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Double Chamber Devices and its Advantages

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ABSTRACT

How to select primary packaging materials for Lyophilized products (Different kinds of Double chamber vial, PFS and cartridges, Rubber stoppers for Lyophilized products. Packaging challenges and Solutions.

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Introduction

Packaging and Polymer Scientist having 30 years' experience in reputed, pharmaceutical companies in USA, Germany, Singapore, India etc., Visiting lecturer in IIP, Mumbai, India. Extensive hand on experience in "Injectable DEVICES", Done research in wide range of "Polymers and its applications in different pharmaceutical products. International speaker for last 15 years. Delivered lecture in Boston, USA, Rome, Italy, Germany, France, Singapore and many places in India. Written "Four Technical Books", published from Germany, "Packaging Innovation for Microgravity Book" is considered as Reference book in "Harvard University, USA", "Packaging Technology An Advance Practical Approach" this book is considered as a Reference book in Indian Institute of Packaging, India. Third book is "Regulatory Audit observations and Responses. Presently doing "Consulting" activities.

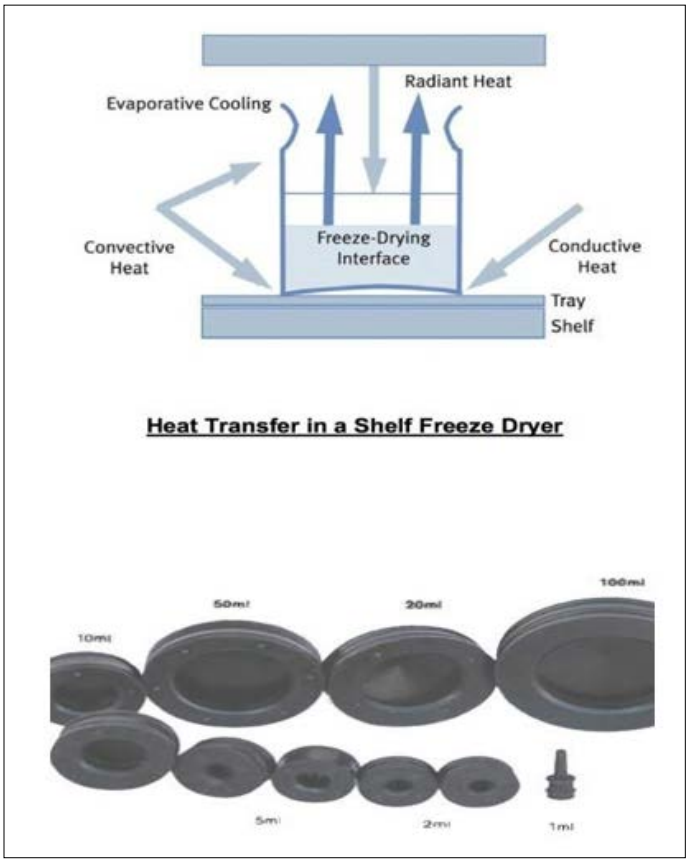
Why Lyophilization required

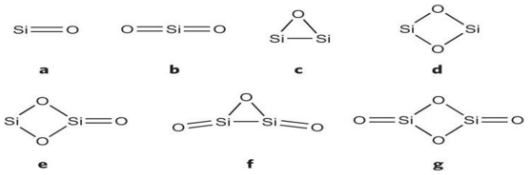
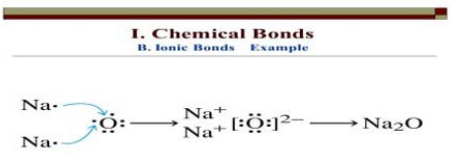
Many parenteral, especially biotherapeutics, are unstable in aqueous based formulations for long periods of time so has to be lyophilized. Lyophilized drug products must be reconstituted with sterile diluent prior to use.

Regular & Double Chamber Vial

- Better to use "Blow back glass vial and blow back rubber stopper. Popping of Rubber stopper during Lyophilization and stopering.
- Selection of right kind of packaging material and innovative design which can be user friendly.
- Primary Packaging material has to be compatible with product.
- Select the right kind of sterilization in which product will be stable and there is no significant change in packaging material
- It's advisable to use "Moulded Vial" with flat bottom surface to avoid hot air circulation at the bottom.
- Lyophilizing a drug in dual chamber systems can be challenging compared with lyophilization in a standard vial due to differences in package configuration, heat flow, and lyophilizer trays.
- One of the main benefits of dual chamber packaging is that the reconstitution step is built into the package and thereby improves patient convenience and safety.

Flat bottom Vial –Right choice for Lyo products



SL#	Composition	Functions
1	Silica (80%) 	Not only forms the glass, but its weight percent is an indication of the thermal expansively of the glass; more silica means lower thermal expansion (and therefore higher resistance to thermal shock)
2	Boric oxide(13%) 	Increases the chemical resistance of the glass
3	Sodium oxide (4%) 	Increases the viscosity of the glass melt at a given temperature.
4	Aluminium oxide (2-3%)	Increase inner strength.

Packaging Challenges and Solutions

- Delamination of Glass and solutions
- Protein absorption on glass and rubber surface and probable solution
- Fluro coated rubber stopper and plunger to use.
- Protein absorption in Needle
- Extractable and Leachable from glass, tungsten needle (for PFS), rubber stopper and polymer
- Popping of Rubber stopper during Lyophilization and stoppering.

Different causes for Delamination of Glass

- Formulations with a high pH include phosphate and citrate buffers increase the risk of glass delamination.
- High alkali content in glass could accelerate erosion.
- High temperature during the vial-forming process increases the risk of glass delamination.
- Terminal sterilization (irradiated at 20-40 kGy for 150 min) also is a risk factor for specific products (veterinary parenteral administration),could cause delamination.
- High product-storage temperatures and long exposure times can increase the rate and severity of glass delamination.

How to prevent Delamination

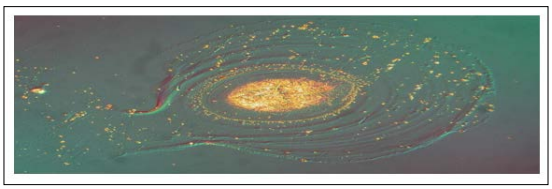
1. Treating the surface of the glass vials with materials, such as ammonium sulfate or siliconization can reduce the rate of glass erosion.
2. Consider alternative sterilization methods only in rare cases.
3. The correct specification for the glass to ensure its suitability
4. for the pH of the product.
5. Use COC/COP vial (Not applicable for Lyo products)
6. Use Alimino silicate glass instead of Borosilicate glass.

Example of Delamination in Glass Vial (50 ml)

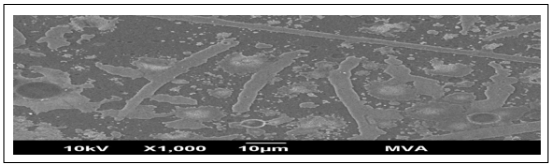
Delamination in Syringe

Solutions	Remark
Hydrophilic (Sulfate treatment)	This coating increased the risk of fogging(i.e undesired creeping of the product upwards along the inner vial surface). Bubling can be controlled by degassing and no need to add a surfactant.
Hydrophobic (Siliconization)	This coating promoted boiling and blow-up phenomena, resulting in unacceptable aesthetic defects in the final product. This can evaluate the application of vacumm-induced surface freezing to Super hydr-philic containers.

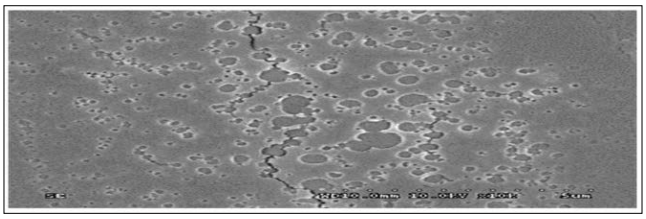
Glass delamination under the carlton Microscope



Optical coating degradation problem



Delamination of Glass under Microscope



Glass Vial VS PFS(Glass)

Sl #	Testing/manufacturing	Glass vial	PFS(Glass)
1	Plasma/mass spectrometry, scanning electron microscopy, atomic force microscopy.	Observed delamination more	Observed delamination very less
2	Glass processing history, including forming and annealing, sterilization and depyrogenation, and surface treatments.	Possibility of delamination is more	Possibility of delamination is very less.
3	Formulation in contact with the container during its shelf life.	Is more	Less
4	For tubing vials, heat is applied to cut and part the glass cane, then to tool the neck, and finally to form and polish the bottom. The most extreme heat is used for forming the vial bottom, the region just above the vial bottom to be more susceptible to delamination.		

Neck & bottom formation of Tubular Glass vial(beginning)

Sl #	Do	Not to Do
1	Recommanding "Tubular vial for " 5ml " capacity	As per stability result no need to go for " COC/COP "vial. Cost of COC/ COP vial is very high compare to Glass vial.
2	Strongly recommending "moulded vial for 100 ml capacity"	Don't use "Tubular vial for 100 ml capacity since " observed delamination during stability study.

Challenge in Production line and Probable Solutions

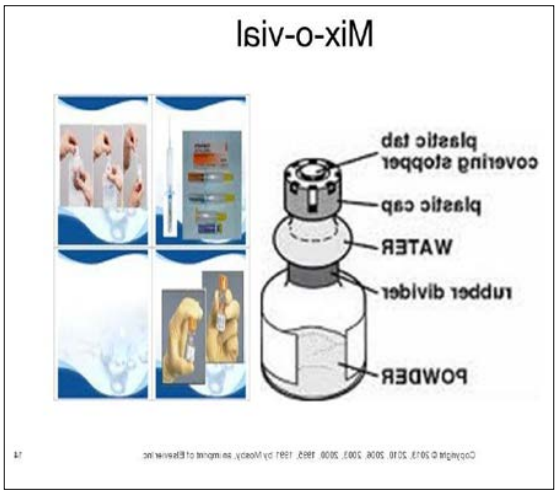
Sl#	Problems	Probable solutions
1	Breakage of vial/PFS/cartridge	Proper handling is required while keeping packaging materials on round table and during washing in case of vial.
2	Improper filling of vial/PFS/cartridge	Right positioning of "Nozzle " is a must. Operator has to be efficient
3	Improper fitment of Rubber stopper	Rubber stopper "pick and place" makcanizam has to work properly. Air compressor need to check as well.
4	Improper sealing of vial	Seal inner dia, sealing head ,height and pressure need to check.
5	Leak test failure	Stoppering and sealing have to be perfect. Sealed vials need to check online or off line "**leak tester**".
6	Leakage observed in PFS	During insertion of "plunger Rod" inside the "Plunger stopper" the height between plunger stoppering part and actual position of plunge need to increase in order to reduce pressure on plunger stopper.
7	Black particle and glass fibre in product	Need to monitor properly Onlineand off line inspection system. Periodic

Things to remember during packaging development

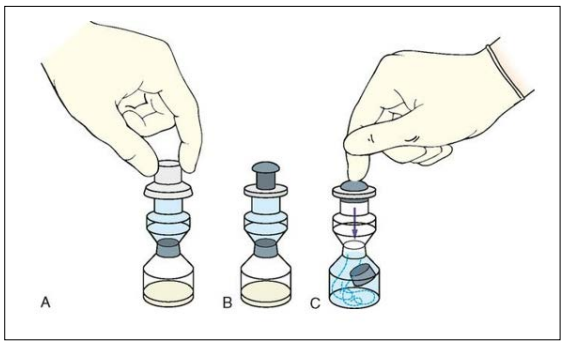
- Blow back vial and blow back rubber stopper to be MUST.
- Better to use RTU (ready to use) rubber stopper to avoid excess moisture contain in rubber stopper.
- If you use RFS (ready for sterilization), then need to take precaution during sterilization.
- Selection of sterilization will play an important role for product stability and shelf life of packaging material as well.
- Proper temperature control inside the "Lyo chamber" will play an important role.
- Storage temperature of product and packaging material need to control properly.
- Protein absorption on glass and Rubber surface and probable solution
- Apply Siliconized coating inside the glass vial/cartridge inner surface.
- Apply Poly glycol coating inside the inner surface of the glass container.
- Possible to use "polymeric coating inside the glass surface.
- Control storage condition is a must.

Siliconization and its advantage

1. It provides good drainage of the solution from the vial wall and thus a better dosage, an easy movement of rubber plunger e. g. in feeding machines.
2. Plunger can move fast inside the cartridge.
3. Stopper can easily go inside the vial mouth.



How to use the DCV



Challenges

These include the increased complexity with respect to freeze-drying and reconstitution. Both processes depend on the container geometry which should provide a big surface area for optimal product drying and wetting. Thus, the use of DCSs with their intrinsically small cross-sectional area is a challenge.

- Increased moisture migration from the diluent chamber and the rubber parts (plunger and closure) to the dried product which might affect stability and
- Presence of silicone oil which can introduce silicone particulates or opalescence.6
- Extractables and leachables, product compatibility, ensurance of device functionality (also and especially over the product shelf life), ensurance and adequate setup for testing of container closure integrity, and other challenges typically encountered when developing drug and device combination products.

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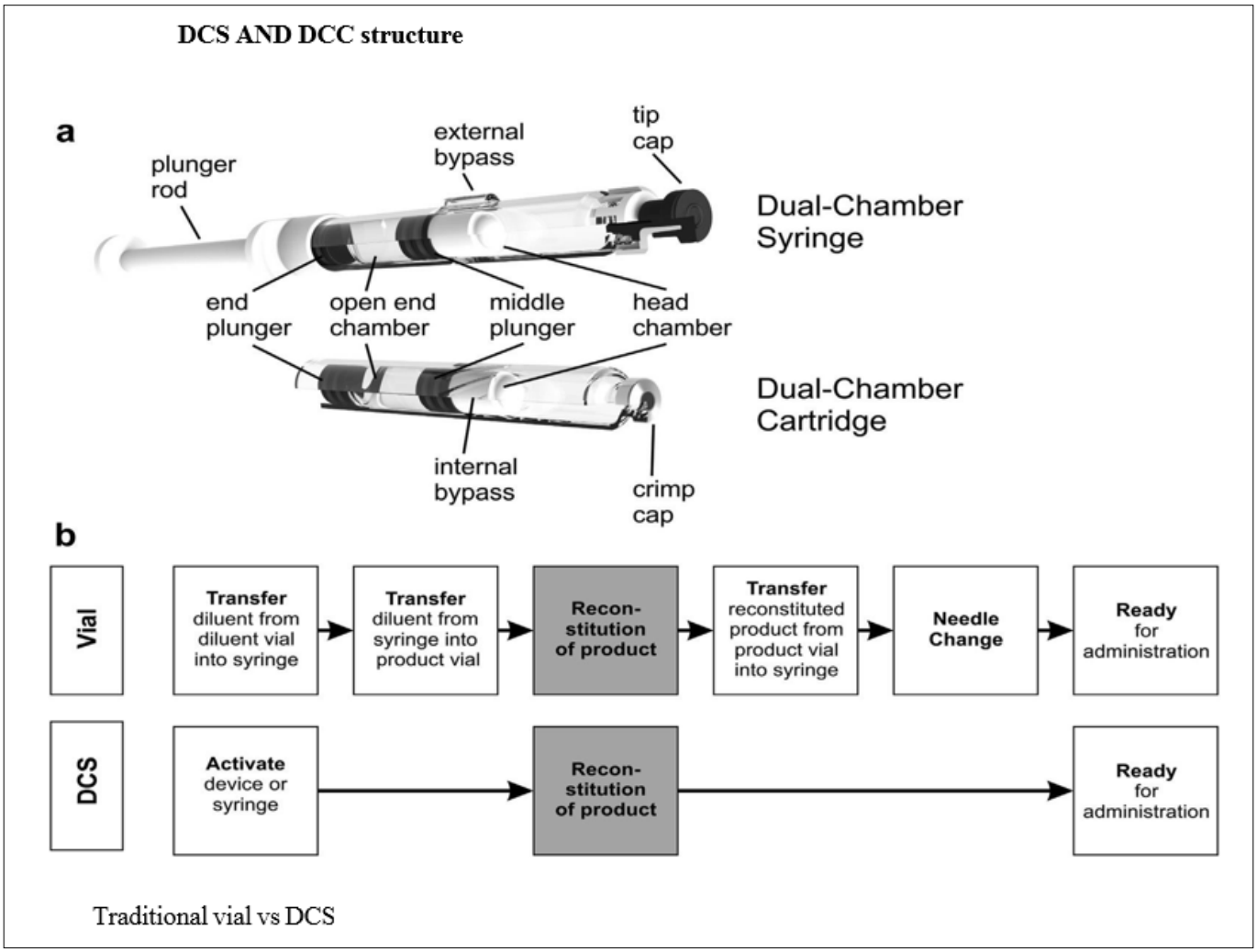
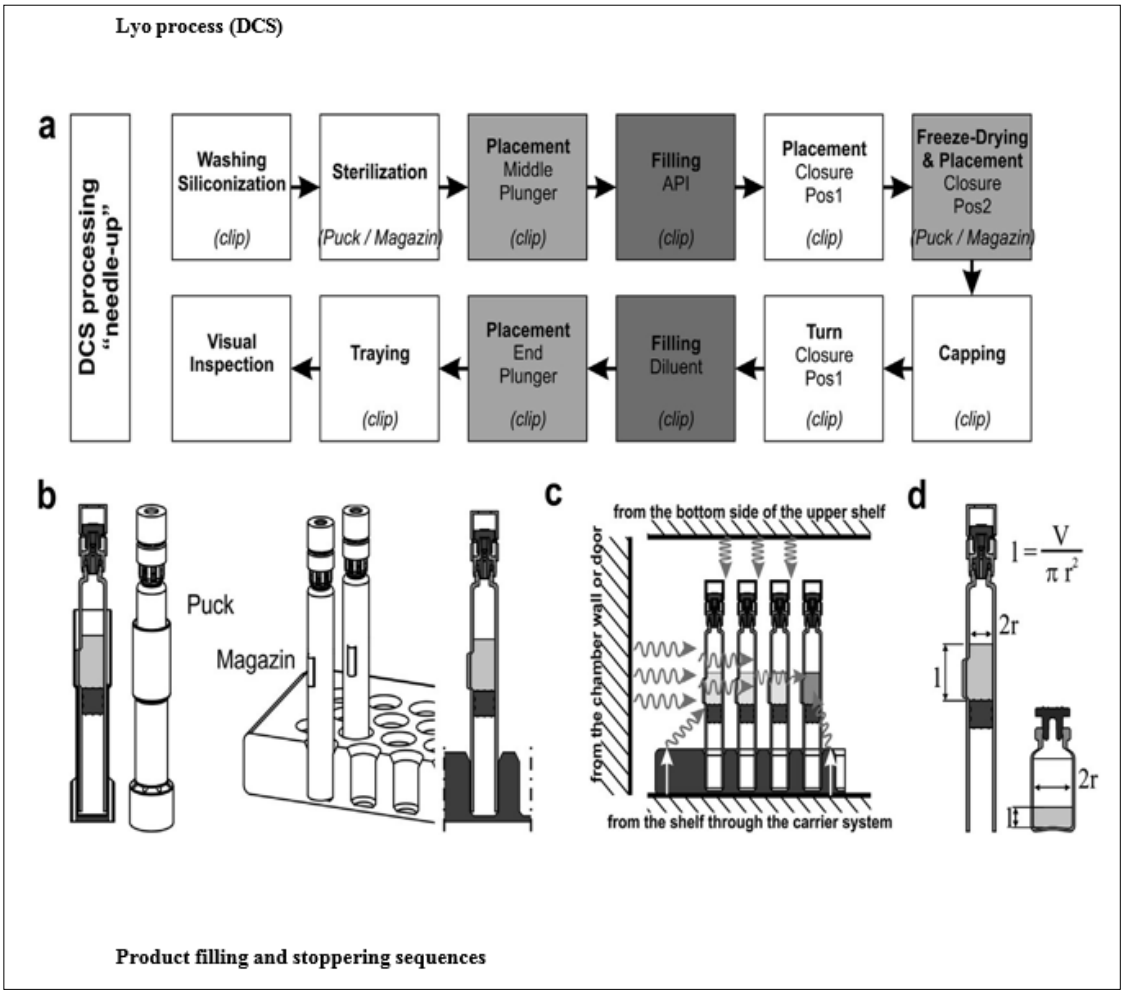
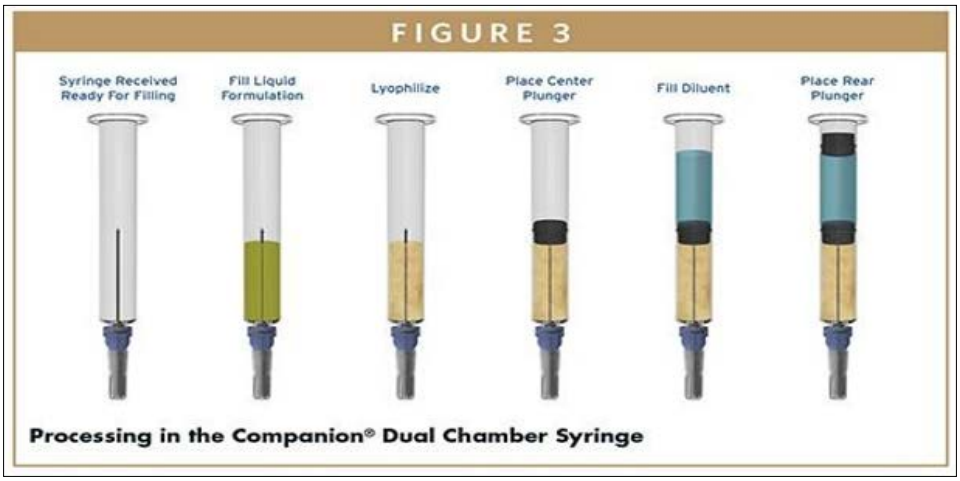


Dual-chamber systems offer multiple user advantages for delivery of sensitive injectable compounds, including:

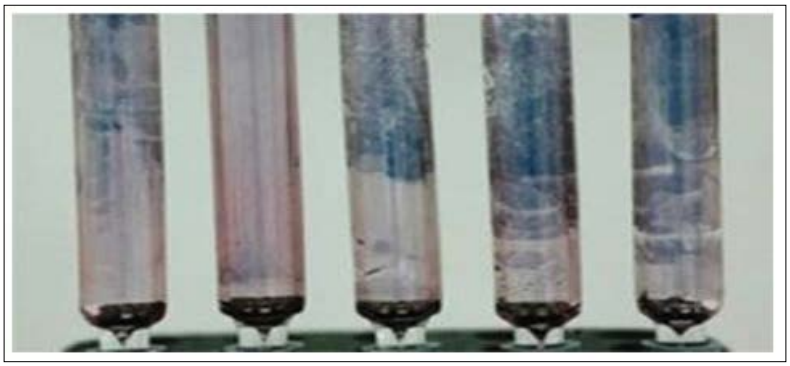
- **Simple administration:** fewer steps required for preparation and
- injection in comparison with traditional vial/syringe combinations
- **Increased patient safety:** more precise dosing and minimized reconstitution errors
- **High product security:** all systems sealed during lyophilization process
- **Versatility:** cartridges designed for single- and multidose applications in pens
- ***Less waste:*** low residual volume with closure system and stopper geometry allows little product loss, reducing overfill, and minimize packaging waste
- **Market differentiation:** dual-chamber technology can provide a compound with greater end-user appeal and a powerful competitive edge.
- **Double chamber syringe testing**
- Adopted deterministic container closure integrity testing (CCIT) methods, such as high voltage leak detection (HVLD) CCIT, dual-chamber syringes with bypass will pose a challenge, even when both chambers are filled with sufficient conductive liquid. This is because the HVLD tester utilizes a traveling probe and rotates the syringe to achieve full coverage, and bypass on traditional dual-chamber syringes will interfere with both.
- DCDs should also provide seal integrity, sterility and compatibility with biopharmaceuticals and avoid leachability and needle stick injuries. DCDs are promising alternatives to traditional containers or devices for biopharmaceuticals. The regulatory and medical practice to choose plastic DCDs as better alternatives over well-established glass syringes will be addressed here.





Ready to use DCS

Direct Visualization of Protein Adsorption



Proteins

1. For proteins and other recombinants, a simple and safe way to maintain bioactivity is to use a liquid formulation. However, simple dilution does not allow sufficient long- term stability for many drugs since water can act as both a medium and a reaction agent that can cause hydrolysis of proteins. In addition, water increases chemical and physical instability in reaction with other substances.
2. One answer is to remove as much water as possible from the liquid formulation to stabilize the substances, which can then be reconstituted with a diluent just before being injected.

Adsorption of protein and Solution

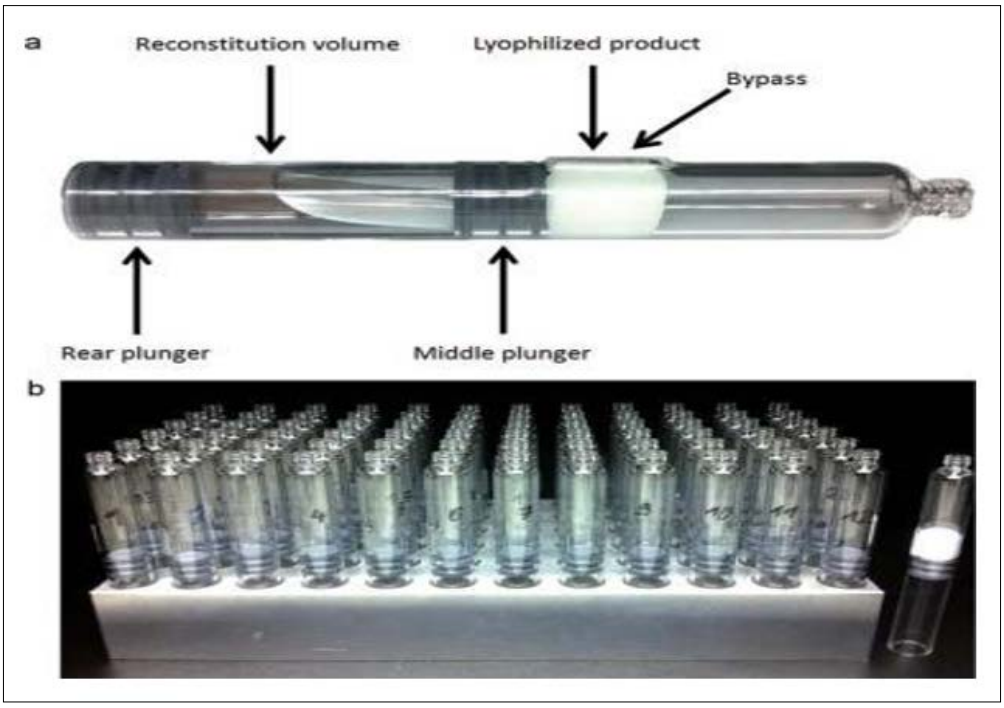
Option1	Methoxylated polyglycerol and hyperbranched methoxylated polyglycerol.
Option2	The hyperbranched non-methoxylated coating performed best.
Option3	Coat with hyperbranched polyglycerol
Option4	Right selection of Sterilization of glass vial/syringe

Dual chamber Cartridges

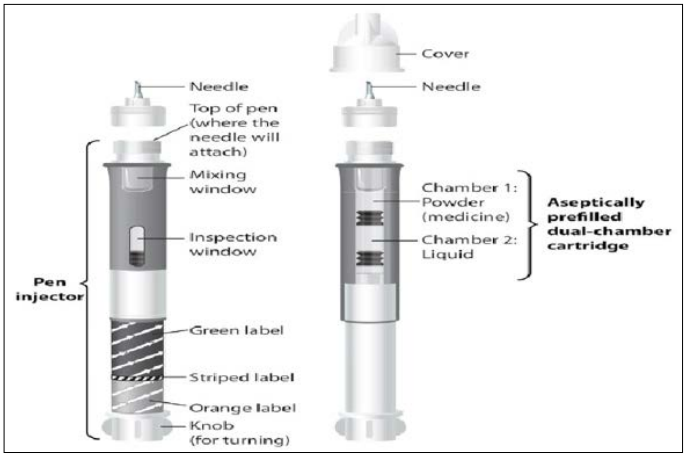
A DCC is typically used in conjunction with a pen injector for reconstitution and delivery to the patient. Pen injectors are available in disposable and reusable formats. The DCC is preloaded in the pen injector for the disposable ready-to-use format. The user/ patient must load the DCC into the pen injector for the reusable format. The first time the pen is utilized the user has to disinfect the rubber septum, attach a pen needle, reconstitute the cartridge, prime the pen to remove air, and set the dose.

Additional uses for this system only require the user to disinfect the rubber septum, attach a pen needle, set the dose, and inject. The needle is removed after each injection. Thus, at time of use there are five steps prior to dosing.

DCC structure



DCC from SCHOTT
Dual chamber cartridge (DCC) PEN



Formulation development for the active-containing chamber
Although formulation development activities for the lyophilized powder in the dual chamber package are similar to those for standard vial systems, there are some activities that are specific to package and process compatibility. Foremost, the formulator must consider the impact of moisture on product quality and ensure the cake mass is sufficient to withstand moisture ingress from the elastomer and diluent chamber.

The formulator must also ensure the formulation is compatible with silicone and the selected elastomer. If the formulation is not compatible with silicone, either the formulation or the siliconization process needs to be optimized. The main concern for compatibility of the formulation with the elastomer is leachable release from the elastomer. This can be controlled with fluoropolymer coating of the elastomer or optimization of the formulation.

Finally, the formulator should attempt to maximize product concentration in the formulation to minimize cake height since this significantly impacts overall lyophilization time.

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