

4000 SERIES CONTROLLED RATE CHAMBER

Innovative freezer technology
revolutionizes biologic drug handling

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INTRODUCTION

The significant growth of the biologic drug market, bolstered by the COVID-19 pandemic and the development of relevant vaccines, along with the growing complexity and fragility of biologic drugs, has led to a need for improved freezing and thawing methods. FARRAR™, a brand of Trane Technologies, has developed the 4000 Series Controlled Rate Chamber to help obtain higher yields and meet demand timelines.



Model 4000-LC Series

IMARC Group, an international market research company, estimated that the global market was worth nearly \$300 billion USD in 2021 and would reach \$501.9 billion by 2027, with a compound annual growth rate of 9.25% during the five-year period from 2022 to 2027. This predicted growth is exciting, but discrepancies in production threaten its success.

Current technologies typically produce batch yields of only 60%–70%, are not repeatable from batch to batch, and face many inconsistencies within a single run (for example, some bottles freeze relatively quickly while others are extremely slow). High variability between batches can lead to less efficient yields, which may result in lower or less predictable earnings.

In addition, freezing materials from ambient temperatures requires the removal of a large amount of heat, which taxes the refrigeration system. Conventional ultra-low temperature (ULT) storage freezers are not designed to handle this process. Such high strain (combined with poor maintenance practices) can greatly reduce service life.

The 4000 Series Controlled Rate Chamber is designed to help resolve these issues.

COMPARISON OF FREEZER DESIGNS

Standard ULT freezers that achieve a temperature of -80°C are designed to maintain temperature with little additional capacity and to store **already frozen material**. When used for freezing from ambient temperatures, their freezing rates vary significantly between product load (from a few hours to several days) and from batch to batch. Given the lack of capacity to remove heat effectively, long run times (48–72 hours) during a pull-down can result in permanent damage to the refrigeration system. Bottles also freeze at different rates, resulting in variability in material quality and yields.

In standard 700L to 800L capacity ULT freezers, the total typical heat transferred into the cabinet from the outside is calculated at 158 watts (W) (assuming a temperature change of more than 100°C [$25^{\circ}\text{C} - (-80^{\circ}) = 105^{\circ}\text{C}$] between the outside ambient air and inner cabinet):

Base cabinet wall (top, back, sides, and bottom) (104 W) + across the face of the door (30 W) + across the door gasket (24 W)

The base cabinet load (Q') is calculated using the following equation:

$$k_f \times A_s \times \Delta T / t = Q'$$

Where

- k_f is the thermal conductivity
- A_s is the area
- ΔT is the change in temperature
- t is the wall thickness

Plugging in the values of a standard ULT freezer results in the following equation:

$$0.020 \text{ W}/(\text{m}\cdot\text{K}) \times 6.3 \text{ m}^2 \times 105^\circ\text{C} (105 \text{ K}) / 0.127 \text{ m} = 104 \text{ W}$$

A conventional ULT freezer's refrigeration system is typically oversized to remove the cabinet heat load by 30%–40%. This equates to a design load between 210 W and 243 W, leaving only 52 W to 85 W to act as a buffer for the loading of warm product and/or temperature recoveries from door openings.

With such a small buffer, the compressor must run constantly during times of high energy expenditure, which can lead to the overheating and premature failure of the refrigeration system. Just eight liters of water at room temperature contain 4.7 million Joules of energy (1 Joule = 1 W/s), which means the refrigeration system must run extensively for a long period of time to remove the heat. In addition, conventional freezers use capillary tubes, which provide a specific amount of refrigerant and only enough to remove the cabinet heat.

The 4000 Series Controlled Rate Chamber removes heat from large volumes of materials using forced air convection. The equipment is purpose-built to be flexible and adaptable to each manufacturer's process needs, and the 4000 Series is programmable for different set-points. Figure 1 shows heat transfer loads (Q') for the cabinet, blower, door, and door jamb.

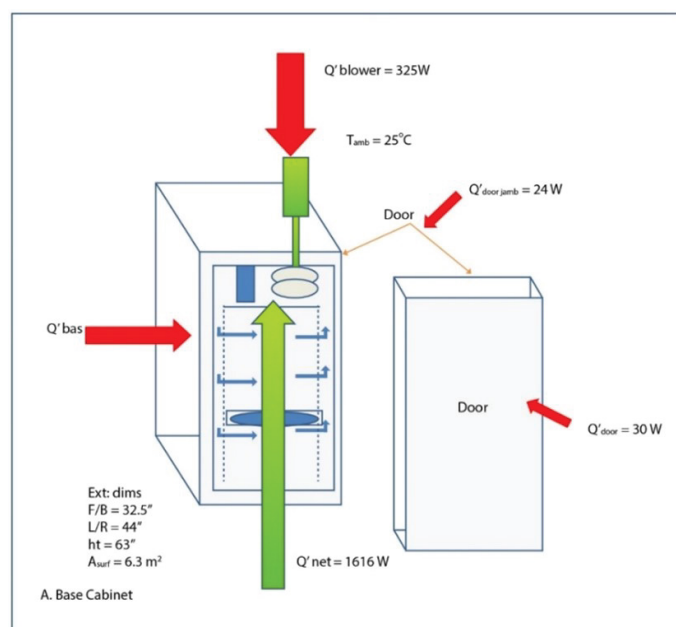


Figure 1: Controlled Rate Chamber schematic.

The 4000 Series refrigeration system is designed to handle a total heat load of 2100 W at -80°C . With a cabinet heat load of 158 W (similar to a conventional ULT) and an added blower heat load of 325 W, the total steady state heat load of the freezer measures 483 W. The leftover 1617 W—an increase of more than 1800% over a conventional ULT freezer's 52 W—makes a much larger buffer to account for product load. At -80°C , this additional energy can remove heat at twice the rate of conventional ULTs that use natural convection.

The following features help achieve this performance:

- Forced air circulation provides both rapid freezing to the desired temperature and uniform cooling throughout the container without false freeze points (where liquid is only partially frozen).
- Five-inch polyurethane foam insulation minimizes heat loss through the wall.
- 60 chamber air changes per minute (1,000 cubic feet per minute) remove heat at double the efficiency of natural convection.

- The expansion valve delivers the exact amount of refrigerant needed to freeze any volume of material by automatically opening and closing for fast and precise temperature control. The unique assembly of specific refrigeration components allows for automatic adjustments throughout the operating range to provide swift and precise temperature control.
- The backward inclined blower wheel can move large volumes of air, even when flow restrictions (such as ice and heavy cabinet loads) are present.

The result is a freezer that is fast, uniform, and reliable under all cabinet conditions from 40°C to -85°C. Temperature uniformity is +/- 2°C anywhere in the chamber under steady-state conditions.

Figure 2 summarizes the differences between standard ULT freezers and freezers with forced air convection.

Customer Value	Model 4000 CR Chamber	Standard ULT
Designed for storage of materials already at setpoint temperature	✗	✓
Freeze material then store in same freezer	✗	—
Temperature uniformity during freezing	✓	✗
Designed for freezing bottles and bulk material bags	✓	✗
Available cooling capacity for small batches or vials	✓	—
Repeatable, consistent freezing results everywhere in chamber	✓	✗
Configurable freeze rates	✓	✗
Adaptable to manufacturing reconfigurations and volume changes	✓	✓
Integrated predictive and preventative maintenance	✓	—
Controlled thaw capability	✓	✗

Figure 2: Differences between forced air convection freezers and standard ULT freezers.

RATE CHAMBER TESTING

To confirm the performance of the 4000 Series, a Farrar 4000-LC unit was used to freeze several bottle sizes: 2L, 4L, and 10L. Each bottle was filled to between 90% and 95% capacity with tap water (1.8L, 3.6L, and 9.4L, respectively). The test setup conditions for all bottle sizes were as follows:

- The chamber was kept at ambient temperature.
- A Kaye Validator System with wired thermocouple probes was used for accurate temperature readings.
 - The times required to freeze bottles were measured.
 - The temperature setpoint varied between -80°C and -85°C.
- The thermocouple was located on a nylon rod in the center of the bottle at the approximate center of bottle mass (see Figure 3).
- The indicated bottles in figures 5, 6, and 7 were measured and timed for speed to reach certain temperature benchmarks:
 - +20°C through completion of phase change at 0°C
 - +20°C to -60°C
 - 0°C (completion of phase change) to -60°C



Figure 3: Nylon rod within bottle mass.

Different loading configurations were used for each bottle size, as shown in Figure 4.



Figure 4: 100 2L bottles (left), 24 4L bottles (center), 12 10L bottles (right).

TEST RESULTS

Table 1 summarizes the time to reach temperature for different temperature ranges for all three bottle sizes.

Table 1: Time to Reach Temperature Per Bottle Size

Bottle Type			
	2L (180L)	4L (86.4L)	10L (112.8L)
+20°C through phase change (0°C)			
Avg time (Hours)	6.27	4.13	7
Range (Hours)	4.1–8.45	3–5.9	5.0–8.6
Phase change (0°C) to -60°C			
Avg time (Hours)	2.9	1.42	1.8
Range (Hours)	1.65–4.8	1.2–1.7	1.5–2.5
+20°C to -60°C			
Avg time (Hours)	9.18	5.54	8.85
Range (Hours)	8.8–10.1	4.4–7.4	7.4–11.1

Note: Phase change to -60°C for 10L bottle test.

Figures 5, 6, and 7 show the cabinet configuration diagram and freeze chart for each bottle size.

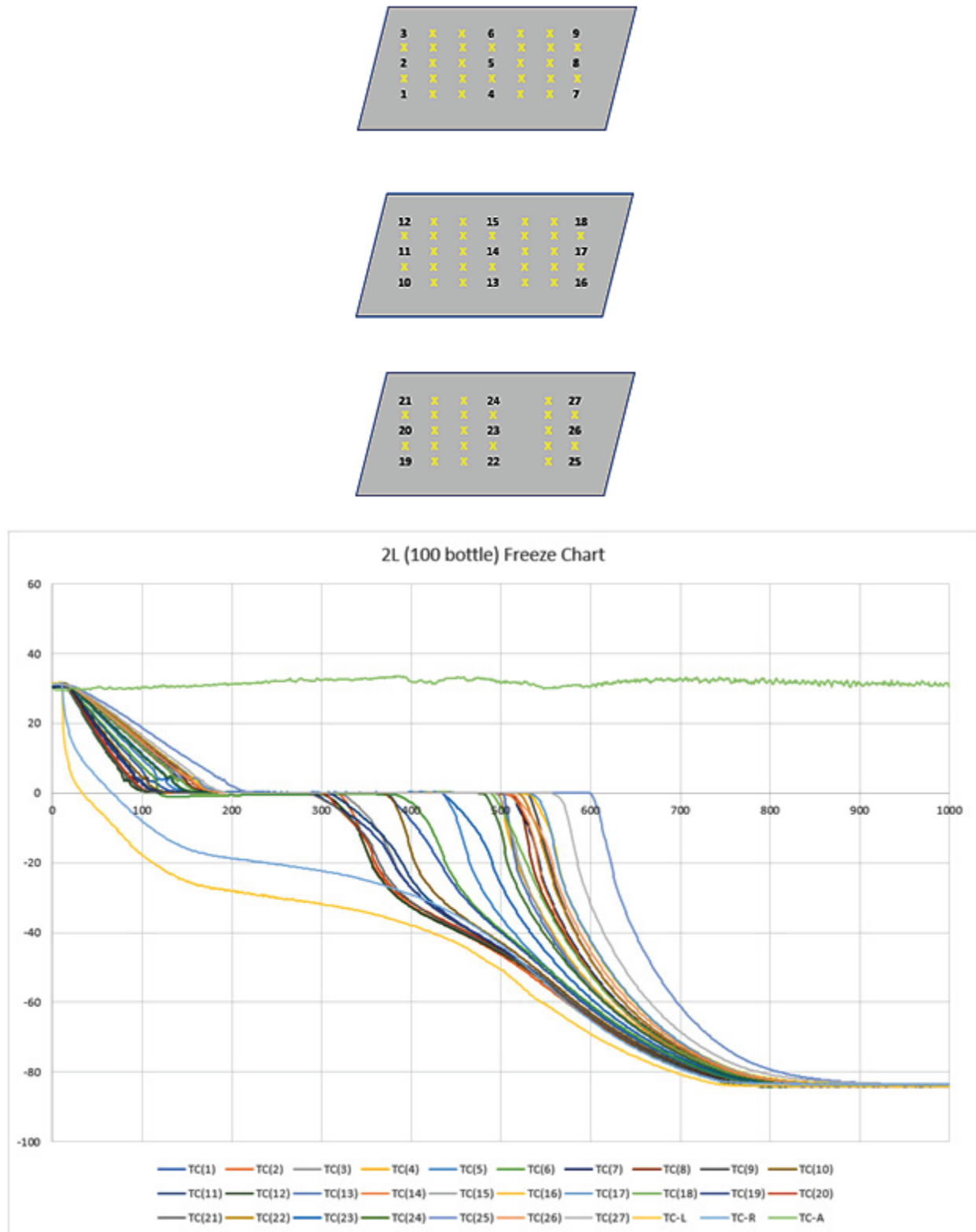


Figure 5: Schematic of the 100 2L bottle configuration (top) and freeze chart (bottom).

In addition to the 27 thermocouples measuring bottle temperatures, three thermocouples measured air temperatures.

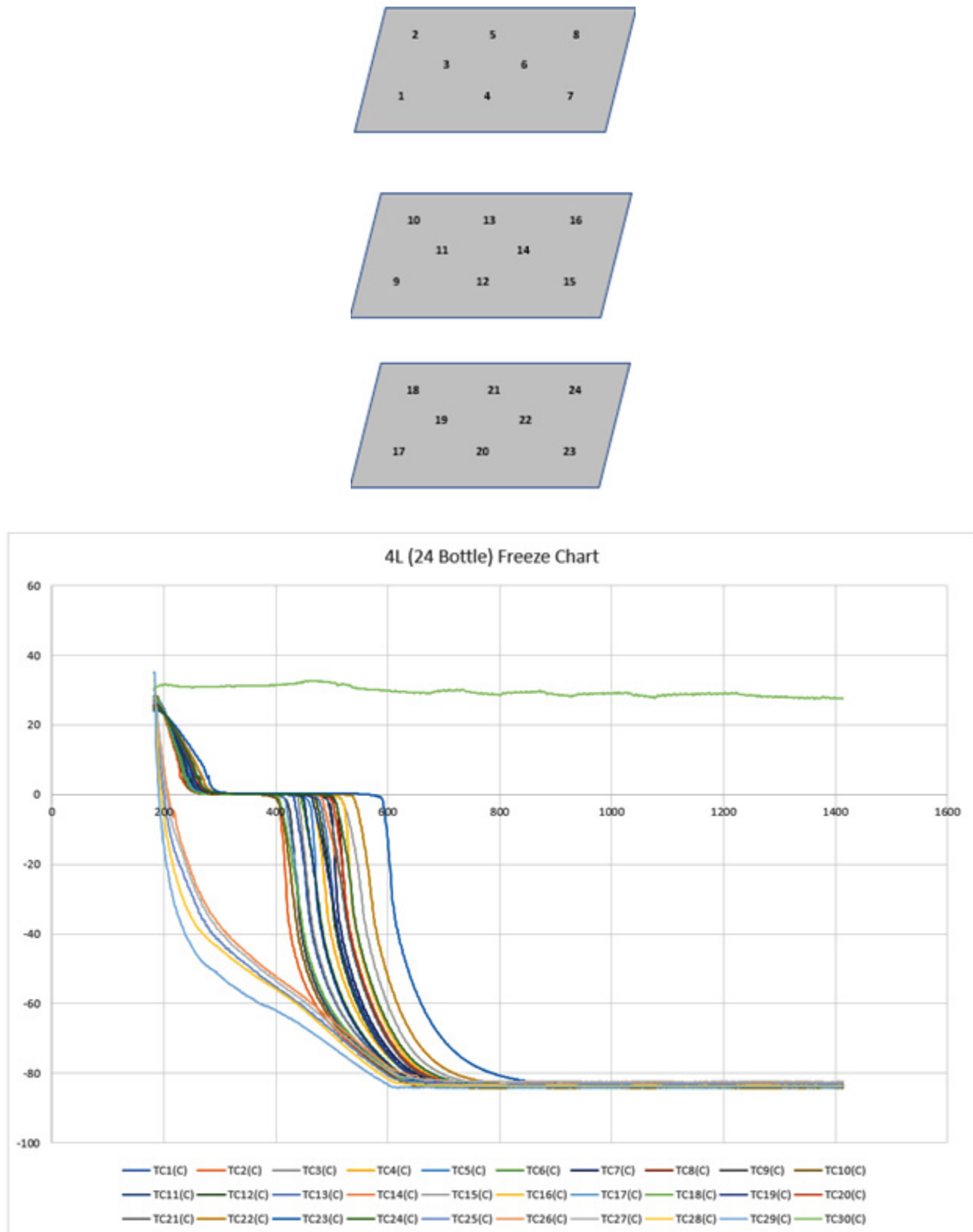


Figure 6: Schematic of the 24 4L bottle configuration (top) and freeze chart (bottom).

In addition to the 24 thermocouples measuring bottle temperatures, six thermocouples measured air temperatures.

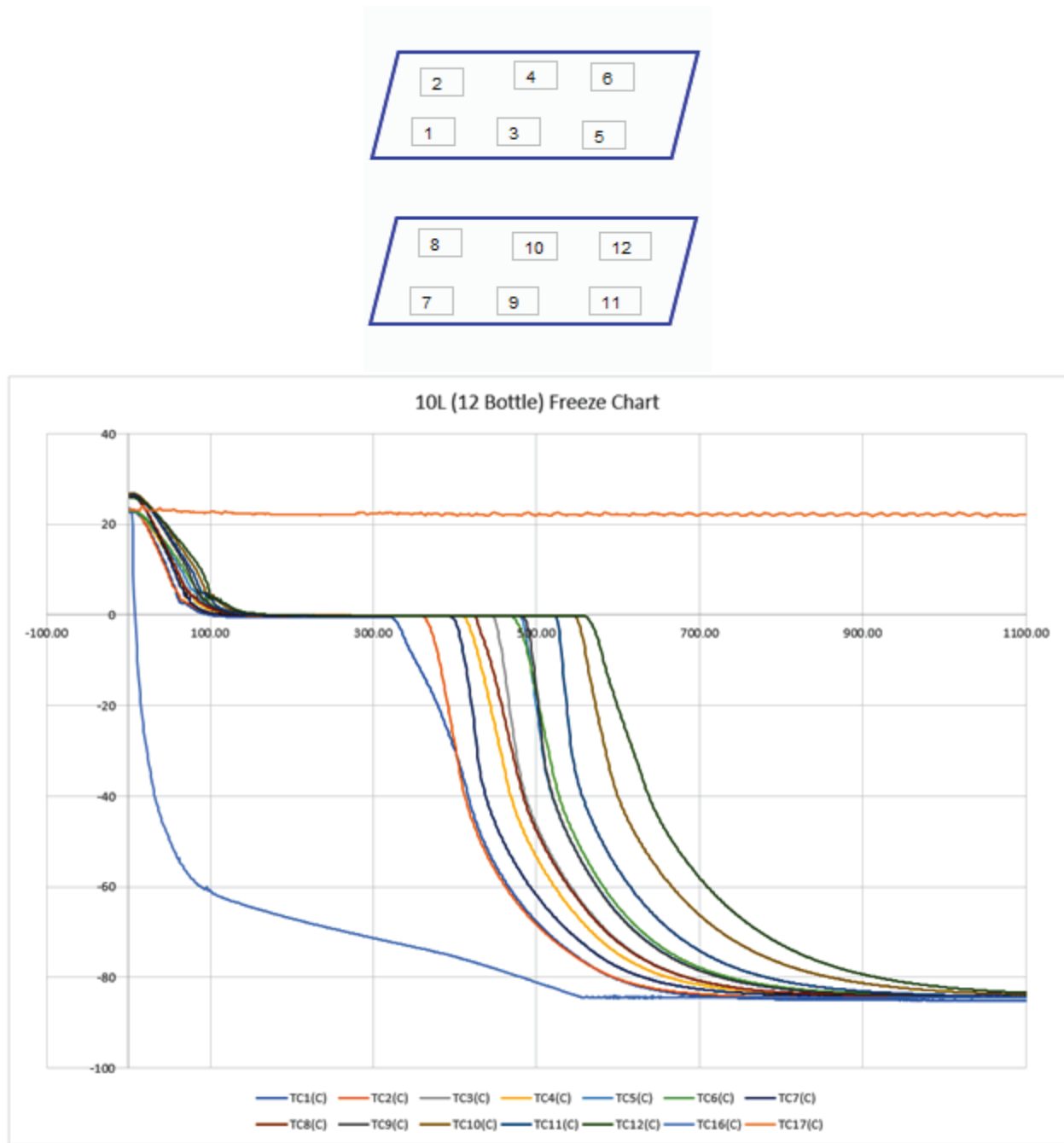


Figure 7: Schematic of the 12 10L bottle configuration (top) and freeze chart (bottom).

In addition to the 12 thermocouples measuring bottle temperatures, two thermocouples measured air temperatures.

For all tests, the right side of the chamber was slower to freeze than the left, based on airflow direction. Analysis of the testing* found that:

- Freeze rates are generally faster at the top versus the bottom of the freezer.
- Freezing rates are faster on the left side of the chamber versus the right side. This is due to the airflow moving left to right.
- Even though freezing rates are initially faster at the top and on the left, freezing quickly approaches uniformity as the samples approach -80°C.
 - Note: The air temperature sensors are represented by TC01 (10L), TC01-05 (4L), TC-R and TC-L (2L).

*Additional test result details are available from FARRAR upon request.

CONCLUSION

Test results confirm that FARRAR's 4000 Series Controlled Rate Chamber can freeze at a much faster rate than conventional freezers despite variations in load, bottle type, and bottle quantity. Although tests show that some temperature gradients among bottles are present within the rate chamber, they are found under transient conditions, generally flow as the air does from left to right, and dissipate as temperature equilibrium is reached.

While biologic drugs are becoming more mainstream as the pharmaceutical industry focuses on their development, maintaining high yields becomes critical to enabling timely introduction to the market and ensuring sufficient supplies. The 4000 Series can help achieve these goals and alleviate problems with conventional technology, such as:

- Low yields, large footprint, and slow freezing rates.
- Overworked refrigeration systems (and the subsequent loss of freezer capability).
- High maintenance costs (such as increased staff counts required for the servicing, validating, and handling of equipment).

Thus, the 4000 Series is a game changer, purpose-built to help support the industry's process intensification goals:

- Simplify freezing steps.
- Increase yields to help achieve industry goals of ≥90%.
- Improve TAKT times during the drug manufacturing process.
- Enable fast freezing runs.
- Provide a more reliable and repeatable method for consistent yields.
- Accommodate a wider range of materials and container sizes.
- Require no preconditioning (reaching setpoint before putting in product).

The freeze-and-thaw technology of the 4000 Series is a marked advancement for the pharmaceutical industry. Its forced air circulation results in quicker freeze times and vastly larger energy buffers. It is versatile, powerful, and robust enough to handle some of the key problems of modern medicine and biologic drug manufacturing.

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