

CLINICAL REVIEW

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Reviewer Name(s)	John Hyde
Review Completion Date	February 26, 2015

Established Name	Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD) (sodium citrate, citric acid, sodium phosphate, glucose)
(Proposed) Trade Name	None proposed
Therapeutic Class	Undetermined
Applicant	MacoProductions S.A.S. (a.k.a. Macopharma)

Formulation(s)	Cord Blood Sterile Collection Bag
Dosing Regimen	None specified
Indication(s)	Collection of umbilical cord blood
Intended Population(s)	None specified

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	7
	Reviewer's Preamble	7
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment.....	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	11
1.4	Recommendations for Postmarket Requirements and Commitments	11
2	INTRODUCTION AND REGULATORY BACKGROUND	12
2.1	Product Information	12
2.2	Tables of Currently Available Treatments for Proposed Indications	13
2.3	Availability of Proposed Active Ingredient in the United States	14
2.4	Important Safety Issues With Consideration to Related Drugs.....	15
2.5	Summary of Presubmission Regulatory Activity Related to Submission	15
2.6	Other Relevant Background Information	18
3	ETHICS AND GOOD CLINICAL PRACTICES.....	20
3.1	Submission Quality and Integrity	20
3.2	Compliance with Good Clinical Practices	20
3.3	Financial Disclosures.....	20
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	20
4.1	Chemistry Manufacturing and Controls	20
4.2	Clinical Microbiology.....	21
4.3	Preclinical Pharmacology/Toxicology	21
4.4	Clinical Pharmacology	21
4.4.1	Mechanism of Action.....	21
4.4.2	Pharmacodynamics.....	22
4.4.3	Pharmacokinetics.....	22
5	SOURCES OF CLINICAL DATA.....	24
5.1	Tables of Studies/Clinical Trials	24
5.2	Review Strategy	24
5.3	Discussion of Individual Studies/Clinical Trials.....	24
6	REVIEW OF EFFICACY	24
	Efficacy Summary.....	24
6.1	Indication	25
6.1.10	Additional Efficacy Issues/Analyses	25
7	REVIEW OF SAFETY.....	26
	Safety Summary	26

7.7	Additional Submissions / Safety Issues	26
8	POSTMARKET EXPERIENCE.....	27
9	APPENDICES	29
9.1	Literature Review/References	29
9.2	Labeling Recommendations	33
9.3	Advisory Committee Meeting.....	34

Table of Tables

Table 1: List of Abbreviations	6
Table 2: Composition of CPD Solution for MSC1207DD.....	13
Table 3: CBER NDAs for Products Including One or More of the Same Drugs.....	14
Table 4: Comparison of CPD Solution Concentrations	19
Table 5: Macopharma UCB Collection Kit Sales 2011 – 2013	28

Table of Figures

Figure 1: Diagram of Configuration MSC1207DD	12
Figure 2: Diagram of Configuration MSC1208DD	13

Table 1: List of Abbreviations

ACD	Anticoagulant citrate and dextrose solution
AE	Adverse event
AP	Approved
BLA	Biologics Licensing Application
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing, and controls
CPD	Citrate, phosphate, and dextrose solution
CP2D	Citrate, phosphate, and double dextrose solution
CPD-A	Citrate, phosphate, dextrose, and adenine solution
CR	Compete Response
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GTT	Glucose tolerance test
HPC	Hematopoietic Progenitor Cell
mmol	Millimole
μmol	Micromole
M.W.	Molecular weight
N/A	Not applicable
NDA	New Drug Application
PK	Pharmacokinetics
PLR	Physician Labeling Rule
PREA	Pediatric Research Equity Act
RBC	Red blood cell
RTF	Refuse to File
UCB	Umbilical cord blood
USP	United States Pharmacopeia

1 Recommendations/Risk Benefit Assessment

Reviewer's Preamble

Applications for blood collection and storage bags containing chemical solutions have been handled by CBER under NDA regulations. This includes at least one umbilical cord blood (UCB) collection system (NDA BN800222). However, the product that is the subject of the current NDA submission has characteristics of a device that make it significantly challenging to apply the clinical requirements of the NDA regulations. The issues are the following:

- The primary role of the product is as a *conveyance* from a site of UCB collection to a site where the UCB will be processed; the chemical solution in the bag supports that role by preventing clotting of blood and maintaining cell viability during transport from site to site (see Section 4.4.1).
- The amount of the involved chemical solution, if any, that might actually find its way into a patient is highly dependent on the subsequent processing of the collected UCB. For the typical processing used in the production of approved HPC, Cord Blood products, much of the chemical solution might be removed. A unit that is subjected to volume reduction prior to cryopreservation and washing prior to administration might contain at most trace amounts of the chemicals by the time the unit is given to a patient.
- The intended use of the chemical solution is to facilitate the production of a useable UCB unit, and it is not meant to achieve its primary intended purpose through a chemical action *within or on the body of man*. In fact, there appears to be no intended purpose, primary or otherwise, for an action within or on the human body for the ultimate UCB recipient. Once the cells have been infused, there is no need for external agents to provide anticoagulation, buffering, or metabolic support of the cells.
- The Indication and Usage section of the labeling does not state an indication for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or for a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.
- Since the proposed indication is for collection of UCB, and no intended clinical benefit to a UCB recipient is claimed, there is no claim of clinical efficacy to be evaluated.

- This is not a product that a physician would prescribe to be directly administered to a patient. Concepts of dosing and administration do not appear to be relevant to a product such as this.
- It is unclear how one could develop meaningful, NDA-type labeling for the product, given the basic nature of the product and the considerations stated above.

Nonetheless, the decision has been made that this product will be regulated as a drug rather than as a device, so that it must be approved under an NDA in order to be marketed. Therefore, the application is being reviewed for compliance with the clinical requirements for an NDA as stated in 21 CFR 314.

1.1 Recommendation on Regulatory Action

Approval Decision

This Reviewer recommends that this application is not an approvable NDA from the clinical standpoint. The application has the following deficiencies that are grounds for refusing to approve the application under 21 CFR 314.125:

1. There is lack of substantial evidence consisting of adequate and well controlled investigations that the drug product will have the effect it purports or is represented to have (21 CFR 314.125 (b)(5)).

Reviewer's Comment: No beneficial clinical effect of the drugs on the UCB recipient is purported, represented, or implied. No clinical investigators were provided to support any clinical effect of the drugs themselves on a UCB recipient. Also, the product is a combination drug product, but the application does not address how each separate component contributes to a clinical effect.

2. There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling (21 CFR 314.125 (b)(4)).

Reviewer's Comment: Although this Reviewer's literature review and other analyses provide some assurance that the product is unlikely to present significant risks to a UCB recipient, the NDA application by itself did not provide sufficient information in the form of clinical studies, literature review, postmarket safety data, or other analyses to permit the comprehensive safety review necessary for an original NDA.

3. The drug product proposed labeling does not comply with the requirements for labels and labeling in 21 CFR 201 (21 CFR 314.125 (b)(8)).

Reviewer's Comment: The proposed labeling deviates substantially and materially from the labeling required for a new NDA under the Physician Labeling Rule (PLR). There is insufficient information in the application to support writing PLR-compliant labeling. See Section 9.2 (Labeling Review) for details of the deficiencies.

The Applicant did not request a waiver of any these requirements under 21 CFR 314.90.

Pediatric Requirements

In NDA Module 5, Section 5.4, p. 13, the Applicant has requested a full pediatric waiver. The Applicant stated in Section 5.4 of the NDA that the requirements regarding pediatric use (under 21 CFR 314.20(d)(7) and 21 CFR 314.55) were not applicable to the product because: "There is no age specific use of the product. This product is applicable to any female who gives birth." It appears the Applicant is viewing the pediatric requirement as applicable to the mother of the UCB donor, rather than any recipient of the UCB.

The Applicant requested a full waiver of pediatric studies stating that "it would be impossible or highly impracticable to conduct studies within this population as the number of patients is very small and the patients are geographically dispersed." However, the Applicant did not provide any further discussion or substantiating documentation regarding those factors.

The application was considered by the CBER PREA Working Group, and the following E-mail regarding this NDA was issued on 8/28/14:

Hi all,

We discussed this NDA in PREA WG yesterday & we have updated RMS-BLA to reflect that this is "PREA-not applicable".

It was noted in the discussion that the rationale for not triggering PREA should be documented in the clinical review. This is not final product that is administered to patients, so the sponsor couldn't design nor conduct pediatric studies. There was some discussion as to whether it falls under "blood and blood components" which historically have not been subject to PREA.

We can revisit this at a future date but we wanted to ensure this was documented.

Thanks-Adrienne

Adrienne Hornatko-Munoz, RAC
FDA/CBER
Review Management/Office of the Director

Reviewer's Comment: It is unclear how this product could be regarded as a blood or blood component product, if it is being regulated as an NDA due to its having drug components. However, the observation that the product is not a finished product that is administered to patients clearly puts it outside the traditional NDA paradigm and makes it difficult to envision how pediatric studies of practical value could be designed or conducted. This Reviewer concurs that the PREA requirements cannot be meaningfully applied in this case.

Exclusivity

There is no basis for granting exclusivity for the drug product or any of its drug components, because there were no clinical trials conducted by the Applicant.

Other Recommendations

The usual course of action when approval is not recommended would be to send the Applicant a complete response (CR) letter citing the deficiencies identified in the course of the review and advising on how the deficiencies could be addressed. However, in view of the nature of the product and its intended use, it is unclear how to advise the Applicant in this case. It is difficult to envision how the clinical deficiencies could feasibly be addressed in a way that would have value for evaluating this product. Because the drugs involved (citrate, phosphate, and dextrose) are intended to support UCB collection and storage during transport, but not have a direct therapeutic effect on any UCB recipient, it is not clear what adequate and well controlled trials the Applicant should be asked to conduct to evaluate a therapeutic effect. Also, it is not clear how the labeling could be revised to make it PLR-compliant.

This reviewer recommends that this product be handled under a regulatory pathway appropriate for a device. Assuming there are no CMC or biocompatibility issues, it would not be unreasonable to have this product available on the market, as it would appear to be as suitable for UCB collection and transport as the currently marketed product (Medsep UCB collection bags, BN800222).

Meeting device approval or clearance requirements appears to be feasible for this product, whereas it is difficult to see how a product of this type could be approved as an NDA without waiving of most of the substantive NDA clinical and labeling requirements in a way that would amount to a tacit acknowledgement that the product does not achieve its primary intended purpose through a chemical mode of action on or in the human body.

1.2 Risk Benefit Assessment

Insufficient information was provided in the NDA to support a risk-benefit analysis.

No claim is made regarding the ability of the product to treat, prevent, mitigate, cure, diagnose, or relieve associated symptoms of a recognized disease or condition or its manifestations. No clinical evidence was presented regarding the existence or magnitude of any direct clinical benefit of the drugs that comprise this product.

Given that CPD has a long history of use in approved products for blood collection, it would be reasonable to infer that CPD is reasonably safe, at least for certain uses. However, the Applicant did not provide data to facilitate any quantitative analysis of the risks of the product.

Without information on the intended clinical benefit, quantitative data regarding the benefit, or a quantitative analysis of safety, any risk-benefit assessment is speculative and does not provide an adequate foundation for approving an NDA.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None. This Reviewer is not recommending that the NDA be approved.

In the absence of the ability to perform an adequate risk-benefit assessment, there is no sound basis for making recommendations regarding postmarketing risk evaluation or risk mitigation strategies, should the NDA be approved.

1.4 Recommendations for Postmarket Requirements and Commitments

None. This Reviewer is not recommending that the NDA be approved.

In the absence of clinical safety and efficacy data, and with no claimed clinical effect, there is no sound basis for making recommendations regarding clinical postmarketing requirements or commitments, should the NDA be approved.

Considerations regarding pediatric postmarketing requirements are discussed in Section 1.1 (Recommendations on Regulatory Action).

2 Introduction and Regulatory Background

2.1 Product Information

Configuration MSC1207DD is a 300 mL bag containing 27 mL CPD, a 40 mL rinsing bag containing 8 mL CPD [35 mL total CPD], and two 12 gauge needles with a protective shield for the used needle. It is intended for collection of up to 250 mL umbilical cord blood.

Configuration MSC1208DD is a 300 mL bag containing 21 mL CPD, a 40 mL rinsing bag containing 8 mL CPD [29 mL total CPD], and two 12 gauge needles with a protective shield for the used needle. It is intended for collection of up to 200 mL umbilical cord blood.

Schematics of each configuration are reproduced in Figure 1 and Figure 2 below:

Figure 1: Diagram of Configuration MSC1207DD

(b) (4)

Figure 2: Diagram of Configuration MSC1208DD

(b) (4)

Each 35 mL of CPD contains 0.92 g sodium citrate (dihydrate) USP, 114.4 mg citric acid (monohydrate) USP, 0.89 g dextrose (monohydrate) USP, and 77.5 mg mono basic sodium phosphate ((b) (4)) USP. The following table displays the total contents and concentrations of the CPD for the MSC1207DD configuration. Configuration MSC1208DD has the same concentrations but the total content of the drugs is (b) (4) less.

Table 2: Composition of CPD Solution for MSC1207DD

	M.W.	g in 35 mL	Conc. g/L	mmol in 35 mL	Conc. mmol/L
Sodium citrate	294.1	0.92	26.3	3.13	89.4
Citric acid monohydrate	210.1	0.1144	3.27	0.56	15.6
Total citrate				3.69	105
Mono basic sodium phosphate (b) (4)	138.0	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Dextrose monohydrate	198.2	0.89	25.4	4.48	128

2.2 Tables of Currently Available Treatments for Proposed Indications

There is no proposed indication for a clinical effect on patients. The proposed Indication and Usage section of the labeling states only that the product is for UCB collection.

The Medsep collection bag (CBER NDA BN800222) is an approved product containing CPD and used for UCB collection. That product is for collection of up to 210 mL of

UCB. The Indication and Usage section of that product's labeling also does not have a statement of a proposed clinical benefit on patients. The Medsep collection bag is the only approved UCB collection product identified through the NIH DailyMed website.

2.3 Availability of Proposed Active Ingredient in the United States

Citrate and phosphate are used as the anion in formulating salts of numerous oral and injectable drug products in which the cation is the active ingredient (e.g., diphenhydramine citrate, codeine phosphate). Phosphate compounds incorporating ³²P are used in medical imaging. Dextrose in varying concentrations, commonly 5% or 10%, is used in countless different intravenous solution products. However, those uses have little in common with the intended use of citrate, phosphate, and dextrose in the product that is the subject of this NDA.

More relevant to the current NDA are the CBER NDA products approved for blood collection or storage. Listings of CBER-approved NDAs for related products (current as of 2/2/15) are given in the table below:

Table 3: CBER NDAs for Products Including One or More of the Same Drugs

Citrate		Citrate Dextrose (ACD*)		Citrate Phosphate Dextrose (CPD)	
NDA	Year AP	NDA	Year AP	NDA	Year AP
BN760305	1978	BN160918	1978	BN170401	1977
BN770923	1978	BA710497	1987	BN781211	1981
BN781214	1980	BA980728	2002	BN800222	1982
BN980123	2000	BN000922	2002	BN811012	1983
BN010409	2003	BN001214	2002	BN811104	1983
		BA010228	2002	BN880217	1988
		BN020037	2003	BN900223	1991
		BA110057	2012	BN900224	1991
				BA070025	2009

* "A" in ACD stands for anticoagulant, not adenine

Citrate Phosphate Double Dextrose (CP2D)		Citrate Phosphate Dextrose Adenine (CPD-A)	
NDA	Year AP	NDA	Year AP
BN820915	1983	BN770420	1978
BN000127	2002	BN800077	1980
		BN820528	1982
		BN940404	1994
		BN950522	1997
		BN040083	2005
		BN110059	2013

2.4 Important Safety Issues With Consideration to Related Drugs

Massive transfusion in trauma settings can result in citrate toxicity from transfused blood units (Sihler and Napolitano, 2010; British Society for Haematology, 1988). However, that adverse reaction is unlikely to be relevant for UCB as it is intended to be used, because use of UCB for hematopoietic reconstitution typically involves administering only one or two units, with each unit being infused over about an hour. Considerations related to the potential for citrate toxicity are discussed further in Section 7.7 (Additional Submissions/Safety Issues).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Pre-NDA Meeting

A pre-NDA meeting between the FDA and the Applicant was held on 2/1/13 (CRMTS 8711, PS001917). The Applicant asked if the application could be submitted as a supplemental application to CBER NDA BN040083 (the Applicant's MTLI Leukocyte Reduction Filter system, which is a collection bag for whole blood). The Applicant also cited CBER NDA BN800222 (Medsep UCB collection bag) as an example of an approved UCB collection system containing CPD. The Applicant was advised that a new NDA would be needed because of the new indication and because the drug product was different from that in BN040083, which includes adenine. The FDA also recommended that the Applicant conduct studies to show there was no negative impact of the product on the quality of UCB units and that the Applicant supply information regarding biocompatibility testing. The FDA stated that NDA requirements under 21 CFR 314.50(d)(5) were applicable, so that the application should include:

- A description and analysis of any data or information relevant to an evaluation of the safety and effectiveness of the product (21 CFR 314.50(d)(5)(iv)).
- A summary and updates of safety information (21 CFR 314.50(d)(5)(vi)).
- An integrated summary of the benefits and risks of the product (21 CFR 314.50(d)(5)(viii)).

RTF of NDA Supplement

Despite the recommendation made at the pre-NDA meeting, the Applicant submitted an efficacy supplement to NDA BN040083 (supplement 36, dated 10/24/13, and received 10/29/13).

The clinical filing review memo recommended against filing due to the following deficiencies (paraphrased from the 12/9/13 clinical filing memo):

1. The product was not the same as the drug product approved under NDA BN40083, because the product approved under BN040083 included adenine.

2. Form FDA 360h was not complete, as it did not specify the type of NDA supplement.
3. Sections of the application were illegible or very difficult to read.
4. The application did not provide product labeling in the required PLR format.
5. The application did not include any adequate and well controlled clinical investigations conducted by the Applicant, nor did it identify any adequate and well controlled investigations not conducted by the Applicant that the Applicant intended to rely upon in support of the efficacy supplement.
6. The application did not include a description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the product.
7. The application did not include an update of postmarketing safety information regarding NDA BN40083, nor did it include an integrated summary of all available information about the safety of the drugs contained in the product.
8. The application did not address adequately the requirements regarding pediatric use.

Deficiencies were also identified in the CMC and nonclinical filing reviews. The FDA refused to file the supplement, and the Applicant was sent an RTF letter dated 12/20/13 stating the following deficiencies (paraphrased from the letter):

1. The application was not for the same drug product approved under NDA BN40083 and thus it cannot be accepted as a supplement.
2. The application form FDA 360h was not complete.
3. The application included illegible text and figures
4. (b) (4) new components were not identified in illustrations to allow the determination of their impact on the UCB collection.
5. It was unclear whether the new components were blood-contacting, which would necessitate biocompatibility testing.
6. The report for the Extractable/Leachable study of the label and ink did not include the study results or a description of the study conduct.

7. It was unclear whether all of the pivotal toxicology studies had been performed in accordance with GLP.
8. There was not an adequate response to CBER comments communicated at the 2/1/13 meeting.
9. The application did not provide product labeling in the required PLR format.
10. The application did not include a description and analysis of any other data or information relevant to an evaluation of safety and effectiveness.
11. The application did not include an update of postmarketing safety information regarding NDA BN40083, nor did it include an integrated summary of all available information about safety of the drugs.
12. The application did not address adequately the pediatric use requirement.

The 12/20/13 RTF letter also recommended additional information that the Applicant should provide and noted that the NDA supplement did not address how the Applicant planned to fulfill the PREA requirement.

Of note, the RTF letter did not include the clinical deficiency relating to the need for adequate and well controlled trials.

Filing of the Current Application

The current application was received on 4/30/14 as a new 505(b)(1) NDA. The clinical filing memo dated 6/9/14 recommended against filing the NDA and noted the following deficiencies (paraphrased from the clinical filing memo):

1. The application did not provide product labeling in the required PLR format.
2. The application did not include adequate and well controlled clinical investigations.
3. The application did not include a description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the product.
4. The application did not include an integrated summary of all available information about the safety of the drugs.
5. The application did not address adequately the pediatric use requirement.

Despite those issues, the FDA decided to file the application, and a filing letter dated 6/26/14 was sent to the Applicant. The letter also requested the following additional product information (quoted from the filing letter):

1. You did not establish whether the bags used in the supporting studies in the literature citations are the same as those proposed for NDA. Hence, it is uncertain if the bags used in the cited literature are the same as those considered under NDA.
2. The cited literature studies do not support the whole range of holding conditions (temperature and time duration) proposed by the sponsor. The sponsor proposes a temperature range of (b) (4) for 48 hours, but the cited studies cover 8°C for 24 -80 hours and 18°C – 26°C for 24 hours.
3. For the (b) (4) studies, the anticoagulant, CPD, used contained **ascorbic acid**; this is different from the CPD used in the cord blood collection bags under NDA. It is uncertain, whether the collection bags used in the studies are the same as those proposed under NDA.

The application was filed, effective June 29, 2014, with Standard review priority and a user fee goal date of April 30, 2015.

2.6 Other Relevant Background Information

The anticipated use of this product is for collection of UCB as a source of hematopoietic precursor cells (HPCs) for use in production of HPC, Cord Blood, products. The currently approved HPC, Cord Blood, products all have indication statements essentially equivalent to the following:

[Product name] HPC, Cord Blood, is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

There are presently five approved UCB products:

HEMACORD, New York Blood Center, BLA 125397, AP 11/10/11

HPC, Cord Blood, ClinImmune Labs, BLA 125391, AP 5/24/12

DUCORD, Duke University School of Medicine, BLA 125407, AP 10/4/12

ALLOCORD, SSM Cardinal Glennon Children's Medical Center, BLA 125413, AP 5/30/13

HPC, Cord Blood, LifeSouth Community Blood Centers, BLA 125432, AP 6/13/13

CPD is listed as an inactive ingredient in the DUCORD and ALLOCORD labelings, but the other three products have no mention of CPD in the labeling.

The processing for all but the ClinImmune product involves volume reduction by removal of RBCs and plasma from the collected UCB. ClinImmune reduces volume only by removing RBCs, so it may have a greater residual amount of the UCB collection solution.

The Applicant's NDA BN40083 (initially approved in 2005) is approved for collection of 500 ± 50 mL of whole blood for pre-storage leukocyte reduction. It includes 70 mL of a CPD solution, but also has a satellite bag with an adenine-dextrose-mannitol additive solution (AS-1). The Medsep NDA BN800222 (initially approved in 1982) is approved for collection of up to 210 mL UCB; it contains 35 mL of a CPD solution. The concentrations of the components of the CPD solutions in these NDAs and in the current product are nearly identical, as shown in the following table:

Table 4: Comparison of CPD Solution Concentrations

	Current NDA	NDA BN040083	NDA BN800222
Total volume (mL)	29, 35	70	35
Sodium citrate (g/L)	26.3	26.3	26.3
Citric acid monohydrate (g/L)	3.27	3.27	3.26
Mono basic sodium phosphate (b) (4) (g/L)	(b) (4)	(b) (4)	2.23
Dextrose monohydrate (g/L)	25.4	25.5	25.5

*The BN040083 NDA review cites 2.51 g/L "sodium phosphate." Assuming that refers to (b) (4) sodium phosphate monohydrate, the phosphate concentration is equivalent to (b) (4) mono basic sodium phosphate (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission consisted of eight pdf “flat” files with bookmarks but no hyperlinks. Bookmarks did not provide much granularity, as some volumes had long sections devoid of bookmarks, and some bookmarks were nonfunctional (e.g., bookmarks for journal articles 9 and 10 in Module 5), but materials in the clinical modules could still be located with reasonable effort. There were no associated electronic clinical data files.

In some parts of Module 5 (pp. 14-25, and multiple scattered examples elsewhere in the module) the page number stamp in the lower right corner overprinted part of the material being presented; however it did not appear to obscure any information critical to this review. In Module 5, the copies of the foreign language labeling (pp. 22 – 25) could not be printed in full despite attempts with various print option settings.

3.2 Compliance with Good Clinical Practices

N/A – The sponsor did not conduct any clinical studies.

3.3 Financial Disclosures

N/A – No clinical trials were included in the application, and no financial disclosures were provided.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviews have not yet been finalized. There are currently no outstanding issues regarding the bag design and materials, the CPD, stability, or the results of performance studies. However, there remain outstanding requests for information regarding sterility and regarding certain observations from the manufacturing site inspections.

4.2 Clinical Microbiology

One notable feature of this blood collection system is that its intended use includes use within the sterile field of a caesarean section. Therefore, the external surfaces of the collection system need to be sterile so that it can be introduced into a sterile field. The product is packaged inside an overwrap to maintain the sterility of the external surfaces.

The CMC reviews have not yet been finalized. There are outstanding requests for information regarding sterility.

4.3 Preclinical Pharmacology/Toxicology

The Nonclinical section of the NDA provided results of biocompatibility testing of the collection bag components to determine effects of extractables and leachables. Testing involved in vivo animal studies and in vitro studies using human blood cells. The Applicant concluded that there were no biocompatibility problems with the product.

In response to the FDA's request, the Applicant provided additional information during the review cycle to address the toxicity of (b) (4) and the extent of phthalate leachables.

The Pharmacology/Toxicology review was finalized on 2/20/15. The Reviewer concluded that the sponsor had provided acceptable evaluations of biocompatibility, ink migration, and the extractables and leachables profile.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

CPD has been used for decades in blood banking for cell collection, transport, and preservation. There are well established scientific principles underlying the use of each component (Henry, 1991, p. 938).

Citrate acts as an anticoagulant for the collected UCB unit. The citrate anions bind calcium, which is required for several steps in the coagulation cascade. No therapeutic direct pharmacologic effect is postulated for the role of citrate in the UCB recipient.

Phosphate is included in the CPD solution to help sustain cellular adenosine triphosphate production, which increases cell viability. Use of phosphate buffer also allows for a less acidic pH, which better maintains 2,3-diphosphoglycerate in red cells.

No therapeutic direct pharmacologic effect is postulated for the role of phosphate in the UCB recipient.

Dextrose (D-glucose) serves as a source of energy to help sustain the cells in the collected UCB unit. No therapeutic direct pharmacologic effect is postulated for the role of dextrose in the UCB recipient.

4.4.2 Pharmacodynamics

N/A – No pharmacodynamic information was provided in the submission.

4.4.3 Pharmacokinetics

No studies relating to the pharmacokinetics (PK) of the drugs in the UCB recipient were provided in the submission. The Applicant did not address PK in the UCB recipient through use of publications or other kinds of analyses.

Reviewer's Pharmacokinetic Analyses

Without any specific information about how the collected UCB would be processed and used, the expected exposure of the UCB recipient to citrate, phosphate, and dextrose from this product cannot be quantified accurately. Although the Applicant supplied references describing the use of UCB units for simple blood transfusion purposes (Eicher, Schaible, et al., 2000; Hassall, Bedu-Addo, et al., 2003), the expected use of UCB units in the United States is as a source of HPCs; the possibility seems remote that there would be any significant use of non-cryopreserved and unprocessed units simply for blood transfusion purposes. As a source for HPCs, units would be stored after undergoing cryopreservation. UCB units are typically volume reduced before cryopreservation, although the currently approved HPC, Cord Blood, products differ in the amount of plasma removed after UCB collection. UCB units also may be washed after thawing, which would further reduce the amount of the original CPD that reaches the UCB recipient. It is possible, at least in some situations, that the UCB recipient might be exposed to only negligible amounts of citrate, phosphate, or dextrose.

Despite the fact that the exposure of the UCB recipient to the drug components of the product depend on a number of unknowns, it is still somewhat informative to perform a “worst case” exposure analysis. Results of these calculations are referenced in Section 7.7 (Additional Submissions/Safety Issues). The worst case assumptions are these:

- The patient receives the entire amount of the drugs present in the configuration with the greater volume of CPD (MSC1207DD, with 35 mL CPD).
- The drugs are all administered intravenously instantaneously, so that elevations in concentrations are calculated without allowance for redistribution or metabolism.

- The drugs are initially all confined to the blood plasma compartment.

It is also assumed that the adult plasma volume is 3 L. In light of the differing molecular weights of the various salts and hydrates, molar concentrations, rather than concentrations by weight, are used in the following calculations.

Dextrose

The normal adult plasma concentration of dextrose is 3.9 to 6.1 mmol/L; peak concentrations at 30 minutes after an oral glucose tolerance test (GTT) dose are 1.7 to 3.3 mmol/L above the fasting concentration, and at 5 minutes after an IV glucose tolerance test, the upper limit of normal is 13.9 mmol/L (McPherson and Pincus, 2011, p. 1494).

If the entire 4.48 mmol of dextrose in 35 mL of CPD is added to 3 L plasma, the concentration would increase by 1.5 mmol/L. This is within the range of the peak effect of an oral GTT and well below the peak for an IV GTT; this would be true even if two units were infused.

Phosphate

The normal adult plasma concentration of phosphate (inorganic phosphorus) is 0.74 to 1.52 mmol/L (McPherson and Pincus, 2011, p. 1496).

If the entire (b) (4) mmol of phosphate in 35 mL of CPD is added to 3 L plasma, the concentration would increase by 0.19 mmol/L. This change is about one fourth of the width of the normal range. Infusion of two units would result in an increase of about half the width of the normal range and would raise phosphate concentrations to at most 25% above the upper limit of normal.

Citrate

The normal adult plasma concentration of citrate is 88 to 156 μ mol/L (McPherson and Pincus, 2011, p. 1493).

If the entire 3.69 mmol of total citrate in 35 mL of CPD is added to 3 L plasma, the concentration would increase by 1.23 mmol/L = 1,230 μ mol/L. This change would result in concentrations about 8-fold higher than the upper limit of normal. Use of two units would result in concentrations about 16-fold higher than normal.

The above calculations are for adults. For children, the concentration change calculations would depend on body weight. For example, in a 10 kg child, who would have a plasma volume of approximately 0.5 L, the analogous elevations would be about 6-fold higher than those calculated above. It should be noted that normal dextrose concentrations are slightly lower in children compared to adults and normal phosphate concentrations are about 50 to 70% higher in children.

5 Sources of Clinical Data

The submission was represented to be a 505(b)(1) application. However, the submission did not provide any original clinical investigations conducted by the Applicant or for which the Applicant had right of reference.

5.1 Tables of Studies/Clinical Trials

N/A – No clinical studies were conducted for this NDA.

In the clinical modules, the Applicant provided a literature summary of 16 references, citing 15 journal publications and 1 company test report. The bulk of the cited material involved in vitro studies. Only two of the references provided any information on clinical outcomes in patients who had received UCB. Neither of these involved a clinical trial, and the extent of clinical data was severely limited. These two publications are described in Section 9.1 (Literature Review/References).

5.2 Review Strategy

The sponsor provided no clinical studies to evaluate efficacy or safety, so there were no efficacy studies to review. The sponsor did not comply with the presubmission request to review the known safety of the drug constituents citrate, phosphate, and dextrose, so a literature review was conducted by this Reviewer.

5.3 Discussion of Individual Studies/Clinical Trials

N/A – The submission did not include any clinical studies.

6 Review of Efficacy

Efficacy Summary

The proposed indication statement for this product (see following section) does not make a claim for a clinical benefit. Specifically, the application does not propose an indication for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or for a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition. Therefore there is no explicit clinical efficacy claim to assess. Further, the application did not include any clinical investigations to evaluate a clinical benefit for UCB recipients.

Because no adequate and well controlled clinical trials were included in the application, this application did not provide substantial evidence of efficacy for any clinical benefit.

6.1 Indication

The proposed indication is (quoted from proposed labeling in Module 1, Attachment 1.4-1, p. 31):

For collection of 40 to 250 ml of umbilical cord blood with MSC1207DD and 40 ml to 200 ml with MSC1208DD from either vaginal birth or within the sterile field of a caesarean section. A minimum collection volume for cord blood has not been established. Collections below 40 ml should be tested for acceptable quality parameters as per facility SOPs.

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

Please refer to Facility SOPs for appropriate instructions.

No clinical effect on UCB recipients is claimed or implied. There were no adequate and well controlled studies that address clinical benefit. Consequently, subsections 6.1.1 through 6.1.9 are not applicable, and those subsections are omitted from this review.

6.1.10 Additional Efficacy Issues/Analyses

This product is a combination drug product composed of three active ingredients: citrate (as two salts), phosphate, and dextrose. There are established scientific bases for the contribution of each of these components in the collection and storage of blood products.

However, The Applicant has made no claim regarding the clinical benefit of the combination product for the UCB recipient and has provided no information regarding the contribution of each drug to a clinical benefit for the UCB recipient. Consequently, the application had not met the condition under 21 CFR 300.50 of showing that "... each component makes a contribution to the claimed effects and the dosage of each component ... is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

7 Review of Safety

Safety Summary

The application did not include any clinical studies conducted by the Applicant, and no clinical safety datasets or other analyses were provided by the Applicant. Thus, there are essentially no clinical study safety data to permit a substantial safety review. Sections 7.1 through 7.6 and the associated subsections are not applicable and are omitted from this review.

The Applicant did provide literature references, two of which included some results of clinical outcomes after administration of UCB. However, safety data from those publications were meager and not amenable to any systematic or comprehensive analysis. They are described in Section 9.1 (Literature Review/References).

7.7 Additional Submissions / Safety Issues

The submission did not include any safety assessment for the UCB recipient of the individual components of citrate, phosphate, or dextrose.

The Applicant explicitly addressed safety issues in two sections of Module 5 of the NDA: NDA Section 5.2 – Summary or Safety Information, and NDA Section 5.3 – Benefits and Risks.

Section 5.2 of the NDA provided the recent postmarketing marketing data for related products, which is described below in Section 8 of this review. The Applicant reported there were more than (b) (4) units marketed in the prior 3 years. There was no information regarding reports of adverse events in UCB recipients.

The Benefit and Risks analyses in Section 5.3 of the NDA stated “There are no risks to mother or baby during the cord blood collection process.” The section also referred to the risk analysis evaluation in Appendix F (Module 5, pp. 49 – 55). That consisted of a device-type risk analysis grid that addressed potential hazards and risk control measures having to do primarily with mechanics, handling, and contamination. There was no presentation or discussion of actual clinical experience regarding adverse events in UCB recipients.

Even by the “worst case” analysis performed by the Reviewer in Section 4.4.3 (Pharmacokinetics), there is some reasonable assurance that the dextrose component and, at least for adults, the phosphate component do not present a significant safety issue for the UCB recipient, even if two units are used. However, the worst case assumptions are unrealistically extreme, in that they ignore redistribution and metabolism and assume a much more rapid administration than would ever be used in

practice. In typical usage, a UCB unit of 100 mL would be infused over the course of about an hour, and any subsequent unit would not be given until all signs and symptoms of an infusion reaction from the previous unit had resolved (e.g., cf. HEMACORD labeling). Therefore, the worst case analysis for citrate must be regarded as uninformative.

More relevant information about the potential risk due to blood collection solutions can be found in the literature regarding the adverse effects of massive blood transfusions. Toxic effects, if any, due to collection solutions have only been described as an effect of the citrate component (Sihler and Napolitano, 2010; British Society for Haematology, 1988). The toxic effects of citrate from blood transfusions is considered to be mediated through its role in producing hypocalcemia, which can have cardiac effects of QTc prolongation and circulatory depression, as well as neuromuscular excitatory effects, but the citrate does not have a clinically evident effect on blood coagulation (British Society of Haematology, 1988; Ludbrook and Wynn, 1958; Sihler and Napolitano, 2010). Citrate is cleared relatively rapidly in a patient with normal liver function, so the approximately 3 g of citrate in a typical unit of packed RBCs can be metabolized in about 5 minutes (British Society for Haematology, 1988), although clearance may be about half as rapid for cirrhotic patients (Kramer, Bauer, et al., 2003). Infusion of blood units at a rate slower than 1 unit every 5 minutes would be unlikely to cause a dangerous elevation of plasma citrate (Bunker, Bendixen, et al., 1962; Ludbrook and Wynn, 1958). Given that the proposed product has about half of the CPD typically used for collecting a unit of whole blood, and that the resulting UCB unit would normally be infused over about an hour, it appears that the citrate component of the product does not present a significant risk.

Reviewer's Comment:

The Reviewer's analysis and discussion immediately above provides some assurance that the drug exposures due to this product will not present a significant risk to UCB recipients, at least when the product is used as anticipated to produce HPC, Cord Blood, products. However, for an NDA application, the Applicant should be expected to provide a more refined assessment of the possible drug exposures and a more complete review of the literature or other sources of clinical data to evaluate the risks and to provide more quantitative data regarding the expected frequency of adverse drug reactions.

8 Postmarket Experience

Neither of the proposed configurations (MSC1207DD and MSC1208DD) has been marketed in the United States or elsewhere.

However, the Applicant stated that the proposed configuration MSC1208DD (containing a total of 29 mL CPD) is similar to marketed Macopharma product MSC1208DU. The

Applicant stated that there have been no adverse event reports for MSC1208DU, but no worldwide sales data for that model number were provided.

The Applicant stated that Macopharma UCB collection systems “with slight modifications” are CE certified and have been marketed by Macopharma since 1996. The Applicant provided a listing of the similar Macopharma products (which have various product codes and slightly differing specifications) used in one or more of the following 19 countries: Australia, Austria, Belgium, Bulgaria, Canada, Croatia, France, Germany, Greece, Italy, New Zealand, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, The Netherlands, The U.K.

The Applicant provided the following sales data for the 3 calendar years preceding the application:

Table 5: Macopharma UCB Collection Kit Sales 2011 – 2013

Product Code	2011	2012	2013	Cumulative
MSC1201DU	(b) (4)	(b) (4)	(b) (4)	(b) (4)
MSC1202PU	(b) (4)	(b) (4)	(b) (4)	(b) (4)
MSC1205DU	(b) (4)	(b) (4)	(b) (4)	(b) (4)
MSC1206DU	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total	(b) (4)	(b) (4)	(b) (4)	(b) (4)

The Applicant reported that, in the period 2011 through 2013, there were 7 complaints regarding product defects, but no complaints regarding adverse events for the donor (baby) or the donor’s mother. The Applicant’s assessment of worldwide postmarketing use of any of these products did not include any statement about clinical safety data pertaining to UCB recipients.

Reviewer’s Comments:

- The lack of AE reports regarding UCB recipients is not surprising, as it seems highly unlikely that such AE reports would find their way back to an equipment manufacturer who is not the provider of the final UCB unit.*
- Given the long marketing history of the Applicant’s similar products, a report of sales numbers and complaints covering only 3 years appears to be substantially incomplete. However, in view of the preceding comment, it is unlikely that a more complete postmarketing assessment would provide any additional information about the clinical safety for UCB recipients.*

9 Appendices

9.1 Literature Review/References

Applicant's Literature Review

The NDA is represented as being a 505(b)(1) application, but no original clinical investigations were provided. The Applicant listed 16 references in the Clinical Section (Module 5). No information was provided about right of reference to the clinical data for any of the journal articles referenced.

The majority of the 16 references describe ex vivo evaluations of cell counts or cell function under various collection or storage conditions, with no clinical data on administration of UCB to patients. Only two of the references were publications that provided information regarding UCB administration and clinical outcomes, but the clinical data were fairly meager. The clinical data from those articles are summarized below:

Reference # 7

Eicher, H, T Schaible, E Richter, et al., 2000, Cord blood as a source of autologous RBCs for transfusion to preterm infants, Transfusion, 40:1111-1117.

This investigation was conducted at a single site in Germany. Rather than collecting UCB for HPCs to use in hematopoietic reconstitution, the UCB was collected as a potential source of autologous RBCs for transfusion. UCB was collected from 47 infants. The collection bags were identified as Macopharma 1206DC systems, which contain a total of 29 mL CPD. UCB units were volume reduced to decrease the amount of CPD.

Only 21 of the infants subsequently received transfusions during the hospital stay. These 21 received a total of 4 autologous RBC transfusions and 62 other transfusions using standard (not UCB) allogeneic RBCs. No difference was seen between autologous and allogeneic transfusions in the change in hemoglobin or hematocrit, either in absolute terms or as a ratio of the transfused dosage. No adverse effects of autologous RBCs were reported.

Reviewer's Comments:

The use of the collection bags reported in this article (for RBC transfusion) differs from the predominant expected use of the NDA product for collecting HPC, Cord Blood, for (b) (4). The changes in hemoglobin and hematocrit were undoubtedly due to the collected cells, rather than any pharmacologic activity of the chemical components of the CPD, so this investigation is not informative regarding any clinical efficacy of the drugs.

The clinical safety experience is very limited in terms of the number of subjects and the detail of clinical data presented.

Reference # 12

Smyth, J, S Armitage, D McDonald, et al., 2007, Directed Sibling Cord Blood Banking for Transplantation: The 10-Year Experience in the National Blood Service in England, Stem Cells, 25:2087-2093.

This report is based on 10 years of experience of the National Blood Service for England and North Wales. In that period (the specific dates are not stated), there were 268 directed UCB collections. UCB was collected using Macopharma collection kits, but model numbers are not identified. The units were cryopreserved with DMSO, but they were not volume reduced. There were 13 units issued for transplantation: 7 were for thalassemia major, 3 were for ALL, and 3 were for other nonmalignant disorders. HLA match was 10/10 in all cases. Recipient ages ranged from 2 to 10.6 years with a median of 5.8 years. Weights ranged from 8 to 31 kg with a median of 19 kg.

Outcome data were collected using a form and telephone follow-up. Of the 12 cases where engraftment data were reported, all engrafted, and the median time to neutrophil engraftment was 18 days. One thalassemia patient had disease recurrence after 4 months. There were 2 deaths; both were due to recurrence of ALL and occurred at 2.5 and 4.4 years after transplantation. No graft-versus-host disease was reported, but it did not appear that reporting was complete. Detailed adverse event data were not provided in the report.

Reviewer's Comments:

The use of the collected UCB for hematopoietic reconstitution is the same as the principal use anticipated for the current NDA product. The efficacy of the transplantation was undoubtedly due to the collected cells, rather than any direct pharmacologic activity of the chemical components of the CPD in the UCB recipient. Thus, this investigation is also not informative as to any clinical efficacy of the drugs.

The clinical safety experience includes more patients than Reference #7 and is more relevant to the expected use of the NDA product. Because the UCB units were not volume reduced (thus not removing CPD) and the median patient weight was only 19 kg, the experience provides some reassurance about the safety of CPD, and for the pediatric population in particular. However, the safety experience is still limited in terms of the number of subjects and the detail of clinical data presented.

The investigations reported in the two clinical references do not contribute to substantial evidence of efficacy for a clinical effect of any of the drug components of the product. The safety experience did not identify any adverse reactions to the drugs, but the data are limited.

Reviewer's Literature Review

Because this Reviewer's PK analysis in Section 4.4.3 (Pharmacokinetics) suggested that citrate was the component that might have some likelihood of producing plasma concentration much higher than the normal physiologic range in the UCB recipient, a limited search was conducted to identify information pertaining to citrate kinetics and the potential for citrate toxicity. Five articles of particular relevance were identified (British Society for Haematology, 1988; Bunker, Bendixen, et al., 1962; Kramer, Bauer, et al., 2003; Ludbrook and Wynn, 1958; Sihler and Napolitano, 2010). These articles are cited in the safety discussion in Review Section 7.7 (Additional Submissions/Safety Issues).

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9.2 Labeling Recommendations

The proposed labeling does not comply with the Physician Labeling Rule (PLR) requirements as set out in 21 CFR 201.56 and 21 CFR 201.57. Several required elements are missing. The deficiencies are not simply matters that can be addressed by reformatting and including omitted information, because some of the omissions are due to the lack of information in the application that would be needed in order to be able to write PLR-compliant labeling.

Specific deficiencies in the labeling are the following:

1. The labeling has no numbered sections and does not comply with the general organization and formatting structure required by PLR.
2. There is no Highlights section at the beginning of the labeling
3. The Indication and Usage section does not state an indication that is for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or for a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition. Given the nature of the product and the role of the chemicals in the product, it is difficult to see how an appropriate NDA-type Indication and Usage statement could be devised.
4. There is no Dosage and Administration section. The application does not provide the information needed for such a section.
5. There is no section on Dosage Forms and Strengths. The application does not provide the information needed for such a section.
6. The information in the Warnings and Precautions section has to do only with issues relating to collection procedures, but does not address safety consideration for a UCB recipient. Of note HPC, Cord Blood, products have a boxed warning and several other warnings pertaining to risks to UCB recipients, although those risks are related to substances in HPC, Cord Blood, that are not the chemicals that are the subject of the current NDA.
7. There is no Adverse Reactions section. The application does not provide the information needed for such a section.
8. No pregnancy category is proposed, and no information addressing the pregnancy category is provided in the application.

9. There is no Pediatric use section that either describes pediatric use or states that pediatric safety and effectiveness have not been established.
10. There is no Description section providing the ingredient information (although a brief description of chemical composition is provided on the container label).

Creation of PLR-compliant labeling is complicated by the following issues:

1. This product is not administered directly to a patient.
2. The amounts of the drug substances that would be received by a patient who receives a cryopreserved UCB unit manufactured using this product depend on unknown factors related to subsequent processing; it is possible that only trace amounts of the drugs would be received in some cases.
3. There is no proposed or intended direct therapeutic pharmacologic effect of the drug components in the product for the UCB recipient.
4. The application does not provide all the information needed to support writing PLR-compliant labeling.

Therefore, this Reviewer is unable to provide recommendations for how to bring the clinical sections of the labeling into compliance with PLR requirements.

No proprietary name was proposed for the product, so there was no trade name review.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held to discuss this application. There was no consultation with Advisory Committee members or other special government employees during the course of the clinical review.

There were no presubmission contacts with clinical consultants or patient representatives.