Celsius® FFT Development Strategy

Technical Note

The Celsius® FFT family of single-use containers provides a platform for secure frozen storage and transportation of biopharmaceutical materials. These containers are pre-assembled, gamma-sterilized, single-use assemblies consisting of a bag enclosed by a protective shell, and are available in nominal volumes of 2L, 4L, 6L, and 12L. A range of insulated shippers provides robust protection to frozen Celsius® FFT containers during international transport.
This document reviews the design method, major tests and risk management strategies used when developing Celsius® FFT and Celsius® FFT Shippers.

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References

- Validation Guide for Celsius® Bags,
  Doc #S--5711-e, 85037-548-94
- Technical Memorandum: Celsius® FFT Shipper
  Qualification Summary, Doc #S--6015-e, 85032-540-49
- Extractables Guide for Celsius® Bags,
  Doc #S--5710-e, 85037-548-93

1. History

Celsius® FFT was developed in response to an established market need for a more robust means of freezing and storing biopharmaceutical material in single-use bags in conventional freezers, such as laboratory freezers and blast freezers. Although single-use bags are generally robust at room temperature, the fragility of the bag film and other components in the bag assembly increases as the temperature drops. It is therefore necessary to add protective packaging to dampen external inputs (e.g. shock and vibration) and to protect the tubing and other components in the assembly.

Although conceptual development for Celsius® FFT started as early as 2005, it was not until 2007 that design activity began in earnest. The project team understood the importance of protecting the bag, but this was a first-in-class product and it was not really clear how best to solve the problem. Furthermore, research with end-users indicated that they could not clearly articulate performance expectations. This was partly due to the fact that nobody could quantify the environment, and partly because there was little consensus on what was actually feasible. As a result, the goal of the development project became to generate successful results against well-known robustness and thermal standards. The team avoided setting hard performance targets in favor of a best-effort-or bracke-ing-approach, with the understanding that the product would be launched if it could be shown to be sufficiently robust to bracket typical handling practices (understanding that handlers of the Celsius® FFT would have substantial training and know-how).

The bracketing method allowed for a practical, achievable iterative process of design, test, and review results until the results consistently met the robustness and thermal standards deemed appropriate for freezing, frozen storage and frozen shipment of high-value drug substances in bioprocess manufacturing.

The first Celsius® FFT container to be developed was Celsius® FFT 6L; after careful qualification it was launched in 2008. All Celsius® FFT containers have the same materials of construction, similar tooling, and similar design approach. The experience gained in development of the 6L container was applied to the 4L (launched 2009), the 12L (2010), and finally the 2L (2012).

2. Life Cycle

The following table outlines the typical life cycle of a Celsius® FFT container. Note that the life cycle will vary according to the application; accordingly, this information is for reference only and is not intended to serve as a specification.

ID	Description	Duration	Temperature	Comment
1	Manufacture	2 weeks	Indoor ambient	
2	Transport to gamma irradiation	3 days		
3	Transport to Sartorius warehouse	1 week		
4	Storage in Sartorius warehouse	Up to 1 year	Indoor ambient	
5	Transport to customer	1 week		
6	Storage in customer warehouse	Up to 1 year	Indoor ambient	
7	Transport to manufacturing suite	4 hours		
8	Filling	1 hour	Indoor ambient	
9	Transport to freezer	1 hour	Indoor ambient	
10	Storage in freezer	Up to 1 year	-70°C to -20°C	
11	Load into shipper refrigerated with dry ice	1 hour	Indoor ambient	
12	Transport shipper by truck | aircraft	Up to 5 days	-70°C to -20°C	
13	Unload from shipper	1 hour	Indoor ambient	
14	Storage in freezer	Up to 1 year	-70°C to -20°C	
15	Transport to manufacturing suite	1 hour	Indoor ambient	
16	Thawing	1 day	+5°C to +30°C	
17	Draining	1 hour	Indoor ambient	
18	Disposal			

3. Risk Review

This section reviews the various risks that were mitigated through the Celsius® FFT design and qualification process. This is not a formal quantitative risk analysis in the style of an FMEA; such an analysis would be of limited value as a design tool because the performance of the Celsius® FFT container and shipper products was only understood after the products were developed.

3.1 Film Compatibility

The Celsius FFT design is essentially a Flexboy® bag design enclosed in a semi-rigid plastic protective shell. The bags are standard 2D Flexboy® pillow designs built from 360-micron S71 (EVA) film that is RF welded with EVA port stubs layouts all common to the Flexboy® product line. The 360-micron film was already the film used in the largest Flexboy® (50L). This was a logical choice to ensure compatibility since Flexboy® had a strong history as an industry standard for many years in bioprocess manufacturing; secondly, the Celsius® CFT platform (FT100) features Celsius® Paks that are also made of 360-micron S71 (EVA) film and used for controlled-rate freezing since 2003.

Biocompatibility tests were performed (ref: Validation Guide for Celsius® Bags, section 8) to demonstrate that all fluid contact components used for the manufacture of S71 film are biocompatible and meet or exceed the current USP and ISO requirements. Tests are carried out on S71 film samples after Gamma irradiation (50 kGy). Film samples were supplied to an independent testing facility for evaluation under the current ISO 10993-5, USP <88> Class VI. All materials used in the construction of the S71 film meet or exceed the requirements of the USP Class VI– 50°C Plastics tests and are considered as non-cytotoxic and non-hemolytic.

3.2 Low Temperature Testing

Most commercial frozen storage applications range between -20°C and -50°C. To further mitigate risks for using Celsius® FFT at low temperatures, many of the qualification tests for Celsius® FFT were performed at -70°C. All qualification tests passed at this ultra-low process temperature further ensuring the robustness and applicability of the materials and designs for low temperature applications (ref: Validation Guide for Celsius® Bags, section 7).

3.3 Testing Approach to Mitigate Risk

ID	Risk	Mitigation | Test	Rationale | Comments
1	Loss of container closure due to mechanical shock and vibration inputs during international transport of frozen container in shipper	Celsius® FFT containers packaged in Celsius® FFT Shippers and tested per transport simulation ASTM D 4169 at Assurance Level I (AL I). All bags including chamber and lines leak tested post-use. Ref: Validation Guide for Celsius® Bags, section 7.4.4	According to ASTM, "There are three levels available for all test methods based on the assurance level one wants to achieve in package performance. For an average level of assurance, one may use Level II with medium test intensities; for highest level of assurance, Level I; and for the lowest level of assurance, Level III. The level selected is based on product value and end-use, desired level of anticipated damage that can be tolerated, number of units to be shipped, knowledge of the distribution environment, or other criteria. Level II is used by most companies for most goods while manufacturers of such products as high value items or critical care products like medical devices may select Level I for the highest assurance that their packaged product will arrive undamaged. There is undoubtedly a higher cost of packaging incurred to meet the requirements of Level I, but the higher assurance of acceptable performance is deemed worth the added cost."
2	Loss of container closure due to freeze or thaw process	Celsius® FFT containers frozen in conventional lab freezer and thawed in water bath. All bags including chamber and lines leak tested post-use. Ref: Validation Guide for Celsius® Bags, section 7.4.1	Water bath is worst case because it has the highest temperature change.
3	Damage to drug product due to thermal inputs during international transport	Celsius® FFT containers packaged in Celsius® FFT Shippers and tested per transport simulation ISTA 7D hot-hot and cold-cold profiles, extended to 96h. Ref: Technical Memorandum: Celsius® FFT Shipper Qualification Summary, pgs 4-5	Found to hold -40°C for 96 hours
4	Mechanical shock during rough handling of liquid container	Challenged liquid Celsius® FFT containers by 50 cm vertical drop. Ref: Validation Guide for Celsius® Bags, section 7.4.1	No industry standard. Adopted 50 cm vertical drop as a reasonable challenge.
5	Mechanical shock during rough handling of frozen container	Challenged frozen Celsius® FFT containers by 20° rotational drop onto bench. Ref: Validation Guide for Celsius® Bags, section 7.4.1	No industry standard. Container cannot routinely survive 50cm vertical drop. Adopted 20° rotational drop as a reasonable challenge.
6	Tipover of stacked containers	Checked stability of stack of 5 containers in both liquid and frozen states. Ref: Validation Guide for Celsius® Bags, section 7.4.2	Maximum number of containers in stack is 5.
7	Damage to product between manufacturing site and customer facility	No specific test.	Packaging methods are controlled and are based on best practices developed over more than a decade of practical experience. Complaint rate due to packaging-related damage is low.

3.4 Custom Design Qualification

Various configurations of tubing, components and termination devices (e.g., Opta® aseptic connector) may be designed into the Celsius® FFT to create customized products that more precisely meet application needs. To reduce potential risks associated with special configurations for freezing applications each component and its engagement are verified against a database that shows all items qualified by Sartorius for freezing applications. If no qualification has been documented the designer will note it on the Technical Drawing and propose immediate qualification for freezing applications. Unqualified components are not allowed without a liability disclaimer.

4. Conclusion

The Celsius® FFT family of single-use containers and shippers provides a robust means of freezing, storing and transporting biopharmaceutical material.

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