محاضرة: Parentral Part 2

الصيدلاني\ة: Rahaf Tyoul

لجان الدُّفعات

Soul Academy

Pyrogen test: Rabbit test (sham test)

No rise in temp (0.5c or more) → No Pyrogen

- 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.

rise in temp (0.5 c° or more) → ارانب ثانية 5 على test يرجع اعيد ال

- If any rabbit shows an individual temperature rise of 0.5°C or more, continue the test using five other rabbits.

عطيه ملاحظه ع test بالمشت ال 3 ارانب اذاً صار المجموع الكلي 8 بعد الإعاده

- 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.

اذا كان 3 من ال 8 ما صار فيهم ارتفاع بدرجه الحرارة بمقدار 5c° + مجموع الإرتفاع

Free from Pyrogen بدرجه الحرارة لل 8 مش اكثر من 3.3c° بقدر اقول عنه

Pyrogen test:
Rabbit test (ohem 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.

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.

صار له coagulation يعني صار صلب

THE INDUSTRIAL PREPARATION OF PARENTERAL: Solutions

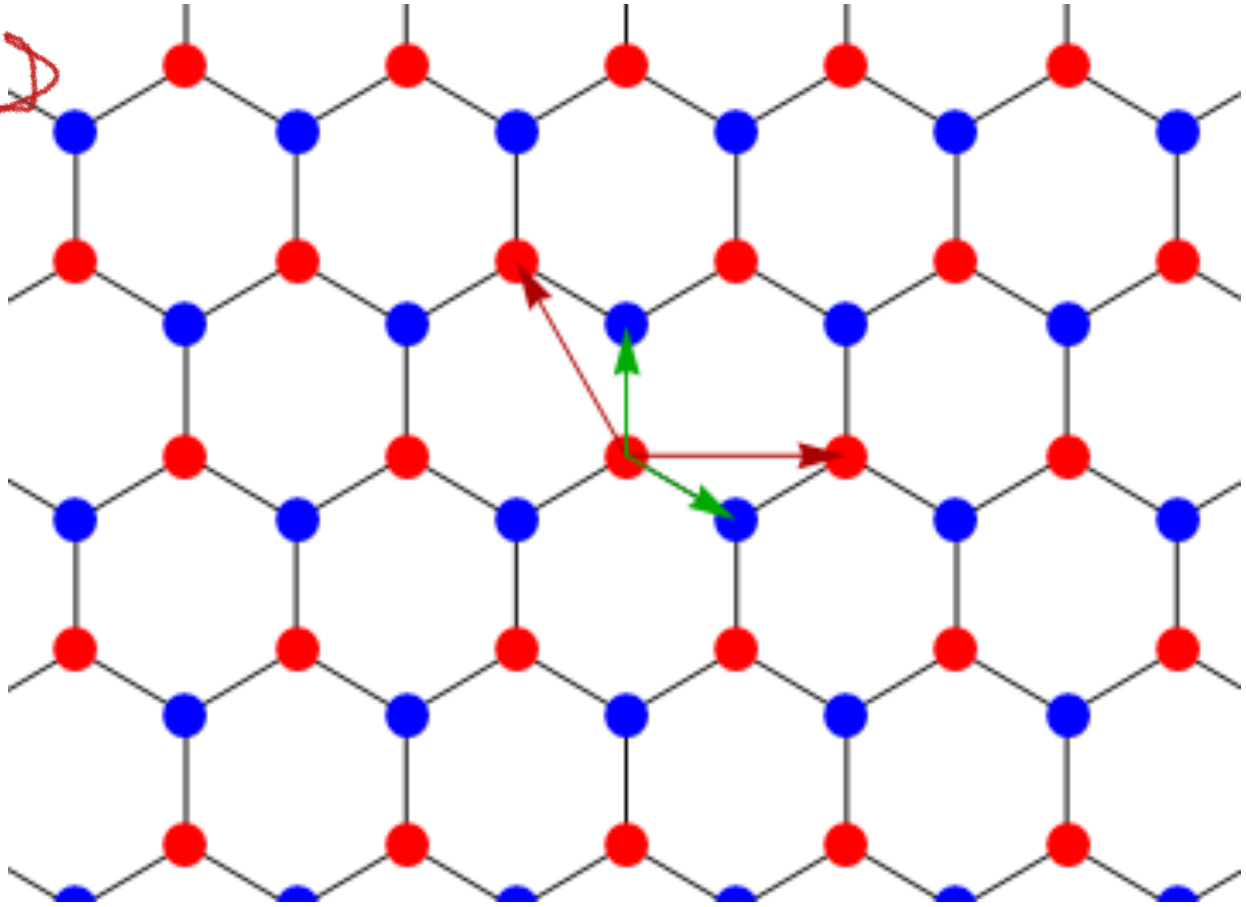
- The solutions are usually filtered through a membrane until sparkling clear.
- After filtration, the solution is transferred as rapidly as possible and with the least possible exposure into the final containers.
- The product is then sterilized, preferably by autoclaving, and samples of the finished 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: Emulsions

الدوا ممكن يكون ذائب بال انه بال water او ممكن يكون معلق

- 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

بخلي بينه فوانات عشان الـ dissolution يطير اسرع



Inspections, Compliance, Enforcement, and Criminal Investigations

Inspection Guides
Inspection Technical Guides

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

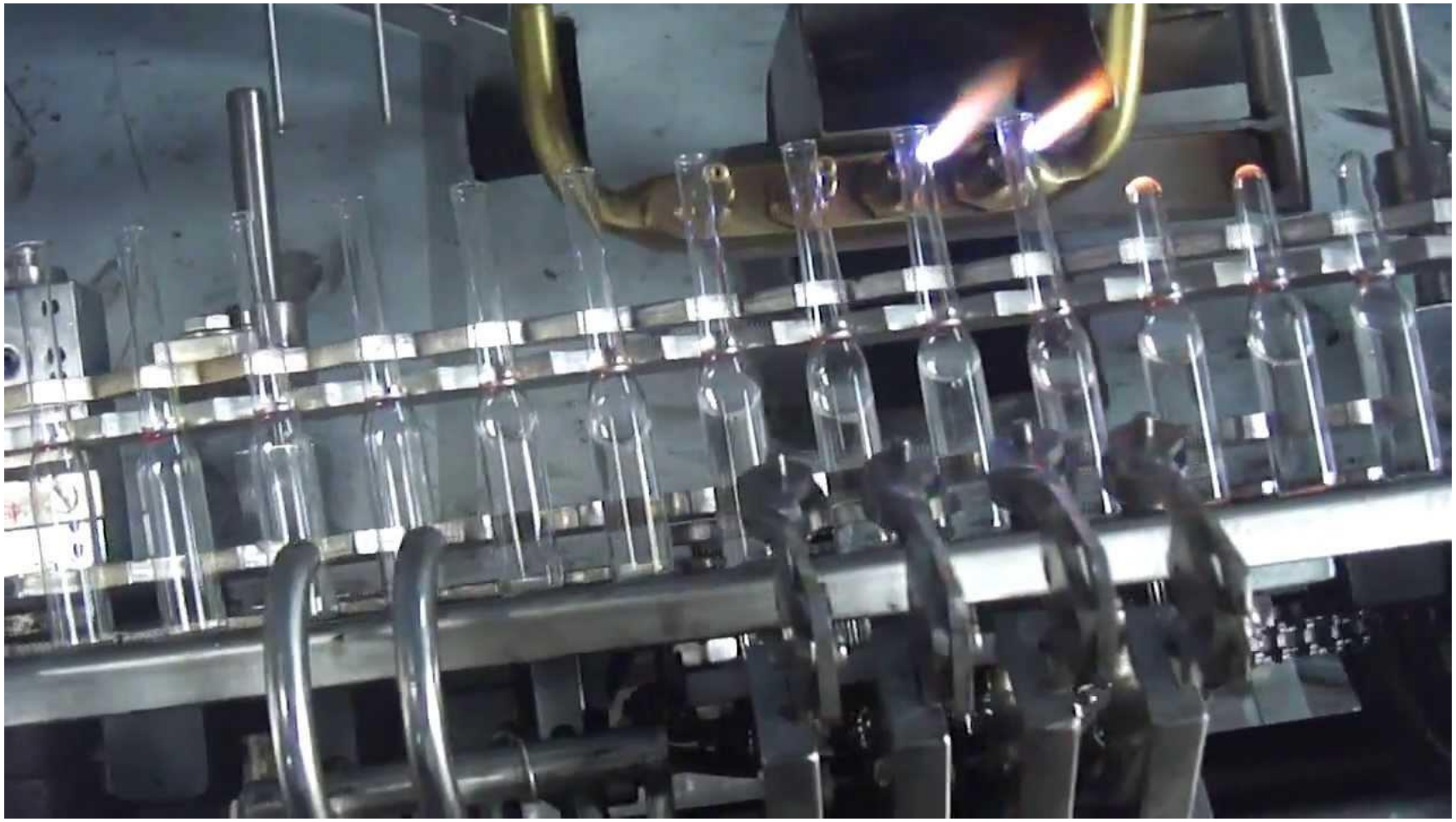
Solid ⟶ gas

Single-dose container

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

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

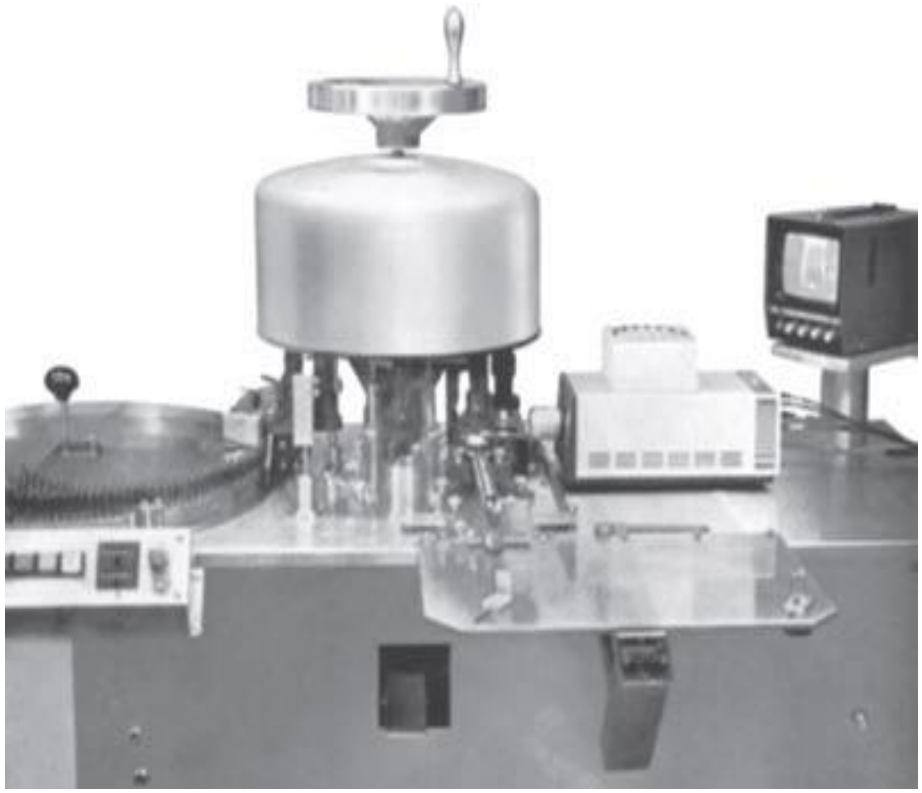


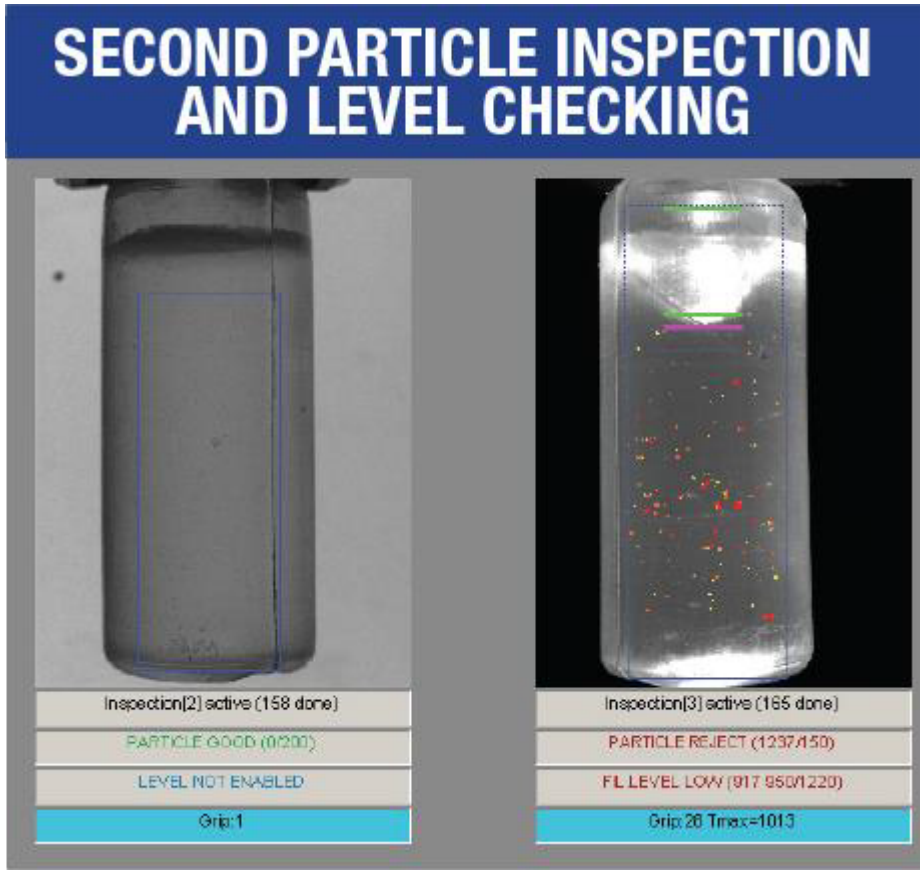
- *Multiple-dose container:* A hermetic container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

يقدر اخذ جرعات اكثر من مرة بدون ما تأثر على ١ و ٢ و ٣

- One of the prime requisites of parenteral solutions is clarity. 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.

Semi-automatic vs automatic particle matter inspection




SECOND PARTICLE INSPECTION AND LEVEL CHECKING
Inspection[2] active (158 done)
PARTICLE GOOD (0/200)
LEVEL NOT ENABLED
Grip:1
Inspection[3] active (165 done)
PARTICLE REJECT (1237/150)
FL LEVEL LOW (917 950/1220)
Grip:26 Tmax=1013

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.

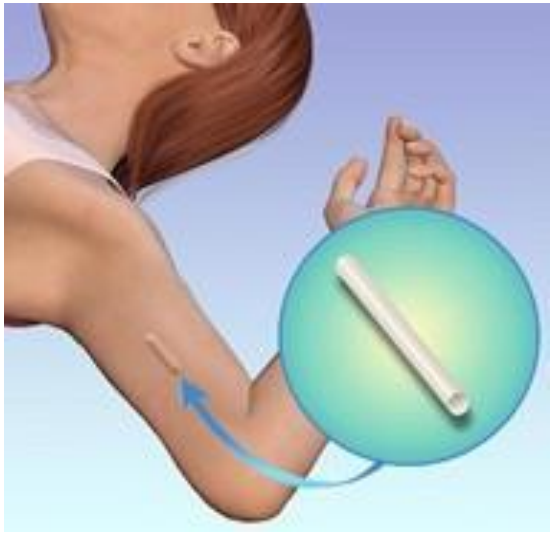
OTHER INJECTABLE PRODUCTS: PELLETS OR IMPLANTS

high dose

- 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.

لانه بدي احطها تحت الجلد وما بدي يضل منها بقايا ولا رح يظهر الطبيب انه يرجع يطلع البقايا

- 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).



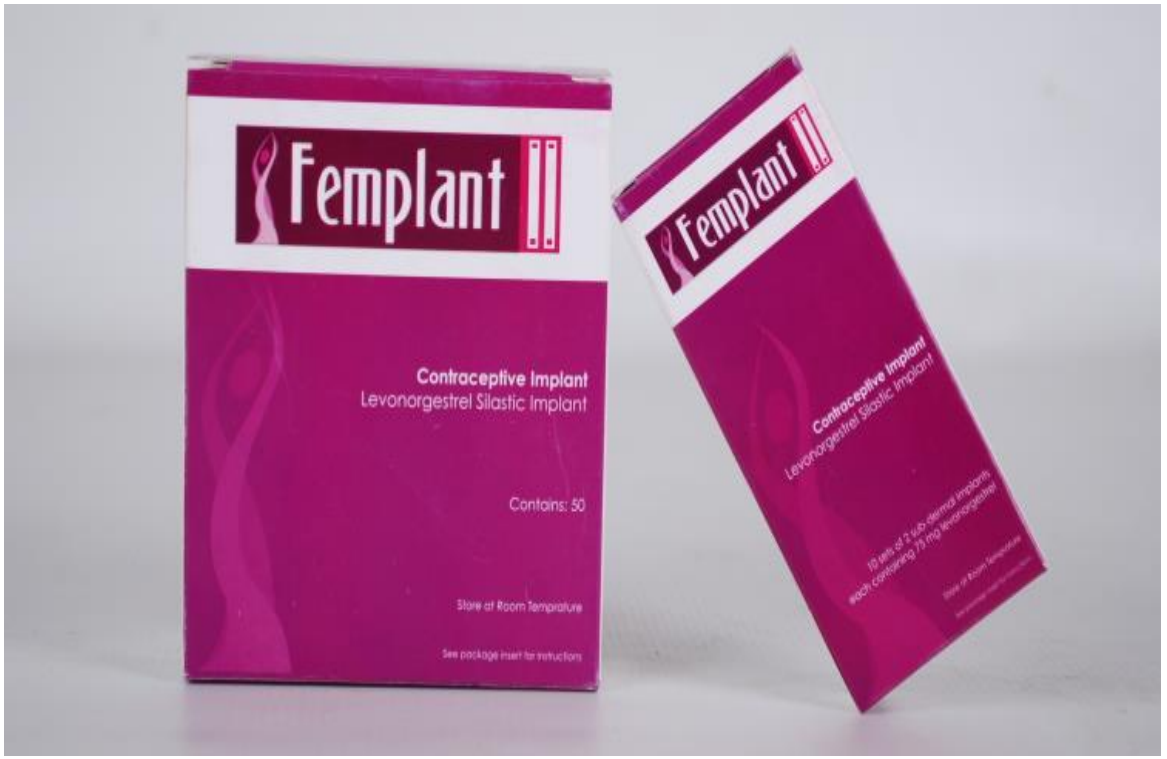

Femplant II
Contraceptive Implant
Levonorgestrel Silastic Implant
Contains: 50
Store at Room Temprature
See package insert for instructions
Femplant II
Contraceptive Implant
Levonorgestrel Silastic Implant

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

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

عشان بمجرد انه شلت الـ Aluminum بعرف انه خلص تم استخدام الـ Irrigation اللي

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

Types:

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

ما في داعي نحفظه، المهم اني تعرف انه كل نوع لازم نعمله test

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

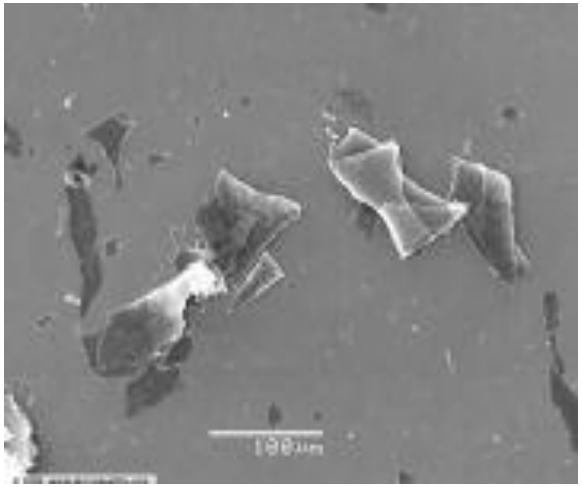
* [Surface glass] Test is present but does not define glass Type

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

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

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



يعني ما يصير adsorption للدوا على العلبة

Adsorption

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

خصوصاً اذا الدوا كان ←

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

Cracks and scratches

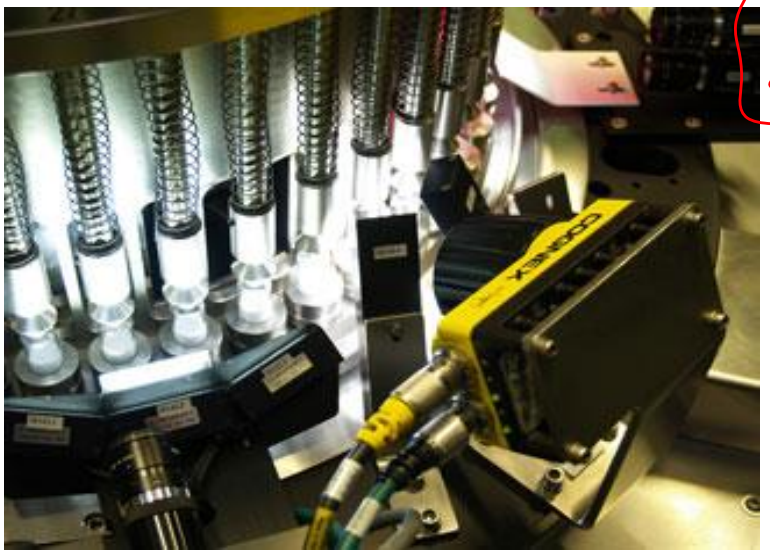
المصنع اللي بصنع الـ Container لازم يوقرم
بـ high quality و لما يدخل كل المصنع لك بدي
امنع الدوا فيه بروحه اتأكد انه ماشي Crack or Scratche

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



هذا السلايد
حكيت هذا ابدي
بس

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.

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, which may act as catalysts for oxidative degradation reactions.
- Silicone coatings are sometimes applied to containers

اذا كان الـ amber فيه mg او iron رح يطير عنه leached الـ amber يكون معنويته الـ si

Rubber closures

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

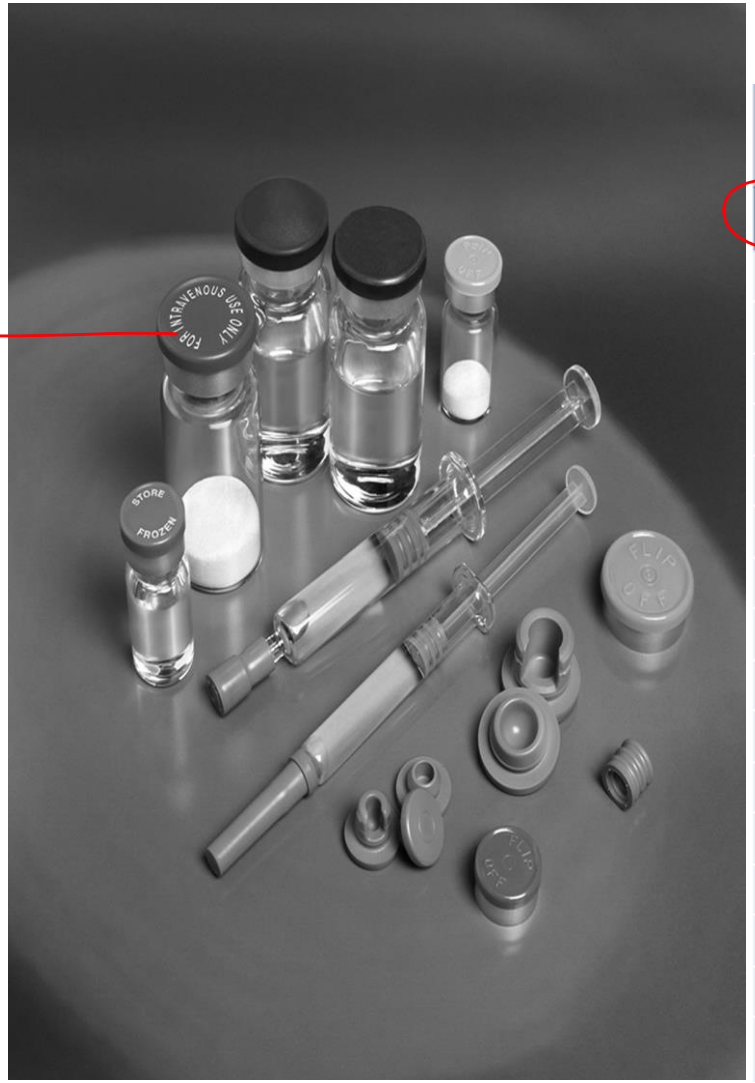


Table 26-3. Examples of Ingredients Found in Rubber Closures

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 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

(مني وعلي ماخ ادرسها) حكت ما رح تدخل بالتفاصيل هون

⟨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

اكتشفوا انه في ماده بال Rubber هي السبب
هذا البثري

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

« Previous | Next Article »
Table of Contents

This Article

Perit Dial Int **June 2007** vol. 27 no. Supplement 2 **S303–S307**

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

[−] Classifications

Part 9: Miscellaneous Complications and Pathophysiologic Mechanisms

[−] Services

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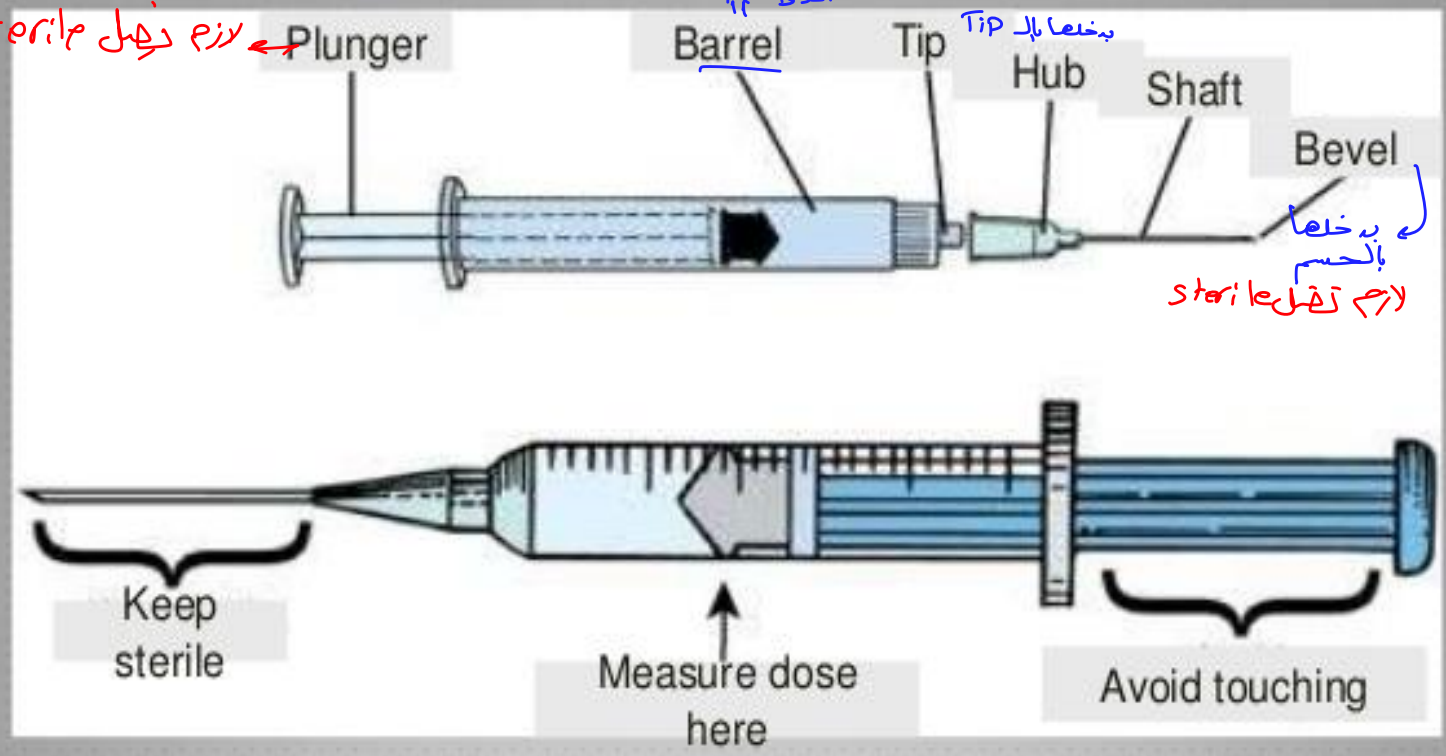
[+] Responses

[+] Citing Articles

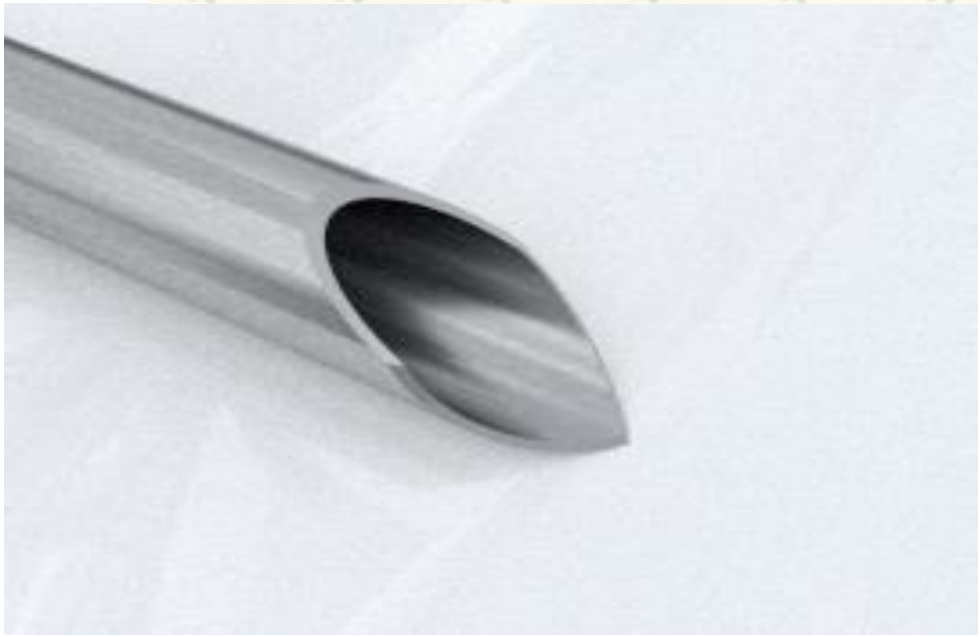
Needles

- 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



هذا ال bevel
بس بشكل اقرب



حكك صافي داي
للتفاصيل

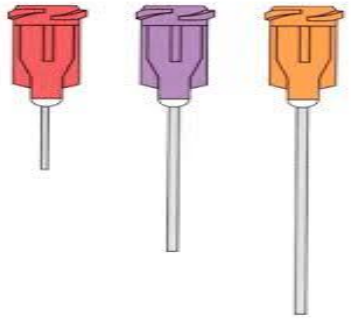
	Outer Diameter (mm)	Gauge Needle	Hub Color
	0.23	32	Orange
	0.25	31	Violet
	0.30	30	Yellow
	0.33	29	Red
	0.36	28	Blue Green
	0.40	27	Medium Grey
	0.45	26	Brown
	0.50	25	Orange
	0.60	23	Deep Blue
	0.70	22	Black
	0.80	21	Deep Green
	0.90	20	Yellow
	1.10	19	Cream
	1.20	18	Pink
	1.60	16	White

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.

ممكن اشتري needle لحالها (يسميها Luer-lok)
او مع syringe

- 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).

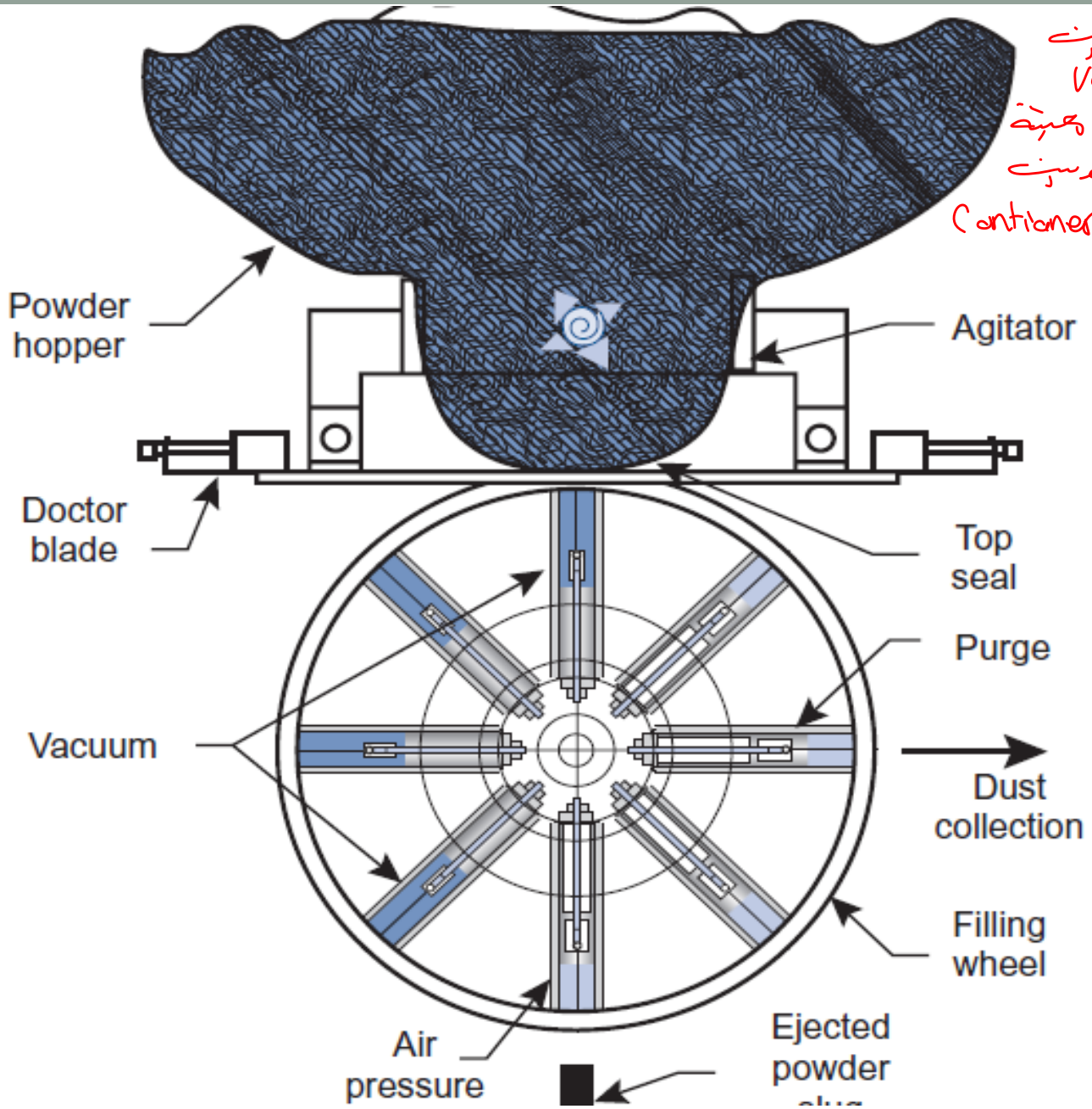


Filling

- 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

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.


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.

3

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.

شفت انه الدكتوره الاداد حاكيه تلتزم بحكي د. سحيي بالفديوهات فالاشياء اكي
حكت انها مش مهمة او مش مطلوبه كتبت كعدها

لاتنسوا زميلنا ايهم من دعائكم بها في الايام الفضيله

(وادعولي بطريقكم)