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Lessons Learned

"Product on Stopper" in a Lyophilized Drug Product: Cosmetic Defect or a Product Quality Concern?

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ABSTRACT

During manufacturing of a lyophilized drug product, operator errors in product handling during loading of product filled vials onto the lyophilizer can lead to a seemingly cosmetic defect which can impact certain critical quality attributes of finished product. In this study, filling of a formulated monoclonal antibody in vials was performed using a peristaltic pump filling unit, and subsequently, the product was lyophilized. After lyophilization, upon visual inspection, around 40% of vials had cosmetic defect with residual product around stopper of the vial and were categorized as "product on stopper" vials, whereas remaining 60% vials with no cosmetic defect were called "acceptable vials." Both groups of vials from 1 single batch were tested for critical quality attributes including protein concentration (ultraviolet absorbance at 280), residual moisture (Karl Fischer), sterility (membrane filtration), and container closure integrity (CCI) (blue dye ingress). Analysis of protein quality attributes such as aggregation, protein concentration, residual moisture showed no significant difference between vials with "product on stopper" and "acceptable vials." However, CCI of the "product on stopper" vials was compromised due to the presence of product around stopper of the vial. The results from this case study demonstrate the following 2 important findings: (1) that a seemingly cosmetic defect may impact product quality, compromising the integrity of the product and (2) that CCI test method can be used as an orthogonal method to sterility testing to evaluate sterility assurance of the product. The corrective action proposed to mitigate this defect is use of a larger sized vial that can potentially minimize this defect that arises because of product handling errors.

Introduction

Of all the injectable products that are in clinical trials or are approved for marketing, roughly half of them are freeze-dried products.[1] Lyophilization or freeze-drying is a process widely used in biopharmaceutical industry to mitigate the stability issue of protein therapeutics.[2] Lyophilized products offer the advantage of better stability, easy handling during shipment, and negate the issue of cold chain storage that is associated with liquid products.[3] The entire freeze-drying process comprises 3 steps: freezing, primary drying, and secondary drying. In the first step, liquid water is converted to ice by freezing the product. During primary drying, the pressure in product chamber is lowered with increase in shelf temperature to assist in sublimation of ice while making sure that the product temperature does not go above the maximum allowable product temperature that can result in product collapse. During secondary drying, the shelf temperature is raised further to remove the remaining water from the product. Typically, a freeze-dried product must have an elegant cake structure with residual water of less than 1%.[4]

One of the desired characteristics associated with lyophilized protein product is "elegant cake structure" upon visual appearance.[5] The term "elegant cake structure" is loosely used while describing a lyophilized cake for the matter that it is a subjective term that may vary from person to person. It is often desired during manufacturing of a freeze-dried product that a freeze-dried cake has the same size and shape as the aqueous product that was originally filled into the vials with a uniform texture and appearance. But, this instance is possible when all the processing steps of freeze-dried product are properly designed and executed without errors. As part of the Current Good Manufacturing Practices requirement, after manufacturing a batch, the freeze-dried product undergoes 100% visual inspection[6] by trained operators where one of the evaluation criteria is cake appearance. Acceptability of cake

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Table 1
Lyophilization Cycle for Freeze-Drying mAb Formulation

Process	Step	Rate/Hold	Temperature (°C)	Time (min)	Ramp Rate (°C/min)	Chamber Pressure (mTorr)
Freezing	1	Hold	5	60	NA	NA
	2	Rate	−40	45	1	NA
	3	Hold	−40	480	NA	NA
Primary drying	4	Hold	−40	60	NA	100
	5	Rate	−23	170	0.1	100
	6	Hold	−23	2650	NA	100
	7	Hold	−23	2000	NA	100
Secondary drying	8	Rate	5	280	0.1	100
	9	Hold	5	60	NA	100
	10	Rate	25	200	0.1	100
	11	Hold	25	600	NA	100

appearance is largely defined based on historical trends observed during freeze-drying of previous batches of the product. If a product is being manufactured for the first time, a broad acceptance criterion for visual appearance of the cake is defined. Even though the freeze-drying process may produce an elegant lyophilized cake with the entire batch passing the visual acceptance criteria, when the product reaches the patient, it might have undergone shipping stress that can lead to chipping or broken lyo cake that may no longer be elegant. In many cases, broken lyo cake or chipped lyo cake with scattered powder in the vial is considered acceptable as it is a cosmetic defect, and furthermore, it does not impact protein quality attributes tested upon reconstitution.

A previous article by Patel et al. outlined the different types of cake appearances and cosmetic defects that are commonly observed for lyophilized products.[7] The range of cosmetic defects vary based on their severity of impact on critical quality attributes (CQAs) such as meltback, collapse,[7,8] product ejection to those that do not impact CQAs such as broken or slanted cake, cake shrinkage, and fogging in vial.[7,9] These cake appearances are largely dependent on individual product and process design. Therefore, the cosmetic defects that arise for individual product have the potential to impact product quality attributes in 1 or more ways. For example, abundant evidence exists in literature that demonstrates that meltback and collapse of lyo cake can impact stability and residual moisture in the finished product,[10-12] and therefore, this type of product appearance should not be acceptable across different product lots. However, for other types of product appearances such as lifted cake, product between vial and stopper, and fogging in vial, no study has shown the probability of product quality attributes to be impacted by such cosmetic defects in lyophilized product.

A regulatory guidance exists on visual inspection of lyophilized products.[13] However, this regulatory guideline on visual inspection of lyophilized product does not provide any specific acceptance criteria upon visual inspection of lyo cakes. This guidance discusses the criticality of meltback and collapse of lyophilized cake but does not provide any guidance on acceptability of other types of lyo product appearances.[13] Nonetheless, it is a regulatory requirement to manufacture a product that is safe, sterile, and efficacious with the goal of ensuring patient safety first.[14] According to the Current Good Manufacturing Practices requirements, a certain number of drug product samples from a manufactured batch are tested for appearance, identity, purity and impurity, potency, quantity, and other general characterization tests.[15] During manufacturing a sterile drug product, a container closure system is selected which provides the critical barrier protecting the drug product contained within. Evidence of sterility is demonstrated by testing a fraction of the manufactured batch for microbial contamination including bioburden and endotoxin levels in the finished drug product.[16] In many cases, the sterility test method may not be practical for testing because the sterility test may only test for viable microorganisms at the time of test or the product may provide potential interference during test.[16] In these scenarios, regulatory agencies also recommend testing for container closure integrity (CCI) as an alternate to sterility.[16] Therefore, in such scenarios, CCI testing may provide better evidence of the safety of the product compared to the sterility test.

Manufacturing of a lyophilized protein product is carried out in a series of steps. First, the vials are filled with product at desired fill volume and partially stoppered. Second, the vials are transported to the lyophilizer and loaded onto the chamber under aseptic conditions. Third, the freeze-drying cycle is allowed to run at set parameters at the end of which the product in vials is capped or stoppered and sealed. Subsequently, the lyophilized product undergoes 100% visual inspection by trained operators[6] and product quality testing. In many cases, it has been speculated that splashing may occur during filling or manual loading of the tray with filled vials that can leave residual product around the neck of the vial and even on stopper of the vial. In this particular situation, an elegant and intact lyo cake may still be observed at the bottom of the vial with the residual product that was freeze-dried around vial neck or around the stopper. In this situation, it is often hypothesized that CCI and product recovery upon reconstitution may be compromised.[7] However, no evidence exists in literature to prove this occurrence of phenomena. In this case study, we provide first evidence demonstrating that the presence of residual product around the stopper of the container closure system may compromise the CCI of the product without affecting product quality attributes including protein concentration, residual moisture, and other protein quality attributes. If this type of cosmetic defect is considered acceptable upon manufacturing, it can impact safety of the product and therefore pose risk to patient's health. We also provide evidence that CCI test method is an orthogonal technique to sterility test to evaluate sterility assurance. Finally, we propose mitigation strategy to “product on stopper” defect by using a larger sized vial to mitigate the product handling errors during operations.

Materials and Methods

Materials

Purified mAb was provided by downstream processing group at Teva Biopharmaceuticals in the final liquid formulation. The formulation contained a standard mAb at high concentration containing buffering agent, stabilizer, and surfactant. The product was sterile filtered using 0.22-μm filter (Millipore). For filling of the product, 5-mL vials and 20-mm Lyo stoppers from West