

# Memorandum

<b>Date:</b>	10-Jan-2019
<b>To:</b>	To whom it may concern
<b>From:</b>	Robin Gubkin and Palvinder Chawla
<b>RE:</b>	Leukapheresis bags assessment

## Objective:

The purpose of this memo is to document the assessment of the physical properties of various cryobags that may be used by apheresis sites to ship patient leukapheresis material to the Novartis (or Novartis CMO) manufacturing facility.

## Background:

The patient peripheral blood mononuclear cells, which are used as a starting material for the CTL019 manufacturing process, are collected at the apheresis sites, formulated, filled into cryobags, cryopreserved, and shipped to the manufacturing facility (under cryogenic conditions to ensure integrity and viability). Upon receipt, the patient cryopreserved leukapheresis material is kept stored frozen at the manufacturing facility until the start of CTL019 manufacturing. At the start of CTL019 manufacturing, each leukapheresis bag is thawed and spiked onto a 6-lead harness.

The Novartis Leukapheresis Reference Manual version 5 states that the maximum allowable size of cryobags is 250 mL, to ensure that all known bag configurations will physically fit into the current shipping cassette of the cryogenic shipper. The preferred cryobags are listed as the following:

- CryoStore™ 250 Freezing Bag
- CELL FREEZE®
- CryoMACS® Freezing Bags

Shipping Validation was performed (PVR5135-7A) using CryoStore™ CS50 and CS250 Freezing Bags and confirmed that cryobags shipped using the validated parameters maintained temperature and integrity during shipment.

## Assessment:

Information was requested from all of the apheresis sites from which patient material is received in order to compile an international database of the cryobags received in order to gather data on the cryobag types currently in use, or planned to be used, at each site. Table 1-1 contains the list of cryobags and sizes compiled from all of the apheresis sites.

**Table 1-1: List of Cryobags and Sizes**

<b>Vendor</b>	<b>Bag Type</b>
Miltenyi Biotec	CryoMACS Freezing Bag 50
	CryoMACS Freezing Bag 250
	CryoMACS Freezing Bag 500
	CryoMACS Freezing Bag 750
	CryoMACS Freezing Bag 1000
Charter Medical	Cell Freeze CF-50
	Cell Freeze CF-250
	Cell Freeze CF-500
Origen	CryoStore CS 50
	CryoStore CS 250
	CryoStore CS 500
	CryoStore CS 750
	CryoStore CS 1000
Nipro	F-050
	F-100
BTC Medical	CordStem CS100
MacoPharma	GSR2001AU
	GSR5001AU
Haemopharm Healthcare / SIAD	Advatis Safe2 StemChoice
Fresenius Kabi	Hemofreeze 100mL

Each of the bag types were assessed for the following physical properties:

- Width: measured across the bag
- Length: measured from below the ports to the end of the bag
- Length with Ports: measured from above the ports to the end of the bag
- Length Folded: measured from above the ports to the end of the fold
- Bag Material: obtained from the vendor
- Tubing Material: obtained from the vendor
- Spike and Visual Leak Test:
  - Each of the bags were filled with approximately 30mL of water using a 60mL luer lok syringe connected to the female port of each bag.
  - One port on each of the bags were spiked with a 6-lead harness.
  - Pressure was applied to each bag by rolling the bag towards the ports and applying pressure by hand.
  - PASS indicates that the bag was spiked successfully and no leakage was observed
  - FAIL would indicate that either the bag could not be spiked successfully, or that leakage was observed.

Each of the bag types were then placed into the current cassette and the Proposed EU cassette to verify physical fit and compatibility to enclose each bag without pinching, scraping, tears or other physical damage that may compromise integrity over the shipment:

- Fit in Current Cassette
- Fit in EU Cassette

After compiling the data on all of the bag types a new cassette was proposed to be compatible with the majority of the bag types assessed and with the new proposed rack. Each of the bag types were then placed into the Proposed Cassette to determine physical fit and compatibility per intended use for shipment in the cassette:

- Fit in Proposed Cassette

Previous evaluations that were performed by the Process Science group were obtained and noted in this assessment (see Annex 1).

Physical dimensions were measured for each of the following to aid in the assessment:

- Current Rack
- Proposed Rack: rack proposed to fit larger bag sizes
- Current Cassette
- EU Proposed Cassette
- Proposed Cassette: cassette proposed to fit larger bag sizes

The results of the leukapheresis bags evaluation are detailed in Annex 1 and the results of the rack and cassette evaluation are detailed in Annex 2.

At the time of this memo samples could not be obtained for the Macopharma or the Haemopharm Healthcare bags. However, the Haemopharm Healthcare Advatis Safe2 StemChoice bag was previously assessed by the Process Science department to be incompatible with the spikes used by Novartis, so this bag type cannot be used for commercial manufacturing and was not considered in the selection of the Proposed Rack and Proposed Cassette dimensions.

## **Conclusion:**

Each cryobag type was assessed for compatibility with the proposed shipping configuration and was determined to be compatible if the bag was made from a cryogenic temperature compatible material (i.e. EVA) and if the bag fit in the proposed cassette and rack. If the bag did not meet these requirements then it was determined to be incompatible.

Each cryobag was also assessed for compatibility with the CTL019 spiking and determined to be compatible if the bag could be spiked with the 6-lead harness and did not exhibit visual leaks after spiking. If the bag did not meet these requirements then it was determined to be incompatible.

Table 1-2 contains the list of bag types that were assessed as being compatible with both the proposed shipping configuration and CTL019 spiking.

Table 1-3 contains the list of bag types that were assessed as NOT compatible with the proposed shipping configuration and/or CTL019 spiking.

Table 1-4 contains the list of bag types that could not be assessed as samples could not be obtained from the vendor.

**Table 1-2: List of Cryobags and Sizes that are Compatible with the Proposed Shipping Configuration and CTL019 Spiking**

Vendor	Bag Type
Miltentyi Biotec	CryoMACS Freezing Bag 50
	CryoMACS Freezing Bag 250
	CryoMACS Freezing Bag 500
	CryoMACS Freezing Bag 750
Charter Medical	Cell Freeze CF-50
	Cell Freeze CF-250
	Cell Freeze CF-500
Origen	CryoStore CS 50
	CryoStore CS 250
	CryoStore CS 500
	CryoStore CS 750
Nipro	F-050 *
BTC Medical	CordStem CS100

\* The spike ports on the Nipro bag are wrapped in plastic packaging. This packaging is difficult to remove in cleanroom attire with double-gloved hands. Therefore, although this bag is compatible with the shipping configuration and with the CTL019 spiking, it is recommended to use alternate cryobags.

**Table 1-3: List of Cryobags and Sizes that are NOT Compatible with the Proposed Shipping Configuration and/or CTL019 Spiking**

Vendor	Bag Type	Reason for Incompatibility
Miltentyi Biotec	CryoMACS Freezing Bag 1000	Bag size too large for cassette and rack
Origen	CryoStore CS 1000	Bag size too large for cassette and rack
Nipro	F-100	Bag size too large for cassette and rack
BTC Medical	CordStem CS100	Bag ports too thick to close cassette
Haemopharm Healthcare	Advatis Safe2 StemChoice	Incompatible with CTL019 spiking

**Table 1-4: List of Cryobags and Sizes that could not be assessed**

Vendor	Bag Type	Reason
Macopharma	GSR2001AU	Sample bags could not be obtained from the vendor
	GSR5001AU	
Fresenius Kabi	Hemofreeze 100mL	Sample bags could not be obtained from the vendor

## Annex 1 - Leukapheresis Bag Evaluation: Physical Properties of the Bags

Table 1-5: Physical Properties of each Cryobag Part 1

Bag Vendor	Bag Name / Product Code	Part Number	Freezing Volume (mL)	Width (cm)	Length (cm)	Length with Ports (cm)	Length folded (cm)	Bag Material	Tubing Material	Connections
Miltenyi Biotec	CryoMACS									
	Freezing Bag 50	74400	10-20	13 (7.6)	12	14.3	N/A	EVA	EVA	2 ports, 1 tube
	Overwrap	N/A	N/A	8.1	18.1	N/A	N/A	EVA	N/A	N/A
	CryoMACS									
	Freezing Bag 250	74401	30-70	12.3	15	17.4	N/A	EVA	EVA	2 ports, 1 tube
	Overwrap	N/A	N/A	13.4	21.5	N/A	N/A	EVA	N/A	N/A
	CryoMACS									
	Freezing Bag 500	74402	55-100	12.1	20.6	23	N/A	EVA	EVA	2 ports, 1 tube
	Overwrap	N/A	N/A	13	25.7	N/A	N/A	EVA	N/A	N/A
	CryoMACS									
Charter Medical	Freezing Bag 750	74403	80-190	12.1	22	24.3	N/A	EVA	EVA	2 ports, 1 tube
	Overwrap	N/A	N/A	13.1	28.2	N/A	N/A	EVA	N/A	N/A
	CryoMACS									
	Freezing Bag 1000	74404	125-270	12.3	30.2	32.5	N/A	EVA	EVA	2 ports, 1 tube
	Overwrap	N/A	N/A	13.2	35.5	N/A	N/A	EVA	N/A	N/A
	Cell Freeze CF-50	CF-50	10-20	7.8	N/A	21.4	13.4	EVA	EVA	2 ports, 1 tube
	Cell Freeze CF-250	CF-250	30-70	12.9	17.3	18.4	N/A	EVA	EVA	2 ports, 1 tube
	Cell Freeze CF-500	CF-500	55-100	13	21	22.4	N/A	EVA	EVA	2 ports, 1 tube
	CryoStore CS 50	CS500	10-30	7.6	N/A	14.1	14.1	EVA	EVA/PVC blend	2 ports, 1 tube
	CryoStore CS 250	CS250	30-70	12.7	15.3	17	N/A	EVA	EVA/PVC blend	2 ports, 1 tube
Origen	CryoStore CS 500	CS500	55-100	12.7	20.1	22.2	N/A	EVA	EVA/PVC blend	2 ports, 1 tube
	CryoStore CS 750	CS750	80-190	12.7	22.9	25	N/A	EVA	EVA/PVC blend	2 ports, 1 tube
	CryoStore CS 1000	CS1000	120-275	15	26.2	27.6	N/A	EVA	EVA/PVC blend	2 ports, 1 tube
	F-050	89-101	Max 25	8.1	12.2	15.6	N/A	EVA	PVC/ Polyethylene	1 port, 1 tube
	F-100	89-100	50-100	15.7	N/A	20.6	N/A	EVA	PVC/ Polyethylene	1 port, 1 tube

Bag Vendor	Bag Name / Product Code	Part Number	Freezing Volume (mL)	Width (cm)	Length (cm)	Length with Ports (cm)	Length folded (cm)	Bag Material	Tubing Material	Connections
BTC Medical	CordStem CS100	CS100	30-60	12.2	N/A	25.6	14	EVA	Not available	2 ports, 1 tube, 3 samples
	Overwrap	N/A	N/A	14.4	31.7	N/A	16	EVA	N/A	N/A
MacoPharma	GSR2001AU	GSR2001AU	30-70	13	N/A	17.9	N/A	EVA	EVA	2 ports, 1 tube
	GSR5001AU	GSR5001AU	60-100	13	N/A	22.4	N/A	EVA	EVA	2 ports, 1 tube
Haemopharm Healthcare	Advatis Safe2 StemChoice	SH-250B	30-70	* Not Available	* Not Available	* Not Available	* Not Available	EVA	EVA	2 ports, 1 tube
Fresenius Kabi	Hemofreeze (100mL)	Z 2002	Not Available	* Not Available	* Not Available	* Not Available	* Not Available	Kapton/ Teflon	* Not Available	3 ports

\* Sample bags could not be obtained to perform measurements and information was not provided by the vendor.

**Table 1-6: Physical Properties of each Cryobag Part 2**

Bag Vendor	Bag Name / Product Code	Fit in Current Cassette	Fit in EU Proposed Cassette	Fit in Proposed Cassette	Spike and Visual Leak Test	Comments
CryoMACS Freezing Bag 50 Overwrap	CryoMACS Freezing Bag 50 Overwrap	Yes	No	Yes	PASS	Label pouch folds over (folded width). With the overwrap it fits very tightly and compresses the ports slightly. The spike port is very tight, so the operator must use more force.
	CryoMACS Freezing Bag 250 Overwrap	Yes	No	Yes	PASS	With the overwrap it fits very tightly and compresses the ports slightly. The spike port is very tight, so the operator must use more force.
Miltenyi Biotec	CryoMACS Freezing Bag 500 Overwrap	No	No	Yes	PASS	With the overwrap it fits very tightly and compresses the ports slightly. The spike port is very tight, so the operator must use more force.
	CryoMACS Freezing Bag 750 Overwrap	No	No	Yes	PASS	With the overwrap it fits very tightly and compresses the ports slightly. The spike port is very tight, so the operator must use more force.
CryoMACS Freezing Bag 1000 Overwrap	CryoMACS Freezing Bag 1000 Overwrap	No	No	No	PASS	Too big for all cassettes. The spike port is very tight, so the operator must use more force.

Bag Vendor	Bag Name / Product Code	Fit in Current Cassette	Fit in Proposed Cassette	Fit in Proposed Cassette	Fit in Proposed Cassette	Spike and Visual Leak Test	Comments
Charter Medical	Cell Freeze CF-50	Yes	No	No	Yes	PASS	Label pouch folds over (length). The ports are very thick, so it fits very tightly in the proposed cassette.
	Cell Freeze CF-250	Yes	No	No	Yes	PASS	The ports are very thick, so it fits very tightly in the proposed cassette.
	Cell Freeze CF-500	No	No	No	Yes	PASS	The ports are very thick, so it fits very tightly in the proposed cassette.
Origen	CryoStore CS 50	Yes	No	No	Yes	PASS	Label pouch folds over (length). Used in Shipping Validation.
	CryoStore CS 250	Yes	No	No	Yes	PASS	Used in Shipping Validation.
	CryoStore CS 500	No	No	No	Yes	PASS	
	CryoStore CS 750	No	No	No	Yes	PASS	
	CryoStore CS 1000	No	No	No	No	PASS	Does not fit in any cassette or either rack.
Nipro	F-050	Yes	No	No	Yes	PASS	If the bag comes with the plastic packaging material on the blue port cover, it will be very difficult to remove in the module double gloved.
	F-100	No	No	No	No	PASS	The port and the tube make the bag too big for the cassettes.
BTC Medical	CordStem CS100	No	No	No	No	PASS	The ports are too thick to fit in any of the cassettes. There are 3 sample bags that are very thick. Are those meant to be detached prior to freezing?
Macopharma	GSR2001AU	** Not Available	** Not Available	** Not Available	** Not Available	** Not Available	Vendor has not provided sample bag
	GSR5001AU	** Not Available	** Not Available	** Not Available	** Not Available	** Not Available	Vendor has not provided sample bag
Haemopharm Healthcare	Advatis Safe2 StemChoice	** Not Available	** Not Available	** Not Available	** Not Available	FAIL *	Vendor has not provided sample bag. However, Process Science evaluation determined that this bag is incompatible with the CTL019 spiking process.
Fresenius Kabi	Hemofreeze 100mL	** Not Available	** Not Available	** Not Available	** Not Available	** Not Available	Vendor has not provided sample bag

\* Process Science evaluation determined that this bag is incompatible with the CTL019 spiking process, so the Spike and Visual Leak Test box was marked as "FAIL"

\*\* Sample bags could not be obtained to perform assessment

## Annex 2 – Rack and Cassette Evaluation

**Table 1-7: Shipping Rack Dimensions**

Rack	Measurement	Height (cm)	Width (cm)	Depth (cm)	Comments
Current Rack	Cassette Fit	23.8	16.3	1.3	Width = front to back (same direction as width of cassette) Depth = cassette slot (rounded down)
	Outside	29.4	17.2	12.3	Width = front to back (same direction as width of cassette) Depth = across the cassette slots parallel with the handle
Proposed Rack	Cassette Fit	28.2	16.3	1.9	Width = front to back (same direction as width of cassette) Depth = cassette slot (rounded down)
	Outside	29.4	17.2	12.3	Width = front to back (same direction as width of cassette) Depth = across the cassette slots parallel with the handle

**Table 1-8: Shipping Cassette Dimensions**

Cassette	Length (cm)	Width (cm)	Depth (cm)	Comments
Current Cassette	20.1	14	1	The cassette only fits 50 and 250 sizes and is too short for the larger sizes
EU Proposed Cassette	27.7	14	0.8 (0.5)	The cassette is too thin to fit the ports on any of the bags. It tightly compresses the ports, bending the side of the cassette, and may damage a frozen bag 0.5 cm is the depth to accommodate the bag, not including the wings
Proposed Cassette	27.8	15	1	Proposed cassette to fit in the Proposed Rack and the most bag sizes. It fits up to and including 750 bag sizes, but not 1000 bag sizes.

**Prepared by:**

**Gubkin Robin**

Digitally signed by Gubkin Robin  
DN: SERIALNUMBER=1735196 + CN=Gubkin Robin,  
OU=TO, OU=people, DC=novartis, DC=com  
Reason: I am the author of this document.  
Date: 2019.01.14 18:20:52 -5:00

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Robin Gubkin, Principal Validation Specialist, MS&T

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**Prepared by:**

**Chawla Palvinder**

Digitally signed by Chawla Palvinder  
DN: SERIALNUMBER=2138998 + CN=Chawla Palvinder,  
OU=TO, OU=people, DC=novartis, DC=com  
Reason: I am approving this document.  
Date: 2019.01.15 07:54:57 -5:00

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Palvinder Chawla, Packaging and Labelling Engineer, MS&T

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**Reviewed by:**

**Elefante Tom**

Digitally signed by Elefante Tom  
DN: dc=com, dc=novartis, ou=people, ou=TO,  
serialNumber=2219262, cn=Elefante Tom  
Reason: I am approving this document  
Date: 2019.01.15 08:44:57 -05'00'

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Tom Elefante, Validation Lead, MS&T

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