Container closure integrity of sterile vials during deep cold storage

INTRODUCTION

Certain sterile pharmaceutical products require deep cold storage, either at dry ice (-80°C) or even cryogenic (–196 °C) temperatures. Live viral vaccines or products that contain active cells (cell therapies) often need deep cold storage to maintain stability. These storage conditions pose a challenge to packaging components, in particular to vial/rubber stopper combinations traditionally used to fill sterile pharmaceutical product. Rubber formulations typically have glass transition temperatures (T_g's) near -65°C meaning that rubber stoppers lose their elasticity at deep cold storage temperatures. This loss of elasticity, coupled with inappropriate capping & crimping, can result in increased risk that the vial seal integrity could be compromised. It is therefore imperative that data is generated to demonstrate the maintenance of seal integrity during deep cold storage and transport.

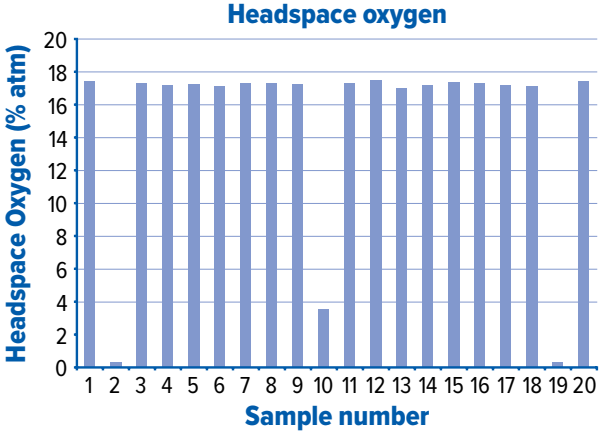
METHOD HIGHLIGHTS

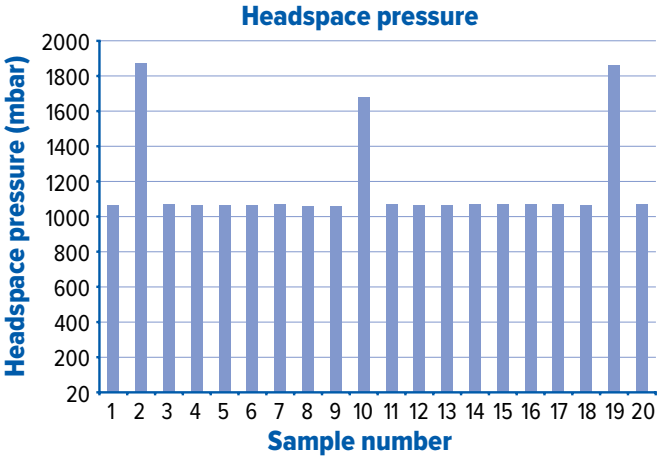
It is not realistic to perform a container closure integrity test at the deep cold storage temperature - integrity tests are usually performed at room temperature after the product vials have been removed from storage. Published studies have shown that leaks occurring in deep cold storage are temporary. Once the stopper loses its elasticity a leak may occur, but when the vial is taken out of deep cold storage and the stopper warms up to

temperatures above the T_g, the vial reseals itself. The only container closure integrity test method which can non-destructively detect these temporary leaks is laser-based headspace. The LIGHTHOUSE laser-based headspace method shines light through the headspace to measure headspace gas concentrations and pressure in finished product containers. Based on spectroscopic methods, the measurement is analytical, rapid, and non-destructive. If seal integrity is lost during cold storage, the surrounding cold dense gas from the storage environment leaks into the vial. The Figures show how headspace measurements are used to detect the drastic change in headspace conditions of vials that have temporarily lost closure during deep cold storage.

BENEFITS

- Laser-based headspace is analytical, rapid, and non-destructive
- Able to detect vials that have (temporarily) leaked during deep cold storage
- Measurement method is robust and independent of operator





Data which identified three media vial samples that temporarily leaked while stored on dry ice. Cold dense carbon dioxide gas ingressed into the vials during cold storage and was trapped after the vials resealed when taken out of storage. This trapped gas resulted in depleted oxygen, and elevated carbon dioxide and pressure levels in the headspace of the vials that leaked.