



November 05, 2014

NDA 125552

INFORMATION REQUEST

MacoProductions S.A.S.
Attention: Ms. Heather Pratt
3675 Crestwood Parkway, Suite 260
Duluth, GA 30096

Dear Ms. Pratt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD).

We are reviewing the product, nonclinical and facilities including the sterility test protocol sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

PRODUCT INFORMATION

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 made of the same material and function the same as MSC1207DD and MSC1208DD. 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.

- 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.

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.
- 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 hub is a blood-contacting component. However, we believe that the (b) (4) may be a blood-contacting component because the CPD in the rinsing/satellite bag can be added to or stripped into the collection bag. Please clarify.
- c. Please submit separate ‘Indications for Use’ directions for each configuration of the MacoProductions CB Sterile Collection Bags (MSC1207DD and MSC1208DD).
- 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.
- 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.

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.

NONCLINICAL INFORMATION

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 a leachable. Please submit detailed toxicological information for (b) (4), including a risk assessment for patient exposure to this compound under worst-case conditions of use.
 - b. The proposed cord blood collection bag (CCB) is composed of (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.

STERILITY TEST

5. Please provide the Bacteriostasis and Fungistasis Qualification Report, for cord blood sterile collection bags with anticoagulant Citrate Phosphate Dextrose (CPD). Please include test method, type of media, conformance lot numbers, incubation conditions and duration, to show suitability of the matrix for the sterility assay.

If you have any questions, please contact Ramani Sista, Regulatory Project Manager, at 240 402 8354.

Sincerely,

Patrick S. Riggins, Ph.D.
Branch Chief
Regulatory Management Staff
Office of Cellular, Tissue & Gene Therapies
Center for Biologics Evaluation and Research