Support Common Sense Regulation of Cord Blood Units:

21st Century Cures Legislation Should Require the FDA To Establish Good Collection, Storage, and Maintenance Practices that Recognize the Unique Nature of Cord Blood Banks

It is common for FDA regulations to be criticized for stifling innovation and adding unnecessary costs. In the case of umbilical cord blood banking, both criticisms are valid. But even more important, current regulations threaten public health by limiting access to cures for serious diseases. The regulations do this by limiting the growth of the national cord blood inventory and causing the needless destruction and disposal of viable tissues. The challenge is licensure requirements that are illogical or based on outdated science.

Our Credentials

The National Marrow Donor Program/Be the Match (NMDP) supports the Committee's efforts to improve the current federal regulatory framework. As the contractor for the C.W. Bill Young Cell Transplantation Program (Program), we understand first-hand the importance of ensuring an efficient and effective pathway for developing innovative treatments. With our partners throughout the world, we have sought to minimize the burdens that can make it difficult for patients to access bone marrow and cord blood transplants. Because of the efforts of physicians, patients and their families, researchers, and the support of the Congress, these cellular transplants have led to the development of treatments and cures for more than 60,000 patients with over 70 blood diseases and genetic disorders. But there is still more that needs to be done.

Cord Blood – It's Not a Drug

Many federal regulations have not kept pace with innovation, which has resulted in a gap between the science of cures and how it is regulated. This is especially true for bone marrow and cord blood transplantation. One of the most difficult barriers to access relates to the recent implementation of licensure requirements for public cord blood banks. The licensure process seeks to regulate cord blood units as if they were drugs, which they are not. Simply put, the current licensing structure does not recognize that the collection, storage, and maintenance of cord blood units is different than the manufacturing process used to create biologics, drugs, and other pharmaceutical products.

This disconnect between the science and the regulations creates a significant burden on cord blood banks, which has led to a slowing of growth of the national cord blood inventory, and has also significantly increased the cost of each unit that

is used in transplantation. Furthermore, it has resulted in many units being needlessly wasted each year either because of disqualification for reasons that do not affect the quality of the cord blood unit or for stability studies which, per the FDA, require use of actual clinical product.

Government Promotion of Cord Blood

Like bone marrow, cord blood can be used to treat and/or cure more than 70 malignant or genetic diseases. In 2005, the Congress formally recognized the importance of collecting, storing, and maintaining an inventory of publicly banked cord blood units by creating the National Cord Blood Inventory (NCBI). The units in the NCBI are listed on the national registry (known as the Be The Match Registry) and available for patients unable to find a matched related or unrelated adult donor.

Through the NCBI, the Health Services and Resources Administration (HRSA) provides grants to cord blood banks that meet certain qualifications to subsidize the costs of collection and storage of public cord blood units. Both the registry and the NCBI are part of the C.W. Bill Young Cell Transplantation Program. It is important to note that each cord blood unit represents a separate and unique 'batch' of product and each cord blood unit is a potential unique match for an individual patient in need. Thus, each banked cord blood unit is a highly valued product.

Currently, licensure is only a requirement for public cord blood banks. Five of the 13 banks in the NCBI have been granted license in the past three years. Others are in the process of applying for their licenses. The licensure regulations are more stringent than those that apply to other blood, hematopoietic stem cell and blood products. The applicable laws and regulation for cord blood licensing, include:

- Public Health Services Act, Section 351, which establishes the licensure requirements for biologic licensing;
- The Current Good Manufacturing Practice for Finished Pharmaceuticals regulations, 21 C.F.R. Pt. 211;
- The Biological Products general regulations, 12 C.F.R. Pt. 600;
- The Biological Licensing regulations, 12 C.F.R. Pt. 601; and
- The General Biologics Product Standard regulations, 21 C.F.R. Pt. 610.

In addition, the FDA issued final guidance in 2009 for "Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications." The FDA updated this guidance most recently in 2014.

Regulation at Cross Purpose with Legislation

While the intent of requiring licensure is to assure the public that the cord blood units are safe and effective, the way it has been implemented has created significant barriers that increase the cost of cord blood units, stifled innovation, and made it more difficult for patients to access these types of cells for transplantation.

The primary problems with the regulation of cord blood banking relate to the FDA's conclusion that collecting and storing cord blood units is the equivalent of manufacturing a pharmaceutical drug. This conclusion imposes a greater burden on banks without meaningfully addressing safety and effectiveness. In essence, the FDA has tried to put a square peg into a round hole and it clearly does not fit. The FDA recognizes that cord blood units do not fit into the precise mold (labeling cord blood units as intermediate products), yet requires compliance anyway. "While there are no specific regulations governing the manufacture of intermediates, drug substances or what are termed active pharmaceutical ingredients, compliance with statutory cGMP (section 501(a)(2)(B) of the FDCA) is required."[1]

The following problems illustrate many that stem from this approach.

1. Barriers to making improvements. The cGMPs establish strict procedural and timing requirements before a manufacturer can implement a change or an improvement to its processes. Cord blood banks are not manufacturing cord blood units the same way that a pharmaceutical company is manufacturing a biologic. Because of the overly strict requirements, the cGMPs inhibit innovation by limiting the ability of the banks to make necessary adjustments in their processes to recognize the unique characterization of each cord blood unit and the rapid innovation in the field. And, applying these requirements to cord blood also makes it extremely difficult to respond to unpredictable shortages of materials/devices used to collect, store, and maintain the cord blood units.

2. Unnecessary, duplicative validation. The cGMPs also require manufacturers to validate their processes *and every product used in the process regardless of whether it was subject to prior validation and clearance*. The FDA has interpreted this requirement for cord blood banks to mean that they must validate products, despite the fact that they have already approved by the FDA for cord blood collection and banking and are purchased from approved vendors by the cord blood bank for processing and testing cord blood units. The interpretation also applies to FDA-approved product for human use, such as Hespan, a volume expander commonly administered to patients in shock, which is also used in preparing cord blood units for storage. This interpretation amounts to a revalidation process that duplicates what the actual manufacturers of the products have already done. The

[1]FDA, "Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications," 19 (2009).

step is unnecessary and adds time and cost without providing any additional benefit or improved safety.

3. Overly burdensome environmental monitoring requirements. Unlike the manufacturing of pharmaceuticals, there are a number of options for assuring safety in the manufacture of a cord blood unit other than strict requirements applied to the entire facility. For instance, the preparation of cord blood is often done in a closed system on the bench-top. The environmental monitoring requirements that apply to pharmaceutical manufacturing are unnecessarily rigorous and simply increase costs without providing benefit.

4. Required creation of an expiration date. The cGMPs also require that all manufactured products to have an expiration date. To meet this requirement, each bank must annually destroy a small part of its inventory to demonstrate that there has been no deterioration in cellular quality even though separate clinical research supporting the use of cord blood units for transplantation has indicated that the cells do not expire. Thus, the requirement for an expiration date is simply not applicable to these cells. Yet, the FDA still requires it.

5. Wasteful stability protocols. The cGMPs also require cord blood banks to use units to comply with stability protocols. These protocols are meant to analyze product potency, integrity, and sterility. Yet, clinical studies have shown that proper storage does not result in a reduction in any of these areas. Applying this requirement means that cord blood units collected using federal dollars are again being taken off the registry and sacrificed for testing to meet this unnecessary requirement. Given that there are still thousands of Americans who cannot find a match today, it does not make sense to take cord blood units, each of which has a unique tissue type, that could provide that match and use them to meet a protocol meant to apply to pharmaceutical manufacturers.

Recommendations

As currently defined, the application of the cGMPs to cord blood units creates unnecessary barriers to accessing this unique and life-saving treatment. Prior to the application of these requirements, this was an area where a strong public-private partnership supported innovation and improved the speed at which this research has been translated to cures that save patients' lives. Removing these barriers is consistent with the intent of "The 21st Century Cures Act." Thus, we encourage you to include language in the next iteration of this legislation to solve this problem.

Specifically, we recommend that a provision be added to Section 5021 in "Subtitle B—21st Century Manufacturing." As currently drafted, this provision would require the Commissioner of the FDA to update the cGMPs. We believe that this Section should be expanded to require the FDA <u>establish good collection, storage, and maintenance practices that apply</u> specifically to cord blood units, which recognize the unique nature of cord blood banks, and remove unnecessary,

duplicative, and costly requirements. Importantly, FDA should be directed to implement this Section in collaboration with the subject matter experts in the hematopoietic stem cell transplantation and cord blood banking communities. We would welcome the opportunity to work with you to develop specific legislative text to authorize this work.