

## How transplant centers deal with the dextran shortage: recommendations for comparing alternatives

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**BACKGROUND:** In the United States, dextran 40 in 0.9% NaCl is the preferred reagent for the thawing and preparation of cord blood units for hematopoietic stem cell transplantation. The recurring nationwide shortage of this reagent could have implications that extend to the avoidance of cord blood for transplantation.

**STUDY DESIGN AND METHODS:** To address the shortage, the National Marrow Donor Program and its Cord Blood Advisory Group sought to identify available alternative reagents or manufacturers. A sample of transplant centers (TCs) were surveyed to determine their process to compare these alternatives. The TCs were then asked to share their comparability protocols for review.

**RESULTS:** The 12 TCs that responded to the survey studied various types of alternative reagents and manufacturers of the standard dextran 40 in 0.9% NaCl. Four TCs submitted their protocols from which a model comparability protocol was created for centers who need assistance.

**CONCLUSION:** Whether comparing dextran 40 in 0.9% NaCl to that of a different manufacturer or a different reagent, the results of the comparability studies submitted by the TCs indicated equivalency. During a shortage, the model comparability study protocol can be used as a reference to establish an alternative to dextran 40 in 0.9% NaCl.

In 1995 Rubinstein and colleagues<sup>1</sup> showed the detrimental effect of retaining the cryoprotectant when thawing cord blood with a nearly 65% decrease in viable white blood cells (WBCs) and 40% decrease in hematopoietic progenitor stem cells. When compared to cord blood progenitor cells and viable WBCs thawed in dextran 40 in NaCl and the cryoprotectant removed, the mean cell count was significantly lower ( $p = 0.0004$ ,  $p < 0.0001$ , respectively). As a result, the use of dextran 40 in NaCl was adopted as a hematopoietic stem cell transplant industry standard for thawing and preparation of cord blood units for infusion.

Over the past 2 years, there has been a recurring, nationwide shortage of dextran 40 in 0.9% NaCl, which is

**ABBREVIATIONS:** IND = investigational new drug; NMDP = National Marrow Donor Program; PBSC(s) = peripheral blood stem cell(s); TC(s) = transplant center(s).

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manufactured by a single-source provider in the United States (Hospira). The potential implications of this shortage range from the need for transplant center (TC) laboratories to validate alternative thawing reagents, change cord blood unit infusion practices, or avoid cord blood as a source of transplantable hematopoietic cells. Furthermore, for cord blood banks holding a biologics license with the Food and Drug Administration (FDA), changes of this nature require a long process with comparability studies, supplements submitted to the agency for approval, and changes made to product labeling and package inserts before implementation.

The National Marrow Donor Program (NMDP)/Be The Match's network cord blood banks under the C.W. Bill Young Cell Transplantation Program initially addressed the shortage by procuring a residual supply of dextran 40 in 0.9% NaCl and making it available for use by the NMDP's network of unrelated donor allogeneic hematopoietic stem cell TCs affected by the shortage. However, the network's residual supply of dextran 40 in 0.9% was depleted before resumption of production by the manufacturer, highlighting the greater importance for TCs to have resources to aid in the selection of an alternative reagent and guidance for performing comparability studies of alternative reagents in compliance with the standards of their accrediting body(ies). The most current versions of the FDA's Guidance for Industry Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications,<sup>2</sup> and accreditation standards specific to the agency governing the TCs, such as the Foundation for the Accreditation of Cellular Therapy<sup>3</sup> and the AABB,<sup>4</sup> should be referred to, when applicable, to develop a comparability study.

Before the recent publication of Reich-Slotky and colleagues<sup>5</sup> regarding a detailed validated alternative to dextran 40 in 0.9% NaCl for the thawing of cord blood, any published guidance on alternative reagents and how to perform a validation did not exist. In this brief report, we describe the actions taken by the NMDP and member unrelated donor cord blood banks of its Cord Blood Advisory Group, to address this challenge and provide general resources to assist TCs in incorporating a dextran 40 in 0.9% NaCl alternative in their laboratory, as a contingency for future shortages or depletions.

## MATERIALS AND METHODS

In anticipation of depleting the supply or reaching the expiration date of the available dextran 40 in 0.9% NaCl in the US market, the NMDP discussed strategies to address solutions to the shortage with the FDA. To assist TCs in assessing comparable reagents to dextran 40 in 0.9% NaCl, members of the NMDP's Cord Blood Advisory Group along with NMDP staff contacted a sample of network TC

laboratory staff. The sample was determined based on the TC having requested a cord blood unit for transplant within the past 6 months. This was to ensure engagement of TCs who are actively transplanting cord blood units and therefore were most affected by the shortage. The goal of the discussions was to determine the extent the TCs had taken to develop a contingency plan to replace dextran 40 in 0.9% NaCl by establishing the following: what the TC had done to replace dextran 40 in 0.9% NaCl or what the TC was planning to do to replace dextran 40 in 0.9% NaCl and what help the TC would like to replace dextran 40 in 0.9% NaCl. If alternative reagents had been compared, the laboratory was requested to complete a questionnaire detailing the process used for their comparability study and to share their study protocol.

The questionnaire was intended to capture the key components of a standard laboratory reagent validation to evaluate reagent comparability. The respondents were instructed to indicate the following:

- Type of product(s) studied, whether peripheral blood stem cells (PBSCs), cord blood, or both and how many of each.
- Variable(s) measured, technique(s) used to measure the variable(s), and acceptance criteria for the variable(s).
- Any significant variations that were observed, especially if specific to any particular reagent and if the procedure was modified based on these observations.
- Whether an alternative thawing reagent was adopted as a result of their study.

The results of the questionnaires from laboratories that had addressed the problem were summarized to share with the broader group. In addition, their shared testing protocols were used to create a model comparability protocol. Both the summary and the model protocol were distributed to the NMDP TC network through a network announcement system and are located at <https://network.bethematchclinical.org/WorkArea/DownloadAsset.aspx?id=13620>. They can serve as a guide to choosing an alternative reagent and performing the comparability study before utilization.

## RESULTS

The NMDP and the FDA agreed that it was imperative to support the TCs in their efforts to establish an alternative to Hospira's dextran 40 in 0.9% NaCl during a shortage. A list of alternatives available at the time of this publication are shown in Table 1.

Thirty-three TCs were identified as having requested a cord blood unit for transplant within the previous 6 months. Of the TCs that had conducted a comparability study, four centers submitted their comparability protocol, and 12 completed and returned the questionnaire detailing the process used for their study.

**TABLE 1. Dextran 40 and non-dextran 40 alternatives**

Alternative option	Manufacturer	Considerations
Dextran powder	Pharmacosmos (Holbaek, Denmark)	Must be reconstituted in a compounding pharmacy. Must be imported under an IND. NMDP's IND has been updated to allow for this, as have some other IND holders. Labeled research use only (RUO).
RUO-labeled dextran 40 in 0.9% NaCl	BioLife Solutions (Bothell, WA)	
Dextran 40 in 0.9% NaCl products licensed outside of the United States	Protide (Lake Zurich, IL) Fresenius (Bad Homburg, Germany)	Must be imported under an IND. NMDP's IND has been updated to allow for this, as have some other IND holders.
Dextran 40 in dextrose	Hospira (Lake Forest, IL)	
Hydroxyethyl starch (HES), 6%	Multiple manufacturers	
PlasmaLyte-A	Hospira (Lake Forest, IL)	
Normal saline (sodium chloride, 0.9%)	Multiple manufacturers	

- Two laboratories performed comparability studies of dextran 40 in 0.9% NaCl from alternative suppliers: cell thawing media (BioLife) and GMP-grade dextran powder (Pharmacosmos) reconstituted in normal saline. The remaining respondents indicated they studied reagents other than dextran 40 in 0.9% NaCl.
- Most studies used cord blood for testing (n = 7), some used cord blood and PBSC products (n = 2), and a few used only PBSCs (n = 3).
- Variables used to measure the comparison between reagents included a variety of the following assays: recovery of total nucleated cells (TNCs), WBCs, and CD34+ cells; viability of TNCs, CD34+ cells, and CD45+ cells; and colony-forming unit (CFU) measurement, sterility checks, and engraftment. TNC and CD34+ recovery and viability were measured by most laboratories (n = 7). All TCs had defined acceptability variables.
- All reagents compared were found to be acceptable alternatives to dextran 40 in 0.9% NaCl for the thawing and washing of cord blood and PBSCs. The results by institution can be found in Table 2.

The four comparability protocols were reviewed and an example protocol was created for use as a guide by TCs. This protocol can be found in its entirety at: <https://network.bethematchclinical.org/WorkArea/DownloadAsset.aspx?id=13620>.

## DISCUSSION

Dilution and/or washing of banked cord blood units using dextran 40 in 0.9% NaCl was adopted to preserve viability and potency of cord blood stem and progenitor cells after thawing.<sup>1</sup> The efforts made by the NMDP and its network cord blood banks and TCs to address the shortage of Hospira's dextran 40 in 0.9% NaCl is indicative of their commitment to keeping open access to cord blood transplantation. Before the guidance provided in this brief

report and on the NMDP/Be The Match website, information on how to address the shortage was limited. This report provides a list of alternative reagents currently available, including research use-only reagents and reagents licensed in another country. Reagents that are not licensed in the United States must be imported under an investigational new drug (IND) application such as the NMDP's Cord Blood IND (<https://network.bethematchclinical.org/cord-blood-banks/policies-and-protocols/cord-blood-protocol-10-cba-/>).

The report also discusses the experiences of multiple TCs comparing alternative reagents and a practical example protocol for performing a comparability study. The authors of this report acknowledge the limitation that three of the survey respondents reported their comparability results based on the use of PBSCs and not cord blood. The collection, processing, storage, and cellular composition of PBSCs is different than cord blood and a comparability study needs to reflect the clinical uses of the reagent. Therefore, it is critical when proving reagent functionality that comparability studies for dextran 40 in 0.9% NaCl should ultimately be performed on the same product type for which the replacement reagent is intended.

The example protocol lists general materials and reagents, a seven-step procedure that allows the use of fresh or frozen cord blood samples, acceptance criteria for results analysis, and important considerations—all of which can be used to create a personalized protocol. The following suggestions are offered for consideration:

- Cord blood aliquots should reflect size, cell concentration, and cellular integrity of clinical-grade units as closely as possible.
- Fresh cord blood products may be pooled to obtain the volume needed to prepare multiple aliquots of sufficient size.
- Due to the biologic nature of cord blood products, aliquots used in the study should be derived from the same original product (pooled or otherwise) to facilitate comparison.

TABLE 2. Survey results

Institution	Dextran alternative(s) compared	Type of HSC product compared	Number of products compared	Variables used to assess comparability	Did the dextran alternative compared meet your requirements for use?
A	Plasmalyte, 5% human serum albumin (HSA)	PBSC	2	Cell counts: TNC, CD34+ viability: TNC, CD34+, CD45+	Yes
B	Dextran 40 in dextrose, HSA	Cord blood	3	Cell counts: TNC Cell viability: CD34+, CD45+ CFU	Yes
C	Dextran prepared from dextran powder, 5% HSA	PBSC	1	Cell counts: TNC, WBC, CD34+ cells	Yes
D	HES, 25% HSA, 0.9% NaCl	Cord blood	2	Cell viability: TNC, CD34+ sterility	Yes
E	BioLife cell thawing medium, HSA	Cord blood	4	Cell counts: TNC Cell viability: CD34+	Yes
F	BioLife cell thawing medium, HSA	PBSC	3	Cell counts: TNC Cell viability: TNC Recovery: TNC	Yes
G	HES, 5% HSA	Cord blood	5	Cell counts: TNC, WBC, CD34+ cells Cell viability: TNC	Yes
H	Dextran 40 in dextrose	PBSC	3	Cell counts: TNC	Yes
I	HES, 5% HSA, dextran 40 in dextrose	Cord blood	33	Cell viability: TNC CFU	Yes
J	HES, 5% HSA	PBSC	2	Cell counts: TNC, WBC, CD34+ cells Cell viability: TNC, CD34+, CD45+	Yes
K	HES, 5% HSA, dextran 40 in dextrose	Cord blood	3	Cell counts: TNC, WBC, CD34+ Cell viability: TNC, CD34+, CD45+ CFU	Yes
L	5% HSA	Cord blood	37	Cell counts: TNC, WBC Cell viability: TNC sterility Engraftment	Yes
M	Multiple alternatives compared: HES and HSA, Plasmalyte and HSA, dextran 40 in dextrose and HSA, normal saline and HSA	Cord blood	10	Cell counts: TNC, CD34+ Cell viability: TNC CFU	Yes
N	BioLife cell thawing medium, HSA	Cord blood	3	Cell counts: TNC, CD34+ Viability: TNC, CD34+	Yes

- Recommended concentration of albumin in final solution, regardless of diluent, is more than 4.2%.
- To evaluate stability, the samples should be removed and tested from a postthaw product at completion of thawing process (T = 0) and subsequent time points, such as T + 30 minutes, T + 1 hour, T + 2 hours, and T + 4 hours.

Dextran 40 in 0.9% NaCl is the preferred reagent for the thawing and preparation of cord blood for transplantation. This reagent was adopted by industry more than two decades ago when Rubinstein and coworkers<sup>1</sup> demonstrated better stability of cord blood cells when thawed with dextran 40 in NaCl. However, it is important that TCs have a contingency plan in the event that a shortage of dextran 40 in 0.9% NaCl recurs. The contingency plan should incorporate a comparability study of an alternative option to the Hospira dextran 40 in 0.9% NaCl reagent. The NMDP and several cord blood banks have collaborated to provide cord blood units at no cost to TCs for use in comparability studies. Whether the study is comparing dextran 40 in 0.9% NaCl from a different supplier, or comparing an alternative reagent, comparability studies have shown acceptable equivalence to Hospira's product. However, the long-term implications on posttransplant

recipient outcomes due to using a reagent other than dextran 40 in 0.9% NaCl remains to be determined.


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**CONFLICT OF INTEREST**

The authors have disclosed no conflicts of interest.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Appendix S1.** Comparability protocol: evaluation of alternative to dextran for preparing cord blood units

**Fig. S1.** Creating duplicate aliquots from fresh cord blood

**Fig. S2.** Creating duplicate aliquots from frozen cord blood