M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

SUMMARY BASIS FOR REGULATORY ACTION
NDA 125552

DATE December 9, 2016

FROM: **Mercy Quagraine, Ph.D., chair of the review committee**

PRODUCT: Sterile Cord Blood Collection kit containing anticoagulant solution of Citrate Phosphate Dextrose Solution (CPD), USP

APPLICANT NAME: MacoProductions S.A.S.

DATE of SUBMISSION: April 30, 2014 (original submission); June 30, 2016 (response to FDA Complete Response letter dated March 30, 2015)

PROPRIETARY NAME: None

INDICATION FOR USE: The bags are indicated for the collection of 40 – 250 ml of umbilical cord blood from either vaginal birth or within the sterile field of a cesarean section.

RECOMMENDATION: Approval

SIGNATORY AUTHORITIES ACTION:

OFFICES SIGNATORY AUTHORITY:

Wilson W. Bryan, Director, Office of Tissues and Advanced Therapies

□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

PRODUCT DESCRIPTION AND DOSAGE FORM:

The system consists of two configurations of Cord Blood Sterile Collection Bags containing Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD); MSC1207DD and MSC1208DD configurations. The product is sterile with a non-pyrogenic fluid pathway.

MSC1207DD Cord Blood Sterile Collection Bag consists 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 consists 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 final container-closure system is terminally sterilized by (b) (4)-steam (b) (4) process.

MANUFACTURING AND CONTROLS:

Drug Substance:

The drug substance is an anticoagulant solution of CPD which is formulated in-house at MacoProductions Polonia SP Z.o.o. in Worclaw, POLAND from raw materials supplied by qualified vendors. The raw materials are manufactured according to the standard ISO 9001:2008 and NF EN ISO 13485:2012 and following the US (b) (4) (USP (b) (4)) methods. The formulation for the drug substance is found in the table below.

Table 2.3.S.1 – 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], (b) (4)

(b) (4)

(Alternate title: Table 2.3.S.1-1 specifies the amounts of raw materials in one liter of CPD)

All lots of the raw materials used in CPD solution are received from qualified suppliers with a Certificate of Analysis, confirming that the materials conform to the required specifications where applicable. In addition to this Certificate of Analysis, MacoProductions S.A.S. France performs all testing on each material. (b) (4) are tested on each lot of incoming raw material. The materials are released by MacoProductions S.A.S. France, and then transported to MacoProductions Polonia SP Z.o.o. Poland. Manufacture of the CPD solutions is conducted under controlled conditions designed to manufacture a product with a low or non-existent bioburden; however, sterilization is not performed on the (b) (4) of manufacturing. MacoProductions Polonia SP Z.o.o. performs all of the tests recommended by the (b) (4) on the CPD solution, to confirm the conformity to the relevant monograph, and performs internal test following SOP. The anticoagulant solution is analyzed to ensure that specifications are met. The solution is monitored by taking samples from (b) (4).
The CPD final product specifications are presented in the following table.

Table 2.3.S.4-2 Analytical Controls for CPD Performed on Final Product

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

(Alternate Title: Table 2.3.S.4-2 shows the test parameters and their limits of acceptance)

Container Closure System:

All the various components of the sterile cord blood collection bags were previously approved under cross-referenced NDA, BN 040083; (b) (4) only the injection site may come into contact with blood. Biocompatibility testing has been conducted. The sterile cord blood collection bags will be manufactured at the MacoProductions facility in Poland: MacoProductions Polonia SP Z.o.o. ,UI Szwajcarska 22, 54-405 Wroclaw, Poland.

The collection bag ((b) (4) is manufactured by MacoProductions Polonia SP Z.o.o., Poland, while the Rinsing bag ((b) (4) is manufactured by MacoProductions (b) (4) . The assembling of needles is performed in the MacoProduction Poland facility. The subassemblies, (b) (4) , can be manufactured in MacoProduction 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.

The plastic component of the container (bag) and tubing is (b) (4) The (b) (4) contains the plasticizer di (2-ethylhexyl) phthalate (DEHP), one of the most widely used plasticizers in containers for medicinal and infusion products, particularly blood bags. DEHP is a widely used plasticizer in (b) (4) products for medical applications for the past 25 years. It has been extensively studied and characterized for its potential toxicity, pharmacokinetics, and metabolism as well as interaction with blood and blood products. The bags conform to monograph of the current (b) (4) and to the standard ISO 3826-1: “Plastics collapsible containers for human blood and blood components Part 1: Conventional containers” Section 6.3 - Chemical requirements. A visual inspection of the overwraps of the materials is conducted by MacoProductions Polonia SP Z.o.o. after receipt.

Stability Studies:

Evaluation of the submitted stability data for the CPD solution stored under the ICH recommended long-term and accelerated conditions indicated that the CPD solution is stable for 12 months stored at ambient temperature and humidity. As per ICH Q1E guidelines, the stability data was extrapolated to

support 24 months of shelf life. The proposed shelf life of 24 months stored at 25°C ambient humidity is supported.

A stability study was performed on 6 independent batches (3 (b) (4) 3 (b) (4)) of the reference MSC1207DD configuration. Stability data for 12 months of long-term and (b) (months of accelerated conditions showed that the drug product conformed to the specification throughout the testing period.

A stability study was performed on three independent batches of the reference (b) (4) (MSC1208DD). Stability data for 12 months of long-term and (b) months of accelerated conditions showed that the drug product conformed to the specification throughout the testing period.

Methods Validation:

All manufacturing steps, including analytical procedures for drug substances, physical inspections, assurance of sterility, freedom from pyrogens, and holds the product in quarantine until all requirements for release have been met and/or validated.

Labeling:

The product labeling (i.e., prescribing information) and the product package and container labels were reviewed, commented, and/or revised by the appropriate discipline reviewers before the Advertising and Promotional Labeling Branch (APLB) conducted its review from a promotional and comprehension perspective. Changes to container and package labels were required in order to be in full compliance with regulations. After discussions with the applicant, the container and package labels were found to be acceptable.

Establishment Inspections:

The sterile cord blood collection kits are manufactured at MacoProductions Polonia SP Z.o.o. (Wroclaw Poland). A pre-licensure inspection of the facility was conducted by the FDA on November 13- 20, 2014. This inspection disclosed numerous objectionable conditions that were listed on a Turbo Form FDA-483 and issued to the firm. The firm submitted an initial response to the observations on December 12, 2014 in which they indicated milestones to complete corrective actions, and a final and complete response on June 30, 2016. The corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

Environmental Assessment Report:

MacoPharma requested categorical exclusion from environmental assessment for the sterile cord blood collection kits containing anticoagulant Citrate Phosphate Dextrose Solution (CPD) pursuant to 21 CFR 25.31. The FDA concluded that the request for categorical exclusion is justified as the product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

In-VITRO STUDIES:

Summary of studies using anticoagulant:

The applicant cited 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 NDA. The study report from the University of Dusseldorf cord blood bank also provided (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). An amendment to the NDA submitted on August 4, 2014 affirmed that the cord blood collection bags used in the cited studies were made of the same materials as the kits that are the subject of this NDA. The amendment further stated that 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, and all configurations were manufactured with the same components or materials and the same ingredients in CPD as those described in this NDA.

These studies supported the proposed 22°C ± 4°C holding/storage condition for the collected cord blood, the established 48 hour time to processing, and (b) (4) performance of the (b) (4) final cord blood product.

The three study citations are listed 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*

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*

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*)

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Biocompatibility Testing:

Biocompatibility testing was performed on the injection site hub, (b) (4) patient-contacting component of the Cord Blood Collection Bags (b) (4) . Testing included cytotoxicity, intradermal and intracutaneous reactivity, and acute systemic toxicity (intravenous and intraperitoneal injection). The results showed the materials in the device component to be safe for the intended use. An ink migration assessment study of the (b) (4) ink used to label the collection bags did not reveal any findings of concern.

Leachables detected in the collection bag were at levels below those found to cause toxicity.

CLINICAL STUDIES:

There were no clinical studies in this application. The recommendation for approval of the NDA stems from the regulatory precedent from numerous NDAs and ANDAs from the Office of Blood Research and Review in CBER for this and similar products, and from the clinical review of the safety of the components of the CPD solution and its anticoagulant and (b) (4) effects. Based on the available data, Sterile Cord Blood Collection kit containing anticoagulant solution of Citrate Phosphate Dextrose Solution (CPD), USP is safe and effective for its intended purpose.

RECOMMENDED REGULATORY ACTION:

The review team recommends the approval of Sterile Cord Blood Collection kit containing anticoagulant solution of Citrate Phosphate Dextrose Solution (CPD), USP as indicated for use in the collection of 40 – 250 ml of umbilical cord blood from either vaginal birth or within the sterile field of a cesarean section.