FDA Streamlines Licensure Approach for Certain Cord Blood Products

By Martha A. Wells, MPH, RAC and Ellen F. Lazarus, MD, FCAP

Minimally manipulated, unrelated allogeneic placental/umbilical cord blood is well recognized as a source of hematopoietic stem/progenitor cells for transplantation in patients with life-threatening conditions such as leukemia, bone marrow failure and primary immunodeficiency diseases. Patients in need of cord blood transplantation can find suitably matched products through national and international registries. The US Food and Drug Administration (FDA) has now developed an approach to licensure of these products that will allow cord blood manufacturers to apply for a Biologics License Application (BLA) using a streamlined approach. This licensure approach was developed in conjunction with the risk-based regulations (21 CFR Part 1271) for human cells and tissue. Until recently, FDA exercised enforcement discretion and delayed implementation of BLAs and Investigational New Drug Applications (IND) for these cell products. This article explains this new licensure process as well as what INDs are now required for other cord blood products not qualified for streamlined BLA approval.

Background

In 1997, FDA announced plans for a more comprehensive, risk-based approach for regulation of human cells, tissues and cellular and tissue-based products (HCT/Ps). Under that approach, FDA included hematopoietic stem/progenitor cells, such as those derived from peripheral or cord blood, in the HCT/Ps category. One of the goals of FDA’s regulatory framework was to ensure demonstration of clinical safety and effectiveness for allogeneic cells and tissues that have systemic effects or that are dependent on the metabolic activity of living cells. Subsequently, the agency proposed and finalized three rules to implement this proposed approach. These requirements are codified as 21 CFR Part 1271 and apply to human cells and tissues recovered on or after 25 May 2005.

Unrelated allogeneic hematopoietic stem/progenitor cells from peripheral and cord blood are considered HCT/Ps, have a systemic effect, and are regulated as HCT/Ps and biological drug products. On 20 January 1998, FDA issued a Federal Register notice that requested information and clinical data to be submitted to a public docket. These submissions were to support development of recommendations for establishment and processing controls and product characteristics to be considered for licensure criteria. At that time, FDA indicated that if adequate information were obtained, including existing clinical trial data that demonstrated the safety and effectiveness of these therapies, it would develop guidance proposing licensure for products shown to meet the standards, and allowing citation of data in the public docket in lieu of requiring separate clinical data for each BLA applicant. FDA received comments and data that focused primarily on cord blood and not on peripheral blood stem/progenitor cell products.

FDA discussed an analysis of cord blood clinical data at a Biological Response Modifiers Advisory Committee on 17 February 2003. After review of that data, as well as information submitted to the docket and the published literature, FDA determined that the data were sufficient to establish the safety and effectiveness of unrelated allogeneic cord blood used for certain clinical indications and published a draft guidance in December 2006. The draft guidance proposed a pathway to licensure for minimally manipulated, unrelated allogeneic cord blood intended for hematopoietic reconstitution in patients with hematological malignancies. Manufacturers could rely upon the data submitted to the docket and would not have to submit additional clinical data if they followed the recommendations in the guidance. This draft guidance was discussed at the FDA Cell, Tissue and Gene Therapy Advisory Committee meeting on 30 March 2007.

Implementation of the Streamlined Licensure Approach

On 20 October 2009, FDA announced the availability of Guidance for Industry; Minimally Manipulated, Unrelated Allogeneic Placental Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications. The most significant change from the 2006 draft guidance...
is the scope, which has expanded to include more intended clinical uses based on public comment, advisory committee recommendations and additional data submitted to the docket. This guidance sets out BLA criteria for certain unrelated allogeneic cord blood products and also contains information on how to comply with applicable regulatory requirements for manufacture. The guidance only applies to certain cord blood products, now referred to as hematopoietic progenitor cells, cord (HPC-C) that are:

- minimally manipulated; and
- intended for hematopoietic reconstitution in patients with any of the following diseases:
  - hematological malignancies
  - certain lysosomal storage and peroxisomal enzyme deficiency disorders (Hurler Syndrome, Krabbe Disease or X-linked Adrenoleukodystrophy)
  - primary immunodeficiency diseases
  - bone marrow failure
  - beta thalassemia; and
- intended to be used in recipients unrelated to the donor

Manufacturers of cord blood for autologous use or use in first- or second-degree relatives are encouraged to follow the recommendations contained in this guidance document for manufacturing and for complying with applicable regulatory requirements, even though their products may not require premarket review.

This guidance explains that FDA will accept BLAs from HPC-C manufacturers that can demonstrate compliance with its recommendations for assurance of safety, purity, potency and effectiveness. Such sponsors can rely upon data in the docket rather than provide their own clinical data. The guidance contains several important parts to assist in preparing the BLA:

- regulatory requirements applicable to these products in 21 CFR Parts 200, 600 and 1271; this section will be especially helpful for newly regulated establishments
- license application procedure and logistics
- chemistry, manufacturing and controls section offering guidance on the content and format of information to be submitted, including:
a helpful table summarizing the characteristics of the cord blood used to obtain the clinical data submitted to the docket to demonstrate safety, purity and potency; sponsors would be expected to obtain similar results if citing the docket data

- manufacturing information to be submitted, including SOPs, validation data (including data on HPC-Cs in inventory demonstrating comparability), control of aseptic manipulations and processing and test methods for validation data

- methods of manufacturing, including all relevant SOPs for donor selection, cord blood collection, transport, processing, testing, storage, registry listing and selection request management and HPC-C shipping and handling; certain validation data summary information must also be submitted

- container closure systems, methods for validation or verification, labeling and environmental assessment

- establishment description section that describes:
  - content and format of general information
  - specific systems such as the source of water used in processing
  - heating, ventilation and air conditioning
  - facility controls
  - computer systems
  - contamination/cross-contamination issues

In addition to a detailed section describing applicable regulatory requirements, the guidance provides details for required postmarket activities such as reporting manufacturing changes, adverse experiences and biologic product deviations. Analysis of clinical outcome data is recommended as an indicator of product quality.

**Draft IND Guidance**

FDA also published a companion draft guidance for comment entitled, *Guidance for Industry and FDA Staff, Investigational New Drug Applications (INDs) for Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic*
Reconstitution for Specified Indications on 20 October 2009. Comments were due within 90 days of publication. This draft guidance sets out criteria for the minimum information to be included in an IND application for the unrelated allogeneic HPC-Cs discussed earlier, when:

- these HPC-Cs are not licensed
- they are needed for treatment of a patient with a serious or life-threatening disease or condition and
- there is no satisfactory alternative treatment

The sponsor may be the manufacturer (generally a cord blood bank), a registry or a transplant physician. There are three categories of HPC-Cs addressed in this guidance that may not be licensable but to which clinical access may be necessary. These are cord blood units:

- manufactured in non-US cord blood establishments, listed in international registries and selected for treatment of a patient in the US
- manufactured in US cord blood establishments before the BLA was approved and not shown to meet licensing criteria (not shown to be comparable to other licensed HPC-Cs in inventory
- prospectively manufactured in the US and not meeting licensing criteria but for which there is no satisfactory alternative (e.g., for the purpose of ensuring diversity of HLA phenotypes)

Conclusions

In addition to the publication of these two HPC-C guidance documents, FDA announced that the phase-in period for implementation of IND and BLA requirements for these products will end two years after the date of their publication (20 October 2011). Sponsors are encouraged to send in IND and BLA applications as soon as possible to ensure they can be processed and approved by that date. Pre-BLA and IND meetings with FDA are encouraged.

Though a lengthy process, this novel licensure paradigm for certain unrelated allogeneic cord blood products is a successful example of FDA’s working with stakeholders to realize a less-burdensome approach to regulatory compliance that will allow continued access to and availability of safe and effective life-saving therapies.

References


Authors

Martha A. Wells, MPH, RAC, recently retired from FDA. She was chief of the Human Tissues and Reproduction Branch in the Division of Human Tissues, CBER. She has more than 30 years of experience at FDA and was involved in the development and implementation of the new regulatory approach for human tissues and cells. She is currently vice president of Regulatory Affairs for Tissue and Biologics at REGLERA LLC in Lakewood CO. She can be reached at wellsm@reglera.com.

Ellen F. Lazarus, MD, FCAP, is currently the director of the Division of Human Tissues, CBER. She has been at FDA for more than 10 years, during which time she has worked in the areas of blood products, human cells and tissues and device regulation. She can be reached at ellen.lazarus@fda.hhs.gov.