



**MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS REVIEW AND RESEARCH**

**NDA 125552
Review of Original Submission**

Date: March 18, 2015

Application: NDA **Status:** Pending Approval

Product: Sterile cord blood collection kit containing anticoagulant solution of Citrate Phosphate Dextrose (CPD), USP

Proposed Use: For the collection of 40 – 250 ml of umbilical cord blood from either vaginal birth or within the sterile field of a cesarean section.

Applicant: MacoPharma, Tourcoing France

Date Received: April 30, 2014

**DIVISION OF CELLULAR AND GENE THERAPIES
OFFICE OF TISSUE, CELLULAR AND GENE THERAPIES**

Reviewed by:	Signature
Mercy Quagraine, Ph.D. Review Committee Chairperson	
Concurred By:	
Steven Oh, Ph.D. Acting Branch Chief	
Kimberly Benton, Ph.D. Deputy Division Director	
Raj Puri, M.D., Ph.D. Division Director	

REVIEW TEAM:

Reviewer	Parts Reviewed	Review Status/Recommendation
Mercy Quagraine, Ph.D. Review Committee chairperson	In vitro data	Review completed; Approval not recommended because of outstanding issues
Ping He, M.D.	CMC (Bags/device and CPD)	Review completed; Approval recommended
Alex Bailey, Ph.D	Pharmacology/toxicology (Biocompatibility)	Review completed; Approval recommended
Ingrid Markovic, Ph.D	Extractables/Leachables	Review completed; Approval recommended
John Hyde, M.D., Ph.D.	Clinical	Review completed; Approval recommended
Xiao-Hong Chen (CDER consult)	Stability (device with CPD)	Review completed; Approval recommended
Ellen Huang, Ph.D. (DMPQ/OCBQ)	Sterilization and Container closure and integrity of final unit	Review completed; Approval recommended
Simleen Kaur, Ph.D. (consult DBSQC/OCBQ)	Sterility testing	Review completed; Approval not recommended because of outstanding issues
Anna Flynn, Ph.D. (DCM/OCBQ)	EIR/483 Responses	Review completed; Approval recommended
Oluchi Elewachi, Pharm D (APLB)	Labeling	Review completed; Approval not recommended because of outstanding issues
Jose Cruz Gonzalez Dennis Cantellops (ORA)	Pre-licensure inspection	Review completed; Approval recommended

Note: See individual review for each review area.

EXECUTIVE SUMMARY

This submission is a new drug application for cord blood collection kit containing the anticoagulant, Citrate Phosphate Dextrose Solution USP, CPD. It was initially submitted as a supplement to an existing NDA (BN 040083) for whole blood collection in OBRR. However, it was refused filing, because the drug

product was not the same as that under BN 040083, and thus had to be submitted as a stand-alone NDA.

The applicant has established that the collections bags used in the supporting literature citations and (b) (4) studies from a cord blood bank, are the same as those proposed under NDA. The performance /in-vitro studies support the applicant's proposed indications for use.

Biocompatibility and extractables/leachables study data submitted are adequate. Real time and accelerated stability studies data submitted support a 2 year expiry.

The steam sterilization procedure used to sterilize the collection kit is adequate, however, parametric release is not approved for product release. Sterility testing will thus be conducted as part of product release. Information requested on February 9, 2015, to evaluate the sterility testing on the (b) (4) is still outstanding.

A pre-licensure inspection has performed and a form 483 citation was issued; a total of 16 citations were issued. Observation #1 cites the lack of impurity profile assessment of the CPD: CPD lots were accepted without analyzing and identifying impurity (b) (4) on the drug product (b) (4). All impurity (b) (4) should be identified, and the impurity profile made part of product release criteria. Observation #2 cites the failure to perform (b) (4) studies for the drug CPD. In the responses to the 483 observations, the applicant had indicated that studies are being conducted to address these citations and the target completion date would be March 31, 2015. The study results will have to be reviewed and approved before corrective actions are implemented. However, without a definitive submission of the additional information addressing the outstanding 483 citation items, the review team agreed that we are no longer able to move forward with the review activity which would need to include labeling discussions with the applicant. Therefore, it has been decided that we send a CR letter to the applicant regarding the outstanding items.

Recommendation: The NDA should not be approved until the corrective actions for 483 observations #1 and #2 are implemented. The applicant proposes to complete studies to address these citations on March 31, 2015. The study data should be reviewed and approved for implementation prior to approval of the NDA. Send a CR letter with the following comments.

Comments to Applicant:

1. Please identify all the impurity (b) (4) on the CPD (b) (4) and establish limits on the amounts that should not be exceeded in the drug CPD. We request that impurity profile assessment and impurity specifications will be a part of your product release criteria.
2. Information on the qualification report for sterility testing of (b) (4) requested on February 9, 2015 is still outstanding.

BACKGROUND

The applicant had a pre-NDA telecon with the agency on February 1, 2013 to request that the cord blood collection kit under this current NDA, be submitted as a supplement to his existing NDA (BN 040083) in the Office of Blood Review and Research (OBRR), a collection kit for whole blood collection. The rationale being the individual components of the cord blood collection bags had been approved under BN 040083, so no additional or supporting studies would be submitted to support the proposed indications under this NDA. The applicant also stated that since CPD is a USP monograph solution and has been approved for the collection and processing of cord blood, its effect on total nucleated cell count (TNC) and CD34 counts had already been confirmed.

The applicant was advised during the pre-NDA meeting that a new stand-alone NDA was required since the drug/anticoagulant CPD under this NDA was not the same as that in BN 040083 (anticoagulant contained additive solution, CPD/AS-1) and the indication for use had changed. During this interaction, the agency further informed the applicant that data needed to be submitted to show that cord blood could be collected in the bags, processed, (b) (4), without impacting the cord blood cells. In response, the applicant requested that this NDA be treated like the MedSep Pall cord blood collection bags, which he claimed was approved as a supplement to an existing NDA without any (b) (4) data. Upon verification, the agency discovered the MedSep Pall cord blood collection bag was indeed approved as a supplement to an existing NDA in OBRR. However, extensive (b) (4) data was submitted to support of the MedSep application.

In October of 2013, the applicant submitted the cord blood collection bag as a supplement to BN 040083; the supplement was “Refused Filing”. The applicant was advised to submit a new stand-alone NDA with supporting data.

INTRODUCTION

MacoPharma, a pharmaceutical laboratory was created in 1977 and has been marketing blood bags since 1980. Currently, the MacoPharma group comprises of 2 companies:

1) MacoPharma – marketing unit, with corporate office located at Rue Lorthiois 59420, Mouvaux France, and 2) MacoProductions – production unit, with corporate offices located at 200 Chaussee Fernand Forest, 59200 Tourcoing, France. MacoProductions is registered with the FDA as Medical Device Manufacturer, #9710488.

The firm’s activities cover two main areas: Transfusion and Biotherapy activities, and Infusion activities; and there are 4 factories: 1) Medical Device Production Unit for blood transfusion in Tourcoing, France, 2) Infusion Solutions Production Unit in Mouvaux, France, 3) Medical Device Production Unit for blood transfusion in Wroclaw, Poland, and 4) Unity of production in Ariana, Tunisia.

The MacoProductions Polonia SP Zo.o., the Poland facility (UT. Szwajcarska 22, 54-405 Wroclaw, Poland)

manufactures the cord blood collection kit and CPD solution under this NDA. This Poland facility is registered with the FDA, FEI# 3011045122. The raw materials used in formulating the CPD are procured and tested ((b) (4)) by the MacoProductions S.A.S. France facility, and then transported to Poland for use. A pre-licensure inspection was performed on this facility in November 13 - 20, 2015 and a 483 citation was issued. The applicant reports that CPD manufacturing follows the US and ((b) (4)) methods and according to the standards ISO 9001:2008 and NF EN ISO 134 85:2012.

PRODUCT

(The preparation of CPD solution and the collection device are reviewed by OBRR consult, Dr. Ping He. See her review)

Product Description:

The system consists of two configurations of Cord Blood Sterile Collection Bags containing Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD); MSC1207DD and MSC1208DD configurations.

Citrate Phosphate Dextrose Solution, USP (CPD):

Established Name: Anticoagulant Citrate Phosphate Dextrose Solution USP

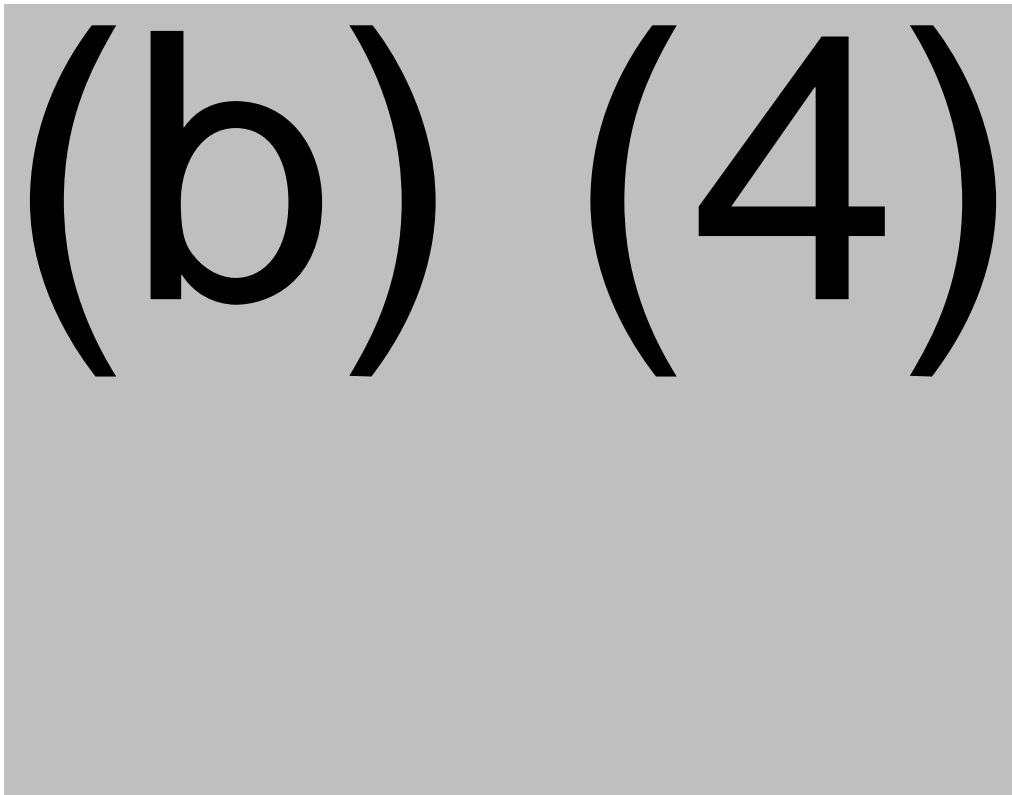
The anticoagulant Citrate Phosphate Dextrose (CPD), is a solution of Citric Acid, Sodium Citrate, Monobasic Sodium Phosphate, and Dextrose in Water for Injection. This solution has been formulated and tested to conform to the USP "Anticoagulant Citrate Phosphate Dextrose Solution" with the specificity of the sodium ((b) (4)) phosphate dehydrate used in formulation which is equivalent to the monobasic sodium phosphate (USP Monograph 37). USP specifies monobasic sodium phosphate (monohydrate) ((b) (4)). The Table S.4.1-2 below shows the release tests and acceptance criteria for product release.

Table S.4.1- 3 Analytical Controls for CPD Performed on Final Product

Tested parameters (and methods)	Limits of acceptance	Standard
(b) (4)	(b) (4)	(4)
pH (pH meter)		
Citric ion, (b) (4)		
(b) (4)		
Glucose, monohydrate (b) (4)		
Phosphate (b) (4)		

The review team does not find the submitted information adequate to approve parametric release, and hence the applicant must conduct sterility testing of CPD as part of product release.

Table S.4.4-1 and S.4.4-2 show the results of batch analysis on the two configurations presented for approval.



Cord Blood Sterile Collection Bags:

MSC1207DD Cord Blood Sterile Collection Bag consist of a 300 ml collection bag containing 27 ml of CPD, a 40 ml Rinsing bag containing 8 ml of CPD and two 12 gauge needles with a protective shield (Secuvam) for the used needle. This configuration permits the collection of approximately 200 ml of cord blood in the 27 ml CPD. If the collection is less than 200 ml, the CPD in the Rinsing bag is used only to rinse tubing and discarded. If the collection is greater than 200 ml. the CPD in the Rinsing bag is used to rinse the tubing and stripped/added into the collection bag, permitting the collection of up to 250 ml cord blood.

MSC1208DD Cord Blood Collection Bag consist of a 300 ml collection bag containing 21 ml of CPD, a 40 ml Rinsing bag containing 8 ml of CPD and two 12 gauge needles with a protective shield (Secuvam) for the used needles. The MSC1208DD configuration allows the collection of up to (b) (4) of cord blood in the 21 ml CPD. If the collection is less than 150 ml, the CPD in the rinsing bag is used to rinse tubing and discarded. If the collection is more than 150 ml, the CPD in the Rinsing bag is used to rinse the tubing and stripped/added into the collection bag and permits the collection of up to 200 ml cord blood. The configuration MSC1208DD is also referred to as (b) (4) in the submission documents.

The dual needle system is for optimum recovery; the second needle is used in case of clots. Each 12 gauge needle has an internal diameter of 2.10 mm and an external diameter of 2.50 mm.

The cord blood sterile collection bags are individually double overwrapped with both a primary and secondary overwrap which allows for the use of the of the collection bags under sterile field conditions of a cesarean section. The primary wrap is made up of an (b) (4) peelable. The primary wrap maintains the sterility of the device. A secondary aluminium wrap (ref.: (b) (4) of the CPD solution. The double overwrapped system is packaged in a transparent packaging and supplied in cardboard boxes (12 kits per box).

The applicant reports that all the various components of the cord blood collection bags were previously approved under BN 040083; (b) (4)

The Cord Blood Sterile Collection Bags will be manufactured at the MacoProductions facility in Poland: MacoProductions Polonia SP Z.o.o. ,Ul Szwajcarska 22, 54-405 Wroclaw, Poland (Vol 1 page 2). The blood bags referenced in BN 040083, were manufactured in France.

The collection bag (b) (4) is manufactured by Macoproducts, Poland, while the rinsing bag (b) (4) is manufactured by Macoproducts, (b) (4). The assembling of needles is performed in Poland. The applicant reports that the subassemblies, (b) (4), can be manufactured in (b) (4) Poland. The subassembly (b) (4) is composed of the needles/Secuvam with clamps and tubing up to the rinsing bag, and (b) (4) is composed of the tubing and clamps from the rinsing bag to the primary collection bag.

(b) (4)

Information on the components of the device/kit and CPD are listed following two tables.

Reference	Quantity	Description
(b) (4)		12G stainless steel needles
		8 mm ring (b) (4)
		(b) (4) blue clamp
		Needle protector
		(b) (4) tubing 3 x 4.1 mm diameter
		Break-away cannula
		Symmetrical Y connector
		Asymmetrical Y connector
		Rinsing (b) (4) bag containing 8 ml of CPD
		Blue clamp (b) (4)
		PVC tubing 3 x 4.1 mm diameter
		Permanent red clamp
		Injection site
		MSC1207DD: (b) (4) bag containing 27 ml of CPD
		MSC1208DD: (b) (4) bag containing 21 ml of CPD

The components of these drug products are:

Components	Materials	References	Suppliers
(b) (4)			

Reviewer comment: (b) (4) injection site may come into contact with blood. Biocompatibility testing has been reviewed.

Proposed Indication:

The bags are indicated for:

For the collection of 40 – 250 ml of umbilical cord blood from either vaginal birth or within the sterile field of a cesarean section. Anticoagulant included.

For optimal cord blood quality it is recommended to maintain the cord blood at an ambient temperature (room temperature, 18°C – 26°C) to a refrigerated temperature (4°C – 12°C) and process within 48 hours of collection.

Cross-Referenced Files:

BN 040083: is for Leucoflex MTL1 whole blood collection set with 70 ml CPD for the collection of 500 ± 50 ml of whole blood, 110 ml of additive solution AS-1, an integral leukoreduction filter, storage containers for blood components and tubing; this NDA is in OBRR. The applicant reports that the individual components of the Cord Blood Collection Bags have been approved under Macopharma's BN 040083. (b) (4)

IND 11076: Collection Set for the Collection and Storage of Leukoreduced Whole Blood and Red Blood Cells (RBCs) in CPD/AS-1. For the collection and storage of leukoreduced whole blood and RBC's in CPD/AS-1, is referenced for biocompatibility information.

(b) (4)

ENVIRONMENTAL ASSESSMENT:

The applicant claims categorical exclusion from environmental assessment under 21 CFR 25.31.

PRE-LICENSURE INSPECTION:

A pre-licensure inspection was performed on this facility on November 13 - 20, 2015 and a 483 citation was issued. The EIR and response to the 483 citations were reviewed by OCBQ.

Observations #1 and #2, listed below, are product issues. The applicant has indicated in the 483 responses that studies are being conducted to address the observations and the target date for completion is March 31, 2015. These studies need to be reviewed and evaluated before approval of the NDA can be granted.

Reviewer comment: *Regarding observation #1, an impurity profile assessment of the CPD should be performed and made part of the product release.*

OBSERVATION 1

Laboratory controls do not include the establishment of scientifically sound and appropriate standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

1) Your firm failed to evaluate the presence of unknown (b) (4) observed during the sample analysis of the Citrate Phosphate Dextrose (CPD) solution for the determination of (b) (4)

During the review of the (b) (4) for the release-testing lots (b) (4) and the stability-testing lots (b) (4) of CPD solution, two large unknown (b) (4) and one unresolved (b) (4) were observed that (b) (4) followed by another unknown (b) (4) the (b) (4). In addition, there is no run for the blank solution to evaluate possible interferences during sample analysis of these batches. This test is used to determine the glucose (b) (4) during release and stability testing.

In addition,

2) Your firm standard operating procedures for the Determination of Citric Acid in CPD solution by (b) (4) (SOP # IS8A0245, used since 02/5/2010), the Determination of (b) (4) in CPD solution by (b) (4) (SOP # IS8G0370, used since 6/01/2009), and for the Determination of (b) (4) (SOP # IS8G0631, used since 10/05/2011), are deficient. None of these methods include system suitability requirements to assure the suitability of the (b) (4) systems used for the testing of these materials. In addition, in none of the three above mentioned methods, there are requirements for the running of blank solutions in order to evaluate possible interferences during sample analyses.

In addition,

3) There is no assurance that the firm has an adequate rationale to justify the sample size for the endotoxin-content test conducted as part of batch-release testing. Currently, (b) (4) blood collecting system is tested for batch release.

In addition,

4) Your firm failed to conduct the qualification and certification of Citric Acid and (b) (4) (b) (4) Reference Standards received from non-certified suppliers. These reference standards have been used since the year 2003 for the evaluation of the anticoagulant CPD solution.

OBSERVATION 2

The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established and documented.

Specifically,

1) Your firm failed to conduct (b) (4) (b) (4) etc.) as part of the method validation (b) (4) for the Determination of (b) (4) (b) (4) in CPD solution. There is no assurance that the test method SOP # IS8G0370, "Determination of (b) (4) in CPD solution", is stability-indicating and that it can be used to evaluate the product throughout its shelf life.

In addition,

2) Failure to have a complete method validation (Validation report #: (b) (4) "Determination of Limit of Detection and Quantitation in case of (b) (4) and Citric Acid Analysis using (b) (4) for the determination of (b) (4) and citric acid level during cleaning validation studies. The method validation does not include specificity, linearity, and recovery to demonstrate that the method is suitable for intended use and that no interferences are observed. Additionally, there are no system suitability requirements to demonstrate that the (b) (4) system is suitable for the determination of (b) (4) and Citric Acid residues.

IN-VITRO TESTING

The applicant cites two studies in the literature and one study report from a cord blood bank at the University of Dusseldorf, Germany, to support temperature and storage/holding time duration to end of processing (48 hours) as proposed in the indication for use. The study report from the University of Dusseldorf cord blood bank also provides (b) (4) data which shows that cord blood can be collected in the kit under this NDA, (b) (4) and infused into patients without any significant impact to the cord blood cells. The collection bag configurations used in the citations were not specified in the studies, except for the studies conducted at the University of Dusseldorf, which used the Macopharma cord blood collection bag configuration MSC1206DU (this configuration is not the subject of this NDA; however, it is marketed in Europe). In an amendment to the NDA submitted on August 4, 2014, the applicant submitted an attestation statement (signed by the Head Pharmacist of Macoproducts, Frederic Lebrun) that affirmed that the cord blood collection bags used in the citation studies were all made of the same materials as the kits that are the subject of this NDA. The bags used in the literature citations were identified in the attestation statement; the collection kits used in the Pope et al. study conducted in Australia used the MQT2205PK configurations, and the Salge-Bartels et al. study conducted in Germany used the MSC1202PU configuration. The statement further attested that all the configurations were manufactured with the same components or materials and the same ingredients in CPD as those described in this NDA (BN 125552) application. Other literature citations submitted are based on the fact that they use Macopharma cord blood collection bags in the studies, but do not support the conditions proposed.

Note: *The applicant has submitted data to demonstrate that the materials used to make the bags used in the citations are the same as those under this NDA(BN 125552) application. The data presented in the citations are hence acceptable to apply to this NDA. See review by OBRR consult, Dr. Ping He. Her comment in the review is appended here: "The sponsor has adequately provided the necessary information about the collection bags that has been referred in the original NDA submission. Based on the available information, I would agree that the base material (b) (4) used for manufacturing the proposed collection bags (MSC1207DD and MSC1208DD) are the same as the MSC1206DU, MSC1202PU and MQT2205PK collection bags. I would recommend that the validation studies carried out in the MSC1206DU collection bag support the proposed Indications for Use statements for the proposed collection bags (MSC1207DD and MSC1208DD)".*

Reviewer comment: *The review team agrees that the Pope et al., the Sarge-Bartels et al. and the University of Dusseldorf cord blood bank studies support the current NDA; the sponsor has established that the bag composition used in the citation studies and those under NDA are the same.*

The three studies that are submitted to support the holding temperature and time to processing for this NDA are summarized below.

1. Pope B., Mitsakos K., Bilgin A., Hokin B. and Grant, R: Predicting overall viability of cord blood harvests. *Transfusion* 2012;52:1079-1085

This group conducted a retrospective analysis of 9918 autologous cord blood collections from 2003 to 2010 (Australian Private Cord Blood Bank) to determine if collection volume and time to freezing (TTF) had significant effect on viability, total white blood cell (WBC) count and total CD34+ count. Triple-collection cord blood collection bags (Mouvan, France) were used, which contained 29 ml CPD. The collected cord blood was transported at 15°C -25°C (with data logger) to the processing facility, and processed (by volume reduction) within 48 hours of collection. However, 0.3% of the CBUs frozen outside of the protocol's 48 hour time frame were included in the analysis pre- and post-processing samples were tested for viability, CD34+ cells counts, and sterility.

Results:

- Viability: Pre-processing = $91 \pm 6.5\%$ (range: 52 – 99.9%); Post-processing = $92.2 \pm 6.1\%$ (range: 52 – 100%)
- Viable CD34+ cells recovery = $102.5 \pm 15.5\%$;
- WBC recovery = $87.3 \pm 11.8\%$
- Collected volume range: 14 ml – 239.5 ml
- Time to freezing (TTF): 29 hr 41 min (SD 8 hr 50 min; range = 3 hr 30 min to 92 hr 45 min). n = 5520. (Note: 0.3% of the CBUs frozen outside of the protocol's 48 hour time frame were included in the analysis)
- Sterility: 3.8% failures overall.

Table shows the summary results of the cord blood units collected.

Variable	After collection		After processing		Recovery (%)	
Volume (mL)	77.1 \pm 31.3	(14.0-239.5)	25.6 \pm 1.9	(15.1-35.9)		
WBC viability (%)	91.7 \pm 6.5	(52.0-99.9)	92.2 \pm 6.1	(52.0-100)		
Total WBCs ($\times 10^6$)	10.5 \pm 5.6	(0.6-76.8)	9.00 \pm 4.72	(0.5-75.8)	87.3 \pm 11.8	(23.0-230.6)
Total viable CD34 count ($\times 10^6$)	4.0 \pm 3.7	(0.1-52.3)	4.0 \pm 3.8	(0.02-51.7)	102.5 \pm 15.5	(24.6-244.4)
%CD34	0.37 \pm 0.22	(0.00-3.22)	0.43 \pm 0.28	(0.01-7.13)		

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Table 3 shows the proportion of cord blood units (CBU) able to achieve more than 95%, more than 90%, and more than 80% viability respectively at various volumes ranges and time to freezing. For example, at volumes of 40 ml – 60ml, if the TTF is more than 37 hours, there is only 15% chance of achieving a viability of 90%, however, there is a 70.3% chance of obtaining a viability of 80%. At higher volumes, the chances of obtaining higher/better viabilities are improved.

TABLE 3. Proportion of CBUs achieving more than 95%, more than 90%, and more than 80% viability for a collected volume						
TTF (hr)	CB volume collected (mL)					
	<40	40-60	60-80	80-100	100-120	>120
>95% viability						
<24	54.0	74.8	82.3	86.7	88.2	92.1
24-36	6.0	23.4	36.1	49.0	57.8	68.9
37+	0.0	1.5	4.6	7.8	12.8	22.3
>90% viability						
<24	90.2	97	96.8	98.3	98.5	100
24-36	44.6	71.2	81.5	88.6	93.6	97.4
37+	4.2	15	25.3	45.5	57.4	76.8
>80% viability						
<24	98.8	99.7	99.8	99.7	100	100
24-36	90.9	98.4	98.3	99.1	99.7	99.7
37+	67.3	70.3	84.7	88.7	95.3	100

The data also show that the WBC viability is affected by the volume of cord blood collected and the TTF. As the collection volumes increased the WBC viability increased. Decreased viability was associated with volumes of less than 60 ml and a TTF or more than 24 hours. The authors explain the low viabilities observed at low volumes to be due to a higher ratio of anticoagulant.

TABLE 2. Relationship between volume and viability, WBCs, and CD34 (mean, 1 SD)						
Volume collected (mL)	Number of CBUs collected	% of CB collections	Overall WBC viability %	Total WBCs ($\times 10^6$)	Total CD34 count ($\times 10^6$)	%CD34
≤ 40	1077	10.9	88.4 (7.4)	4.0 (1.8)	1.4 (1.2)	0.36 (0.25)
40.1-60.0	2142	21.7	90.8 (6.6)	7.0 (2.5)	2.3 (1.7)	0.34 (0.21)
60.1-80.0	2471	25.0	92.2 (6.0)	9.6 (3.3)	3.4 (2.4)	0.35 (0.21)
80.1-100.0	2049	20.8	93.2 (5.1)	12.3 (4.1)	4.6 (3.5)	0.38 (0.23)
100.1-120.0	1226	12.4	94.1 (4.4)	14.9 (4.9)	5.8 (4.0)	0.39 (0.21)
120.1-140.0	548	5.6	94.6 (3.7)	17.0 (5.0)	7.2 (4.6)	0.42 (0.23)
140.1-160.0	229	2.3	95.2 (3.0)	20.6 (6.2)	9.3 (6.1)	0.44 (0.23)
160.1+	127	1.3	95.5 (2.8)	22.3 (7.1)	11.4 (8.7)	0.50 (0.31)

Table 2 shows a strong correlation between volume and CD34+ count.

Reviewer comments: The data partially supports the applicant's proposed holding condition of [REDACTED] - 25°C.

2. *Salge-Bartels U, Huber M, Kleiner K, Volkers P, Seitz R, Heiden M: Evaluation of quality parameters for cord blood donations. Transfus Med Hemother 2009;36:317-324*

This group evaluated how the conditions for collection and storage of cord blood before processing, might impact the quality of cord blood preparations including viability and clonogenic potential. These studies were performed on 82 cord blood collections in Germany using Macopharma (Langen, Germany) bags containing 21 ml of CPD in the primary bag and 8 ml in the satellite bag. The donations were stored at 18°C – 26°C or at 8°C (4°C – 12°C) and 4 storage periods and conditions were defined as follows:

- a. Group A: (0 – 24 hours at 18°C – 26°C)
- b. Group B: (0 – 24 hours at 8°C (4°C – 12°C)
- c. Group C: (25 hours – 48 hours) at 8°C (4°C – 12°C)
- d. Group D: (49 hours – 80 hours at 8°C (4°C – 12°C)

The study evaluated unprocessed blood, i.e. the cord blood units were held under specified temperature conditions and times and then analyzed. For CFU analysis, mononuclear cells were isolated by density gradient prior to inoculation into culture. Pre- and post-processing samples were tested for viability, total nucleated cell counts (TNC), CD34+ cells counts, colony forming units (CFU), and sterility.

Result summary:

- a. There was no significant difference between samples stored at both study temperatures (18°C – 26°C or at 8°C) during the first 24 hours within all groups.
- b. Loss of WBC viability was observed after storage for 25- 48 hours and particularly after 49 – 80 hours (storage at 4°C – 12°C only).
- c. CD34+ cell content and CFU did not show any significant difference throughout the tested storage periods.

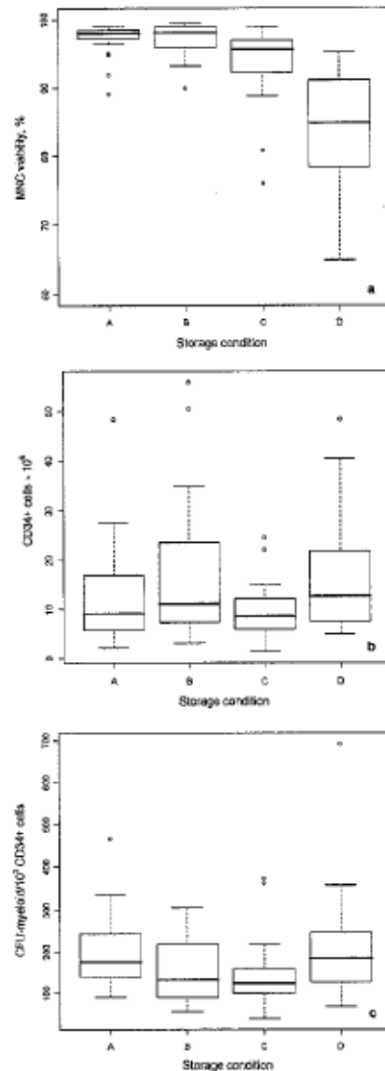


Fig. 4. a Influence of temperature and storage time on leukocyte viability in MNC, **b** content of viable CD34/CD45+ cells in CB donations, **c** CFU-myeloid / 10⁵ CD34/CD45+ cells. Before analysis, CB donations had been stored either (A) 0–24 h at room temperature (n = 31); (B) 0–24 h at 8 °C (n = 22); (C) 25–48 h at 8 °C (n = 19), or (D) 49–80 h at 8 °C (n = 10). There was a significant decline in viability with increasing storage time: group B versus C p = 0.002, group B versus D p < 0.0001; group C versus D p = 0.0018. Amongst others the box plots provide the 1st, 2nd (median) and 3rd quartile of the data.

Reviewer comments: This study supports storage conditions for collected cord blood at 4°C – 12°C and processing within 48 hours

3. Prof. Gesine Kogler, Jose Carreras CBB, Medical Center, University of Dusseldorf: General information on the institution and the production facility of the Jose Carreras Cord Blood Bank: Macopharma Summary Report. February 10, 2014 (b) (4) studies)

This study was performed at the Jose Carreras Cord Blood Bank at the University of Dusseldorf, Germany. Twenty four (24) cord blood units (CBU) studied, were randomly selected from transplanted cord blood units on the basis that Macopharma collection kit (MSC1206DU) was used. The MSC1206DU kit is single needle kit containing 29 ml of CPD (21 ml in primary bag and 8 ml in satellite bag) for the collection of up to 200 ml cord blood. A minimum TNC of 1.30×10^9 cells were used for the study. The collected cord blood was stored and transported at $22^{\circ}\text{C} \pm 4^{\circ}\text{C}$ and processed within 48 hours of collection. (b) (4)

(b) (4)

(b) (4)

Note: In the original submission in May 2014, the applicant stated that the anti-coagulant CPD contained ascorbic acid. However, in a response to the filing communication, the applicant has submitted an attestation statement from Dr. Gesine Kogle, who performed the studies, that the "ascorbic acid was a typing error. The correct word as in my report (as of February 2014, page 6) is citric acid"

Results summary:

The results of this report are summarized in Table 2 below.

(b) (4)

Reviewer comments:

- *These studies provide data to support the proposed $22^{\circ}\text{C} \pm 4^{\circ}\text{C}$ holding/storage condition and (b) (4) performance.*
- *The (b) (4) viabilities obtained are acceptable. (b) (4)*

Review of responses to Information Request letter to applicant. Our letter was dated Nov 5, 2014 (responses received Dec 22, 2014)

1. You have provided two literature citations and a summary report regarding the cord blood collection bags. The agency recommends that performance studies be carried out with the proposed bags, MSC1207DD and MSC1208DD, to demonstrate the safety and efficacy of the bag system. The information cited in the literature citation and summary report you have provided may be considered if you establish that the bags used in the studies are the same as those under NDA. We note that you have provided an attestation statement that states that the materials

used in the cited bags and CPD are the same materials. However, this is insufficient to establish sameness. We also note that all the bags used in the studies cited contained up to 29 ml of anticoagulant CPD, when the NDA contains 29 ml and 35 ml of CPD.

- a. Please provide a table to compare the proposed bags MSC1207DD and MSC1208DD containing CPD, with the bags studied by Pope et al., Salge-Bartels et al., and the MSC1206DU bag used for the (b) (4) studies. The table should compare the bag configuration, measurements, size, compound raw materials, references, suppliers, and thickness of the film and tubes for both CPD and plastics. Please note that the collection bags cited in the two literature reports did not provide information on the bag information as mentioned above.

Note: Table was provided and reviewed by CMC consult. She finds that the bags used in the literature citations and those under NDA are the same.

- b. Please clarify or comment.
 - i. Some study results include data from cord blood units that were processed outside the 48 hour time limit proposed under NDA.
 - ii. There are differences in kit configuration and amounts of CPD; for example, the Pope et. al. study uses a Triple-collection, containing 29 ml CPD, and the bag used in Salge-Bartels et.al. study contains 21 ml + 8 ml CPD, while the collection bag is described only as a Macopharma (Langen Germany). These studies do not cover the 27 ml + 8 ml configuration.

Applicant response:

1b (i): The studies were performed to evaluate quality parameters of Cord Blood function on the volume collected and the time to (b) (4). The testing and results obtained beyond 48 hours is how the 48 hour limit was established.

1b (ii): The volume of cord blood to be collected should be such as to maintain a cord blood/CPD ration of (b) (4). The ratio of (b) (4) is generally recognized to be optimal as per (b) (4). Both configurations have identical functions; the 27 ml + 8 ml configuration is for customers who target collecting 240 ml of cord blood whereas the 21 ml + 8 ml is for customers who target collection volumes of 200 ml.

Reviewer comment: the applicant's responses are adequate.

2. Regarding the Cord Blood Collection kit:

- a. You indicated “Most of the individual components of these products have been approved under MacoProductions’s NDA BN040083 for the Leucoflex MTL1 and CGP Leukocyte Reduction Filter System”. Please provide a table to compare the CB bags and the bags approved under BN040083 for compound raw materials, references, suppliers, and thickness of the film and tube for both CPD and plastics.

Applicant Response: The tables below provide a comparison of the cord blood bags MSCv1207DD and MSC 1208DD to the bags approved under BN040083 for compound raw materials, references, suppliers and thickness of the film and tube for both CPD and plastics.

Component	Characteristics	Reference	Cord blood collection medical devices				
			MSC1207DD	MSC1208DD	MSC1202PU	MSC1206DU	MQT2205PK
Anticoagulant solution	Citric acid monohydrate Supplier : (b) (4)	Citrate Phosphate Dextrose (CPD)	27 ml + 8 ml (USP)	21 ml + 8 ml (USP)	21 ml + 8 ml (USP)	21 ml + 8 ml (USP)	21 ml + 8 ml (USP)
	Sodium citrate Supplier : (b) (4)						
	Sodium (b) (4) phosphate dihydrate Supplier : (b) (4)						
	Dextrose monohydrate Supplier : (b) (4)						

(b) (4)

Reviewer comment: the CMC consult agrees that the responses are adequate.

- b. In response to an agency query during the February 1, 2013 pre-meeting, you indicated that out of the (b) (4) the Injection site may come into direct contact with blood; the other components have been approved under Macopharma's BN 040083. On the contrary, we believe that the (b) (4) may be considered a blood contact component because the CPD in the rinsing/satellite bag can be added to or stripped into the collection bag, and thus may require biocompatibility testing. Please comment. (*Pharmtox may edit or replace this comment*)

Applicant response: We confirm that the (b) (4) is outside the fluid pathway and it is not a blood contacting component. The purpose of the (b) (4) stays in position.

Reviewer comment: adequate response.

- c. Please submit a separate 'Indications for Use' directions for the each configuration of the MacoProductions's CB Sterile Collection Bags (MSC1207DD and MSC1208DD).

Applicant response: submitted

- d. Please clarify whether the range of volume of cord blood collected as stated in the 'Indication for Use', i.e., 40 – 250 ml, includes anticoagulant.

Applicant response: The range of cord blood collected as stated in the 'Indications for Use' does not include the anticoagulant

- e. Please clarify the following discrepancy: In Vol 1 page 55, you stated that the MSC1208DD configuration allows the collection of about 147 ml and the MSC1207DD allows the collection of 189 ml. If the collected volume is higher than these values, the extra 8 ml CPD in the rinsing bag is added for a final volume of (b) (4) ml (MSC1208DD) or 245 ml (MSC1207DD).

This differs from the kit description on the same page and elsewhere: the MSC1207DD containing 27 ml CPD permits the collection of approximately 200 ml; and for collections more than 200 ml, the 8 ml CPD in the rinsing bag is added. The MSC1207DD containing 21 ml CPD permits the collection of approximately 150 ml; for collections more than 150 ml, the 8 ml CPD is added.

Applicant response: The collection volumes of 147 and 189 ml are based on the theoretical ratio between CPD and blood which is (b) (4). Specifically, for MSC1208DD: Collection bag 21 ml CPD (b) (4) and Rinsing bag: 8 ml (b) (4). Therefore the final volume would be (b) (4). For MSC1207DD: collection bag - 27 ml CPD (b) (4) blood and Rinsing bag: 8 (b) (4). Therefore, the final volume would be (b) (4) = 245 ml.

Reviewer comment: adequate response

3. You cite master file (b) (4) for the (b) (4), however, you have not provided a letter of authorization to reference this file. The letter should specify the information that is applicable to your file.

Applicant response: letter of authorization is attached.

Review of responses to telecon comments on 11-20-2014: (responses received Dec 22, 2014)

- a. Your (b) (4) data from the MSC1206DU version of the MacoProductions CB collection kit indicated that the collection bag must weigh (b) (4). Please clarify what part of this weight is cord blood.

Applicant response: The (b) (4) are calculated as follows: Collection bag (b) (4) which results in (b) (4) pure cord blood (b) (4)

Reviewer comment: adequate response.

- b. On page 3 of Vol 8, you state that: "Macopharma is seeking approval of the following two configurations. MSC1207DD is the collection set which will be provided for sale for customers in the United States" It appears the MSC1208DD configuration will not be marketed in the US. Please comment.

Applicant response: It is Macopharmas intention to market both configurations MSC1207DD and NSC1208DD in the US.

- c. Please clarify the following discrepancies:

- i. Table 1 (Vol 8, page 6) identifies the MSC1207DD as having a collection volume of 200 ml and containing 21 ml + 8 ml CPD. This information conflicts with description of this configuration in Vol 1 page 1, Vol 8 page3 and elsewhere, which describe this configuration as having 27 ml + 8 ml CPD. Please clarify.
- ii. Although, Table 1 (Vol 8 page 6) identifies the major differences in the various configurations, MSC1208DD is not listed.

Applicant response: The 21 ml volume listed for MSC1207DD in Table 1, Volume 8, page 6, is a typographical error. The correct volume is 27 ml. The table has been updated to also include MSC1208DD; attached below.

- d. Based on the information you have provided, FDA recommends revising the Indications for Use as follows:
- i. Remove the statement “A minimum collection volume for CB has not been established. Collections below 40 ml should be tested for acceptable quality parameters as per Facility SOPs”.
 - ii. Based on the cited data please add the following statement to your Indications for Use: If the collection volume is less than 60 ml, the unit should be processed within 24 hours of collection.

Applicant response: *The instructions for use has been revised accordingly.*

Reviewer comment: adequate response.