIAN SEE DIRECTIONS CAUTIONS SQUEEZE AND INSPECT INNER BAG WHICH MAINTAINS PRODUCT STERILITY DISCARD IF LEAKS ARE FOUND MUST NOT BE USED IN SERIES CONNECTIONS DO NOT ADMINISTER SIMULTANEOUSLY WITH BLOOD DO NOT USE UNLESS SOLUTION IS CLEAR **Rx ONLY** STORE AT ROOM TEMPERATURE (25°C/77°F) UNTIL READY TO USE AVOID EXCESSIVE HEAT SEE INSERT

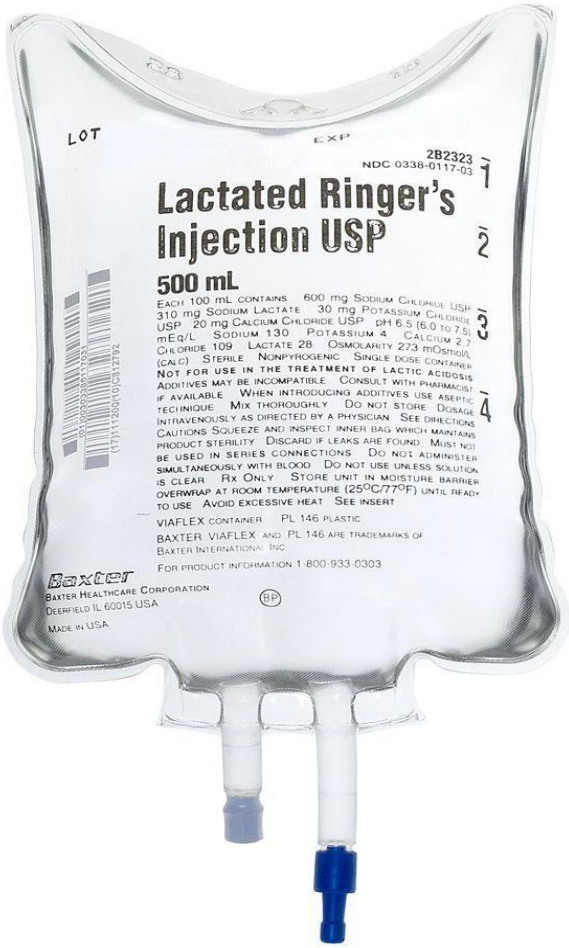
Baxter
BAXTER HEALTHCARE CORPORATION
DEERFIELD IL 60015 USA
MADE IN USA

BAXTER AVIVA AND THE AVIVA CRESCENT DESIGN ARE TRADEMARKS OF BAXTER INTERNATIONAL INC

FOR PRODUCT INFORMATION
1-800-933-0303

AVIVA CONTAINER

~~PVC~~ SOLUTION CONTACT | ~~LATEX~~ | ~~DEHP~~ SOLUTION CONTACT



NONAQUEOUS VEHICLES Not used for IV

- restrictions on the fixed vegetable oils in parenteral products:
- For one thing, they must remain clear when cooled to 10°C (50°F) to ensure the stability and clarity of the injectable product during refrigeration. الزيت العادي بصير turbid بس تبرده
- The oils must not contain mineral oil or paraffin, as these materials are not absorbed by body tissues.
- Oils to be employed in injections must meet officially stated requirements of iodine number and saponification number.
- Some patients exhibit allergic reactions to specific oils→label must state the specific oil. Such as : peanut oil
- The most commonly used fixed oils in injections are corn oil, cottonseed oil, peanut oil, and sesame oil.

- oleaginous injections are administered intramuscularly
- Not IV→ the oil will occlude the pulmonary microcirculation

Pyrogens and Pyrogen Testing

- **Pyrogens**: A pyrogen is a substance that induces fever. These can be either internal (endogenous) or external (exogenous) to the body

يعني خارج الدم

- **Endotoxin**: An "endotoxin" is a toxin that is a structural molecule of the bacteria that is recognized by the immune system. "endotoxin" are, in fact, due to lipopolysaccharide found in the outer membrane of various Gram-negative bacteria→ is **thermostable and water soluble**, it may remain in water even after sterilization by autoclaving or by bacterial filtration.

ال pyrogen هي جزء من البكتيريا حيث انها lipopolysaccharides (LPS) موجودة بال outer membrane ولكن ال endotoxin يقع تعريفها تحت ال pyrogen ومشكلتهم اصعب ال endotoxin لانه صعب قتلهم بأي طريقة لانهم thermostable and water soluble

Pyrogens and Pyrogen Testing

- USP injection monographs state a bacterial endotoxin unit limit, USP EU. Thus, **injections are not pyrogen or endotoxin free but are limited.**

ited. The following are examples from the USP 32-NF 27 (12):

Dextrose Injection: Contains not more than 0.5 USP EU per mL for injections containing less than 5% dextrose and not more than 10.0 USP EU per mL for injections containing between 5% and 70% dextrose.

Digoxin Injection: Contains not more than 200.0 USP EU per mg of digoxin.

Gentamicin Injection: Contains not more than 0.71 USP EU per mg of gentamicin.

Maximum acceptable endotoxin level [edit]

Because endotoxin molecular weight may vary a great deal (10,000 to 1,000,000 Da), endotoxin levels are measured in "endotoxin units" (EU). One EU is approximately equivalent to 100 pg of E. coli lipopolysaccharide—the amount present in around 10^5 bacteria. Humans can develop symptoms when exposed to as little as 5 EU/kg body weight. These symptoms include, but are not limited to, fever, blood pressure, increased heart rate, and low urine output; and even small doses of endotoxin in the blood stream are often fatal.

The FDA has set the following maximum permissible endotoxin levels for drugs distributed in the United States:

- Drug (injectable, intrathecal) - 0.2 EU/kg body weight
- Drug (injectable, non-intrathecal) - 5 EU/kg body weight
- Sterile water - 0.25-0.5 EU/ml (depends on intended use)

عشان نعرف اكم جسمنا بتحمل EUبنضرب الوزن بـ 5 EU ، ففوق هالرقم بصير عنا اعراض ال endotoxin

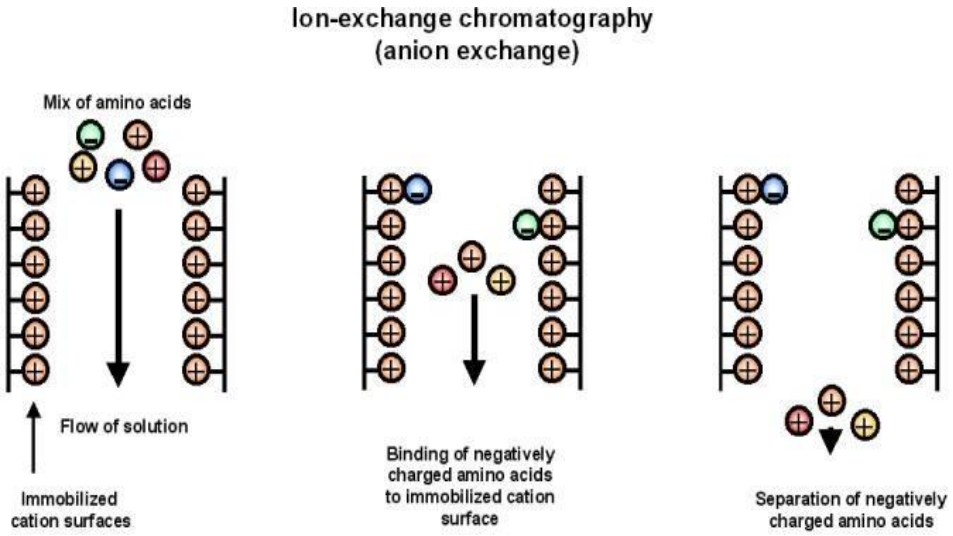
يعني كمية ال LPS الموجودة بـ 10 to the power 5 هي تعادل 1EU ، فهي يعني اكم الكمية الموجودة بـ 10 to th power 5 of bacteria

1EU equal 100 pg Ecoli

Pyrogen removal (depyrogenation)

- **Ion exchange chromatography:**

Endotoxins are negatively charged, and will bind to an *anion exchanger*

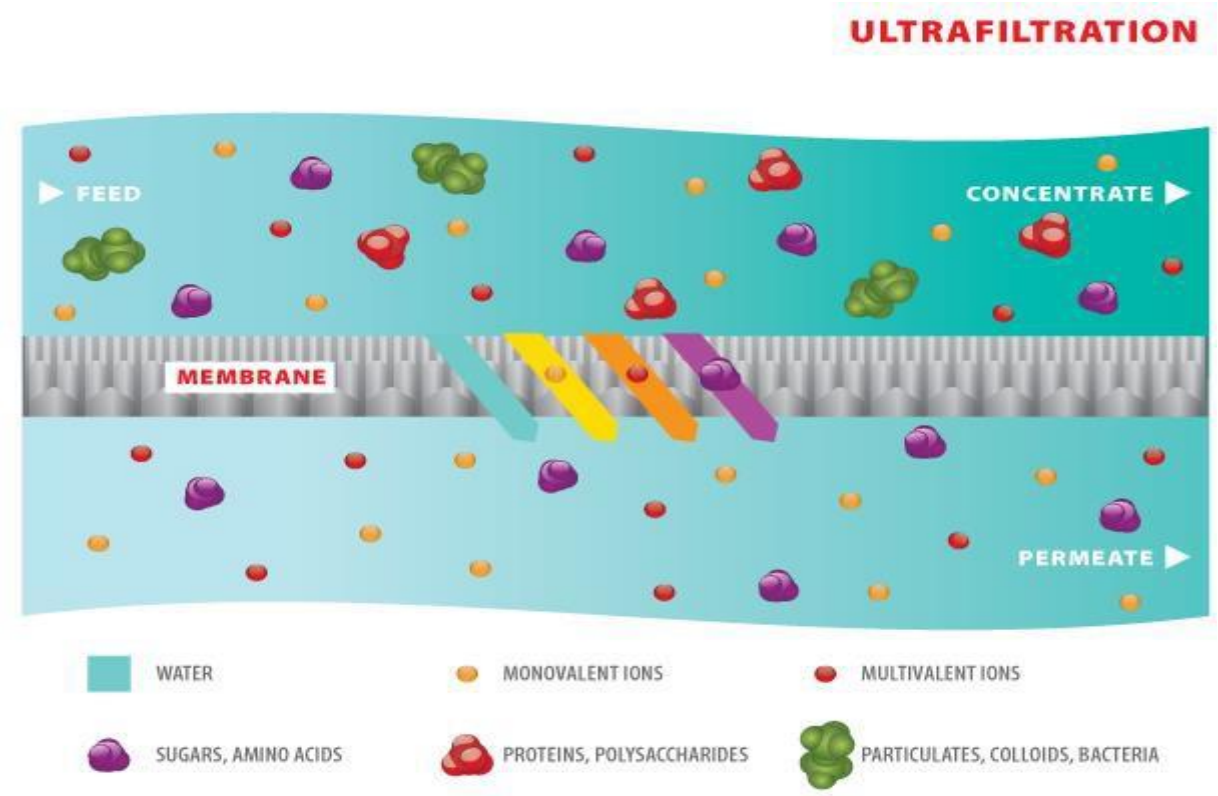


من احد طرق ازالتهم انه نمررهم على chromatography column تحتوي عليى ion exchanger يعني اله positive charge لانه ال endotoxin هي negative charge فبالتالي بطلع الدوا بدونهم

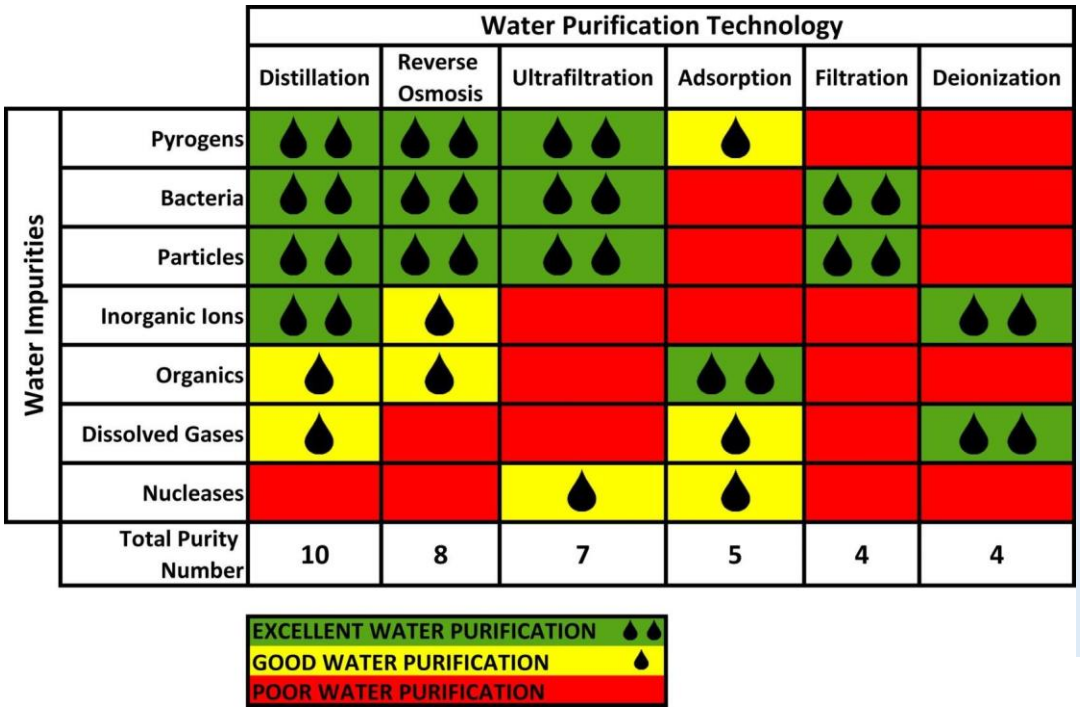
Pyrogen removal (depyrogenation)

هي بنستخدمها اذا كانت ممكنة لنوع ال endotoxin هاد لانه في انواع ما بتزبط معهم

- **Ultrafiltration**:
- this method is best used only when all endotoxins present are larger than 300,000 Da



- **Distillation**:
- The large LPS molecules do not easily vaporize, and are thus left behind in the heating vessel



الجدول مش حفظ، لكن الفكرة المي LPS لا تتبخر لكن بدنا نعرف ال تتبخر

يعني مثلا كيف رح نفهمه خلينا ناخد مثال اللي هو اول سطر:
ال pyrogen ما رح ينفع معها ال filtration and deionization

ال bacteria مثلا ما رح ينفع معها ال adsorption and deionization

De-pyrogenation

Emphasis is placed on prevention of introduction of pyrogens

Removal

- glassware, metals
  - 250 °C for 45 minutes
- water
  - oxidation to nonvolatile solvents using potassium permanganate, then distill
  - reverse osmosis
- plastics
  - protect against contamination

هون بدكم تعرفوا لمين بنعمل هي العملية فهي الصورة حفظ و بدكم تعرفوا انه العملية تتم على درجة حرارة عالية و كمان بدكم تعرفوا ال plastic ما اله هيك طريقة لانه ما بنقدر نحطه على درجة حرارة عالية

B. Amsden

Pyrogen test:
Rabbit test (sham test)

- Render the syringes, needles, and glassware free from pyrogens by heating at 250°C for not less than 30 minutes or by other suitable method.
- Warm the product to be tested to 37°C ± 2°C.
- Inject into an ear vein of each of three rabbits 10 mL of the product per kilogram of body weight, completing each injection within 10 minutes of the start of administration.
- Record the temperature at 30-minute intervals 1 to 3 hours subsequent to the injection.

لازم كلشي بنسخدمه للـ test يكون free of pyrogens بعدين بنعمل warming
للإبرة و من ثم بندخلها لجسم المريض حسب وزنه و طبعا مش مرة وحدة ، بندخلها مرات عدة لمدة 10 دقايق

Pyrogen test:
Rabbit test (sham test)

- If no rabbit shows an individual rise in temperature of 0.5°C or more, the product meets the requirements for the absence of pyrogens.
- If any rabbit shows an individual temperature rise of 0.5°C or more, continue the test using five other rabbits.
- If not more than three of the eight rabbits show individual rises in temperature of 0.5°C or more and if the sum of the eight individual maximum temperature rises does not exceed 3.3°C, the material under examination meets the requirements for the absence of pyrogens.

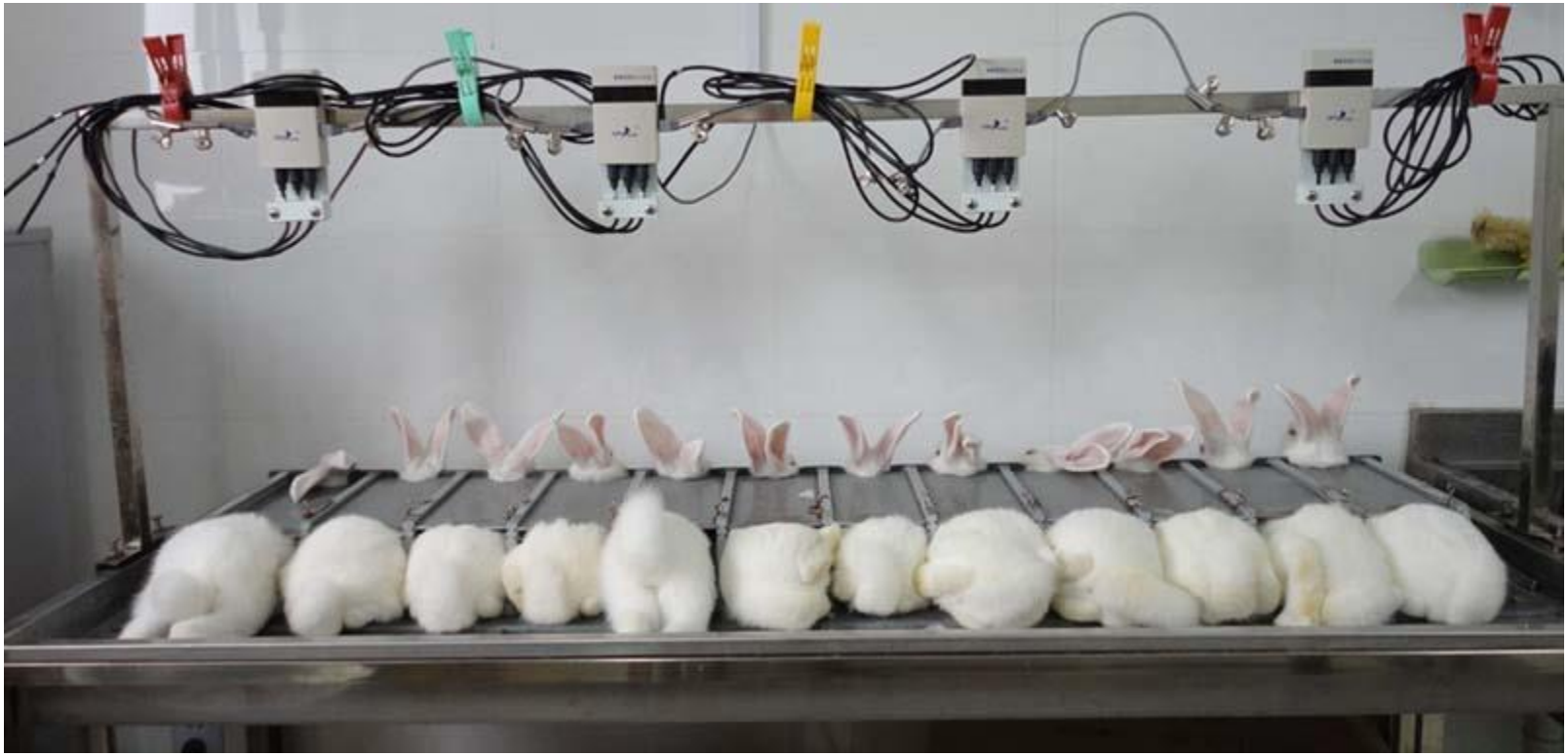
هسا اذا ال product اللي حقنته ما رفع درجة الحرارة 0.5 C او اكثر معناها المنتج ما فيه pyrogens

هسا اذا واحد منهم ارتفعت درجة حرارته بروح بجيب كمان 5 هسا برجع بشوف بعدها اذا sum 3 من اصل ال 8 (3 من قبل و 5 اللي جبتهم بعدين) هسا اذا 3 ارتفعت باخد وقتها بنعتبره 3.3C للارتفاع اللي صار و هاد المجموع اذا كان اكثر من free of pyrogen

Pyrogen test:

Rabbit t est (sham test

Pyrogen test:
Rabbit test (sham test)



Pyrogen test:
LAL test (Bacterial endotoxin test)

- An extract from the blood cells of the horseshoe crab (*Limulus polyphemus*) contains an enzyme and protein system that coagulates in the presence of low levels of lipopolysaccharides.
- This discovery led to the development of the ***Limulus*** **amebocyte lysate (LAL)** test for the presence of bacterial endotoxins.
- The Bacterial Endotoxins Test, USP, uses LAL, and is considered generally more sensitive to endotoxin than the rabbit test.
- The FDA has endorsed it as a replacement for the rabbit test, and it is used for a number of parenteral products.

ميزته انه ما رح نحتاج حيوانات هون فـ عم نحميهم، هون بجيبوا extract from
اسمه Limulus polyphemus بحتوي على انزيمات و بروتينات ففي حالة blood
وجود كمية قليلة من ال endotoxins(LPS) بصيرلها coagulations

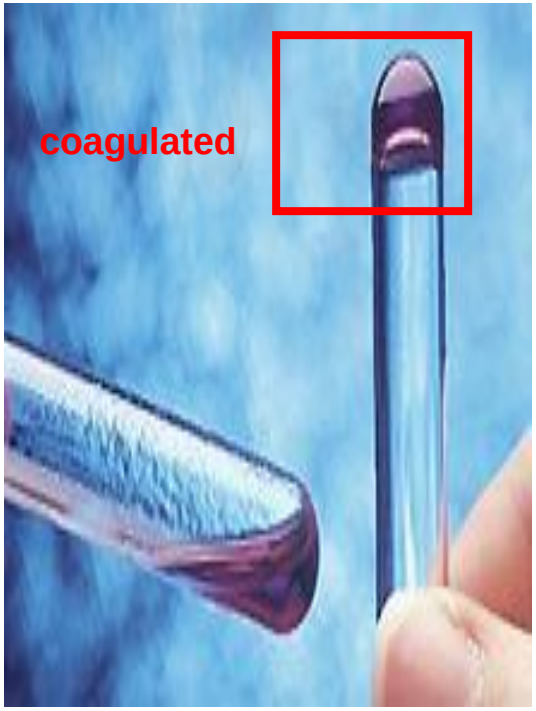
Why is horseshoe crab blood so vital to pharmaceuticals?

Every drug certified by the FDA must be tested with an extract from the animal's blood, but the biomedical harvest is affecting horseshoe crab populations.

LAURA MOSS

March 11, 2014, 1:50 p.m.

340 19



طبعا رغم انهم حكوا انها ما بتأذي الحيوانات بس زي ما انتوا شايفين عملية استخراج المادة هي تاعهم عملية كمان مؤلمة ، فهون هي حيوانات دمها ازرق لما يكون في شوية blood من ال coagulation hgil مباشرة بتعمل endotoxins

B- Pyrogen testing

C. Bacterial Endotoxins Test (LAL Test)

1. Equal volumes of test solution and LAL reagent are mixed in glass test tubes.
2. After incubation at 37 C for 1 h, the tubes are observed for clot formation after inverting them.
3. Formation of a solid gel clot that withstands inversion of the tube constitutes a positive test.

THE INDUSTRIAL PREPARATION OF PARENTERAL: Solutions

- The solutions are usually filtered through a membrane until sparkling clear.
- After filtration, the solution is transferred as rapidly as possible and with the least possible exposure into the final containers.
- The product is then sterilized, preferably by autoclaving, and samples of the finished product are tested for sterility and pyrogens.
- If sterilization by autoclaving is impractical because of the nature of the ingredients, the individual components of the preparation that are heat or moisture labile may be sterilized by other appropriate means and added aseptically to the sterilized solvent or solution of components that can be autoclaved.

THE INDUSTRIAL PREPARATION OF PARENTERAL: Suspensions

- Suspensions of drugs for parenteral use may be prepared by reducing the drug to a very fine powder with a ball mill, micronizer, colloid mill, or other appropriate equipment and then suspending the material in a liquid in which it is insoluble.
- It is frequently necessary to sterilize separately the individual components of a suspension before combining them, as frequently the integrity of a suspension is destroyed by autoclaving.
- Autoclaving of a parenteral suspension may alter the viscosity of the product, affecting the suspending ability of the vehicle, or change the particle size of the suspended particles, altering both pharmaceutical and therapeutic characteristics.
- If a suspension remains unaltered by autoclaving, this method is generally employed to sterilize the final product

- حكينا انه ال parenteral بكونوا اما : solution or suspension or emulsions
- هسا ال solution طرق تصنيعه ليكون sterile بنعمله filtration under aseptic condition
- اذا الـ autoclave ما بزبط (زي suspension عارفين انه بخرب بال autoclave)فبالتالي محتاجين من البداية يكون التصنييع under aseptic condition

هسا فس طرق ثانية لكن بضل ال aseptic conditionاحسن شي بهيك حالة لكن اذا فش مشكلة مع ال autoclaveبنستخدم ال autoclave

THE INDUSTRIAL PREPARATION OF PARENTERAL: Emulsions

- Because parenteral emulsions, which are dispersions or suspensions of a liquid throughout another liquid, are generally destroyed by autoclaving, an alternative method of sterilization must be employed for this type of injectable

نفس حكينا عن ال suspension

THE INDUSTRIAL PREPARATION OF PARENTERAL: Dry powders

- Some injections are packaged as dry solids rather than in conjunction with a solvent or vehicle because the therapeutic agent is unstable in the presence of the liquid component.
- These dry powders are packaged in the final container to be reconstituted, generally to a solution or less frequently a suspension.
- The method of sterilization of the powder may be dry heat or another appropriate method.
- Sometimes a liquid is packaged along with the dry powder for use at the time of reconstitution.

العينات اللي فيها unstability بتعملها as dry powder وهي عادي بنعقمها بال dry heat
و بيجي معها liquid

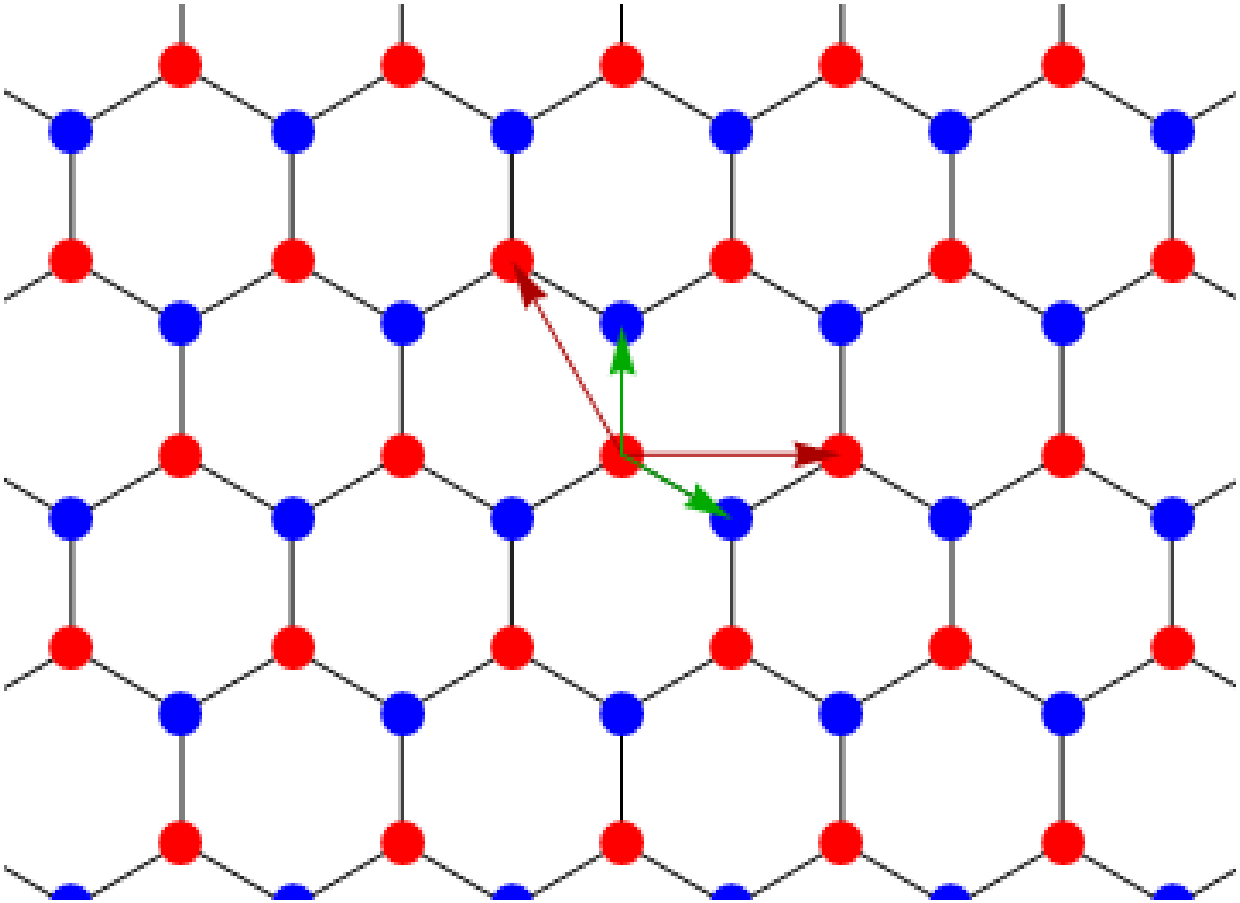
THE INDUSTRIAL PREPARATION OF PARENTERAL: Dry powders

- More frequently, the solvent or vehicle is not provided, but
- the label generally lists suitable solvents.
- Sodium chloride injection and sterile water for injection are perhaps most frequently employed to reconstitute dry- packaged injections.
- The dry powders are packaged in containers large enough to permit proper shaking with the liquid.
- To facilitate dissolution, the dry powder is prevented from caking upon standing by the appropriate means, including lyophilization.
- Powders form a honeycomb lattice structure that is rapidly penetrated by the liquid, and solution is rapid because of the large surface area of powder exposed.

نتذكر مش اي مي بنستخدمها و نتذكر ال lyophilization هي freeze drying فبتخلي الدوا more soluble

ال freeze drying بخليها على شكل honeycomb يعني سداسي زي خلية العسل وهاد بساعد على دخول ال powder بال solution

Saja



Lyophilization of Parenteral (7/93)

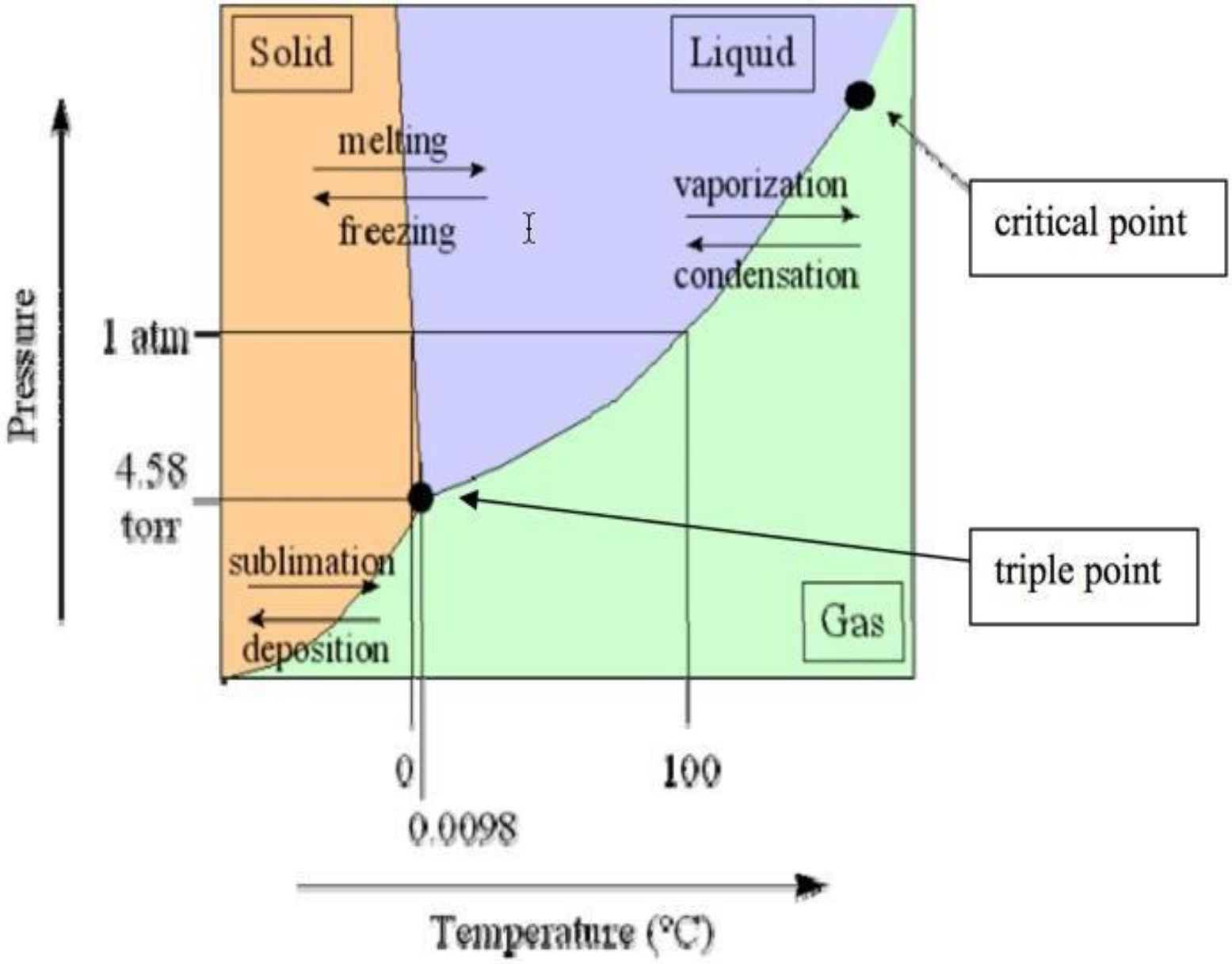
GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does no confer any rights, privileges, benefits, or immunities for or on any person(s).

INTRODUCTION

Lyophilization

- Lyophilization or freeze drying: Freeze-drying works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublimate directly from the solid phase to the gas phase


Solid
Liquid
melting
freezing
vaporization
condensation
critical point
Pressure
1 atm
4.58
torr
sublimation
deposition
triple point
Gas
0
0.0098
100
Temperature (°C)

Lyophilization

- **The advantages of lyophilization include**:
- Ease of processing a liquid, which simplifies aseptic handling
- Enhanced stability of a dry powder
- Removal of water without excessive heating of the product
- Enhanced product stability in a dry state
- Rapid and easy dissolution of reconstituted product
- **Disadvantages of lyophilization include**:
- Increased handling and processing time
- Need for sterile diluent upon reconstitution
- Cost and complexity of equipment

ال Lyophilization : بتكون عينة liquid بنحطها بال freeze dryer
فهاد بقلل من ال pressure الداخلي وبعمل freezing فتتحول ل solid
عن طريق ال sublimation يعني من solid ل gas مباشرة

ال sublimation يحدث على حرارة و ضغط قليل !

هسا شغلات مهمة ركزوا فيها:
*هسا ال lyophilization من فوائدها انه ال liquid المستخدم بيكون تابع لـ aseptic condition
*كمان بحقق ال stability of powder
- كمان ما في حاجة نعرضه لحرارة عالية للتخلص من المي الزيادة
- و بصير ال Dissolution اسرع لانه على شكل honeycomb

لكن عيوبه:
*زدنا هيك كمان step انه صرنا نحتاج dry freezing
*علبة sterile تم اضافتها مما تعني عبئ اكبر
*التكلفة والصعوبة

Lyophilization

*بنسكر نص تسكيرة عشان يضل فرصة لل sublimation

*و شغلة ثانية كمان لاحظوا تم تحويله من liquid ل freeze state ثم لـ dry state

PACKAGING, LABELING, AND STORAGE OF INJECTIONS

- Containers for injections, including the closures,
- must not interact physically or chemically with the preparation so as to alter its strength or efficacy
- If the container is made of glass, **it must be clear and colorless or light amber to permit inspection of its contents.**

لكن لازم يكون كمان بسمح نشوف ويبين اذا انه clean او لا عشان مش مزحة نعمل
injection لـ solution مش clean

- The type of glass suitable for each parenteral preparation is usually stated in the individual monograph.

Single-dose container

- *Single-dose container:* A hermetic container holding a quantity of sterile drug intended for parenteral administration as a single dose; when opened, it cannot be resealed with assurance that sterility has been maintained.

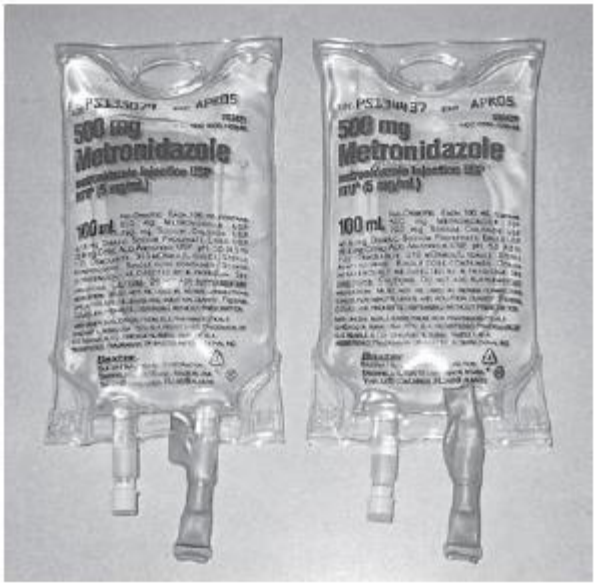
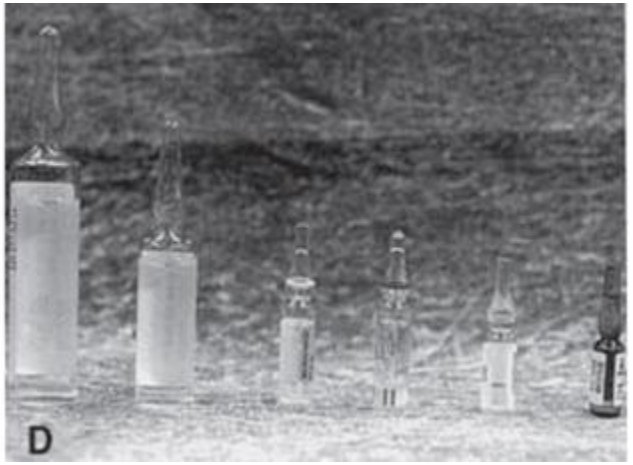


FIGURE 15.15 Two 100-mL single-dose plastic bags for intravenous infusion. (Courtesy of Mr Akinwale O. Onamade.)

عبوة بتكون محكمة الاغلاق وهاد النوع من ال dose بكون لمرة واحدة فقط يعني المريض بفتحها بستخدم بكبها !



Single-dose container

- ampules or single-dose vials.
- Ampules are sealed by fusion of the glass container under aseptic conditions.

Need heat

- The glass container is made so as to have a neck that may be easily separated from the body of the container without breaking the glass.
- After opening, the contents of the ampule should be withdrawn into a syringe with a 5-µm filter needle or straw apparatus. The filter needle is replaced with a regular needle.

بتتعقم و بتتنظف بسرعة و يتم ازالة ال neck بدون كسر الزجاجة

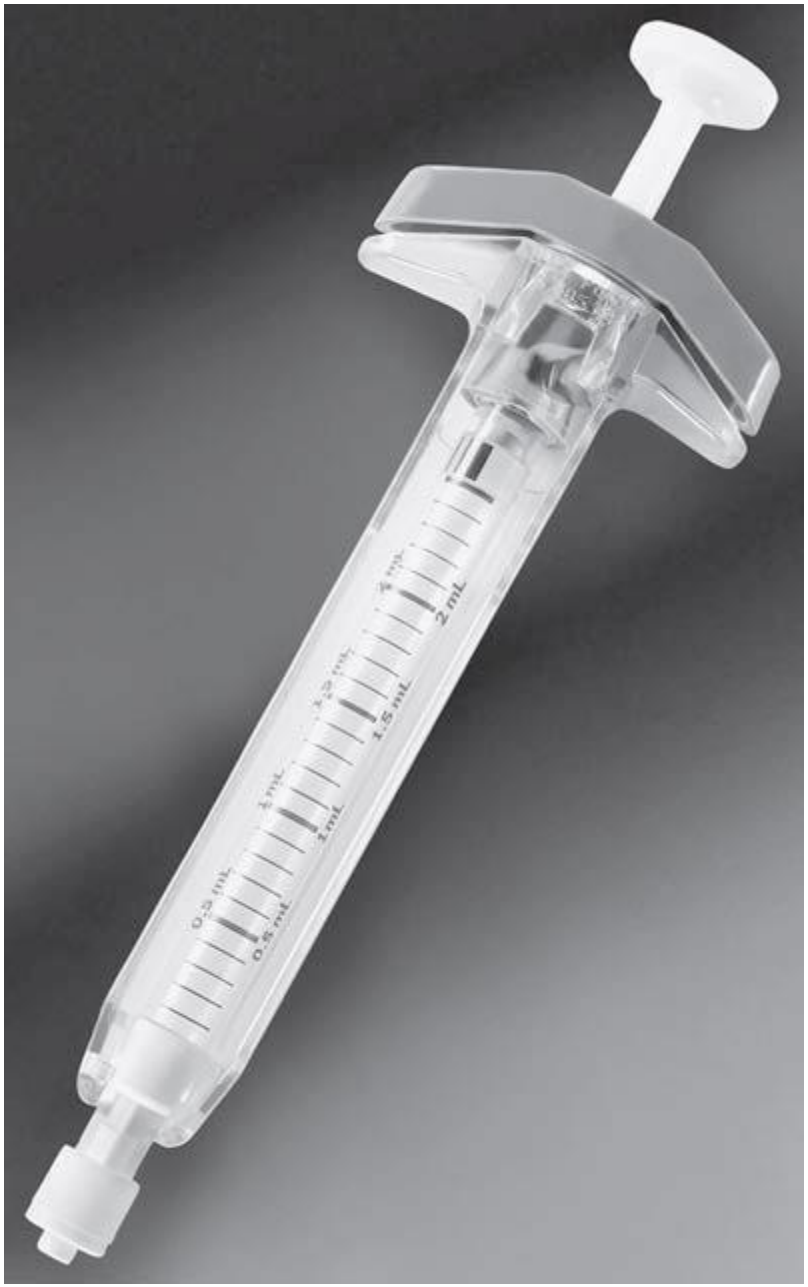
- If a filter needle is not available, withdrawal of glass can be minimized by holding the ampule upright, tilted slightly, when inserting the needle, and avoiding the outer surface of the neck of the ampule. The needle should not be lowered to the bottom of the ampule but held slightly above to avoid drawing glass into the syringe.

بدنا نعرف انه The filter needle is replaced with a regular needle عشان بعد الكسر ما ينسحب قزاز فيها ولازم بس نسحب ما نخلي ال needle ما تضرب بـ neck of ampoule و برضه بنخلي ال ampoule مايلة شوي و لا بنسحب من القاع عشان ما نسحب بقايا زجاج

بتروح ال sterility بس نفتحها

Single-dose container

- Once opened, the ampule cannot be resealed and no unused portion may be retained and used later, as the contents would have lost sterility.
- Some injectable products are packaged in prefilled syringes, with or without special administration devices



Single-dose container

- In addition, preparations intended for intraspinal, intracisternal, or peridural
- administration must be packaged only in single-dose containers as a precaution against contamination.

متى ما عبوا ال ampoule بتمر على حرارة عالية ليصير fusion للـ ampoule زي ما حكينا قبل و يتم برضه تحت aseptic condition

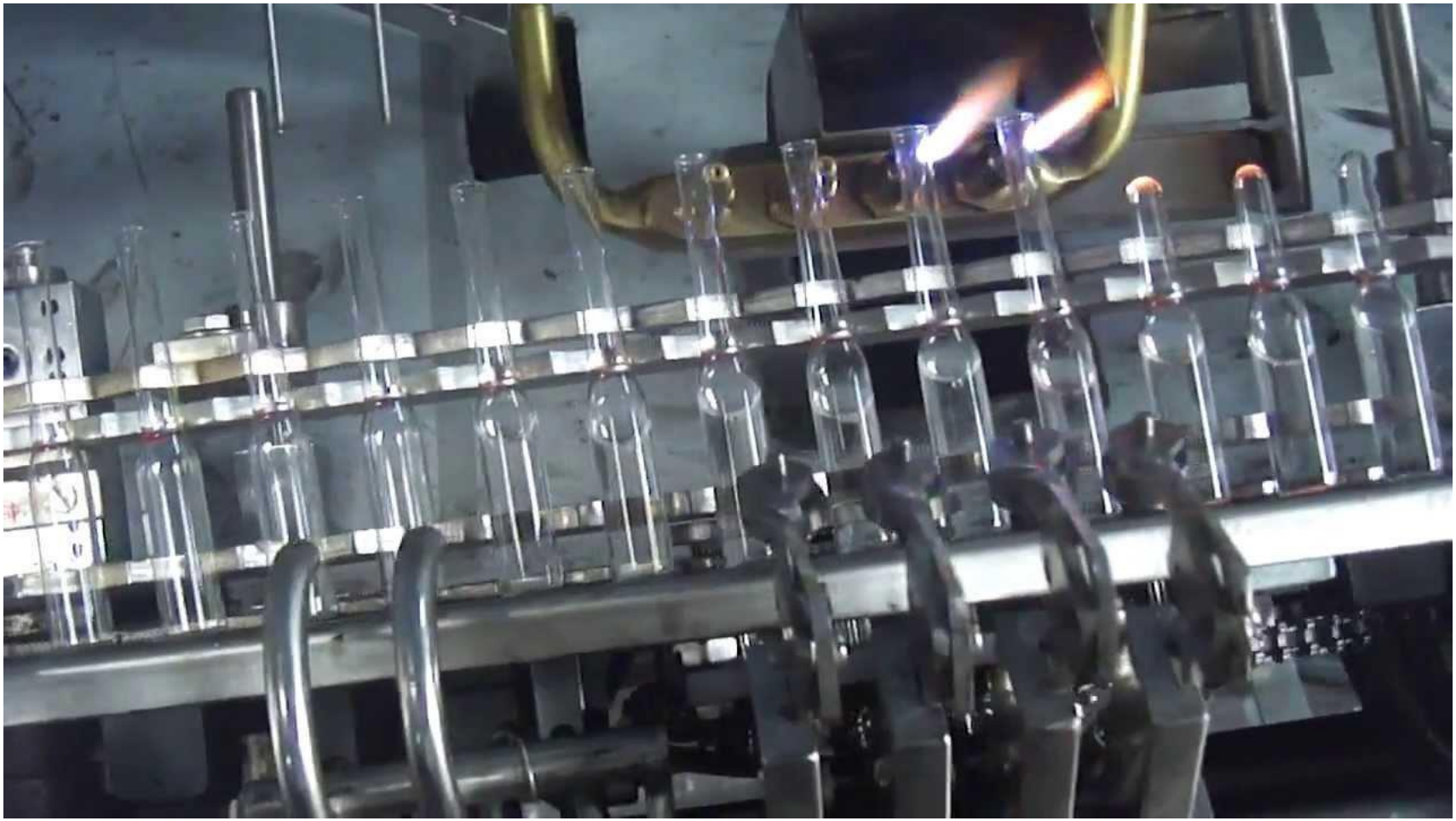


Table 2. Glass Types and Test Limits

Type	General Description[1]	Type of Test	Limits	
			Size,[2] mL	mL of 0.020 N Acid
I	Highly resistant, borosilicate glass	*Powdered Glass*	All	1.0
II	Treated soda-lime glass	*Water Attack*	100 or less	0.7
			Over 100	0.2
III	Soda-lime glass	*Powdered Glass*	All	8.5
NP	General-purpose soda-lime glass	*Powdered Glass*	All	15.0

- The type of glass to be used for a particular injection is indicated in the individual monograph for that preparation.

لكن ال general description & type of test اللي حفظ بالجدول السابق بس ال limit مش مطلوب

- هسا بدنا نشوف شو بدنا نصنع دوا و بنشوف شو المسموح من الزجاج نستخدمه
- بروحوا بطحنوا الزجاج و بعملوا test موجود بال pharmacopeia و بكون very strick و اله limit معين بال pharmacopeia

- *Multiple-dose container:* A hermetic container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

- One of the prime requisites of parenteral solutions is clarity (clear). They should be sparkling clear and free of all particulate matter
- Such contaminants include dust, cloth fibers, glass fragments, material leached from the glass or plastic container or seal, and any other material that may find its way into the product during manufacture or administration or that develop during storage.

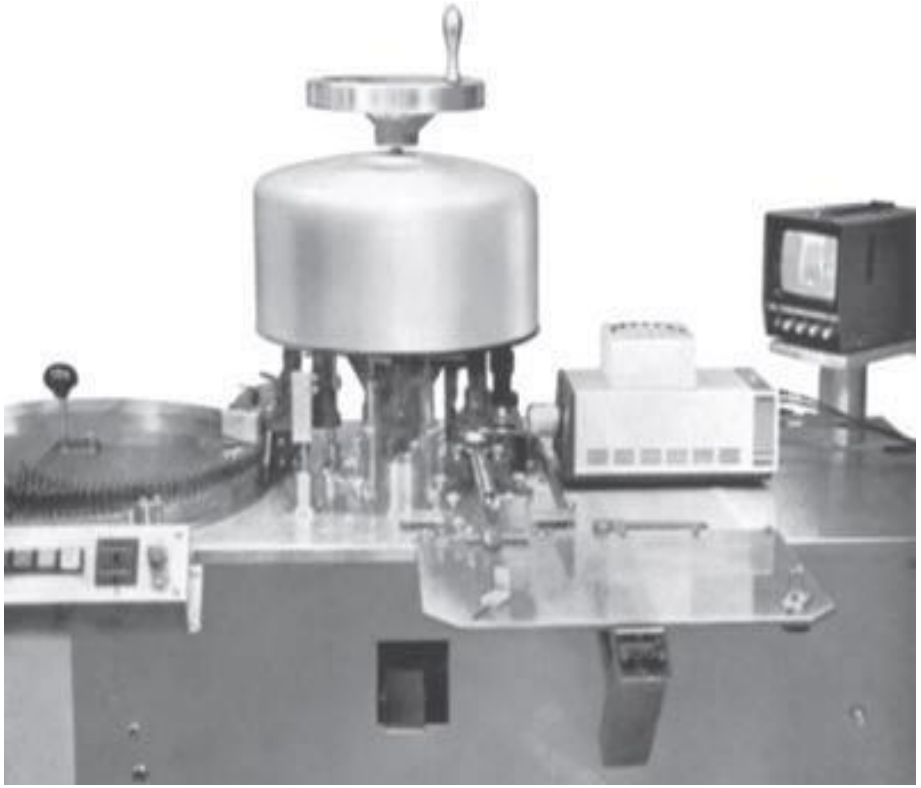
Leached :

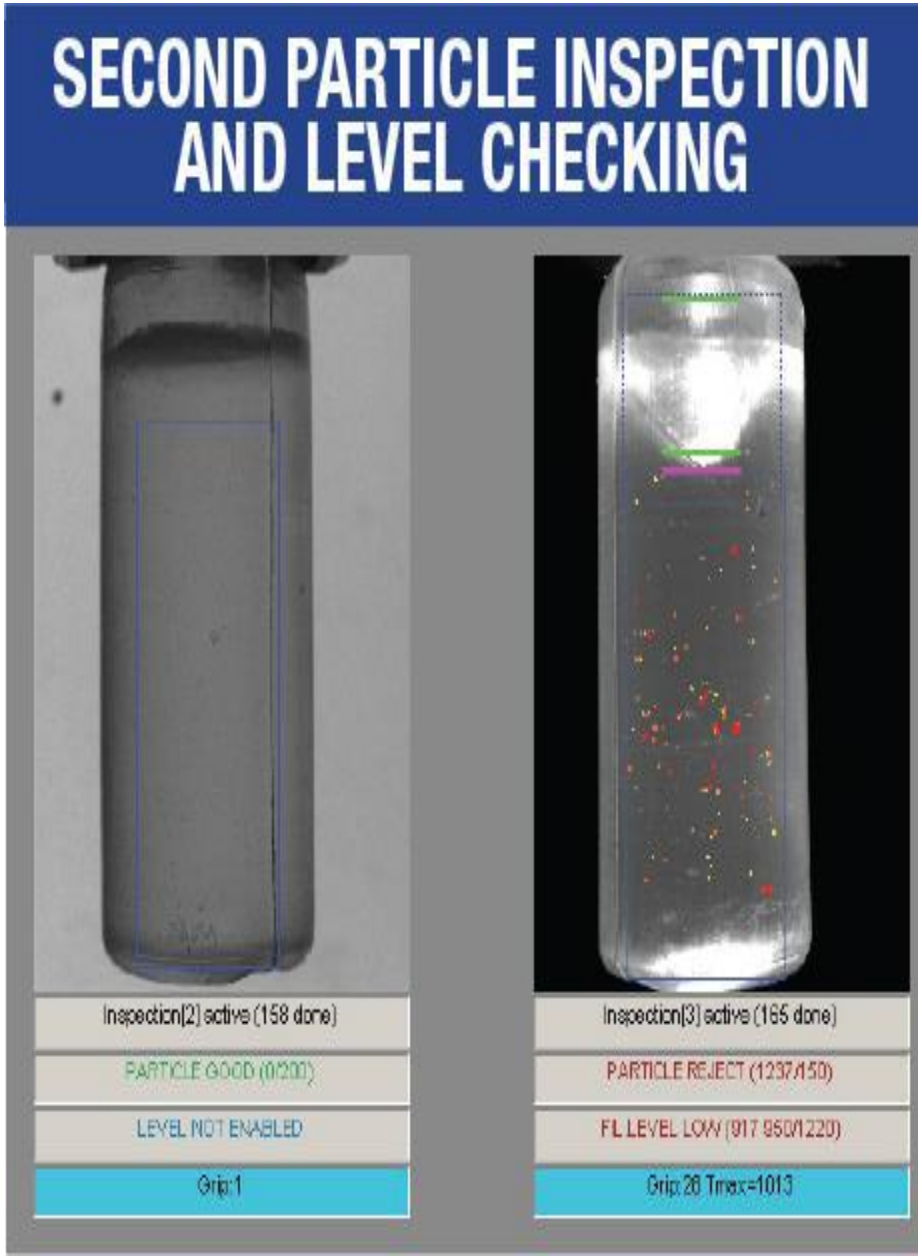
يعني تطلع ال material من ال container للـ Dosage form

- After the containers are filled and hermetically sealed, they are visually or automatically inspected for particulate matter. Usually, an inspector passes (شخص مسؤول) the **filled container past a light source with a black background to observe for mobile particles. Particles of approximately 50 µm may be detected in this manner**.
- Having passed the inspection, the product may be labeled. However, the pharmacist should inspect each parenteral solution for evidence of particulate matter.

بعد ما يعبوا ال container بحطوا المنتج ورا شاشة سودا ليلاحظوا وجود اي particle

Semi-automatic vs automatic particle matter inspection





Electronic بياخد صورة للمنتج و بشوف
اذا في particle material او لا

Multiple-dose container

- Multiple-dose containers are affixed with rubber closures to permit penetration of a hypodermic needle without removal or destruction of the closure.
- Upon withdrawing the needle from the container, the closure reseals and protects the contents from airborne contamination.
- Non-latex closures are being developed and manufacturers will provide a list of their latex-free products.

نظام اغلاقها بسمح بدخول ال needle و بسمح بإنه مكان دخول ال needle يسكر بعد ما نطلعها

Multiple-dose container

- Unless otherwise indicated in the monograph, multiple-dose injectables are required to contain antibacterial preservatives.
- Also, unless otherwise specified, multiple-dose containers are not permitted to allow withdrawal of more than 30 mL to limit the number of penetrations into the closure and thus protect against loss of sterility.
- The usual multiple-dose container contains about 10 usual doses of the injection, but the quantity may vary greatly with the individual preparation and manufacturer.

10 dose بس مسموح

فرضا size of ampoule كان 6 ،هسا حسب ال pharmacopeia في زيادة
شوي لانه بس نسحبها رح يروح جزء من الحجم فقاعات ففي slight excess

- Because it is impossible in practice to transfer the entire volume of a single-dose container or the last dose in a multiple-dose container into a hypodermic syringe, a slight excess in volume of the contents of ampules and vials over the labeled size or volume of the package is permitted.

TABLE 15.2 RECOMMENDED OVERAGES FOR OFFICIAL PARENTERAL PRODUCTS IN MILLILITERS

LABELED SIZE	EXCESS VOLUME FOR MOBILE LIQUIDS	EXCESS VOLUME FOR VISCOUS LIQUIDS
0.5	0.10	0.12
1.0	0.10	0.15
2.0	0.15	0.25
5.0	0.30	0.50
10.0	0.50	0.70
20.0	0.60	0.90
30.0	0.80	1.20
50.0 or more	2.00%	3.00%

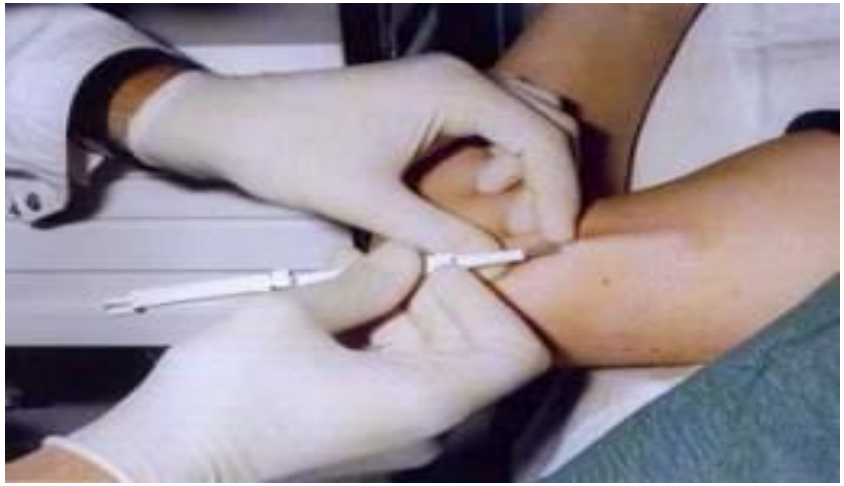
OTHER INJECTABLE PRODUCTS: PELLETS OR IMPLANTS

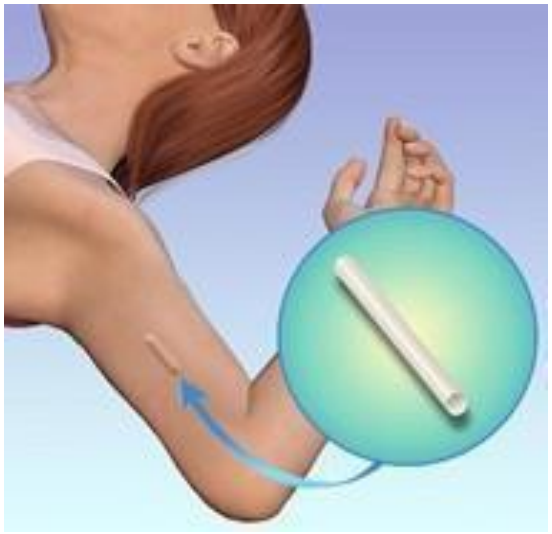
هون للي بنقدر نزرعهم، يعني dose يتم زراعتها مثل موانع الحمل بتنزرع لـ 5 شهور

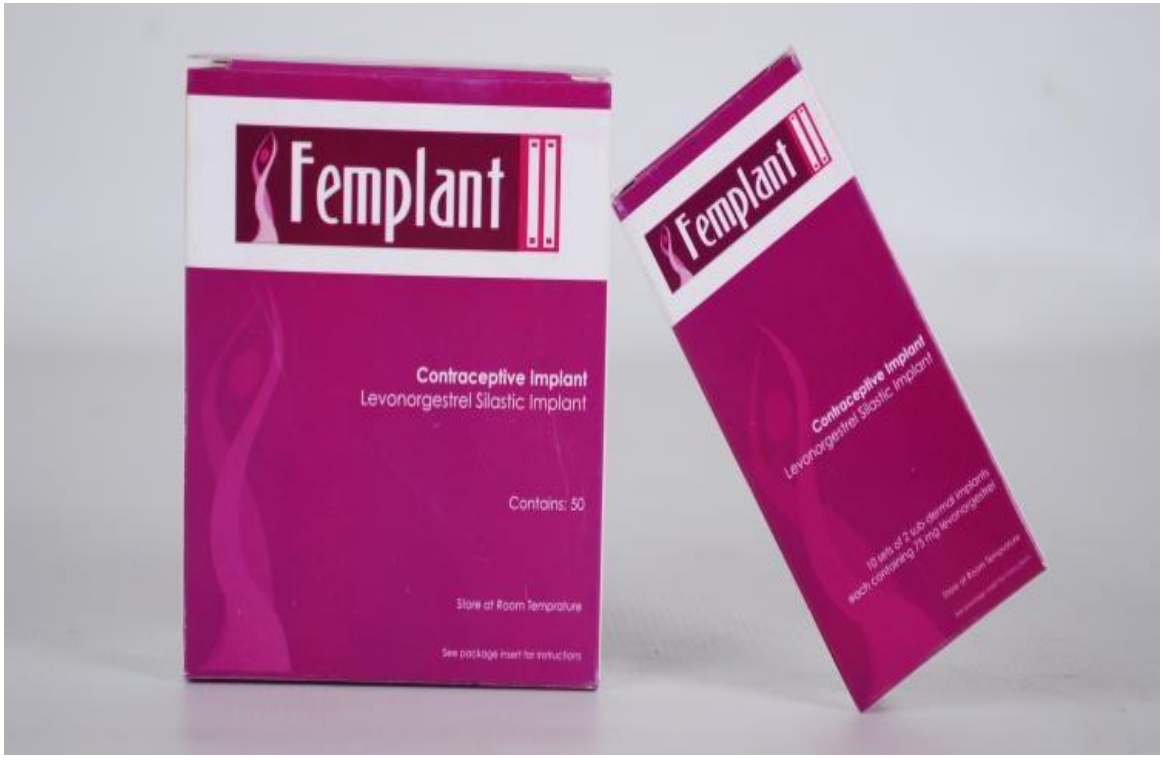
- pellets or implants are sterile, small, usually cylindrical solid objects about 3.2 mm in diameter and 8 mm long, prepared by compression and intended to be implanted subcutaneously to provide continuous release of medication over time.
- The pellets, which are implanted under the skin (usually of the thigh or abdomen) with a special injector or by surgical incision, are used for potent hormones.
- Implantation provides the patient with an economical means of obtaining long-lasting effects (up to many months after a single implantation) and obviates frequent parenteral or oral hormone therapy.

OTHER INJECTABLE PRODUCTS: PELLETS OR IMPLANTS

- The implanted pellet, which may contain 100 times the amount of drug (e.g., desoxycorticosterone, estradiol, testosterone) given by other routes of administration, release the drug slowly into the general circulation.
- Pellets were formulated with no binders, diluents, or excipients, to permit total dissolution and absorption of the pellet from the site of implantation.
- Recently, a levonorgestrel implant contraceptive system was developed. Rather than dissolve entirely, the surgically implanted capsules are intended to be removed by surgery after an appropriate amount of time (up to 5 years).






Femplant
Contraceptive Implant
Levonorgestrel Silastic Implant
Contains: 50
Store at Room Temprature
See package insert for instructions
Femplant
Contraceptive Implant
Levonorgestrel Silastic Implant

حكت الدكتورة ما في داعي ندخل فيهم

TABLE 15.8 EXAMPLES OF IRRIGATION SOLUTIONS

SOLUTION	DESCRIPTION
Acetic acid irrigation, USP	0.25% solution applied topically to bladder for irrigation; pH 2.8–3.4, calculated osmolarity 42 mOsm/L; during urologic procedures, washes away blood, surgical debris while maintaining suitable conditions for tissue and permitting unobstructed view
Neomycin and Polymyxin B sulfates solution for irrigation, USP	Sterile urogenital solution contains 57 mg neomycin sulfate (40 mg neomycin) and polymyxin B sulfate 200000 U/mL; topical antibacterial in continuous irrigation of bladder; pH 4.5–6; 1 mL added to 1 L 0.9% NaCl, administered via three-way catheter at 1 L/24 h (40 mL/h approx.)
Ringer's irrigation, USP	NaCl 8.6 g/L, potassium chloride 0.3 g/L, calcium chloride 0.33 g/L in purified water, in same proportions as in Ringer's injection. Sterile and pyrogen free; used topically to irrigate; must be labeled NOT FOR INJECTION; pH 5–7.5, calculated osmolarity 309 mOsm/L
Sodium chloride irrigation, USP	NaCl in water for injection; 77, 154 mEq/L of each sodium, chloride in 0.45% and 0.9% solutions, respectively; NaCl irrigation pH 5.3 approx.; 0.45%, 0.9% solutions calculated osmolarity 154, 308 mOsm/L, respectively. Employed topically to wash wounds and body cavities where absorption into blood not likely; also employed as enema; for simple evacuation, 150 mL; for colonic flush, 1500 mL may be used
Sterile water for irrigation, USP	Sterilized and suitably packaged. Label designations FOR IRRIGATION ONLY, NOT FOR INJECTION must appear prominently. Must not contain any antimicrobial or other added agent

PARENTERALS-II

اللي جاي رح تلاحظوا ما في حكي كثير ف اقرأوا السلايد منيح بعدين شوفوا شو النوتس اللي سجلتهم مع الدكتورة بالسلايد

Containers and Closures

Containers and Closures

- Ampoules, vials, syringes, cartridges, bottles, bags
- Ampoules are all glass
- Bags are all plastic
- The other containers can be composed of glass or plastic and must include rubber materials such as rubber stoppers for vials and bottles, and rubber plungers and seals for syringes and cartridges
- Irrigation solutions are packaged in glass bottles with aluminum screw caps

- Properties of container materials to be considered:

1. Leaching
2. Permeation
3. Adsorption
4. Integrity of container/closure

Table 26-2. Comparative Compatibility Properties of Container Materials

	Leaching		Permeation		Adsorption (Sele
	Extent[a]	Potential Leachables	Extent[a]	Potential Agents	Extent[a]
Glass					
Borosilicate	1	Alkaline earth and heavy metal oxides	0	N/A	2
Soda-lime	5	Alkaline earth and heavy metal oxides	0	N/A	2
Plastic polymers					
Low density	2	Plasticizers, antioxidants	5	Gases, water vapor, other molecules	2
High density	1	Antioxidants	3	Gases, water vapor, other molecules	2
PVC	4	HCl, especially plasticizers, antioxidants, other stabilizers	5	Gases, especially water vapor and other molecules	2
Polyolefins	2	Antioxidants	2	Gases, water vapor	2
Polypropylene	2	Antioxidants, lubricants	4	Gases, water vapor	1
Rubber polymers					
Natural and related synthetic	5	Heavy metal salts, lubricants, reducing agents	3	Gases, water vapor	3
Butyl	3	Heavy metal salts, lubricants, reducing agents	1	Gases, water vapor	2
Silicone	2	Minimal	5	Gases, water vapor	1

Container Types
Glass

- Composed of silicone dioxide with varying amounts of other oxides (other oxides only loosely bound→ free to migrate) اشي بتركيبة الزجاج بفك و بصير بال solution
- These migratory oxides may be leached into a solution in contact with the glass especially during increased reactivity of thermal sterilization
- The dissolved oxides may:

1. hydrolyze to raise the pH of the solution
2. and catalyze or enter into reaction

- Some glass compounds attacked by solution and dislodges glass flakes into solution فتافيت زجاج تدخل على ال solution
- Such problems can be minimized by the selection of proper glass type

Container Types
Glass

Types:

1. Types I: a borosilicate glass
2. Type II: a soda-lime treated glass
3. Type III: a soda-lime glass Not treated
4. NP: a soda lime glass not suitable for containers for parenterals Not for parenteral

هي اقل نوعية

Table 1. Determination of Glass Types in European and United States Pharmacopeias

Container Type	General Description	EP Tests	USP Tests Current	USP Tests Proposed
Type I	Borosilicate glass	• Glass grains • Surface glass • Surface etching	• Powdered glass * [Surface glass]	• Glass grains • Surface glass • Surface etching
Type II	Treated soda-lime glass	• Glass grains • Surface glass • Surface etching	• Water attack at 121°C * [Surface glass]	• Glass grains • Surface glass • Surface etching
Type III	Soda-lime glass	• Glass grains • Surface glass	• Powdered glass * [Surface glass]	• Glass grains • Surface glass

* [Surface glass] Test is present but does not define glass Type

http://www.americanpharmaceuticalreview.com/Featured-Articles/37187-Parenteral-Products-Pharmacopeial-Control-of-Containers-Storage-and-Distribution/

مش حفظ بس بدنا نعرف كل واحد لازم نعمله test

- Type I glass → suitable for all products اغلى نوع
- Type II glass → buffered solutions or has a (pH < 7)
- Type III glass → anhydrous liquids or dry substances

عشان هيك مش دايما بنستخدم اول نوع لانه السعر مهم ننتبهله

Leachable/extractables

- If product is sensitive to ions (boron, sodium, calcium..)→
- Presence of formulation components that can act as metal chelating agents (EDTA, citrate) → تسمح بخروج ال metal من ال solution
- great care must be taken in selecting appropriate type of glass container
- These ions may interact with the product:

1. Reduce chemical stability
2. Induce formation of particulate
3. Alter pH of solution

- **Extractables – Potentials**
  - Determined in Laboratory Experiments using Neat Solvents under Conditions that Predict the "Worst Case" Conditions of Exposure.
    - Contact Time, Temperature, Solvating Power of Drug. etc
- **Leachables – Actuals**
  - In the Presence of the Drug or Drug Components During Normal Use
    - Processing, Shelf-Life, Stability Studies, etc.

Extractables

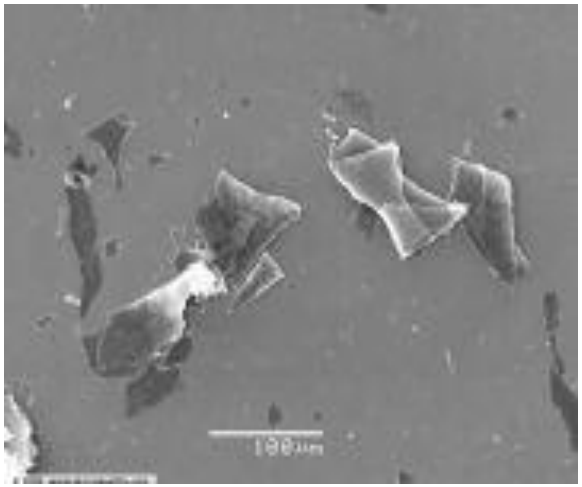
تحت ظروف صعبة (worsen condition) و بنشوف شو ممكن يطلع

Leachables

هي بدون اي force بنلاقيها لحالها طلعت لل solution

Delamination: glass particulate formation

- Caused by chemical attack on the glass matrix by the formulation solution
- This results in weakening of the glass and dislodgement of flakes from the glass surface



Adsorption

- Adsorption of drugs to contact surfaces and consequent loss of potency
- Proteins, small drug products at low concentration
- Solution/container evaluation
- Stability studies

http://www.plastics.gl/packaging/viable-for-vials/

Cracks and scratches

High speed pharmaceutical glass vial inspection with Cognex In-Sight vision systems

Few industrial sectors have such stringent quality requirements as the pharmaceutical industry. To meet these exacting specifications, companies are increasingly utilizing intelligent vision systems.

For over 30 years, EISAI Machinery GmbH, located in Cologne, Germany, has been an expert in the field of high speed pharmaceutical product testing Its latest device, the AIM 596, can inspect delicate glass vials in fractions of a second, thanks to two Cognex In-Sight vision systems.

Depending on the application and customer requirements, the machine can check approximately 6,000 packages and in its fastest version, the device, with its imposing inspection towers and star wheels, can even

Physical characteristics

- Glass containers must be strong enough to withstand:
- The physical shocks of handling and shipping
- the pressure differentials that develop, particularly during the autoclave sterilization cycle.
- the thermal shock resulting from large temperature changes during processing, for example, when the hot bottle and contents are exposed to room air at the end of the sterilization cycle.

مش منطقي تتكسر بسرعة

Physical characteristics

- Preparations that are light-sensitive must be protected, by placing them in amber glass containers
- amber color of the glass is imparted by the incorporation of potentially leachable heavy metals, mostly iron and manganese(بعطوا لون), which may act as catalysts for oxidative degradation reactions.
- Silicone coatings are sometimes applied to containers

بمنع ال solution to get in contact with metal

Rubber closures

- vial is sealed with a rubber closure held in place by an aluminum cap

حيث عنا انواع كثيرة

We have to be careful in choosen right rubber closure

Table 26-3. Examples of Ingredients Found in Rubber Closures

Ingredient	Examples
Elastomer	Natural rubber (latex)
	Butyl rubber
	Neoprene
Vulcanizing (curing agent)	Sulfur
	Peroxides
Accelerator	Zinc dibutyldithiocarbamate
Activator	Zinc oxide
	Stearic acid
Antioxidant	Dilauryl thiodipropionate
Plasticizer/lubricant	Paraffinic oil
	Silicone oil
Fillers	Carbon black
	Clay
	Barium sulfate
Pigments	Inorganic oxides
	Carbon black

Rubber held in its place by aluminum cap

مجرد ما فتحته و استخدمته بصيرش ترجع تستخدمه وبكون مبين من فوق اذا العلبة انفتحت او لا

Rubber closures

- The physical properties considered in the selection of closures include:

1. Elasticity: The elasticity is critical in establishing a seal with the lip and neck of a vial or other opening and in resealing after withdrawal of a hypodermic needle from a vial closure
2. Hardness: The hardness should provide firmness, but not excessive resistance to the insertion of a needle through the closure,
3. tendency to fragment, and minimal fragmentation of pieces of rubber should occur as the hollow shaft of the needle is pushed through the closure
4. and permeability to vapor transfer: Although vapor transfer occurs to some degree with all rubber formulations, appropriate selection of ingredients makes it possible to control the degree of permeability

مش مطالبين فيها

⟨381⟩ ELASTOMERIC CLOSURES FOR INJECTIONS

Change to read:

INTRODUCTION

Elastomeric closures for containers used in the types of preparations defined in the general test

tempt to change a closure that does not meet compendial requirements to one that does conform. Therefore, all *Physicochemical Tests* apply to the base formula of such closures, as well as to the coated or laminated closure. To obtain *Physicochemical Tests* results, the tests are to be performed on uncoated or non-laminated closures of the same elastomeric compound, as well as to the laminated or coated closure. The *Functionality Tests* apply to and are to be performed using the

هاد الدوا كان منيح واموره تمام لحد ما اكتشفوا مادة فيه بتسبب تكسر صفائح دم الاطفال

PURE RED-CELL APLASIA "EPIDEMIC"—MYSTERY COMPLETELY REVEALED?

Francesco Locatelli[1], **Lucia Del Vecchio**[2] **and Pietro Pozzoni**[1]

[+] Author Affiliations

Correspondence to: F. Locatelli, Divisione di Nefrologia e Dialisi, Ospedale A. Manzoni, Via Dell'Eremo 11, Lecco 23900 Italy. nefrologia@ospedale.lecco.it

Abstract

Starting in 1998, the number of pure red–cell aplasia (PRCA) cases in patients treated with recombinant human erythropoietin (rHuEPO) increased dramatically. Most cases were observed in patients treated with epoetin alfa produced outside the United States. The peak was observed in 2002; since then, the PRCA incidence has declined.

Many factors are likely to have contributed to this upsurge. The molecular structure of the various epoetins and patient characteristics do not seem to play a major role. The route of administration holds some importance, because most PRCA patients received rHuEPO subcutaneously. The peak of

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This Article

Parit Dial Int **June 2007** vol. 27 no. Supplament 2 **S303–S307**

Abstract *Free*
» **Full Text**
Full Text (PDF)

[–] **Classifications**

Part 9: Miscellaneous Complications and Pathophysiologic Mechanisms

[–] **Services**

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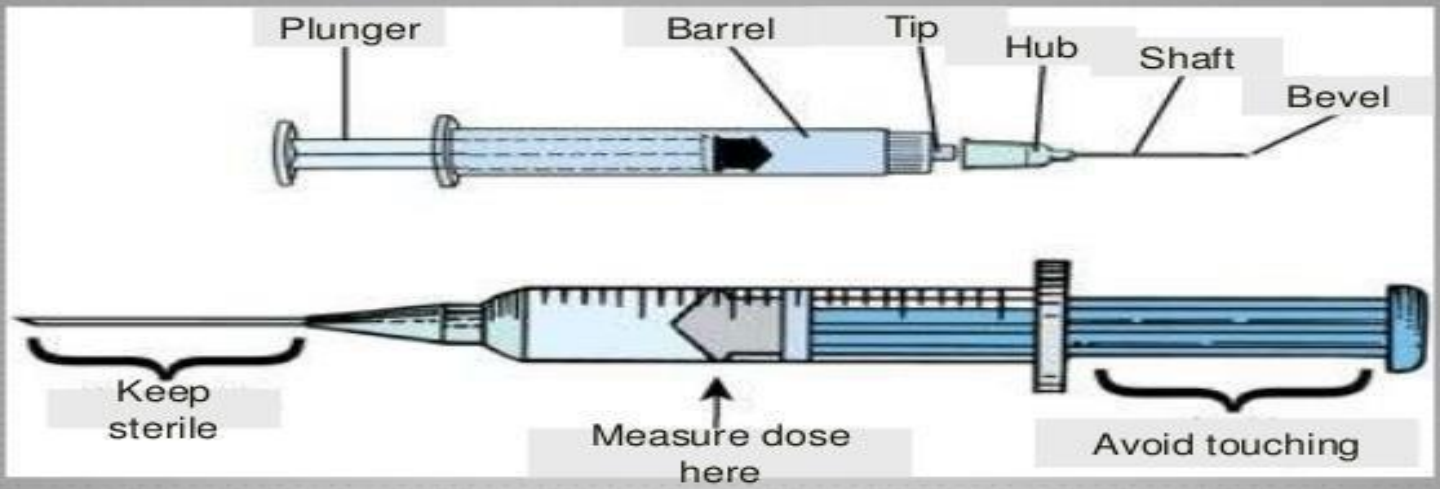
Higher G so lower outside diameter

Needles

- Needles are hollow devices composed of stainless steel or plastic.
- Needles are available in a wide variety of lengths, sizes, and shapes.
- Needle lengths range from 1/4 inch to 6 inches.
- Needle size is referred to as its gauge (G), or the outside diameter (OD) of the needle shaft.
- Gauge ranges are 11 to 32 G,
- 16 G needles have an OD of 0.065 inches (1.65 mm), whereas 32 G have an OD of 0.009 inches (0.20 mm).
- Needle shape includes regular, short bevel, intradermal, and winged.
- Needle shape is defined by one end of a needle enlarged to form a hub with a delivery device, such as a syringe, or other administration device.
- The other end of the needle is beveled, meaning it forms a sharp tip to maximize ease of insertion.

PARTS OF THE SYRINGE



Barrel:

بدخل الدوا فيه

Bevel:

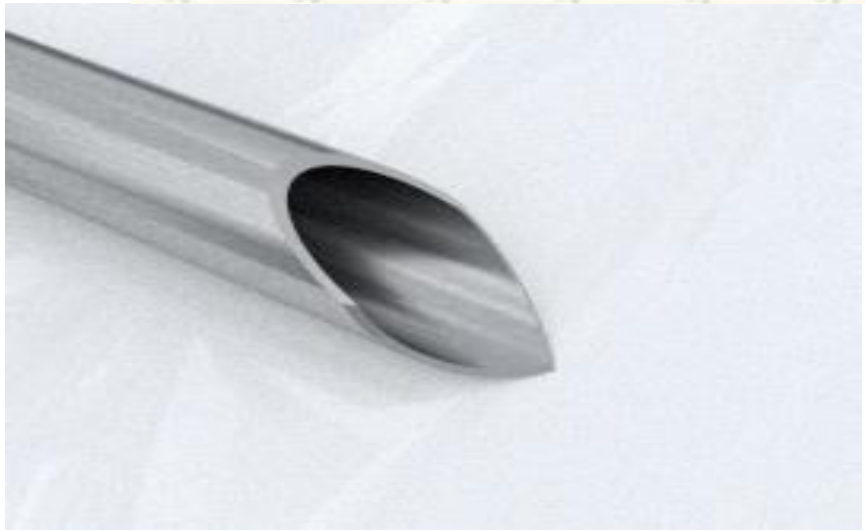
بندخلها جوا الجلد

Keep sterile :

هي ال needle

Avoid touching:

هون ما بصير نقرب ايدنا لأنه رح يدخل هالمكان داخل الجرعة الدوائية



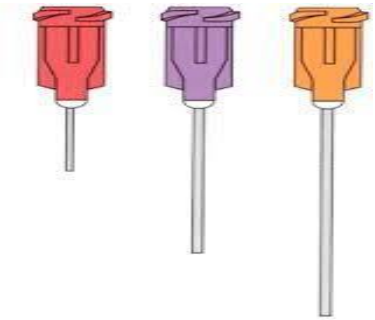
Higher G so lower outside diameter

	Outer Diameter (mm)	Gauge Needle	Hub Color
	0.23	32	Orange
	0.25	31	Violet
	0.30	30	Yellow
	0.33	29	Red
	0.36	28	Blue Green
	0.40	27	Medium Grey
	0.45	26	Brown
	0.50	25	Orange
	0.60	23	Deep Blue
	0.70	22	Black
	0.80	21	Deep Green
	0.90	20	Yellow
	1.10	19	Cream
	1.20	18	Pink
	1.60	16	White

مش للحفظ

- Intravenous injections use 1–2 inch 15–25 G needles. Intramuscular injections use 1–2 inch 19–22 G needles.
- Subcutaneous injections use 1/4–5/8 inch 24–25 G needles.
- Needle gauge for children rarely is larger than 22 G, usually 25–27G.
- Winged needles are used for intermittent heparin therapy.

- Needles are purchased either alone (e.g., Luer-Lok) to be attached to syringes, cartridges, and other delivery systems,
- or, for syringes, can be part of the syringe set (stake needle).



Filling

- Most frequently, the compounded product is in the form of a liquid. However, products are also compounded as dispersed systems (e.g., suspensions and emulsions) and as powders

التعبئة لل solution سهلة ، لكن لل solid صعبة لانه بدنا نحافظ على ال rate of flow

Filling

- Sterile solids, such as antibiotics, are more difficult to
- subdivide evenly into containers than are liquids:

1. The rate of flow of solid material is slow and often irregular.
2. Even though a container with a larger-diameter opening is used to facilitate filling, it is difficult to introduce the solid particles, and the risk of spillage is ever-present
3. The accuracy of the quantity delivered cannot be controlled, as well as with liquids.

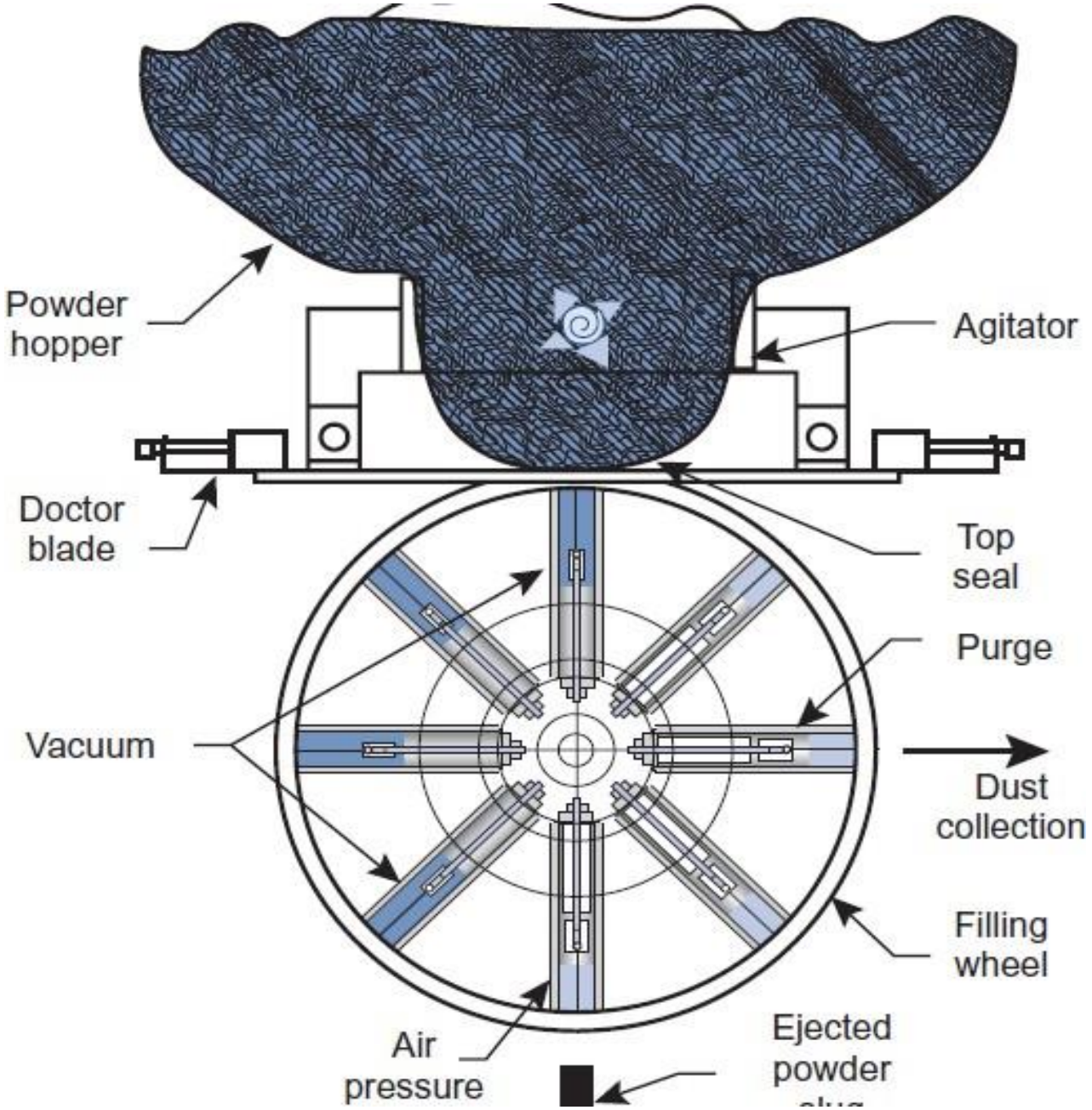
- Due to these factors, the tolerances permitted for the content of such containers must be relatively large.

Filling

1. quantity filled into the container is weighed on a balance
2. measurement and delivery of a volume of the granular material that has been calibrated in terms of the weight desired.

الطرق للتعبئة كالتالي :

يا بنوزن و بنعمل تعبئة او بنستخدم جهاز اله
Pressure معين بحيث انها بتولد vacuum
بسحب الكمية الصح من ال powder وبنعمللها
injection to container


Powder hopper
Agitator
Doctor blade
Top seal
Purge
Vacuum
Dust collection
Filling wheel
Air pressure
Ejected powder

- aluminum caps:

1. Rubber closures are held in place by means of it
2. The caps cover the closure, crimped under the lip of the vial or bottle to hold them in place.
3. The closure cannot be removed without destroying the aluminum cap; it is tamperproof→ an intact aluminum cap is proof that the closure has not been removed intentionally or unintentionally.

B

Container-closure integrity test

- Container-closure integrity testing: measures the ability of the seal between the glass or plastic container opening and the rubber closure to remain tight and fit and to resist any ingress of microbial contamination during product shelf life.
- Container-closure integrity test requirements are covered in USP <1207>

Container-closure integrity test

- Ampoules that have been sealed by fusion must be subjected to a test to determine whether or not a passageway remains to the outside; if so, all or a part of the contents may leak to the outside and spoil the package, or micro-organisms or other contaminants may enter.

Container-closure integrity test

- This test is usually performed by producing a negative pressure within completely sealed ampoule, while the ampoule is submerged entirely in a deeply colored dye solution.
- Most often, approximately 1% methylene blue solution is employed.
- After carefully rinsing the dye solution from the outside, color from the dye will be visible within a leaker. Leakers, of course, are discarded

هاد ال test الهدف منه نتأكد من احكام الاغلاق فبروحوا بجيبوا الdrug و بنعبيه in container ومن ثم بنحطه و بنعمله immersion بصبغة اللي هي methylene blue solution ، هسا اي vial بصير لونه ازرق معناها ما في integrity يعني في دخول من برا لجوا يعني ممنوع نستخدمها لأنه صار Leakage