



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

**NDA 125552**  
**Review of Re-Submission**

**Date:** October 5, 2016

**Application:** NDA **Status:** Approval Recommended

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

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

**Applicant:** MacoPharma, Tourcoing France

**Date Received:** June 30, 2016

**Submission Type:** Resubmission in response to April 25, 2015 CR letter Comments. 125552/10

**CELL THERAPIES BRANCH**  
**DIVISION OF CELLULAR AND GENE THERAPIES**  
**OFFICE OF TISSUES AND ADVANCED THERAPIES**

<b>Reviewed by:</b>	<b>Signature</b>
<b>Mercy Quagraine, Ph.D.</b> <b>Review Committee Chairperson</b>	
<b>Concurred By:</b>	
<b>Steven Oh, Ph.D.</b> <b>Branch Chief</b>	

## Review of June 2016 Resubmission

Reviewer	Section Reviewed	Recommendation
Xing Wang, Ph.D. (CDER consult)	CR letter comment 1	Approval recommended
Simleen Kaur, Ph.D. (consult DBSQC/OCBQ)	CR letter comment 2	Approval recommended
Ping He, M.D. (DHT consult)	CR letter comment 5	Approval recommended
Loan Nguyen, Pharm D (APLB)	Labeling: CR letter comments 3 and 4	Approval recommended
Anne Pilaro, Ph.D. (Informal OBRR consult- Pharm/Tox)	CR letter comment 1: Expert opinion	Approval recommended
Mercy Quagraine, Ph.D. (Review Committee Chairperson)	Overall Summary	Approval Recommended

*Note: see individual reviews*

### **EXECUTIVE SUMMARY**

This resubmission contains response to a request for information in a complete response (CR) letter to the applicant on April 25, 2015, after review of the original NDA submission. The sponsor satisfactorily addressed all of the outstanding issues: impurity (b) (4) on CPD (b) (4) are glucose degradation products and pose minimum risk, validation of sterility testing of (b) (4) is adequate; all 483 citations and labeling information requests have been adequately addressed.

Stability data submitted in the original submission supports a 2 year expiry for the product. Regarding sterility testing, parametric release is not approved for product release. Sterility testing will thus be conducted as part of product release. All impurity (b) (4) (both identified and unidentified) in the CPD have established limits which will not be exceeded in a product lot to be released.

There are no more outstanding issues with this NDA.

**Recommendation:** The NDA may be approved. All the information requested in the complete response (CR) letter have been submitted and reviewed and found adequate. All the 483 citations have been adequately addressed and corrective actions implemented.

### **INTRODUCTION**

Macopharma's NDA submitted on April 14, 2014 was not approved due to deficiencies. The applicant was informed in a CR letter on April 25, 2015, in which recommendations to address the deficiencies were communicated to the Macopharma (*Refer to CBER letter: 125552\_CR\_2015330.pdf*). This resubmission (received June 30, 2016) is in response to the CR letter.

## Review of Resubmission

The CR letter comments were as follows:

- 1. Please identify all the impurity (b) (4) on the CPD (b) (4) and establish limits on the amounts that should not be exceeded in the drug CPD. We request that impurity profile assessment and impurity specifications will be a part of your product release criteria.*
- 2. Information on the qualification report for sterility testing of (b) (4) requested on February 9, 2015 is still outstanding.*
- 3. Submit draft labeling that addresses our proposed revisions in the attached comments on labeling. Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.*
- 4. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.*
- 5. During a recent inspection of the MacoProductions Polonia SP Zo.o., the Poland facility (UT. Szwajcarska 22, 54-405 Wroclaw, Poland) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

The reviewer assignments for the responses to the CR letter comments are listed in the table above. All of the Agency comments were adequately addressed and approval was recommended by all the reviewers as indicated in the table. The NDA committee chair has also reviewed the reviewers' memos and agree with their recommendation.

### 1. Complete Response to letter comment #1

#### Summary on Impurities in CPD:

During the pre-licensure inspection, the Macopharma was cited for unidentified/unknown (b) (4) observed on (b) (4) of CPD lots that had been released (CR letter comment 1). The applicant reports that all the impurity (b) (4) (known and unknown) are glucose degradation products that results from heat sterilization of CPD. (b) (4) known glucose

degradation products, (b) (4)

(b) (4) are described. Impurity (b) (4) have not been identified because of their very low levels, but limits have been imposed for product release. The CDER consult reports that the risks associated with the impurities is low. However, he also recommended that an additional Pharm/Tox review be performed to assess the risks; the rationale being that the glucose degradation product/impurities are known to be genotoxic.

#### **Impurity Profile of Macopharma CPD with Established Limits**

(b) (4)

In accordance with the CDER consult recommendation, an informal Pharm/Tox consult review was requested and conducted (see review by Anne Pilaro, PhD (OBRR)). The Pharm/Tox review demonstrated that the margins of the glucose degradation products in Macopharma CPD are reasonably safe and recommended approval of the NDA. A copy of her email memorandum is appended at the end of this summary. A formal memorandum documenting this consult review will also be generated to the NDA.

#### **Informal Pharm/Tox Consult Review Email**

**From:** Pilaro, Anne

**Sent:** Thursday, October 06, 2016 5:13 PM

**To:** Quagraine, Mercy

**Cc:** He, Ping; Sista, Ramani V; Riggins, Patrick; Oh, Steven

**Subject:** RE: Review of NDA 125552 CBER consult

Hi Mercy and Ping –

I am sending you this e-mail as the informal consult from OBRR regarding the presence of the glucose degradation products (b) (4)

(b) (4) in the MacoPharma's citrate phosphate dextrose (CPD) additive solution, contained in their Sterile Collection Bags product #MSC1207DD and #MSC1208DD (NDA #125552). The Sterile Collection Bags containing the CPD are terminally sterilized by steam sterilization, which results in the degradation of the dextrose (glucose) to the impurities mentioned above that were detected in the final Drug Product and container closure system.

The CDER consult reviewer, Dr. Xing Wang from the Center for Drug Evaluation (CDER), Office of Product Quality (OPQ), Office of New Drug Products (ONDP), Division of New Drug Product Integrity (CDER/OPQ/ONDP/DNDPI/NDPBII) initially identified these impurities being present in the final Drug Product at the following levels (Data are excerpted from Dr. Wang's final review):

(b) (4)

If a "worst-case" scenario is envisioned where for the each of the unidentified impurities their concentration in the CPD Drug Product is considered to be at the limit of detection of its specific assay, and (b) (4) of aqueous solution of CPD, then the total level of both the known and unknown impurities is approximately (b) (4). This level of impurities translates to a total patient exposure of (b) (4) per bag if the total, 35 mL maximal 'dose' of CPD used to store the stem cells (27 mL) and rinse the bag (8 mL) during their recovery prior to infusion is infused into the patient. If a patient received stem cells stored in the 21 mL storage bags and rinsed with 8 mL of CPD rinsing solution, their exposure to the total impurities would be (b) (4) per bag. However, both the consult reviewer and the Applicant state that the stored stem cell will be recovered by (b) (4) which will remove the majority of the CPD solution (data not included to quantify the magnitude of removal) and effectively reduce the concentrations of each impurity.

Therefore, in a "worst-case" scenario in which a patient receives the full 35 mL amount of CPD together with their dose of umbilical stem cells, the amount of total impurities will be (b) (4) (b) (4) per bag. (b) (4) is reported in the literature to be genotoxic in in vitro assays, but not in in vivo testing; (b) (4) are reported as potential mutagens (Class 2 compounds, by ICH M7), and the unknown impurities are also treated as potential mutagens. As documented in the CDER consult reviewer's memorandum, the individual levels of each impurity fall within the allowable limits set forth by the ICH M7 guidance of 120 micrograms per day for single, or short-term (i.e., less than 30 days) dosing. However, the total level of all of the glucose degradation products (b) (4) (b) (4) does exceed the acceptable limits set forth in the ICH M7 guidance document for impurities with the potential to damage DNA.

Additional research shows that (b) (4) and other, structurally related but as yet unidentified degradation products are byproducts of heating sugars, including glucose, sucrose, maltose, fructose and starches. These compounds are major components of the food additive caramel coloring, which is Generally Recognized as Safe (GRAS) by the US FDA for use as color additive, and exempt from certification. Although the US FDA has no limit on the human exposure to

caramel coloring, the United Nations Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) has set the Acceptable Daily Intake (ADI) of Class I caramel color as "not specified"; that of Class II as 0–160 mg/kg body weight; and 200 mg/kg body weight for Class III and Class IV caramel colorants. Because the glucose degradation products present in Maco's Drug product resulted from steam sterilization of the CPD solution in the absence of added ammonium or sulfites (Class II, III, and IV caramel colorants), there is no specified ADI (i.e., Class I) for the related glucose degradation products present in Maco's CPD Drug Product. However, if the ADI for Class II caramel colorants is applied to the Maco CPD solution, there is an appropriate safety margin of at least

**ADI** = 160 mg/kg x 70 kg model "average" human = 11200 mg total allowable intake for Class II caramel colorant, per day

**Safety margin** = 112000 mg total ADI / <sup>(b) (4)</sup> mg total impurities per dose = <sup>(b) (4)</sup>

Because the ADI for caramel colorants is calculated after oral exposure and the planned route of exposure for the CPD and stem cells is intravenous, an additional uncertainty factor of 10 is applied to the safety margin, bringing it to <sup>(b) (4)</sup>. A further uncertainty factor of 10 is applied to address potential increased susceptibility of umbilical cord blood stem cells to DNA damage by these impurities. The final safety margin after application of the two uncertainty factors is <sup>(b) (4)</sup>. This margin is appropriate and reasonably safe, considering the conditions of use for the Maco CPD product and that further processing (<sup>(b) (4)</sup>) is expected to remove the majority of the CPD solution from the final stem cell preparation. The recommendation from the nonclinical pharmacology discipline in DHCR is that this NDA may be **approved**.

A formal memorandum documenting this consult review will be provided to the NDA file following supervisory concurrence. Please let me know if you need any additional information

Thanks,

Anne

## 2. Complete Response to letter comments #2, 3, 4, and 5:

Please see individual review memos for detail.