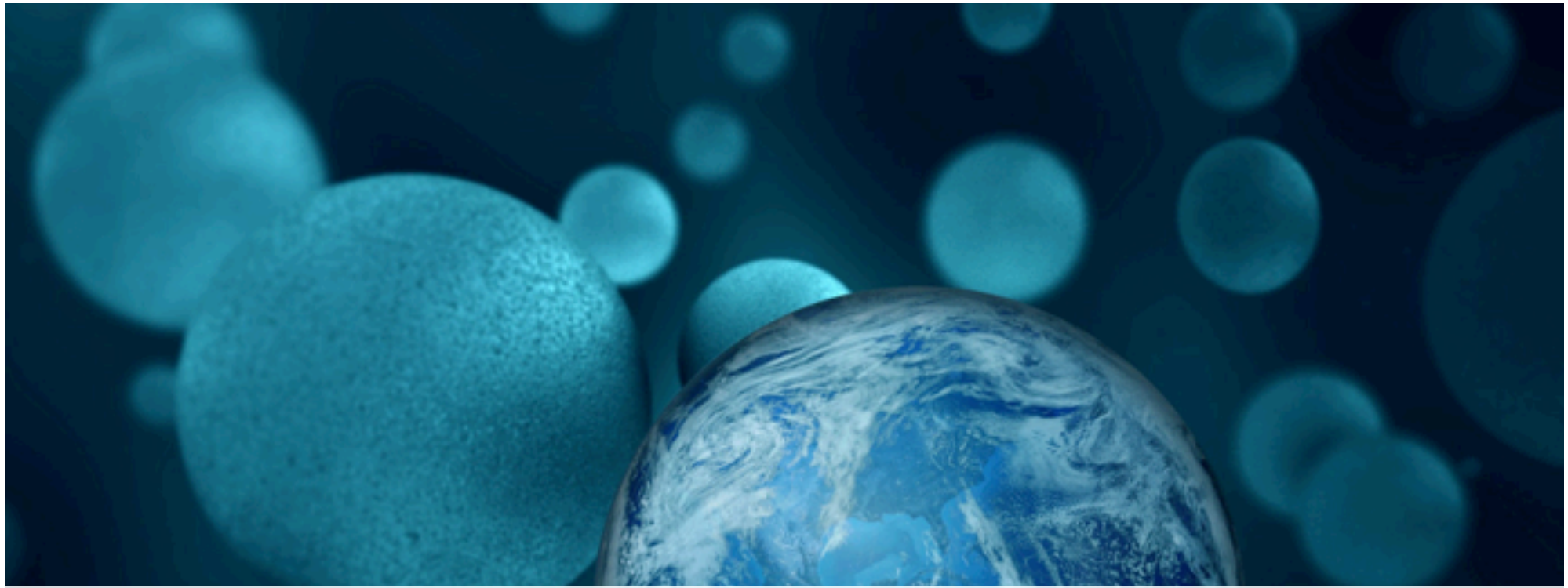


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New Technologies to Improve Throughput and Product Integrity

Cameron B. Haring
Sr. Global Product Manager
LN2 Cryo and Sample Preparation
IPFA/BCA Global Symposium 9/29/2015

The World Leader in Serving Science



- $17 billion in revenues
- $700 million spent on R&D
- 50,000 employees
- 50 countries
- 5 premier brands

ThermoFisher SCIENTIFIC

Thermo SCIENTIFIC | applied biosystems | invitrogen | Fisher Scientific | Unity Lab Services

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Our Business Segments

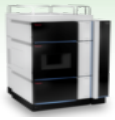
Analytical Instruments

Mass Spectrometry



Q-Exactive HF mass spectrometer

Chromatography



Vanquish Ultra HPLC

Chemical and Environmental Analysis



Gemini handheld analyzer

Life Science Solutions

Clinical Oncology



Next Gen Sequencing

Genetic Sciences



QuantStudio Dx R qPCR

Biosciences



Life Science Reagents

Human Identification

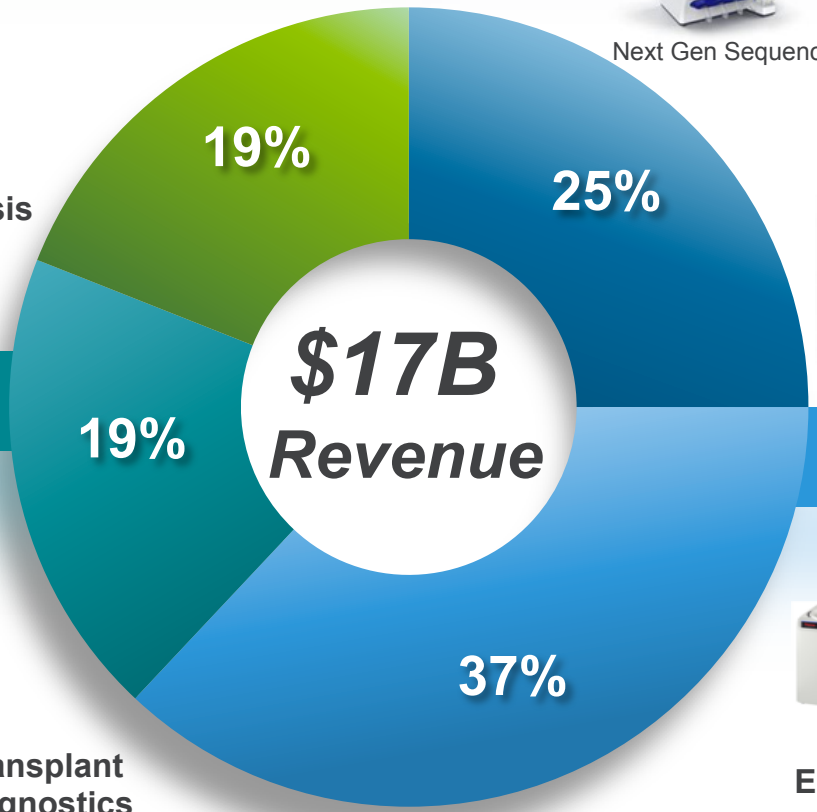


GlobalFiler PCR Amplification Kit

BioProduction



Cell Culture Reagents



Specialty Diagnostics

ImmunoDiagnostics



ImmunoCAP Allergy and Asthma Tests

Clinical Diagnostics



Oral-Eze Oral Fluid Collection System

Microbiology



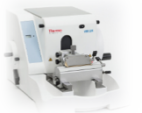
Antimicrobial Susceptibility Testing Solutions

Transplant Diagnostics



NXType High Resolution Genotyping

Pathology



Rotary Microtome

Laboratory Products and Services

Lab Equipment



Sorvall WX+ Ultracentrifuge

Distribution and BioPharma Services



Chemicals



Enterprise and Instrument Services



Lab Consumables

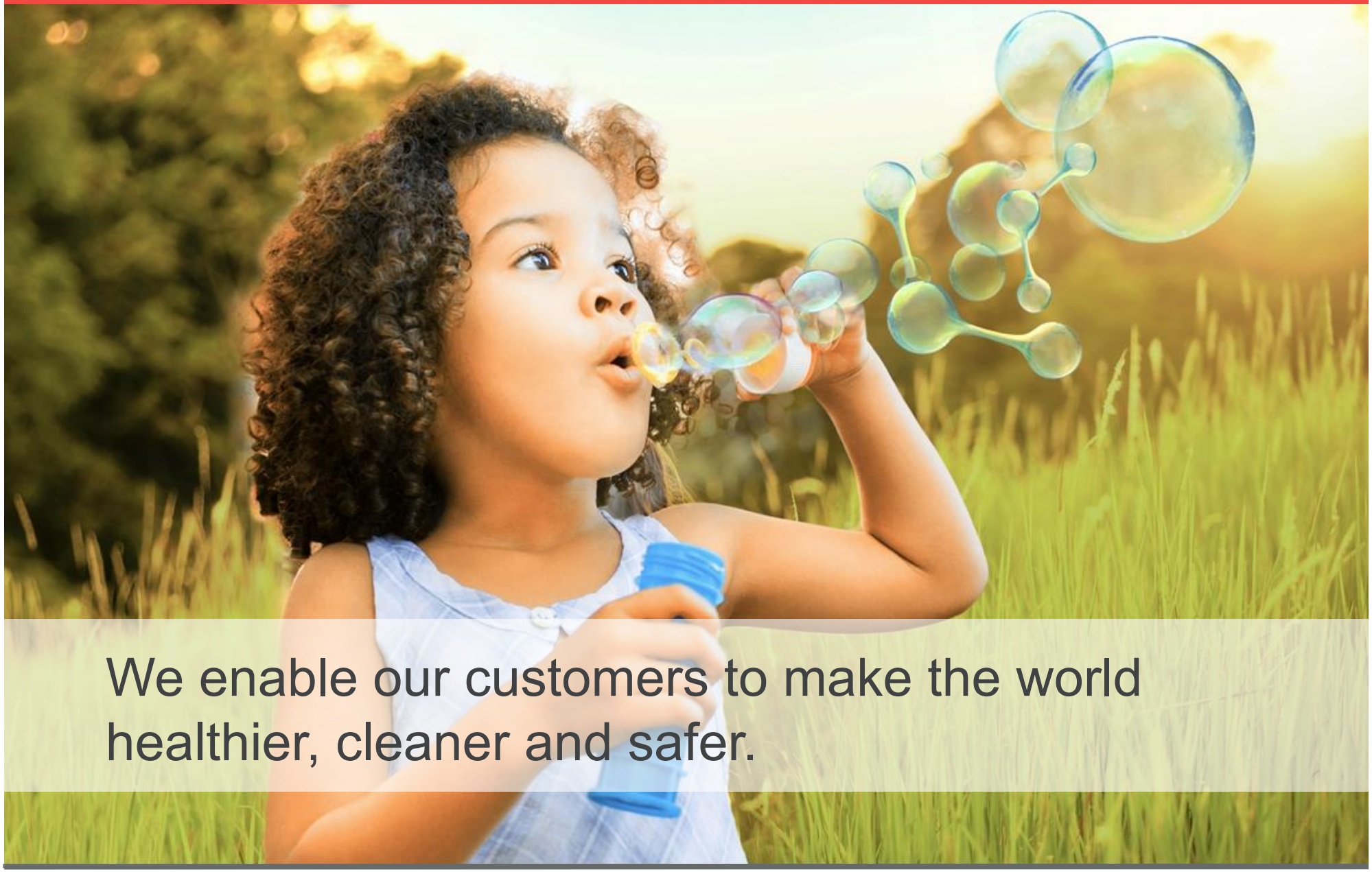


E1 ClipTip Pipette system

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A Mission We are Proud of



We enable our customers to make the world healthier, cleaner and safer.

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The *Future* of Blast Freezers…Thermo Scientific **XBF40D**









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XBF40D ‘Sample Preparation’ Summary

- Free standing, turn-key blast freezing solution for sample preparation
- **NO** costly or cumbersome installation
- Better performance and reliability
- Superior throughput relative to footprint
- Suitable for blood plasma as well as other applications that require quick cooling



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Legacy Blast Freezer vs. New XBF40D



- **Eliminate the need for remote compressors** unit that is often installed outside, or in a machine room away from the lab where the freezer is located.
- XBF40D Blast Freezer design concept is based around our 600 box ULT cabinet (14.9cf), with a 2.5 HP hermetic reciprocating compressor, driving a large forced-air evaporator located inside the payload area.
- Used to rapidly freeze centrifuged blood plasma or other products prior to long term storage



Legacy Product
(Marietta)



New Product
(XBF40)

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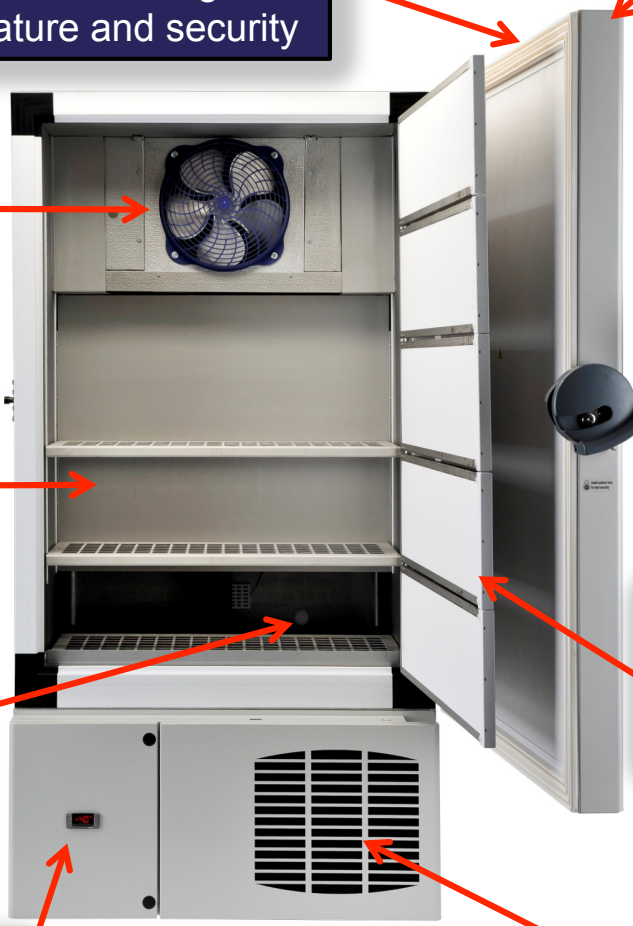
ThermoFisher SCIENTIFIC

Self-contained Forced-air -40C Xtreme Blast Freezer

- Sized for 3 loads of 12x 325ml blood bags (36 Bags Total)
- 208/230V 60Hz 20A input power
- Onboard air-cooled refrigeration system
- High-velocity air flow in refrigerated space, no contact plates or fluid bath
- Inner doors allow multiple parallel loads
- Condensate evaporator
- UL 61010 / FDA KSE864.9700 Registered Medical Device
- **No connections to building infrastructure required besides power**

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XBF40 Series Blast Freezer – Features



Outer door, multi-point gaskets, maximizing temperature and security

Durable, cold-rolled steel exterior

High-performance, forced-air circulation

Ergonomic door handle for one-hand operation

Versatile cabinet interior with adjustable, stainless steel shelves

Polystyrene, insulated inner doors featuring rare earth magnets

Standard access port

Easy-to-use digital controller

Easy-to-remove, washable filter

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FAST – Flexible Design

- 3 separate compartments allow customers to stagger product loads



- 3 stainless steel adjustable shelves and 6 aluminum baskets accommodate a wide variety of vessels
  - 2ml vials = **4,776**
  - 5L bottles = **25**
  - 10L carboys = **6**
  - 500ml Plasma Bags = **36 (72 Double Stacked*)**

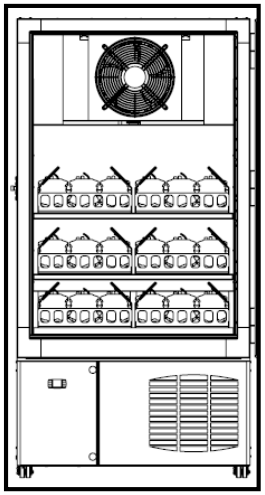


** Double stacking bags doubles freeze time*









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FAST – Accelerated Airflow

	XBF40 Blast Freezer	Typical -30 Lab Freezer
Fan Diameter (in)	12	5
Fan Surface Area (in^2)	110	20
Fan Unloaded Airflow (cfm)	650	240
Fan Motor Size (W)	60	24



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FAST – Self Contained Refrigeration System



- External to the building
- Complex and costly installation



- Plug-and-play
- No installation costs

Quality Bristol Compressor
Made in USA

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FAST – Trusted

- All Thermo Scientific XBF40 freezers are manufactured with pride in Asheville, NC with high-quality materials and high-performance technology
  - Backed by a 2-year parts & labor warranty (NA)
  - Every XBF40 series blast freezer will go through a full end-of-line test via Smart Factory, which is filed as part of the design history file
  - All units undergo Final Inspection once they have completed testing – to verify units meet engineering specifications and quality requirements

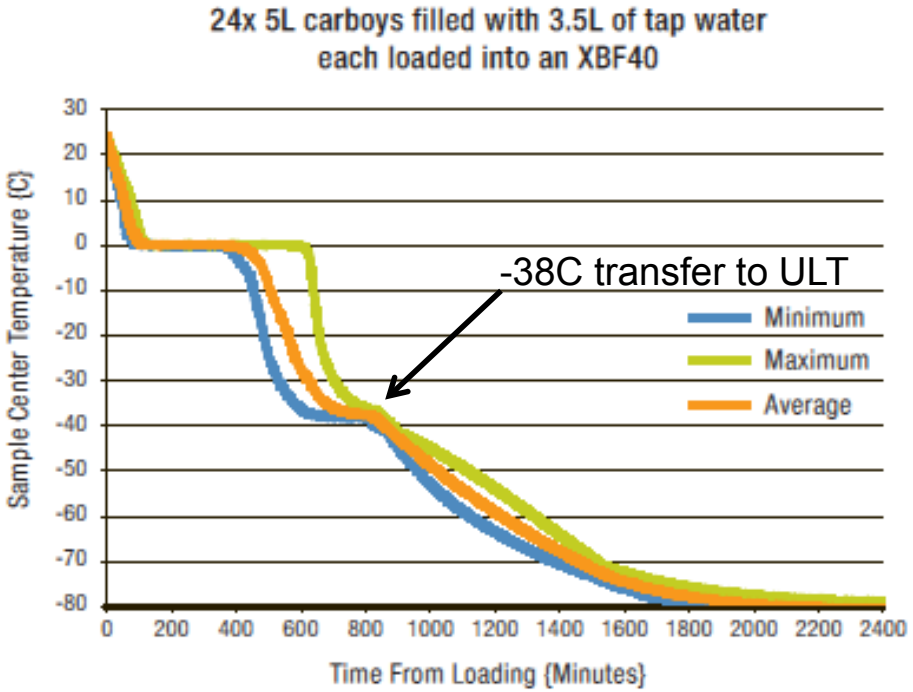


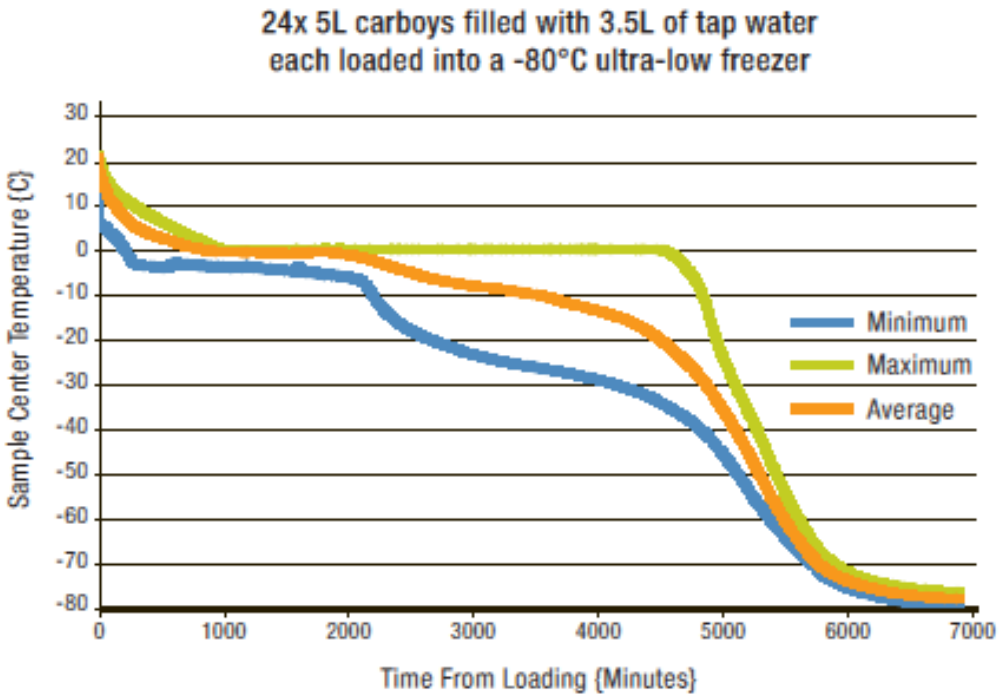
Asheville, NC U.S.A.

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XBF vs. ULT: Pull Down Applications to -80C

In a test comparing freezing times between the XBF40D and a -80°C ultra-low freezer, a group of 5L carboys on average reached -70°C in the XBF40D 75% faster than an ultra-low freezer.







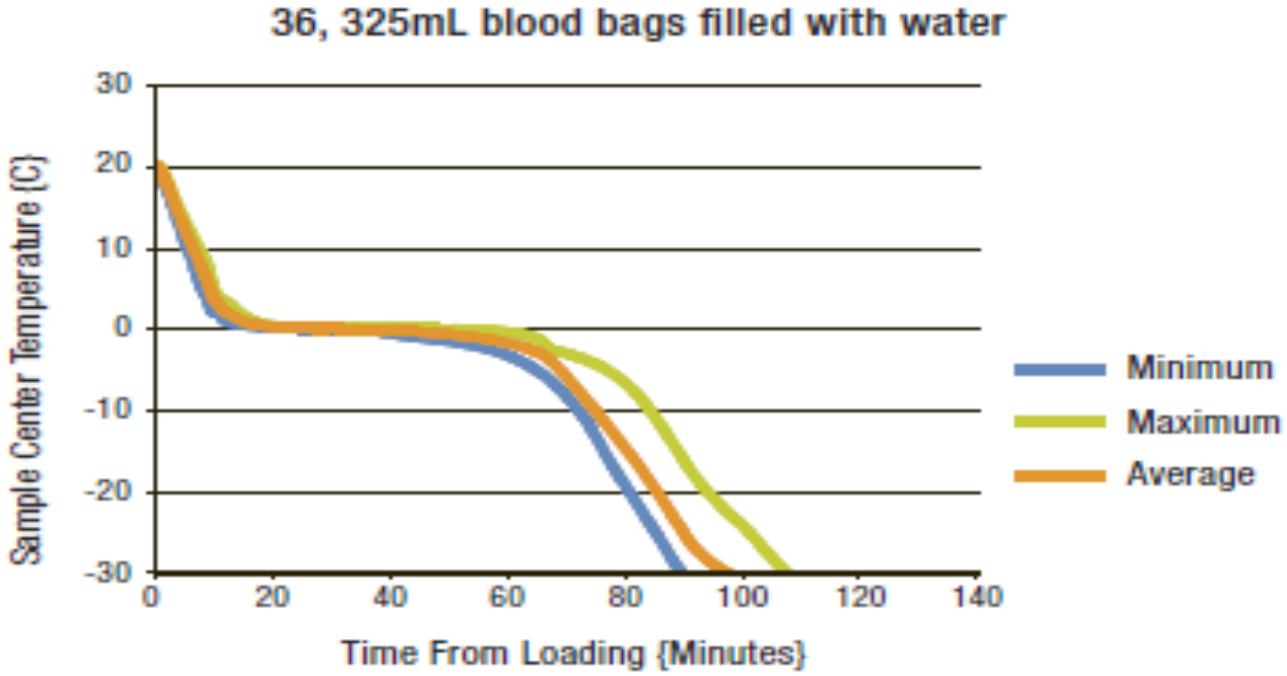


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Pull Down Applications to -30C

In a test of plasma bags filled with tap water, the XBF40D-MD reached 0°C in 27 minutes and -30°C in as fast as 90 minutes*



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XBF40 Accessories

Stainless Steel Shelf
Part Number = 6640
List Price = $275 ea.



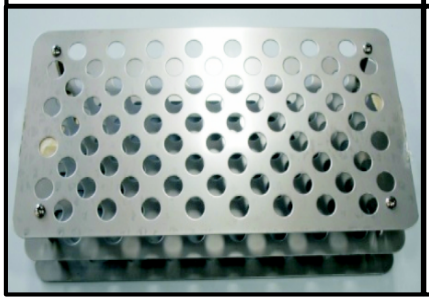
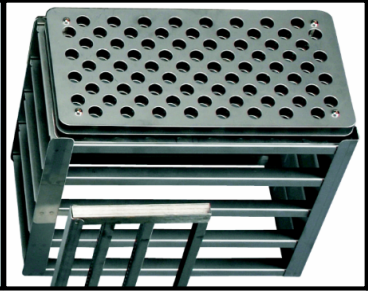
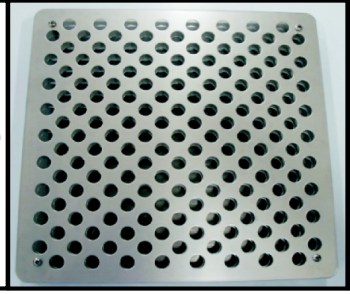
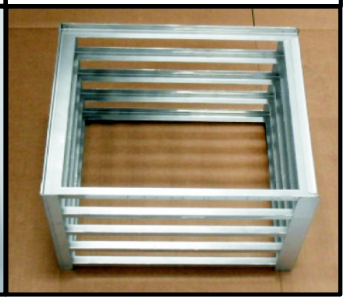
Aluminum Basket
Part Number = 6641
List Price = $325 ea.



Wireless Triple Timer
Part Number = 6642
List Price = $80 ea.



Maximize the 2ml Vial Capacity in the XBF40 Blast Freezer (4,776 Vials):
(3) – 6” Vial Rack Holders (1 per shelf); part number 4000702
(12) – 6” Vial Racks (4 per Vial Rack Holder); part number 4000701
(6) – 12” Vial Rack Holders (2 per shelf); part number 4000704
(24) – 12” Vial Racks (4 per Vial Rack Holder); part number 4000703

Vial Rack (6”) Part Number = 4000701 List Price = $224 ea.	Vial Rack Holder (6”) Part Number = 4000702 List Price = $274 ea.	Vial Rack (12”) Part Number = 4000703 List Price = $268 ea.	Vial Rack Holder (12”) Part Number = 4000704 List Price = $284 ea.
			

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Conclusion

- Free standing, turn-key blast freezing solution for sample preparation
- **NO** costly or cumbersome installation
- Better performance and reliability
- Superior throughput relative to footprint
- Suitable for blood plasma as well as other applications that require quick cooling



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Thank you!

Thank you for your time today,
Questions, comments or concerns?

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Appendix

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Reliability Testing

- Evaporator fan
  - 250,000 off-balance start/stop cycles in -40C cabinet
  - 24 hours cycling in -50C cabinet
  - 24 hours blocked fan in -40C cabinet
  - No failures or performance degradation observed



- Compressor
  - Valve design optimized for high-load reliability, heated accumulator prevents flooding
  - ~10 years of cumulative hours on high compression ratio life test stands
  - 12 months field testing in plasma freezing application
  - No failures or performance degradation observed



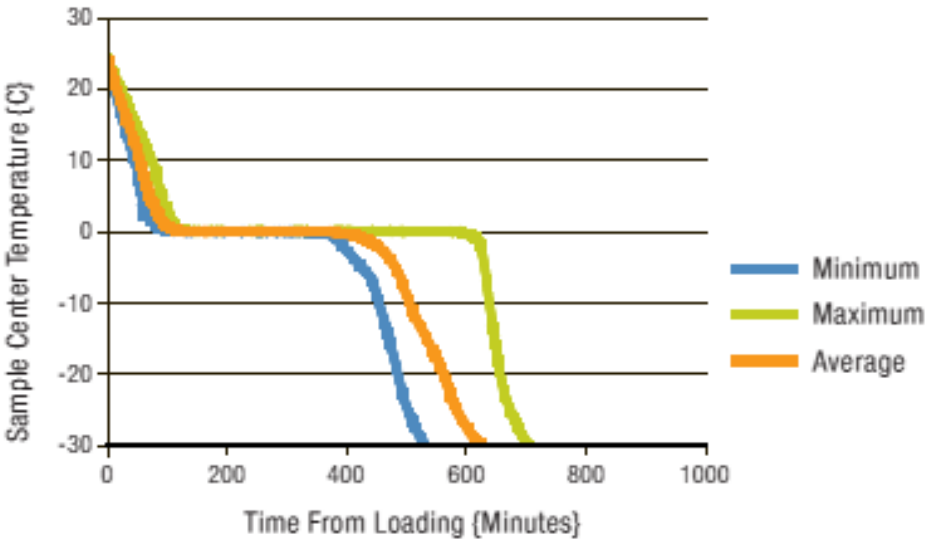
- Starting
  - Designed to minimize electrical load at compressor start
  - Tested for reliable starting under worst–case NEMA voltage and impedance

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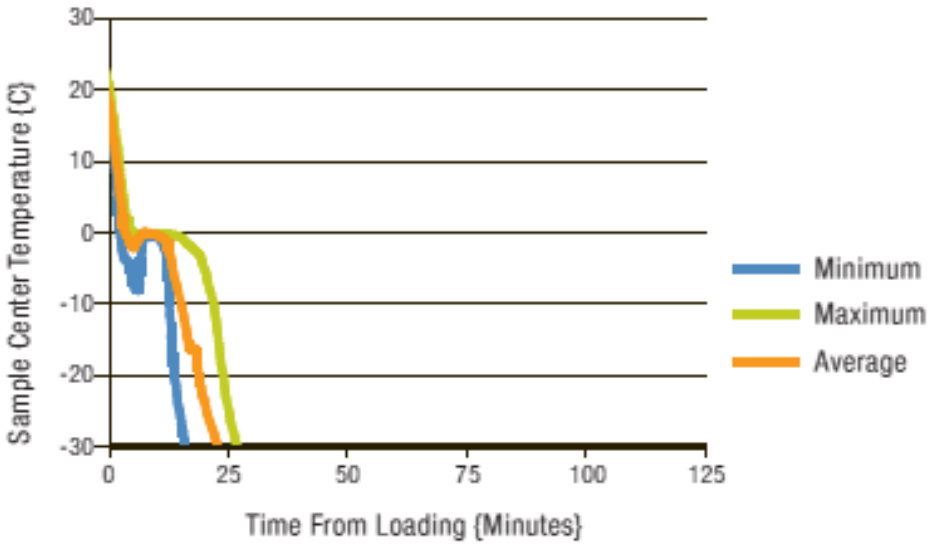
Pulldown Applications to -30C

As shown below, a test of 5L carboys filled with 3.5L of tap water reached 0°C on average of 100 minutes and -30°C on average of 600 minutes. A grouping of 2mL vials reached 0°C in 5 minutes and -30°C in 25 minutes.*

24x 5L carboys filled with 3.5L of tap water each loaded into an XBF40



500x 2mL vials filled with 1.8mL of tap water; Plus 12x 6" racks and 24x 12" racks and holders loaded into an XBF40

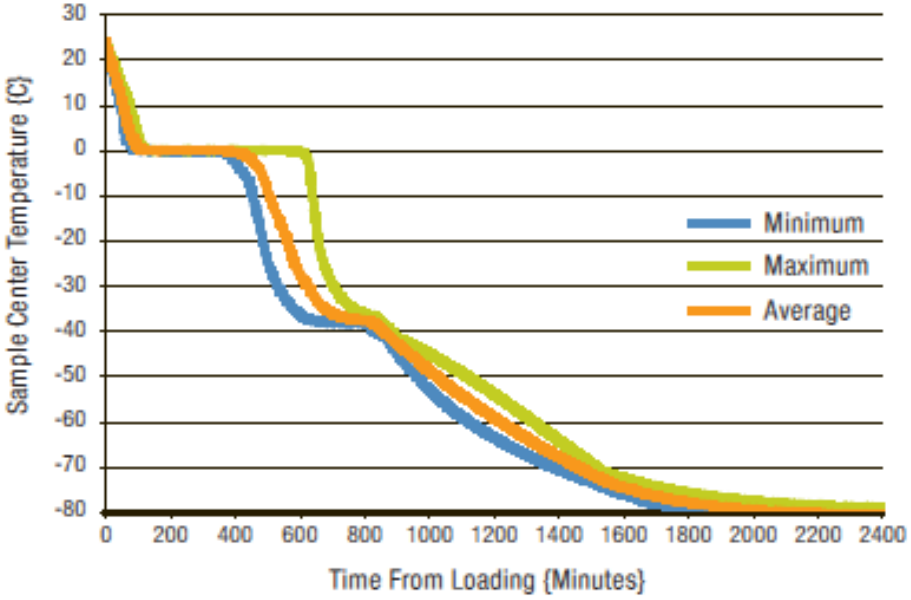


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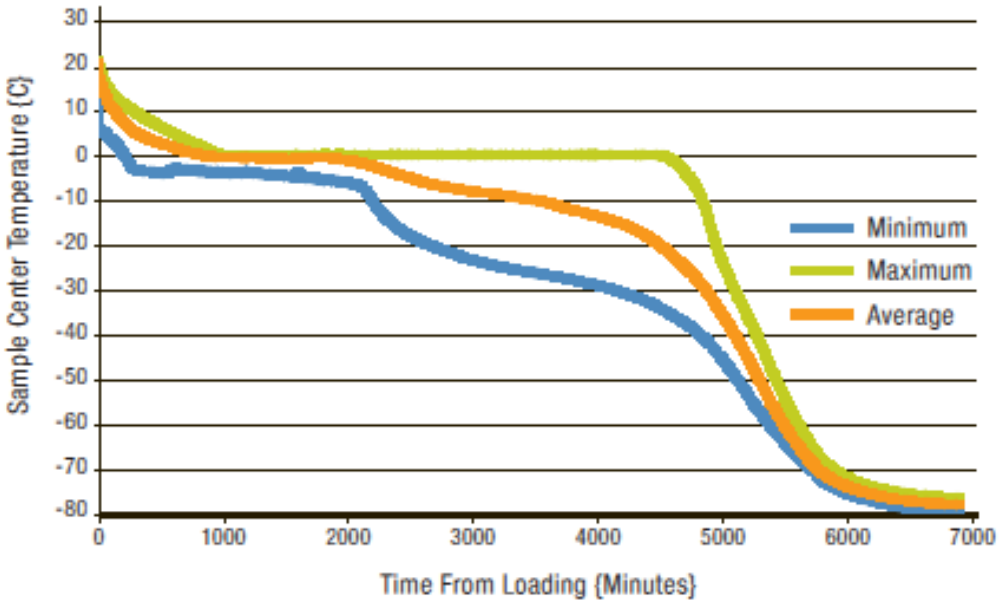
Pulldown Applications to -80C

In a test comparing freezing times between the XBF40D and a -80°C ultra-low freezer, a group of 5L carboys on average reached -70°C in the XBF40D 75% faster than an ultra-low freezer.

24x 5L carboys filled with 3.5L of tap water each loaded into an XBF40



24x 5L carboys filled with 3.5L of tap water each loaded into a -80°C ultra-low freezer



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Thermo Scientific Has Redefined Sample Preparation

…and it's ***FAST***

Flexible Design: The XBF40D accommodates staggered loads and a variety of vessels such carboys, bottles, racks with vials and more. For rapid plasma freezing, the XBF40D-MD accommodates plasma bags, boxes and bottles.

Accelerated Air Flow: A large, forced-air circulation freezes the product – fast!

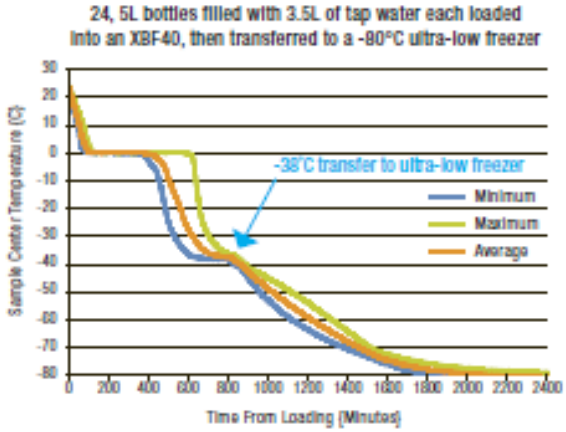
Self-Contained Refrigeration System: Unlike previous generation blast freezers, the XBF is a plug and play requiring no customized installation and no remote compressors.

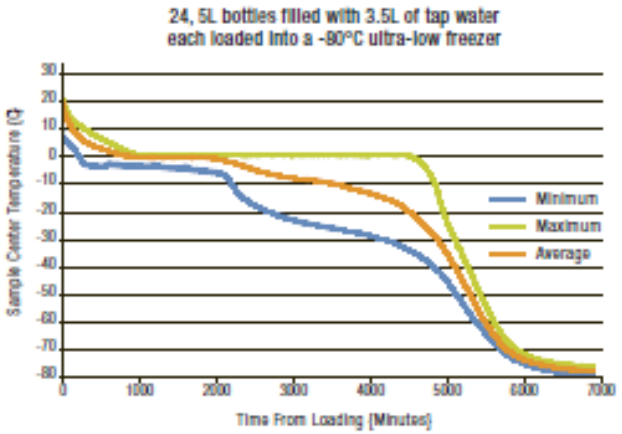
Trusted: All XBF freezers are manufactured with pride with high-quality materials and high-performance technology.



- 500ml Plasma Bags = **36**
- 2ml vials = **4,776**
- 5L bottles = **25**
- 10L carboys = **6**

In a test comparing freezing times between the XBF40D and a -80°C ultra-low freezer, a group of 5L bottles on average reached -70°C in the XBF40D 75% faster than an ultra-low freezer.





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ULT Versus XBF Blast Freezer

ULT (UXF60086D)

- **Heat Rejection:**
  - 2,516 - 3,028 BTU/hr (energy savings vs. high performance mode)
- **Power / Energy Consumption:**
  - 17.7 - 21.3 kW-hr/day (energy savings vs. high performance mode)
- **Pulldown time to -40C:**
  - ~275 minutes

VS.

XBF40 Blast Freezer

- **Heat Rejection:**
  - 3,000 BTU/hr
- **Power / Energy Consumption:**
  - 24 kW-hr/day
- **Pulldown time to -40C:**
  - ~60 minutes

(24) 5L Carboys Filled with 3.5L of Tap Water (+20C)

	ULT		Blast Freezer		Time Savings	
	Min	Hr	Min	Hr	Min	Hr
Time to -5C	4,500	75.0	600	10.0	3,900	65.0
Time to -20C	5,000	83.3	700	11.7	4,300	71.7
Time to -30C	5,150	85.8	750	12.5	4,400	73.3
Time to -38C	5,300	88.3	800	13.3	4,500	75.0
Time to -70C	5,850	97.5	1,500	25.0	4,350	72.5

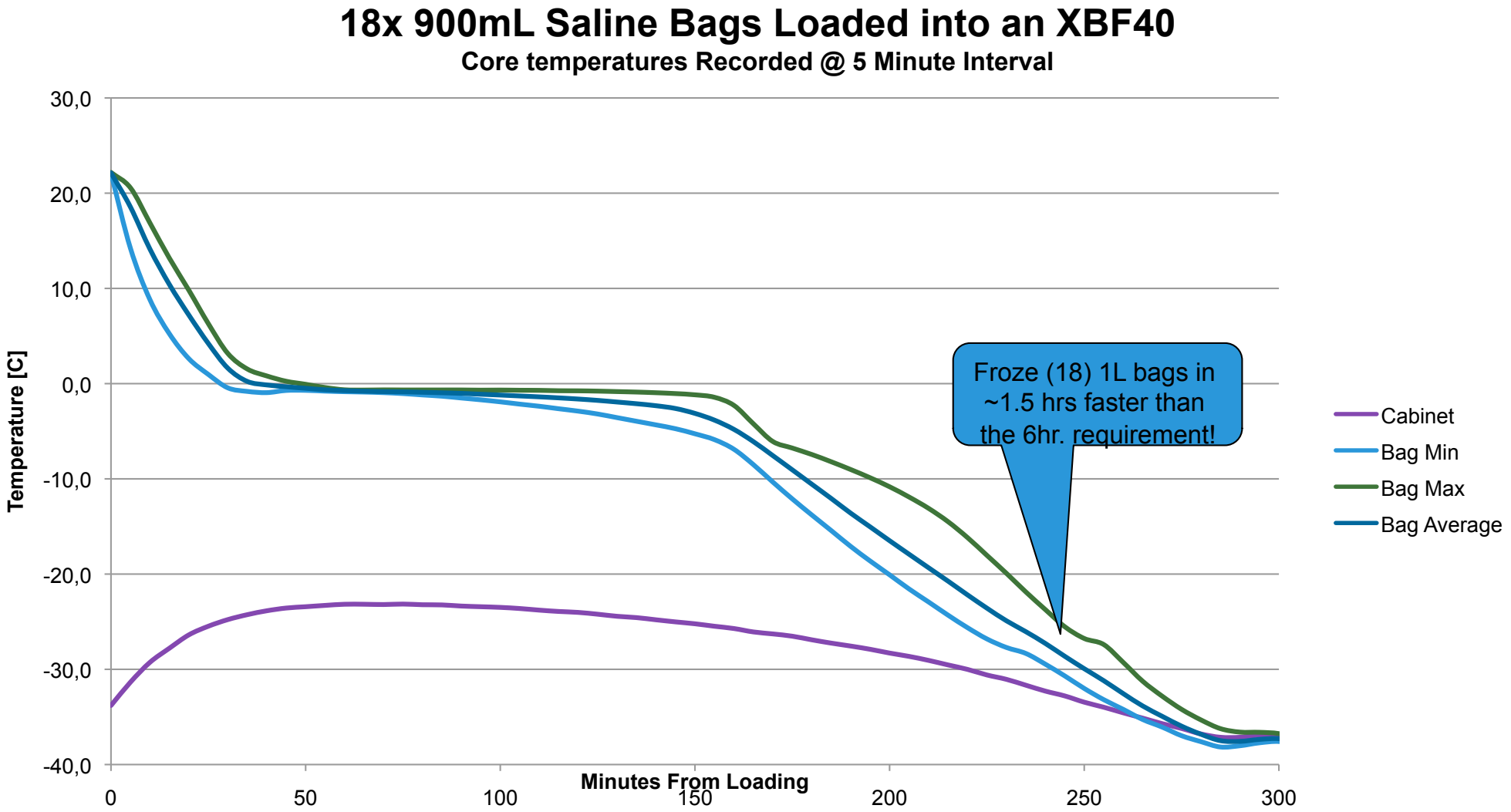
Note: Product transferred from the blast freezer to a ULT at -38C





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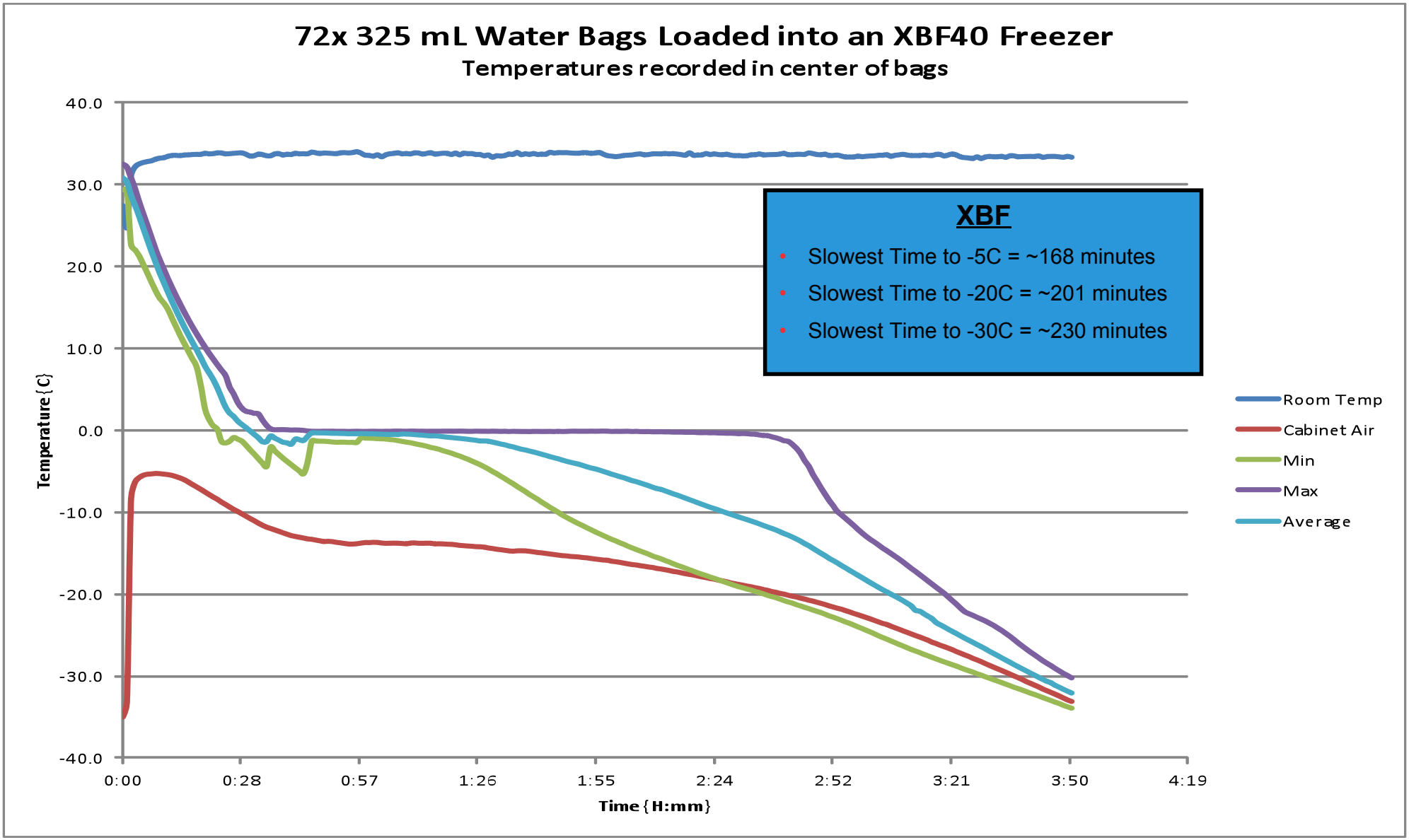
Independent Test Results – Sourced Plasma



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XBF40 Internal Test – (72) 500ml Plasma Bags



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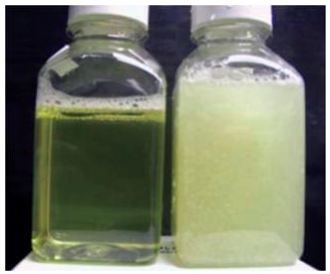
Why is Sample Preparation Important?

http://www.bioprocessintl.com/manufacturing/antibody-non-antibody/use-of-blast-freezers-in-vaccine-manufacture-322317/

- Maintaining the stability and viability of the active ingredients throughout production, distribution, and administration is a major challenge in vaccine manufacturing.

- Study conducted by Medimmune comparing the potency of samples using different freeze methods of live virus vaccines

- Why is rapid freezing necessary?
  - The rate at which drug substances is frozen (degrees reduced per hour) can be important in maintaining viability of the viruses (which constitute the active ingredient)
  - Determined that freezing samples in a ULT led to a reduced potency and was statistically different compared to freezing samples in a blast freezer



Slow vs. Fast Freeze
Visual difference between two thawed samples of the same lot of a live influenza virus

- Medimmune's conclusion:
  - "Efficient freezing of the vaccine drug substance (DS) is an essential manufacturing step in most cases to realize the full potential of vaccines"
  - "Freezing of a live-virus vaccine DS in the blast freezer resulted in little to no significant product losses. We conclude that air-blast freezers are an attractive option for freezing medium scale volumes of vaccine DS in disposable containers.

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Examples of Sample Preparation

- **“Direct Plunge” Freezing:**
  - Place sample directly into LN2
  - Pros:
    - Extreme freezing profile (-196C)
    - No mechanical system
  - Cons:
    - Footprint/Logistics of storing and refilling LN2
    - Extreme cold temperatures of -196C can cause thermal stress
    - Container options limited, such as commonly used bags



- **“Step-Down” Freezing**: +4C → -20C → -80C long term storage
  - Uses conventional freezer technologies (UGL2320, ULT2330, UxF600)
  - Pros:
    - Cost effective compared to other options
    - Self contained, no custom installation or need to refill LN2
  - Cons:
    - Very slow process of freezing – cannot account for things like latent heat of fusion
    - Not best for many sample types; uniformity issues during the freeze process
    - Reduced viability of samples due to the slow freeze process – product losses/lower potency

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Examples of Sample Preparation (continued)

- **Historical "Blast" Freezing**:
  - Mechanical system utilizing either forced air circulation or submersion into a silicone solution
  - Pros:
    - Effective for rapidly freezing plasma in bags
    - Temperature range more suitable for bags (typical operating range of -40C)
  - Cons (until now!):
    - Typically requires custom installation
    - Very expensive
    - Limited to accommodate bags – designed around the plasma freezing market



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Research pulled from Web - Considerations

- Need to define “fast” and “slow” freeze conditions.
- Increasing the rate of freezing plasma decreases the loss of FVIII activity up to a point, beyond which the rate has little effect.
- The amount of FVIII, vWF, and fibrinogen in cryoprecipitate is highly dependent on the thaw method as well as the freezing rate.
- Under defined conditions there is little advantage in freezing to -30 ^{o}C within 1 h compared to 2 h.

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Research Pulled from Web Requests to the Committee

- Please discuss the extent to which the available literature on plasma processing may support changes to improve the clinically relevant safety, purity, potency or consistency of various plasma products for use in transfusion, e.g. time to plasma separation, time from collection or separation to freezing, freezing rate and target temperature, storage temperature, allowed temperature excursions, cellular content.
- What additional scientific studies are needed?
- What recommendations do you have for the next steps forward?

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