



Advancing Transfusion and  
Cellular Therapies Worldwide

08 April 2010

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

RE: Docket No. FDA-2006-D-0157 (Formerly Docket No. 2006D-0514), 20 October 2009, "Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications", Guidance for Industry

Via electronic submission: <http://www.regulations.gov/>

Dear FDA Dockets Manager:

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, and developing and delivering programs and services to optimize patient and donor care and safety.

The organizing committee of the Cord Blood Licensure Workshop held 8-10 March in Rockville, MD appreciates the opportunity to submit the attached questions to the docket referenced above. The workshop provided a unique and valuable opportunity for manufacturers and transplant practitioners to better understand the requirements of the regulations behind the BLA process for HPC-Cs and to understand use of the IND process in order to continue using those products that are not licensed. Of equal value was the increased understanding FDA gained of challenges that remain in order for establishments to submit BLAs in time for the agency to complete the review process by the October 2011 deadline. The organizing committee believes that the IND questions might help FDA understand points that could be clarified in a final guidance document and the other questions may be useful to FDA in understanding questions some cord blood banks have about BLA content and documentation.

AABB strongly supports initiatives that improve the safety of patients and donors and stands ready to interact with FDA as necessary. Questions concerning these comments may be directed to M. Allene Carr-Greer, Director, Regulatory Affairs, [acarrgreer@aabb.org](mailto:acarrgreer@aabb.org).

Sincerely,

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**Questions for panel discussions – submitted by participants in the March 8-10, 2010 Cord Blood Licensure Workshop, Rockville, MD**

Panel A. Overview, Product Characterization, Assay Validation, CMC, Comparability

1. What would be the potential status of units from hepatitis B core antibody positive donors (currently considered 'exception' units) prior to availability of hepatitis B nucleic acid testing?
2. Are media fills required (per cGMP regulations)? Are media fills an appropriate method to validate aseptic manufacturing process? What other methods could be used to demonstrate aseptic processing?
3. Regarding validation, must all validation studies of equipment be done with a sample of the material that will be tested? For instance, do all of the validation studies on the cell counter have to use HPC, Cord? Is it acceptable to include some HPC, Apheresis samples?
4. How extensive does lot to lot testing of approved materials need to be?
5. For non-FDA approved materials or materials approved for a different use (i.e. DMSO), is review of certificate of analysis sufficient or would one need to actually repeat some of the tests?
6. Please comment on whether common approaches by industry such as the ones described below will satisfy the requirements to validate manufacturing methods / processes.
  - a. Microbiological methods – potentially reference previous work of full validation and each establishment /site perform a verification to demonstrate equivalent sensitivity/sensitivity in their hands.
  - b. Expiration dating – combine published and unpublished data (including what was previously submitted to the docket) to support a common expiration date.
  - c. Post-thaw expiration for varieties of product preparation (thaw, reconstitute, wash, etc)?
7. Please comment on development of common approaches for validation of assays such as CD34+ and viability assays where established proficiency testing programs have shown that interlaboratory variation is high.
8. Documentation of processes used in manufacture of some historical cord blood products (SOPs, training and competency, validation, environmental controls / aseptic processes monitoring, label control, etc) is not as detailed with regard to GMPs as current regulations require. Many facilities can demonstrate comparability in TNC, CD34+, CFU, recovery, sterility, etc and similar outcome of historical units consistent with medical literature. Is this considered enough to demonstrate processes are "in conformance with CGMP"?
9. In the context of collection sites that operate under contract / agreement with the licensed bank, will a copy of the contractor's SOP addressing collection have to be submitted with the BLA or is it enough that the agreement specifies that the licensed bank will have access to the applicable SOP(s) to ensure collection is compliant with the BLA? What is FDA's expectation regarding the license holder's responsibility in monitoring significant collection container/process changes?

What additional information should be submitted for collectors operating under agreement?

10. Will pre-licensure inspection meetings include collection sites? If so, will all sites be visited?
11. Regarding the Chemistry, Manufacturing, Controls Chart found in Section V of the licensure guidance:
  - a. How will units (before and after 5/25/05) be evaluated for safety if CMV testing was performed using IgG antibody tests and/or research PCR?
  - b. What about hemoglobinopathy testing in units where there is no sample left but other required tests are done?
  - c. What if tests have been invalidated and cannot be repeated due to test sample suitability requirements? Note: invalidated might apply to a situation where diagnostic rather than donor screening tests were performed.
  - d. Would cord blood units be eligible for licensure if the bacterial detection testing has not been validated for fungal culture by the facility?
12. Is a bank expected to submit their maternal risk questionnaire and the action form with their BLA? How would a bank communicate that the forms may have changed over time and what would the FDA expect a bank to do related to the questions that might be different, to prove comparability of older inventory?

Panel B. Labeling, Applicable Regulations, Establishment, Computers

1. Labeling – What is the role of ISBT 128 in the labeling and naming of licensed products? What about National Drug Code?
2. Will licensed products need to be physically segregated from non-licensed products?
3. Shared facilities
  - a. Will a cord blood bank that currently operates in an FDA licensed blood bank facility be required to move the cord blood banking operations to a separate facility dedicated to cord blood processing and banking?
  - b. When cord blood processing occurs in a cell therapy facility where other cellular products are manufactured, is campaign manufacturing required for each cellular product? That is, can HPC, Apheresis and HPC, Marrow be processed in the same area as HPC, Cord?
4. Please define a functionally-closed processing system.
5. Is environmental monitoring required in context of viable and nonviable particles/ surface monitoring, etc? If not, what evidence can be submitted to show it is not routinely required?
 

Would a facility need to perform monitoring with every product or would it be sufficient to do this at regularly defined intervals?
6. If retained samples are stored in a different freezer or at a different temperature than the product, is the sample still considered acceptable as the ‘retained sample’? When there is no properly stored retained sample for testing does the product have to go under IND?

7. What is the validation requirement for a database that produces a summary document from information originally captured on paper records?
8. When a facility uses an excel spreadsheet to calculate and store values as part of the manufacturing process, what validation/verification is required?
  - a. If the database provides "alerts" to user such as ineligible status, abnormal test result or TNC below a defined parameter, what validation/ verification is required?
  - b. If laboratory equipment or software interfaces with data base (example: transfer of test results), what testing is required?
  - c. How will FDA approach an Access data base (not validated) used to store manufacturing information (lot #s, equipment, eligibility data) and later create a record/ report(s) which is then verified manually as part of manufacturing record and release?
9. How detailed does a cleaning policy need to be? For non-classified areas, is it necessary to include types of cleaning agents, rotate them and prove effectiveness against known organisms - or is frequency and documentation of performance sufficient?
10. What is the expectation of how quickly records should be retrievable once they have been placed in long term storage?

Panel C. IND, Post Market, Post Approval Inspection Process, Business

1. We are an international private/public bank: Would we have to apply for an IND?
  - a. Will it still be acceptable to import these units into the U.S. under the Exceptional Distribution provisions, even though they do not meet current regulatory requirements?
  - b. If we are FDA registered but will we have to be FDA assessed?
2. Regarding cost Recovery – how will cost recovery be handled for units under IND?

How should we approach cost accounting/ cost recovery in context of licensure for only certain indications and requirements for IND for “ineligible” domestically and internationally?
3. Clinical issues – will new approved indications (if this happens) apply to all banks as they are approved or just for those that submit the data?
4. Is it an option for a bank to operate under IND until it is “ready” to apply for BLA? This might take it past the two year deadline. Would this scenario be permitted?
5. Will license holders be required to determine if the clinical site is using the HPC-C for one of the indications listed in the guidance document, and if they have all of the appropriate documentation?
6. How should all the “other indications” be handled? Do we have to have a broad IND to support eventual labeling claim extensions (like other licensed drugs that are under trial for new potential indications per CFR 312) or is off-label use of a licensed drug acceptable and allowed?
7. What would be the expected level of oversight for the INDs in the draft guidance?

8. Please provide examples of events that would be reportable under BPD regulations or be subject to recall. What are the requirements when there are labeling mix-ups or SOP violations that call into question a batch of products and a clear assessment of individual products cannot be made?
9. In some instances a non-licensed HPC-C may pass through three different IND holders – the cord bank, the registry, the transplant center. Which one is the primary IND holder? How would inconsistencies be resolved so as not to delay use of product? Is reporting required through only one of them or all three?
10. The IND states that labeling needs to be part of the submission. If the Transplant Center is submitting the IND, how can they have control of what is on the labels?
11. Can a Transplant Center submit a Masterfile rather than an IND? If they already have a Masterfile in place can they just submit an amendment?
12. If the Cord Blood Bank is submitting the IND, how can they attach a clinical protocol? Or is the intention of the agency that the Bank would submit an IND for each protocol?
13. What is the timeline for the final Guidance on IND submission?
14. The draft IND guidance assumes that a comparable non-licensed unit is not available. If the holder of an IND is a cord bank or registry do they somehow have to document that the non-licensed unit was “better” or the “best” one for a patient? The concern is that a single CBB or registry will not know what other units might have been selected and what the rationale was for the selection of a particular non-licensed unit. This should be a physician issue as part of the practice of medicine.

**Questions from the floor—submitted by participants in the March 8-10, 2010 Cord Blood  
Licensure Workshop, Rockville, MD**

IND Questions

1. Will currently active cord blood bank INDs need to be closed on October 20, 2011?
2. If a cord blood unit is requested from a private (family) cord blood bank, should the cord blood bank apply for an IND or will the transplant center using the cord blood unit be required to file an IND?
3. In a private (family bank) situation, possible uses of cord blood extend beyond the currently defined indications in the Cord Blood Licensure Guidance. Does this mean that the bank needs to have both a BLA and an IND?
4. Does a non-US stem cell facility need to file an IND or any other application with the FDA to receive a cord blood product from the US?
5. If cord blood products meet the requirements listed in Table A (page 9) of the Final Guidance for Cord Blood Licensure, except that the CD34+  $<1.25 \times 10^6$ , will an IND be required for use of the product or is the product to be discarded?

Manufacturing Questions

1. Does sterility testing need to be performed in an FDA registered lab?
2. What are the requirements for endotoxin testing of the final product? Can facilities accept vendor data concerning endotoxin testing of ancillary products and components used in cord blood processing?
3. If cord blood products are stored in liquid nitrogen and retention samples are stored in the vapor phase of liquid nitrogen, does FDA consider this as equivalent storage conditions?
4. Is a Certificate of Analysis needed for BacT Alert bottles?
5. Is compliance with GMPs a requirement for demonstrating comparability?
6. Are establishments required to use clean rooms in cord blood manufacturing steps?
7. If a closed system is used for cord blood processing, are any HVAC controls required? Is gowning required?
8. Is the laboratory that a biological safety cabinet resides in considered as the supporting clean area, class 10,000?
9. Is a full electronic batch record sufficient for cord blood products?

10. For vendor qualification of IT systems, how often should a cord blood facility perform vendor qualification? Should it be performed every two years or only after major system changes?
11. Can ineligible units be kept in quarantine to be used for research later, or must the units be discarded?
12. What type of sample is considered an acceptable reserve sample?

### BLA Questions

1. Please describe the fee structure and costs for a BLA submission.
2. In the BLA application, do all cord blood collection sites need to be listed and described?
3. After BLA approval, what data are needed if a bank needs to change from one 510(k) cleared cord blood processing system to another system? Is it sufficient to validate the new method, or is it necessary to show comparability of the two systems?