

I concur with this review. M. Serabian

**FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Cellular, Tissue and Gene Therapies
Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch**

Final Review Memo

NDA NUMBER: NDA #125552
DATE PHARM/TOX MODULE RECEIVED BY CENTER: 30-April-2014
DATE REVIEW COMPLETED: 20-February-2015
DUE DATE: 30-April-2015
PRODUCT: Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD)
SPONSOR: MacoProductions S.A.S.
PROPOSED INDICATION: For the collection of 40 to 250 ml of umbilical cord blood from either vaginal birth or within the sterile field of a Cesarean section
PHARM/TOX REVIEWER: Alex M. Bailey, PhD
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DMPQ REVIEWER: Nancy Waites, MS
CONSULT REVIEWERS: Ingrid Markovic, PhD; CBER/OD/RM
Ping He, MD; CBER/OBRR

Formulation and Chemistry:

The drug substance is an anti-coagulant solution of Citrate Phosphate Dextrose (CPD) which is formulated in-house at MacoProductions Polonia SP Z.o.o., from raw materials supplied by qualified vendors. The CPD components are manufactured according to the standard ISO 9001:2008 and NF EN ISO 13458:2012 and following US (b) (4) methods.

The following table was provided by the sponsor:

Table 1: CPD Formulation

Raw Material	Formulation
Citric acid monohydrate	3.27 g (b) (4) / USP
Sodium citrate	26.3 g (b) (4) / USP
Sodium (b) (4) phosphate dihydrate*	2.51 g (b) (4) / USP*
Glucose monohydrate	25.5 g (b) (4) / USP
Water for Injections	qs to 1000 mL (b) (4) / USP

*Note: USP specifies monobasic sodium phosphate (monohydrate) [Molecular Weight (MW) = 138], whereas (b) (4)

(b) (4)

Table 2: Application History

pre-NDA Type B teleconference	01-February-2013
NDA 40083/036	Refuse to File (RTF) issued 20-December-2013
NDA 125552 submitted	30-April-2014
Teleconference to request additional information (AI)	11-June-2014; sponsor submission provided in response to AI request on 19-June-2014
NDA 125552 Filing Action Letter Issued	27-June-2014

Comments:

- The sponsor previously submitted NDA BN40083 Supplement #036 for approval of two new configurations for Cord Blood Sterile Collection Bags (CCB) containing CPD. The sponsor was subsequently issued a RTF decision on 20-December-2013 for this supplement, primarily due to differences in the drug product. Specifically, the CPD solution did not contain the adenine additive solution (AS-1) that was part of the previously approved product. Thus, the sponsor was informed that a new NDA would be required.

- *At the time of the original NDA 125552 submission, the sponsor failed to provide the complete study report for an Extractables & Leachables (E&L) study of the collection bag, which was listed as 'ongoing' in the Table of Contents. The sponsor was contacted by this reviewer and the RPM via telephone on 11-June-2014 to request this information, and the sponsor submitted the complete study report via email on 19-June-2014.*

Cross-referenced files: N/A

Background:

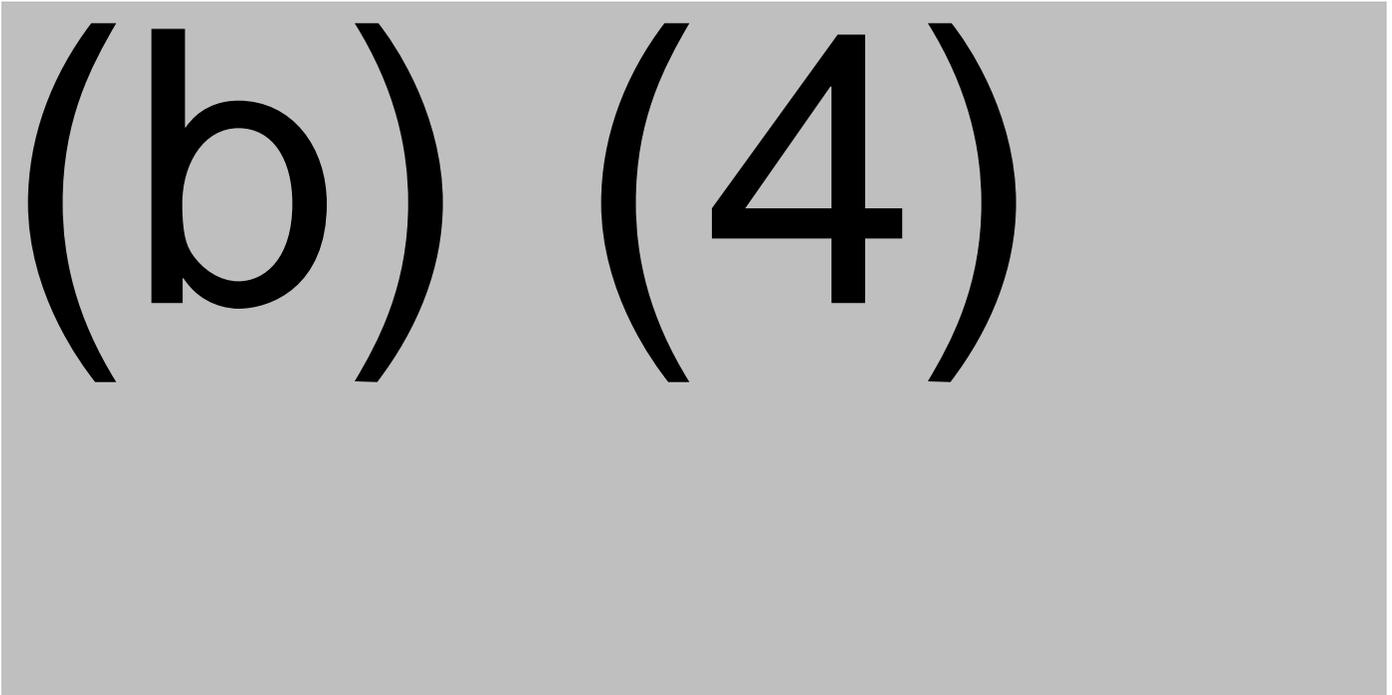
The CCB, termed MSC1207DD and MSC1208DD, are intended for the collection of umbilical cord blood obtained from a vaginal birth or within the sterile field of a Caesarian section. Briefly, cord blood is collected directly into the CCB, which allows collection of about 147 ml (MSC1208DD) or 189 ml (MSC1207DD). Each CCB is a wholly integrated set of blood bags with anticoagulant solution CPD.

The following summary information of the two new configurations was provided by the sponsor:

- 1) MSC1207DD – product components:
 - a. 300 ml collection bag containing 27 ml of CPD
 - b. 40 ml rinsing ((b) (4) bag containing 8 ml of CPD
 - c. Two 12-gauge needles with a protective shield (Secuvam) for the used needle

The following schematic of MSC1207DD was provided by the sponsor:

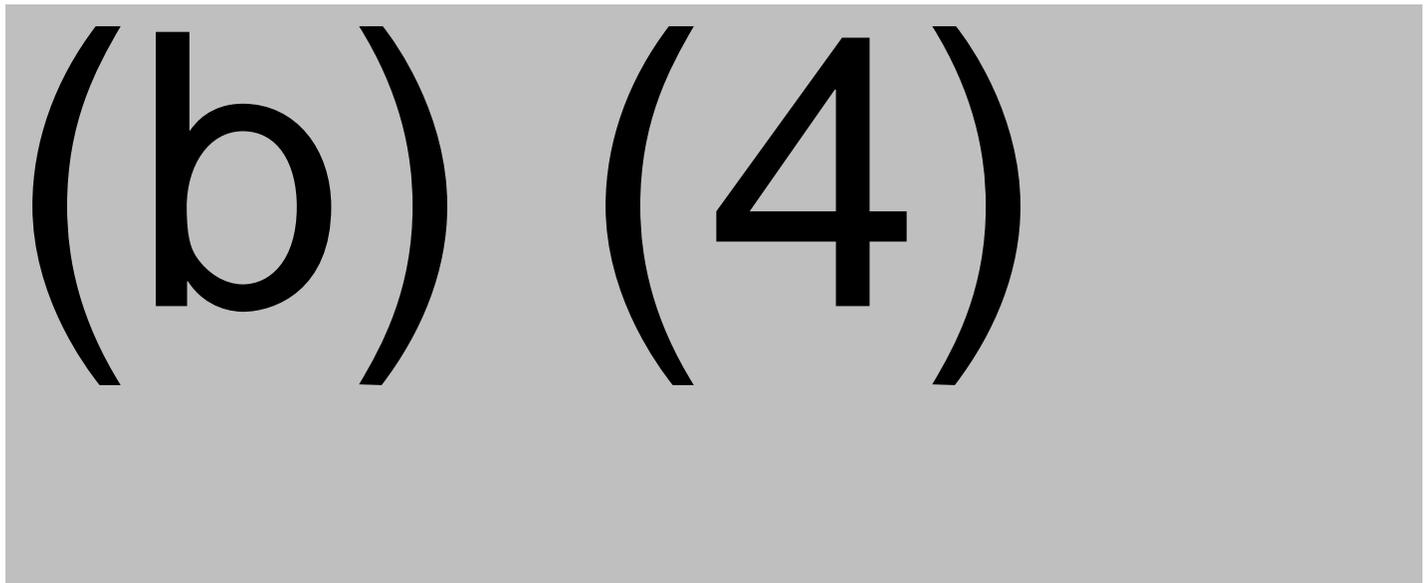
Figure 1: MSC1207DD components



- 2) MSC1208DD – product components:
- a. 300 ml collection bag containing 21 ml of CPD
 - b. 40 ml rinsing ((b) (4)) bag containing 8 ml of CPD
 - c. Two 12-gauge needles with a protective shield (Secuvam) for the used needle

The following schematic of MSC1208DD was provided by the sponsor:

Figure 2: MSC1208DD components

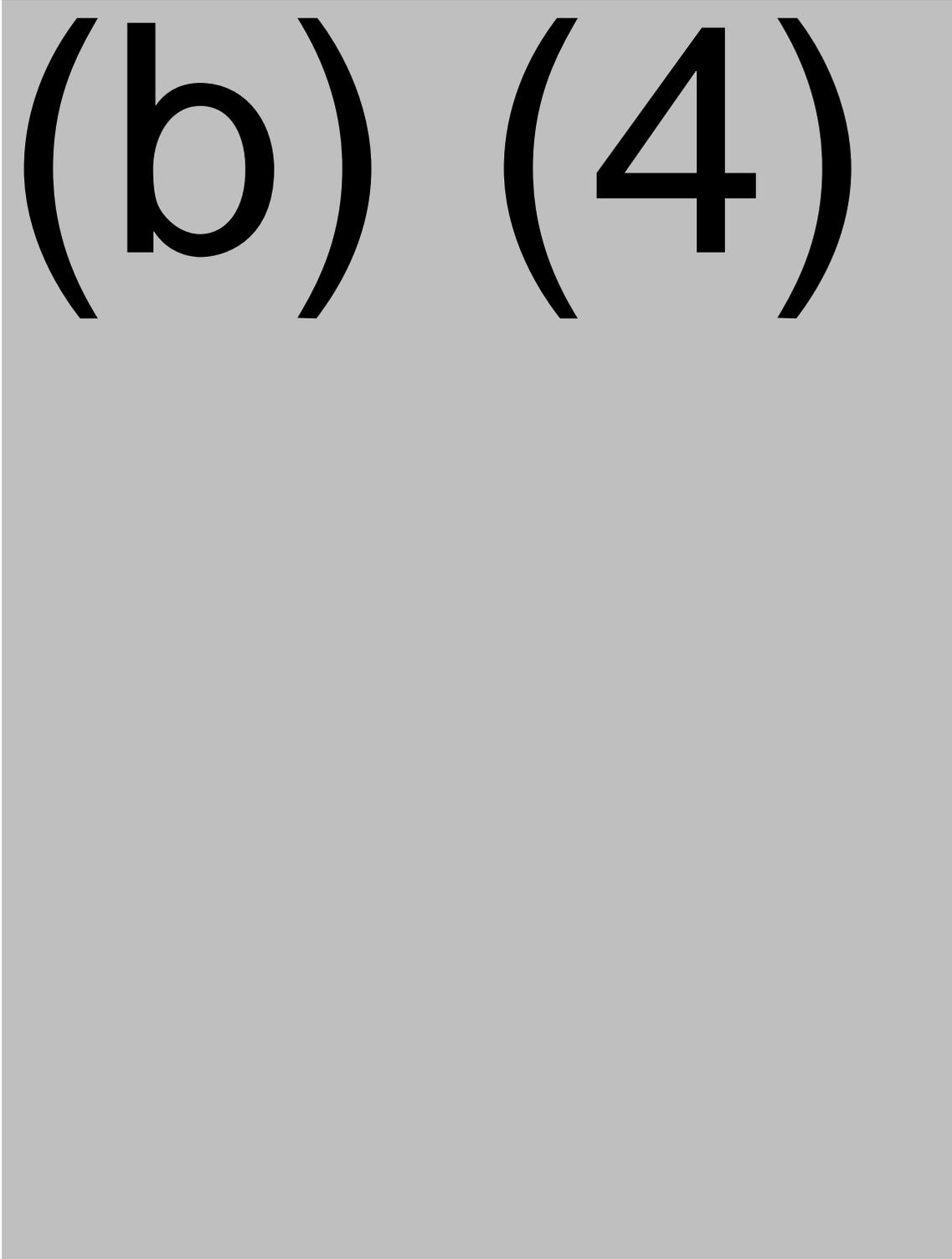


The sponsor provided the following tables of component quantities, descriptions, materials, and suppliers:

Table 3: CCB component quantities and descriptions

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

Table 4: CCB component materials and suppliers



According to the sponsor, the majority of the individual components of MSC1208DD and MSC1207DD have been previously cleared or approved in the following applications:

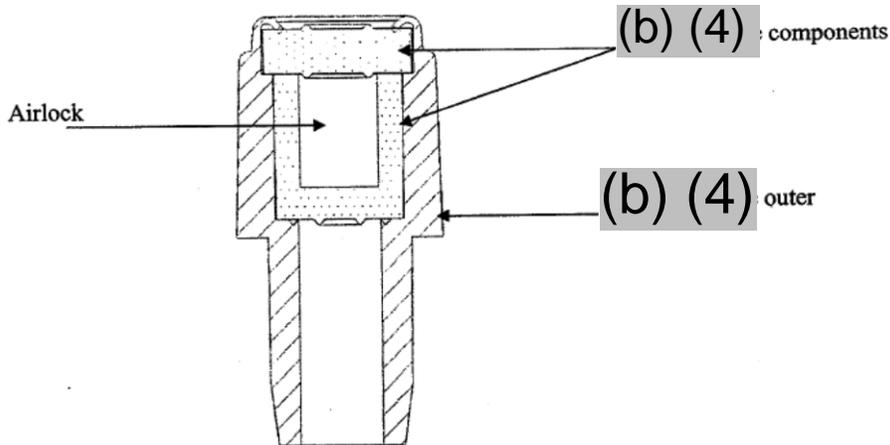
- BN040083 for the Leucoflex MTL1 Leukocyte Reduction Filter System for Whole Blood
- BN040083 for the Leucoflex CGP Leukocyte Reduction Filter System for Red Blood Cells
- BK080060, BK03008, BK080060, and BK120071 for the Leucolab Leukoreduction System for AS01, AS-3, and AS-5 Red Blood Cells

According to the sponsor, the only differences between the components of the new proposed CCB (MSC1208D and MSC1207DD) and the previously approved CCB are the: 1) CPD formulation; 2) volume of the CPD contained in the collection bags; (b) (4)

injection site hub is the only new patient-contacting component.

The following schematic of the injection site hub and materials of construction was provided by the sponsor:

Figure 3: Injection site hub



Biocompatibility Testing

Biocompatibility (BC) testing was conducted on the Leucoflex Leukoreduction Filter System which is similar to the CCB ((b) (4) ; Table 5), tubing ((b) (4) ; Table 6), and injection site hub material components (Membrane: (b) (4) ; Hub: (b) (4) Table 7). The following summary tables of BC testing were provided by the sponsor:

5 Pages Determined to be Non-Releaseable: (b)(4)

Comments:

- *The Leucoflex Leukoreduction Filter Systems and tubing are composed of the (b) (4) materials as the CCB (i.e., (b) (4)) and tubing (i.e., (b) (4)) submitted under this NDA #125552. Thus, BC tests previously conducted on the materials constituting the approved Leucoflex Leukoreduction Filter Systems and submitted under this NDA as support for the BC of the CCB and tubing (Tables 5-6) are applicable. No additional BC testing on these components is recommended at this time.*
- *The proposed CCB incorporates new device components that not have been previously cleared or approved, specifically (b) (4) the injection site hub (Figure 3) is (b) (4) patient-contacting component. Thus, the sponsor conducted additional BC testing on the materials that constitute this component (Table 7).*
- *Complete BC testing study reports were submitted under Module 4 of the NDA submission.*

BC testing conducted on the material components of the injection site hub (i.e., (b) (4)) are reviewed below:

Study title: Acute toxicity study by single intravenous injection (mice)

Report number: Not specified

Reference standards:

- (b) (4)

Testing facility: (b) (4)

GLP compliance: Non-compliant

Articles tested:

- Test article: (b) (4) (Lot/Batch #: Unknown)
- Controls: Extraction vehicles
- Extraction vehicles: NaCl and 1:20 ethanol/NaCl

Test system:

- *Animal species:* (b) (4) mice
- *Number of animals:* 20 (5 mice/group)
- *Sex:* Female
- *Age:* Unknown
- *Body weight:* 22-26 grams

Route of administration (ROA): Intravenous (IV) injection

Study design:

Mice were injected with either test article extracts or with the extraction vehicles and observed for signs of toxicity immediately after injection and at 4, 24, 48, and 72 hours post-injection. Mortality, body weights, and clinical observations were recorded.

Results:

None of the animals were adversely affected following injection of the test article extracts. All animals survived for the duration of the test.

Study title: Acute systemic toxicity after single intra-peritoneal (IP) injection

Report number: Not specified

Reference standards:

- (b) (4)

Testing facility: (b) (4)

GLP compliance: Non-compliant

Articles tested:

- Test article: (b) (4) (Lot/Batch #: Unknown)
- Controls: Extraction vehicles
- Extraction vehicles: NaCl and vegetable oil

Test system:

- *Animal species:* (b) (4) mice
- *Number of animals:* 20 (5 mice/group)
- *Sex:* Female
- *Age:* Unknown
- *Body weight:* 22-28 grams

ROA: Intraperitoneal (IP) injection

Study design:

Mice were injected with either test article extracts or with the extraction vehicles and observed for signs of toxicity immediately after injection and at 4, 24, 48, and 72 hours post-injection. Mortality, body weights, and clinical observations were recorded.

Results:

None of the animals were adversely affected following injection of the test article extracts. All animals survived for the duration of the test.

Study title: Local toxicity study in rabbits

Report number: Not specified

Reference standards:

- (b) (4)

Testing facility: (b) (4)

GLP compliance: Non-compliant

Articles tested:

- Test article: (b) (4) (Lot/Batch #: Unknown)
- Controls: Extraction vehicles
- Extraction vehicles: NaCl, 1:20 ethanol/NaCl, polyethylene glycol 400 (PEG 400), vegetable oil

Test system:

- *Animal species:* (b) (4) rabbits ((b) (4))
- *Number of animals used:* 8 (2 rabbits/group)
- *Sex:* Unknown
- *Age:* Unknown
- *Body weight:* Average body weight of 2 kg

ROA: Intradermal injection

Study design:

Each rabbit was injected with five 0.2-ml injections/test article extract (anterior) and five 0.2-ml injections/extraction vehicle (posterior). Clinical signs, body weights, and evidence of erythema, necrosis, and edema were recorded immediately after injection and at 4, 24, 48, and 72 hours post-injection.

Results:

There were no test article-related findings at any time point.

Study title: Cytotoxicity using the (b) (4) Method
Report number: Not specified

Reference standards:

- (b) (4)

Testing facility: (b) (4)
GLP compliance: Non-compliant

Articles tested:

- Test article: (b) (4)
- Negative control article: High Density Polyethylene
- Positive control article (b) (4)
- Extraction vehicle: NaCl

Test system used: Mouse fibroblast cells ((b) (4) cells) and standard methods

Results: Under the conditions of the study, the test article extract showed no evidence of cell lysis or cytotoxicity.

Study title: Biological reactivity test in vivo (b) (4) study
Report number: 20000372 ST

Reference standards:

- (b) (4)

Testing facility: (b) (4)

GLP compliance: Non-compliant

Articles tested:

- Test article: (b) (4)
- Controls: Extraction vehicles
- Extraction vehicles: NaCl, 1:20 ethanol/NaCl, PEG 400, sesame oil

Intracutaneous test in rabbits*Test system:*

- *Animal species:* (b) (4) rabbits (b) (4)
- *Number of animals:* 8 (2 rabbits/group)
- *Sex:* Female
- *Age:* Unknown
- *Body weight:* 2.0-2.4 kg

ROA: Intracutaneous (IC) injection

Study design:

Each rabbit was injected with five 0.2-ml injections/test article extract (anterior) and five 0.2-ml injections/extraction vehicle (posterior). Clinical signs, body weights, and evidence of erythema, necrosis, and edema were recorded immediately after injection and at 4, 24, 48, and 72 hours post-injection.

Results: None of the animals were adversely affected following injection of the test article extracts. All animals survived for the duration of the test.

Systemic injection test in the mouse*Test system:*

- *Animal species:* (b) (4) mice (b) (4)
- *Number of animals:* 40 (5 mice/group/ROA)
- *Sex:* Female
- *Age:* Unknown
- *Body weight:* 17-23 grams

ROA: IV and IP injection

Study design: Mice were injected with either test article extracts or with the extraction vehicles and observed for signs of toxicity immediately after injection and at 4, 24, 48, and 72 hours post-injection. Mortality, body weights, and clinical observations were recorded.

Results: None of the animals were adversely affected following administration of the test article extracts via IV or IP injection. All animals survived for the duration of the test.

Comments:

- *Regarding the BC evaluation of the injection site hub materials:*
 - *The BC of the (b) (4) seal was evaluated in vitro as well as in mice and rabbits per (b) (4), and results indicate acceptable BC.*

- *The BC of the (b) (4) outer component was evaluated in accordance with the specifications of (b) (4), which includes systemic toxicity testing in mice and IC toxicity testing in rabbits. These data provide adequate evidence of the BC of the (b) (4) outer component.*
- *The BC of the other components of the CCB is supported by data generated from the BC evaluation of previously cleared and approved components of the Leucoflex and Leucolab Leukocyte Reduction Filter Systems. No additional BC testing is recommended at this time.*

Ink Migration and E&L Testing:

The sponsor conducted ink migration on the (b) (4) ink (used in the printed labels on the bags) and E&L testing of the CCB, which is summarized in the table below:

2 Pages Determined to be Non-Releaseable: (b)(4)

- (b) (4) [Redacted]
- [Redacted]

Comment:

- *Ink migration testing is adequate, and no additional testing is recommended at this time.*

E&L Testing:

A consult review of the sponsor’s E&L testing of the CCB was performed by Dr. Ingrid Markovic, Ph.D. (FDA/CBER/OD/ADRM).

Comments:

- *The complete E&L study report was submitted on 19-June-2014. Please see the comment at the beginning of this review for additional information.*
- *Following her initial review of the submission, Dr. Markovic recommended that a request for AI be sent to the sponsor to seek clarification on numerous issues. Please see the Pharmacology/Toxicology Mid-Cycle Review memo for additional information.*
- *An AI letter was sent to the sponsor on 04-November-2014 with the following IR requests pertaining to the E&L assessment of the CCB:*

4. **Regarding the study titled "Risk Assessment of Extractable Compounds from the Sterile Cord Blood Collection Bag" that was submitted on June 19, 2014, please provide the following:**

- a. **You identified (b) (4) as the most abundant extractable component, which we note contains a (b) (4) functional group and may be associated with high acute toxicities. However, you did not provide sufficient information to assess the risks to the patient that may be posed by the presence of this compound as leachable. Please submit, detailed toxicological information for (b) (4), including a risk assessment for patient exposure to this compound under worst-case conditions for use.**

- b. **The proposed cord blood collection bag (CCB) is composed of (b) (4) (b) (4), which is a material commonly manufactured using plasticizers containing various phthalates. However, phthalates were not detected as extractable components (Table 2, page 8 of the study report). Please clarify if plasticizers are used during the manufacture of the CCB and, if phthalates are expected to be extracted in aqueous Citrate Phosphate Dextrose buffer, whether they could be present as leachables.**

- *The sponsor responded to the IR request on 29-December-2014. Please see the Pharmacology/Toxicology Mid-Cycle Review memo for additional information.*

In response to the IR Request #4a, the sponsor submitted an Amended Report No. 14-01306-N1 titled “Risk Assessment of Extractable Compounds from the Sterile Cord Blood Collection Bag” that included additional toxicologist information for (b) (4). Per the sponsor, there was no available toxicity information for (b) (4) following review of all available sources of toxicity information, and the US EPA AIM software did not identify any appropriate surrogate compounds. Thus, the sponsor submitted information on the acute, genetic, and repeat dose toxicity of other substances that contain the (b) (4) functional group - specifically (b) (4) - as support for the safety of (b) (4). This approach to the risk assessment of (b) (4) is acceptable, and the submitted data are acceptable.

Dr. Markovich reviewed the sponsor’s response to IR Request #4b, which she found acceptable. This reviewer concurs. Please see Appendix 1 for additional information.

Reviewer Conclusion:

The sponsor’s evaluation of the BC, ink migration, and E&L profile of the proposed product is acceptable.

Appendix 1:
E&L Consult: E-mail Communication

Primary Reviewer: Alexander Bailey, Ph.D.

Special Advisor to the Associate Director for Review Management providing E&L consult: Ingrid Markovic, Ph.D., FDA/CBER/OD/ADRM

From: [Markovic, Ingrid](#)
To: [Bailey, Alexander](#)
Cc: [Serabian, Mercedes](#)
Subject: RE: E&L consult follow-up
Date: Wednesday, February 18, 2015 4:40:55 PM

Hi Alex,

The sponsor has adequately addressed IR 4.b. pertaining to the presence of phthalate leachables. According to the Sponsor, phthalate leachables are monitored on stability throughout product expiry (i.e., end of the shelf life) at 24 months, which is an optimal approach. The Sponsor measured that DEHP is leaching during storage at a concentration below (b) (4), which is the level expected to leach from a (b) (4) bag (source: (b) (4) devices and published literature). While the level of leachables tends to increase over time, the Sponsor indicated that stability study is underway and their final stability report will be provided for review and will include DEHP concentration at the end of the shelf life. When evaluating leachables impact to the patient and product, one is generally concerned about the direct toxicity and impact to product quality most often observed on stability. While I defer the toxicological evaluation to you guys, my own review of the available information seem to suggest that DEHP levels released during storage are well below the NOEL or LOEL for by IV administration in rats. The assessment of product quality is similarly deferred to the CMC reviewer, although it may be worth to point out that published findings noted that phthalates have stabilizing effect on cells during storage minimizing lysis. Therefore, the risks from the phthalates appear adequately controlled and are acceptable.

I defer Sponsor's response to IR 4.b. to you guys since it pertains to toxicological assessment of the (b) (4).

Please let me know if you have any questions. Thank you!

Best,
Ingrid