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Mini Review

# Packaging Challenge for Lyophilized Products

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## Abstract

Scope of the Problem

This topic is going to cover type of vial and rubber stopper is ideal for Lyo products. Wrong formulation and design of glass vial, cartridge, rubber stopper and plunger can spoil product quality before shelf life. wrong design of glass vial neck caused popping of rubber stopper, improper sealing and leak test failure.

Impact or Importance it has for Industry and Market;

This has huge impact on product quality as a result of fact market recall and huge loss of the company.

**Keywords:** Packaging; Lyophilized

## Introduction

Presently Packaging plays a significant role for Lyophilized products. The process of selecting materials and the type of packaging also offers an opportunity for the Packaging scientist to look for new biological delivery choices. Most injectable protein products were supplied in some sort of glass vial, prefilled syringe, and cartridge. That product having high Ph. content there is a chance of "delamination "from inner surface of glass vial. With protein-based drugs, the biggest issue is the effect of packaging derivatives on the protein's three-dimensional and surface structure. These are effects that relate to denaturation or aggregation of the protein due to oxidation or interactions from contaminants or impurities in the preparation. The potential for these effects needs to be carefully considered in choosing the container and the container closure system to avoid putting patients in jeopardy.

## Purpose and special role

- Better to use "Blow back glass vial and blow back rubber stopper.
- 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.

## Lyophilized Product

Those products are highly unstable in liquid form, better to go ahead with frozen form i.e. in lyophilization.

## Probable packaging Challenges:

- Delamination of Glass and solutions
- Protein absorption on glass and rubber surface and probable solution
- 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.

## Delamination of Glass

This is a serious issue in most of the pharmaceutical companies. Tubular vial has few manufacturing limitations like during manufacturing of the vial along the shoulder and along the bottom circumference of the vail flaming applications are high as a result of that evaporation of boron and sodium, at that place accumulation of silica happen. When the product having high Ph. contain come contact at those places glass flex are coming out and float into the product. This is the cause of delamination.

## Different type of Glass

- **Borosilicate Glass (Type-I Glass):** This glass is most suitable for pharmaceutical products packaging because it is most durable, less alkaline and most clear. Delamination observed at the bottom surface and shoulder of the Tubular vial.
- **Soda-Lime-Silicate Glass (Type- II Glass):** This type of glass is using for packaging of selected pharmaceutical products. Not using for Lyophilized product packing. This is more alkaline compare to Borosilicate glass.

## Different causes of Delamination

- Formulations with a high pH, and those that include phosphate and citrate buffers increase the risk of glass delamination,
- Phosphate and citrate buffers can corrode glass, for example, the active molecule may require the attributes of those ingredients. "Any change to the formulation may affect the safety and efficacy of the product.
- High alkali content in glass could accelerate erosion, so manufacturers should choose vials with low alkali content if possible.
- High temperatures during the vial-forming process increase the risk of glass delamination. Appropriate control of temperatures during the glass-forming process is especially important when the containers will store corrosive product formulations. Drug manufacturers should ask vial vendors about their process control, and also test vials to ensure their suitability for the product in question.
- Terminal sterilization also is a risk factor that, together with specific products, could cause delamination.
- High product-storage temperatures and long exposure times can increase the rate and severity of glass delamination.

## How to prevent Delamination of Glass

- Ammonium sulphate Treatment can reduce the rate of glass erosion.
- Consider alternative sterilization methods only in rare cases.
- During Autoclaving, temperature control is most important.
- Siliconized coating can apply uniformly inside the glass vial/cartridge inner surface.

**Figure 1:** Example of Delamination in Glass Vial.

**Figure 2:** Delamination in Syringe.

**Figure 3:** Delamination in Syringe.

**Figure 4:** Glass delamination under the Carlton Microscope.

**Figure 5:** Optical coating degradation problem.

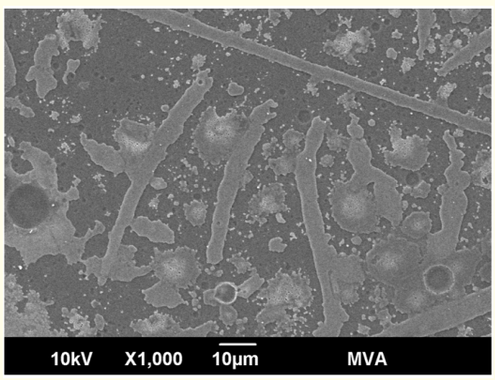


**Figure 6:** Delamination of Glass under Microscope.

**Figure 7:** Delamination of Glass under Microscope.

**Figure 8:** Seal Integrity Problem and Failure of Lyophilized Product.

**Figure 9:** Excess moisture into the vial and improper Lyo cake.

**Figure 10:** Improper Rubber stopper fitment cause Lyo product Failure.

**Figure 11:** Improper crimping of flip-off seal cause failure of seal integrity test.

**Figure 12:** Perfect fitment of Rubber stopper.

Figure 13

## Things to remember during packaging development for Lyophilized products:

1. Blow back vial and blow back rubber stopper are MUST.
2. Better to use RTU (ready to use) rubber stopper to avoid excess moisture contain in rubber stopper.
3. If you use RFS (ready for sterilization), then need to take precaution during sterilization.
4. Selection of sterilization will play an important role for product stability and shelf life of packaging material as well.
5. Proper temperature control inside the "Lyo chamber" will play an important role.
6. Storage temperature of product and packaging material need to control properly.

## Glass Vial VS Cartridge(Glass)

**Table 1**

| Sl # | Testing/manufacturing | Glass vial | Cartridge( 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. | Delamination observed from neck and bottom | Delamination possibility is less |
| **5** | Product "Ph." value more than 6.5 | Recommending | Not recommending |

## Challenge in Production line and Probable Solutions

**Table 2**

| Sl# | Problems | Probable solutions |
|---|---|---|
| 1 | Breakage of vial | Proper handling is required while keeping packaging materials on round table and during washing in case of vial. |
| 2 | Improper filling of vial | Right positioning of "Nozzle "is a must. Operator has to be efficient |
| 3 | Improper fitment of Rubber stopper | Rubber stopper "pick and place" system has to work properly. Air compressor need to check as well. Blow back rubber stopper and glass vial to use. |
| 4 | Improper sealing of vial | Seal inner diameter, 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 | Black particle and glass fibre in product | Need to monitor properly Online and off line inspection system. |

## 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.
- Use coated rubber stopper.
- Possible to use "polymeric coating inside the glass sur face.
- 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.

### Inner surface Modification of Glass (for reduction of protein absorption)

1. Coating of glass vials with thin layers of SiO2
2. Poly- or oligoethylene glycol (PEG/OEG).-Coating
3. Coatings with polyglycerols, zwitterionic.

### Silicone Oil

Proteins can be easily adsorbed onto the silicone oil droplet surface, leading to a loss of soluble proteins, lysozyme, abatacept, and trastuzumab.

- The adsorption of protein at the silicone oil/water inter face can be irreversible and protein concentration dependent.
- Silicone induced surface adsorption.
- Silicone-induced protein aggregation.
- Several approaches can be taken for mitigation of the impact of silicone oil.

### Extractable and Leachables

This is one of the key tasks during the drug development process and through product approval

- Different types of metal ions can leach from different glass or plastic packaging materials. Metal Leachables are dependent on the type of containers, incubation temperature, and formulation composition
- Tungsten is inserted during syringe manufacturing and can leach out in significant amounts in the funnel region of a prefilled syringe and facilitate formation of protein particles.
- Especially Borosilicate Glass surfaces can leach alkali components causing pH changes over time, especially under basic conditions [1-8].

## Conclusion

- Right formulation and right design of rubber stopper to use.
- Blow back vial and blow back rubber stopper to use.
- The correct specification for vial and rubber stopper is a must.
- Need to maintain all necessary parameters during Lyophilized cycle.
- Glass manufacturers ensuring that appropriate process controls are in place.
- Forming temperatures and correct annealing and due diligence in the quality testing and assurance of their glass.

Durability analyses are conducted to assess the compatibility of the glass with the specific product that will be stored within the container.

### Understanding

- Innovator product characterization need to carryout in detail to know design of vial, design and formulation of rubber stopper and plunger.
- Correctly decide the “sterilization” is best suited for product stability and low risk.

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