

## FARRAR - ASI ACCLIMATE RATE CHAMBER STUDY SUMMARY

Evaluation of ASI Acclimate Freeze Rates in Farrar Scientifics Model 4002 Rate Chamber

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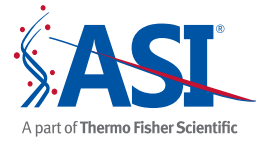
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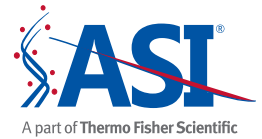


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# FARRAR - ASI ACCLIMATE RATE CHAMBER STUDY SUMMARY

Evaluation of ASI Acclimate Freeze Rates in Farrar Scientifics Model 4002 Rate Chamber



## EXECUTIVE SUMMARY

The purpose of the study was to determine the rate at which the Farrar Scientific Model 4002 -80°C to +40°C Rate Chamber could freeze and thaw 2 L, 6 L, and 16 L ASI Acclimate Freeze / Thaw Containers. The integrity of the Acclimate Freeze / Thaw Containers was evaluated by visual observation of physical changes and the identification of leakage caused by freezing and thawing of potable water before and after one cycle in the Farrar Scientific -80°C to +40°C Rate Chamber. The internal core temperature at the last point of freezing (LPF) was monitored throughout the cycle. The ASI products used in this study were:

- 2 L Acclimate bag Part number B107874-I
- 6 L Acclimate bag Part number B107875-I
- 16 L Acclimate bag Part number B107876-I
- 2 L Acclimate tray assembly Part number S3363
- 6 L Acclimate tray assembly Part number S3364
- 16 L Acclimate tray assembly Part number S3365

None of the bags showed any loss of integrity after undergoing one cycle of freezing and thawing in the Farrar Scientific -80°C to +40°C Rate Chamber. As expected, the largest (16 L) bags took the longest to freeze and thaw. The average time for a bag to freeze, regardless of load or bag size was 437 minutes. The average time for a bag to thaw, regardless of load or bag size was 905 minutes. Thus, it took on average 2.1 times longer for a bag to thaw than to freeze, regardless of the load or the bag size. However, the rate of freezing and thawing for the 6 L containers was least affected by the load size. The rates of freezing were more uniform than the rates of thawing for all of the containers. The variability in the rates of thawing did not seem to depend on the position of the bag in the rate chamber.

## INTRODUCTION

ASI is a leading global provider of advanced single-use systems for the Healthcare and Life Sciences Industries. The Acclimate Single-Use Freeze Thaw Containment System from ASI is a single-use bag and container combination used for freezing / thawing of bio-pharmaceutical fluids in commercial equipment such as walk-in freezers, cold rooms, temperature controlled cabinets or water baths.

The Acclimate system has a range of features that offer users both efficiency and practicality. The bag is integral to the protective container and holds 2, 6 or 16 liters of fluid while the container fits easily into commercial freezing equipment and stacks, maximizing freezer space. The system is also available with an optional sample bag that can be safely stored on the outside of the container for easy access to a representative sample.

The Acclimate Freeze Containment System (bag and container) is capable of withstanding temperatures as low as -70°C and thaw conditions to ambient room temperature while maintaining the integrity.

The Acclimate bags are designed with patent-pending tuft(s) which uniformly distributes the fluid as it expands during freezing. Initial freezing studies have indicated that the tufted design has improved fluid distribution and expansion during the freezing / thawing cycles.

The Acclimate system has been designed for the freezing, thawing and long-term frozen storage of bio-pharmaceutical fluids such as:

- Process Intermediates
- Bulk Drug Substances
- Product in Clinical Phases
- Vaccines

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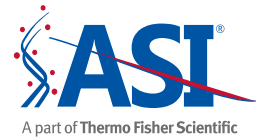


Figure 1 - 2 L, 6 L and 16 L Acclimate Single-Use Freeze Thaw Containment System bags in the Acclimate Freeze Container.



Figure 2 - The Acclimate Single-Use Freeze Thaw Containment System container.



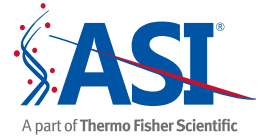
The Acclimate Single-Use Freeze Thaw Containment System containers were inspected for defects, deformations, or damages such as cracking. The containers were filled with 2 L, 6 L or 16 L of potable water by weight and placed in a Farrar Scientific  $-80^{\circ}\text{C}$  to  $+40^{\circ}\text{C}$  Rate Chamber in various configurations. The temperature in each Acclimate Freeze / Thaw Container was independently monitored with a thermocouple located in the center of the bag. This position was considered as the last point to freeze (LPF). The rate chamber freeze cycle was started, and the temperature inside the bags was monitored until the temperature of the LPF reached  $-80^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and that temperature was maintained for  $\geq 10$  minutes. The temperature set-point on the rate chamber was then set to  $+30^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and internal core temperature of the containers was monitored until the internal core temperature of the last point to thaw (LPT) reached  $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ , and that temperature was maintained for  $\geq 10$  minutes. The containers were again visually inspected for any defects caused by the freezing/thawing cycle.

The study was conducted between February 17 and June 6, 2014 at Farrar Scientific.

All of the data for this study is in the Farrar Scientific executed protocol ASIRC2014 - Evaluation of ASI Acclimate Freeze Rates in Farrar Scientific Model 4002 Rate Chamber.

# FARRAR - ASI ACCLIMATE RATE CHAMBER STUDY SUMMARY

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## MATERIALS

### MATERIALS USED IN THE STUDY

#### Acclimate Single-Use Freeze Thaw Containment System

- 2 L Acclimate bag Part number B107874-I
- 6 L Acclimate bag Part number B107875-I
- 16 L Acclimate bag Part number B107876-I
- 2 L Acclimate tray assembly Part number S3363
- 6 L Acclimate tray assembly Part number S3364
- 16 L Acclimate tray assembly Part number S3365

#### Instruments Used in the Study

- Farrar Scientific -80°C to +40°C Rate Chamber,
- Serial Number: 4000003-1, 4000006-1, 4000006-2, 400000-3

#### Data Acquisition Equipment

- Manufacturer/Model Number: Fluke NetDaq 2640A  
Serial Number: 7850013, 9090017, 6619914, 9090016, 8642001  
Calibration Expiration Date: November 23, 2014
- Manufacturer/Model Number: Agilent 34980A  
Serial Number: MY44006591  
Calibration Expiration Date: December 10, 2014

#### Scale

- Manufacturer/Model Number: Inficon Wey-TEK  
Serial Number: 12470184  
Range/Resolution: 100Kg/220 pounds, .01 ounce  
Calibration Expiration Date: December 19, 2014

#### Chemicals Used in the Study

- Potable water

## TEST METHODS

Prior to and after the freeze-thaw cycle, the exterior protective shell was inspected for visual defects, deformations, or damages such as cracking. All bags were also inspected for any visual blemishes or defects.

The Acclimate Freeze / Thaw Containers were filled with 2 L, 6 L or 16 L of potable water by weight and placed in a Farrar Scientific -80°C to +40°C Rate Chamber in various configurations.

In total, nine different tests were carried out to evaluate the performance of the Acclimate Single-Use Freeze Thaw Containment System in the Farrar Scientific -80°C to +40°C Rate Chamber for freezing and thawing a full load, a half load and a minimum load. The number of containers in each of the different loads tested is shown in **Table 1** and the configurations of the containers in the chamber are shown in **Figure 3**.

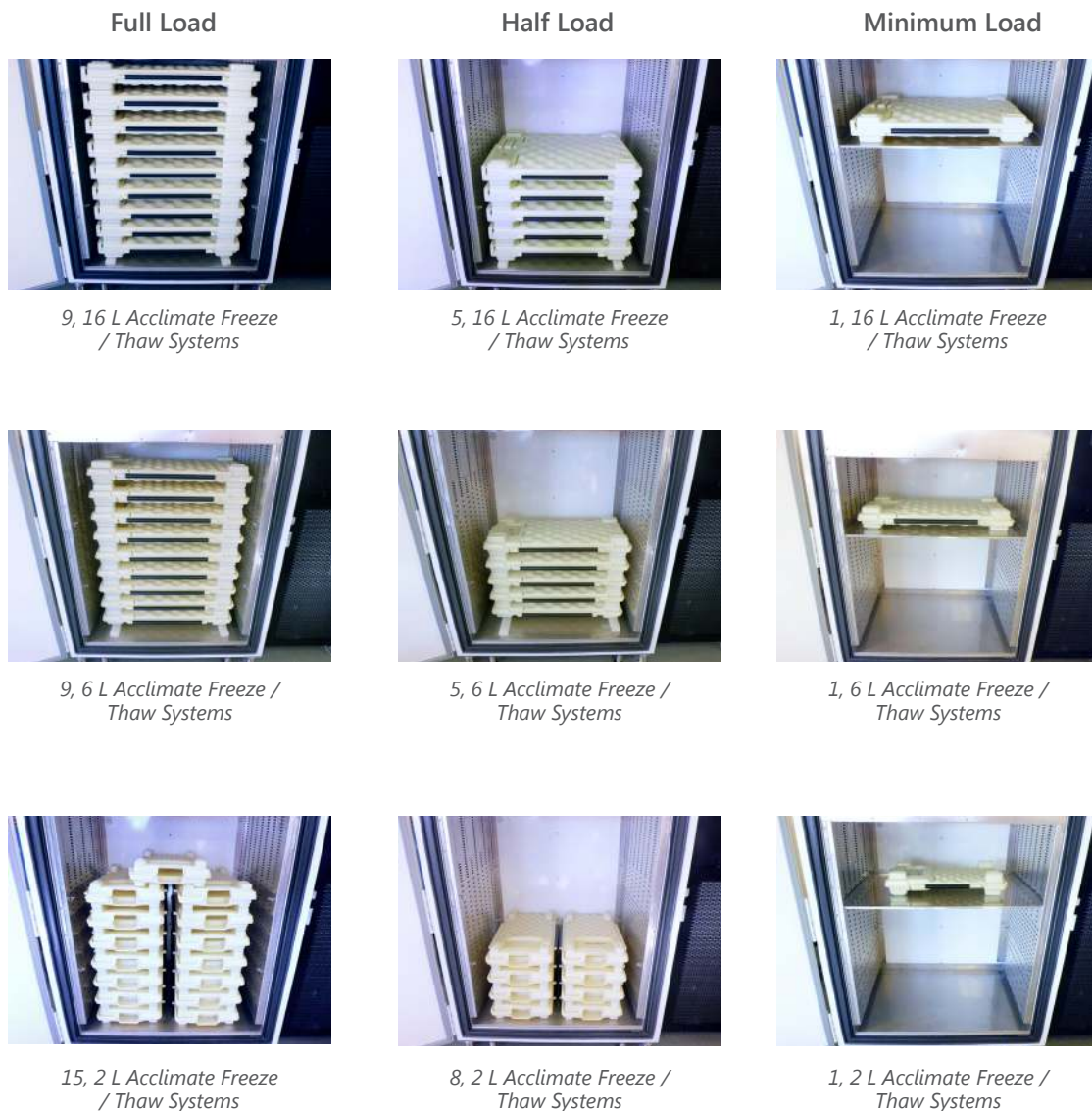
# FARRAR - ASI ACCLIMATE RATE CHAMBER STUDY SUMMARY

Evaluation of ASI Acclimate Freeze Rates in Farrar Scientifics Model 4002 Rate Chamber

Table 1 – Numbers of Acclimate Single-Use Freeze Thaw Containment System containers in the Farrar Scientific -80°C to +40°C Rate Chamber during the tests

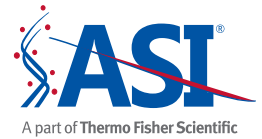
Load Size / Container Volume	Number of Containers in Load		
	16 L	6 L	2 L
Full Load	9	9	15
Half Load	5	5	8
Minimum Load	1	1	1

Figure 3 – Configuration of Acclimate Single-Use Freeze Thaw Containment System containers in the Farrar Scientific -80°C to +40°C Rate Chamber during the tests



# FARRAR - ASI ACCLIMATE RATE CHAMBER STUDY SUMMARY

Evaluation of ASI Acclimate Freeze Rates in Farrar Scientifics Model 4002 Rate Chamber



## PROTOCOL

### TESTING OF THE ASI ACCLIMATE FREEZE / THAW CONTAINERS

An appropriate number of complete Acclimate Freeze / Thaw Containers of the volume to be tested were acquired, and the outer shell and the bag were inspected to ensure they were free of defects and/or damage. Each bag and shell was labeled with a black permanent marker.

Each container was filled with potable water to the appropriate volume by weight.

- The scale was set up and levelled, and its calibration expiration date was checked.
- The bag was placed on a rigid tray and then on the scale platform.
- The scale was tared to zero.

The container was filled with potable water. The weights used for the various tests were 16kg ± 0.2kg, 6kg ± 0.2kg or 2kg ± 0.2kg.

The temperature in each container was independently monitored with a thermocouple located in the center of the bag. This position was considered as the last point to freeze (LPF).

The rate chamber freeze cycle was started and the temperature inside the bags was monitored until the internal core temperature of the LPF reached -80°C +/-2°C, and that temperature was maintained for ≥ 10 minutes.

The temperature set-point on the rate chamber was then set to +30°C +/-2°C and the temperature inside the bags was monitored until the internal core temperature of the LPT reached 30°C +/-2°C and that temperature was maintained for ≥ 10 minutes.

The containers were again visually inspected for any defects caused by the freezing/thawing cycle. All containers were placed on a flat surface, and the shells were inspected for damage.

- The shell clamps and the top half of the shell were removed.
- The exterior of the bag was dried and inspected for visual damage or blemishes and/or leaks.
- The bag in the second half of the shell was removed, and the inspection was repeated.

## RESULTS

The rates of freezing and thawing of the Acclimate Single-Use Freeze Thaw Containment System containers in the Farrar Scientific -80°C to +40°C Rate Chamber are shown in **Table 2**.

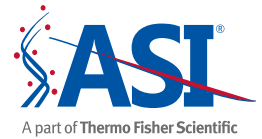
*Table 2 – Rates of Freezing and Thawing of Acclimate Single-Use Freeze Thaw Containment System containers in the Farrar Scientific -80°C to +40°C Rate Chamber*

Load Size / Container volume	16 L		6 L		2 L	
	LPF time (min)	LPT time (min)	LPF time (min)	LPT time (min)	LPF time (min)	LPT time (min)
Full Load	763	1852	469	916	348	742
Half Load	653	1352	346	777	315	692
Minimum Load	512	762	330	629	197	424
Average for All Loads	643	1322	382	774	287	619

*Abbreviations: L=liters; LPF=last point to freeze (-80°C); LPT=last point to thaw (30°C); min=minutes*

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The size of the container was the most important factor that determined the freeze/thaw rate.

The 16 L bags took 2.2 times as long to freeze as the 2 L bags did, regardless of load size. The differences in the freezing times between the 6 L and the 2 L bags were not as great as those between the 2 L and the 16 L bags; the 6 L bags took only 1.3 times as long to freeze as the 2 L bags, regardless of load size. The 16 L bags took 1.7 times as long to freeze as the 6 L bags, regardless of load size.

The 16 L bags took 2.1 times as long to thaw as the 2 L bags did, regardless of the load size. The difference in the thawing time between the 6 L and the 2 L bags was not as great as that between the 2 L and the 16 L bags; the 6 L bags took only 1.2 times as long to thaw as the 2 L bags, regardless of load size. The 16 L bags took 2.1 times as long to thaw as the 6 L bags, regardless of the load size.

The average time for a bag to freeze, regardless of load or bag size was 437 minutes. The average time for a bag to thaw, regardless of the load or the bag size was 905 minutes. Thus, it took on average 2.1 times longer for a bag to thaw than to freeze, regardless of the load or the bag size.

All of the bags were visually inspected after the freeze/thaw cycle was completed, and all of them were found to be intact. No leaks were detected.

Table 3 shows the fold differences in the rates of freezing and thawing of the Acclimate Single-Use Freeze Thaw Containment System containers in the Farrar Scientific -80°C to +40°C Rate Chamber for different loads. Figure 4 shows the graphs of the freezing/thawing of the individual containers of different sizes when the rate chamber was fully loaded. The fold difference values were calculated by dividing the LPF or LPT times for the full or half loads by the corresponding time for the minimum load for each container size.

The bags took longer to freeze and thaw as the load size increased.

The 16 L containers took longest to freeze or thaw (Table 2). However, the rate of freezing and thawing for the 6 L containers was least affected by the load size (Table 3).

Table 3 – Fold Differences in the Rates of Freezing and Thawing of Acclimate Single-Use Freeze Thaw Containment System containers in the Farrar Scientific -80°C to +40°C Rate Chamber for Different Loads

Load Size / Container volume	16 L		6 L		2 L	
	LPF fold difference	LPT fold difference	LPF fold difference	LPT fold difference	LPF fold difference	LPT fold difference
Full Load	1.5	2.4	1.4	1.5	1.8	1.2
Half Load	1.3	1.8	1.0	1.2	1.6	1.1
Minimum Load	1.0	1.0	1.0	1.0	1.0	1.0

Abbreviations: LPF=last point to freeze (-80°C); LPT=last point to thaw (30°C)



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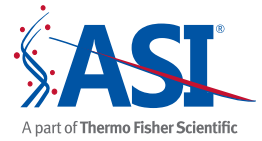
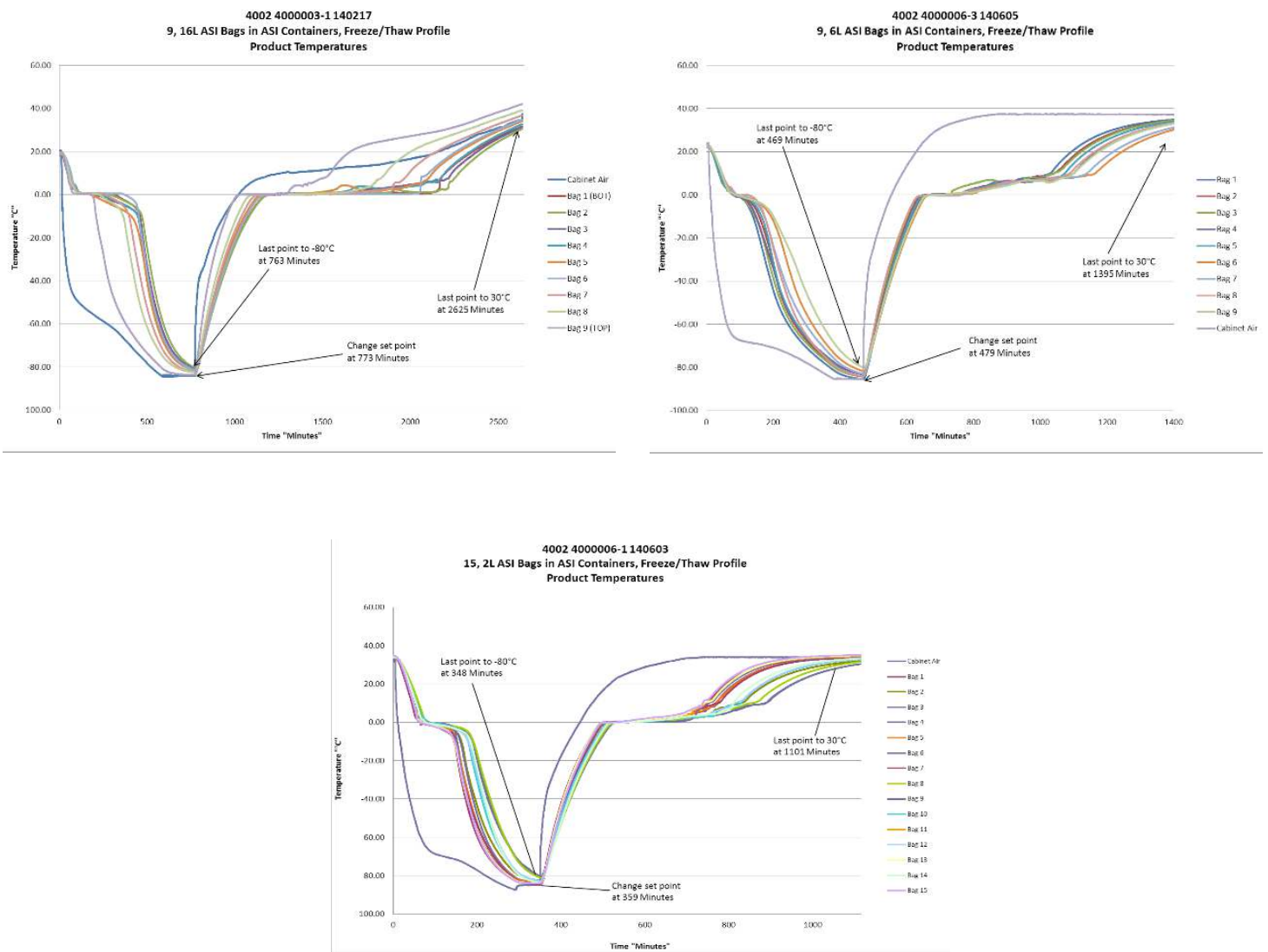


Figure 4 indicates that the rate of freezing was fairly uniform for all of the containers, regardless of size. Conversely, Figure 4 also indicates that the thawing rate was more variable than the freezing rate, and did not seem to depend on the position of the container in the freezer.

The graphs for the freezing/thawing of the individual containers of different sizes for the half load and minimum load sizes were similar to those for the fully loaded rate chamber, so they are not included in this summary. However, these graphs can be found in the Farrar Scientific executed protocol ASIRC2014 - Evaluation of ASI Acclimate Freeze Rates in Farrar Scientific Model 4002 Rate Chamber.

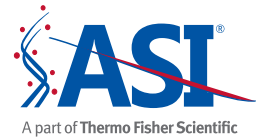
Figure 4 – Graphs of Freezing and Thawing of Full Loads of Acclimate Single-Use Freeze Thaw Containment System containers in the Farrar Scientific -80°C to +40°C Rate Chamber



No deviations were recorded during the execution of the protocol.

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## CONCLUSION

The primary Critical Process Parameters (CPPs) for the ASI Acclimate Freeze / Thaw Containers are the ability to maintain their integrity before, during, and after the freeze thaw process. The rate at which the Farrar Scientific -80°C to +40°C Rate Chamber could freeze and thaw 2 L, 6 L, and 16 L ASI Acclimate Freeze / Thaw Containers was determined in this study. The integrity of Acclimate Freeze / Thaw Containers was evaluated by visual observation of physical changes and the identification of leakage caused by freezing and thawing of potable water before and after one cycle in the Farrar Scientific -80°C to +40°C Rate Chamber.

All of the bags tested maintained their integrity during and after one cycle of freezing and thawing in the Farrar Scientific -80°C to +40°C Rate Chamber.

The effects of handling of the containers were not evaluated in this study.

The largest (16 L) bags took the longest time to freeze and thaw, and the 2 L bags took the least. The difference between the freezing and thawing times between the 6 L bags and the 2 L bags was not as great as that between the 6 L and the 16 L bags

The time for the bags to freeze and thaw increased as the load size increased. The 6 L bags showed the most uniformity of freezing and thawing rates across different load sizes.

In general, the rate of freezing was more uniform than the rate of thawing.

A worst-case scenario has not been defined for freeze and thaw rates. Specifications against regulatory requirements should be addressed during proper equipment and/or process validation activities if deemed necessary. Technical assessments may be suitable for implementation.