Cord Blood Banking and Biologic License Application (BLA)

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Webinar Presenters

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These speakers have indicated no conflict of interest to disclose.

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CORD BLOOD BANKING BIOLOGICS LICENSE APPLICATION

Tara Sadeghi, BS
Michele Carbone MS, CLS, MT(ASCP)
Objectives

• Review of the regulations to include 1271
• NMDP – IND
• Validation Plan to the FDA and a pre- BLA meeting prior to BLA submission
• BLA 356h Form
• Details based on standards to meet the BLA requirements
REVIEW OF THE REGULATIONS
Cord blood from unrelated donors is a biologic drug product

- FDA regulations for cord blood apply to CB units manufactured in the U.S. or *distributed to the U.S.*
- Relevant regulations are many
  - Listed at the end of this presentation
- Two guidance documents released in October 2009
  - **Final guidance regarding licensure**
  - **Draft guidance regarding investigational new drugs**
    - *Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (Draft HPC-C IND Guidance)* - 10/20/09
Time Line

• With publication of these HPC-C guidance documents, FDA announce that phase-in implementation for IND and BLA requirements will end 10/20/11

• Sponsors are encouraged to send in IND and BLA applications as soon as possible to allow sufficient time for review, comment, and resubmission as needed to complete all actions
  – Does not actually have to be approved by this time
  – Expected that all units distributed after October 2011 be under BLA or IND
    • For non-U.S. banks, only applies to those units coming to the U.S.
Scope of the Guidance Documents

• Placental/umbilical CB units that are:
  – Minimally manipulated
  – Intended for hematopoietic reconstitution in patients with a specified list of diseases
  – Intended for unrelated use
Applicable Diseases and Conditions

- Hematological malignancies
- Certain lysosomal storage and peroxisomal enzyme deficiency disorders
  - Hurler Syndrome
  - Krabbe Disease
  - X-linked Adrenoleukodystrophy
- Primary immunodeficiency diseases
- Bone marrow failure
- Beta thalassemia
Biologics License Application (BLA)

- **Guidance for Industry:** *Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications*

- **How the guidance helps:**
  - FDA intends to grant a license for CB units shown to follow recommendations in the guidance and meet applicable regulatory requirements
  - License would apply to all HPC-Cs manufactured after approval of license and those previously manufactured that are demonstrated to be comparable
  - Guidance explains: Scope (products covered), historical background, lists and explains the applicable regulatory requirements
    - License application procedure – Form FDA 356h, information to include, and actions that FDA will take
Information in the HPC-C Licensure Guidance – CMC

• Table summarizes characteristics of the cord blood used to obtain the clinical data submitted to the docket to demonstrate safety, purity, and potency of HPC-C; applicant expected to obtain similar results if citing docket

• Manufacturing information to be submitted
  – SOPs
  – Processing validation data
  – Control of aseptic manipulations
  – Test methods and validation
Special Issues for BLAs

- Banks are not required to follow recommendations in guidance, but must still submit a BLA
- Units already stored can be used as long as:
  - HPC-C manufactured using the same procedures where documentation is provided:
    - Demonstrating their comparability, and that they were manufactured in accordance with CGMP
  - HPC-C in inventory that were previously manufactured using different procedures, provided that:
    - Manufacturer submits a separate validation summary, and
    - Includes data demonstrating comparability of previously manufactured HPC-C to the currently manufactured HPC-C, and providing evidence that methods, facilities, and controls used for manufacture conformed to CGMP
Establishment Description

• Guidance on the content and format of information to be submitted in this section of the BLA

• Floor diagram, personnel and product flow, HVAC, facility controls, computer systems

• Contamination/cross-contamination issues including equipment cleaning and validation; containment features
Investigational New Drugs Application

- **Draft Guidance for Industry and FDA Staff:** Investigational New Drug Applications (INDs) for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications

- Intended for unlicensed CB units that are a suitable match for recipients with serious or life-threatening disease for which there is no satisfactory alternative treatment
Applicable Scenarios for Cord Blood INDs

• Manufactured in non-U.S. banks, listed in international registries, and selected for U.S. patient
• Manufactured in U.S. banks before BLA has been approved and not shown to meet licensing criteria
• Prospectively manufactured in U.S. banks and do not meet licensing criteria but for which there is no satisfactory alternative
Non-U.S. Cord Blood Banks

• Non-U.S. banks may choose not to apply for licensure
  – If so, must export CB units to U.S. under an IND
• Products from non-U.S. banks will often not meet the criteria for licensure, for example:
  – Donor eligibility determination
  – Release criteria
U.S. Cord Blood Banks’ Pre-licensure Inventory

• For CB units that cannot be shown to be comparable to licensed CB units
• Needed for treatment of patients with the diseases or conditions applicable to the guidance
U.S. Cord Blood Banks’ Prospectively Manufactured CB Units Not Meeting Licensure Requirements

- CB units for under-represented populations
- Intended to maintain diversity of HLA phenotypes of units in inventory
Minimal Information to Include in IND

• Outlined in Table A of Draft Guidance
  – Column A: Non-U.S. Cord Blood Banks
  – Column B: Pre-licensure inventory
  – Column C: Prospectively manufactured unlicensed inventory
IND Responsibilities

• INDs can be submitted by:
  – Cord Blood Banks
  – Registries
  – Sponsor/Investigators

• Responsibilities for maintaining the IND are listed in part IV of the guidance

• Communication with the FDA Center for Biological Evaluation and Research is encouraged prior to submission of IND
Back to Options for Non-U.S. Banks

• Submit a BLA or IND to the FDA

• Advantage:
  – All units are permitted to enter U.S. regardless of whether or not they are through an IND-holding registry

• Disadvantage:
  – Arduous process requiring demonstration that ALL units meet licensure or IND requirements even if not distributed to the U.S.
Back to Options for Non-U.S. Banks

• Distribute CB units to U.S. exclusively through a registry, affiliated U.S. establishment, or clinical program that holds an IND

• Advantage:
  – Primary responsibilities for submitting and maintaining IND fall on registry, affiliate, and/or clinical program
  – Do not have to meet stringent requirements for all CB units

• Disadvantage:
  – Can only distribute units to U.S. if found via an IND-holding registry or by an IND-holding clinical program
National Marrow Donor Program

• Plans to submit an IND for CB units from non-U.S. banks
  – Sponsor would be NMDP and investigators would be U.S. transplant physicians
• Non-U.S. bank responsibilities would include:
  – Registration with FDA
  – Qualification process by NMDP (prefers accreditation by FACT-NetCord or AABB, may be alternatives)
  – Report adverse events to NMDP and participate in investigations
  – Comply with NMDP procedures for establishing donor eligibility, etc.
• Some “unknowns” and challenges related to cost recovery and oversight
How FACT-NetCord Accreditation Helps

• Potential qualification criterion for registry INDs, such as NMDP
• Requirements for INDs and/or licensures are already required in the Cord Blood Standards
• Peer-reviewed inspections verify compliance to Standards requirements
Applicable U.S. FDA Regulations

– 21 CFR Parts 201, and 610 Subparg G – Labeling
– 21 CFR Parts 210 and 211 – cGMPs
– 21 CFR Part 600 – Biological Products: General
– 21 CFR Part 610 – General Biological Products Standards
– 21 CFR Part 1271
Selected Guidances Useful for INDs

- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)
- Guidance for Industry CGMP for Phase 1 Investigational Drugs
NMDP INVESTIGATIONAL NEW DRUG (IND)
Investigational New Drug (IND)

• Based on the Guidance Document
  – Biologic License Application (BLA)
  – Compliance with the regulations
  – Licensed product
  – Defined the intended use

• IND
  – NMDP
  – Off label use
  – Manufacture cord blood units that do not meet the regulations and guidance standards and BLA requirements
  – NMDP and changes
VALIDATION PLAN AND THE PRE-BLA MEETING
Validation Plan / Pre- BLA Meeting

• Establish and Maintain
  Define, document and implement and review and as needed revise on an on-going basis
  – Quality Plan (Quality Program)
    • Designed to prevent, detect and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission or spread of communicable diseases
  – Level 2 documents
  – Level 3 documents
Validation Plan / Pre- BLA Meeting

- Level 2 Documents (Quality Management Systems)
  - Personnel
  - SOP on SOP
  - Equipment (Qualification)
  - Training and Competency
  - Supplier Qualification/ Supply Qualification
  - Validation (Assay, Process)
  - Labeling
  - Transport
  - Good Documentation Practices
  - Environmental Monitoring
  - Occurrence Reporting
  - Audit
Validation Plan / Pre-BLA Meeting
Quality Systems

- Audit
  - SOP Document Control
  - Equipment
  - Occurrence Management
  - Record Management
  - Facilities and Environment

- Cord Blood
  - Personnel
  - Training Competency
  - Validation
  - Supplier and Supply Qualification
  - Labeling

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Quality Management Tools

- Quality Management Plan
- Standard Operating Procedures
- Supporting Documents
Validation Plan / Pre-BLA Meeting

• Level 2 Documents
  – Personnel
    • Education, training, experience to enable that person to perform the assigned functions - qualified with GMP
    • Supervising capacity
    • Perform their functions in such a manner to provide assurance that the product has the safety, identity, quality, purity, and potency
  – Quality Unit
  – Labeling
    • Product Insert
    • Distinct Identification Code - DIN – ISBT- register with ICCBBA
    • Labeling requirements for donor eligibility (biohazard and warning labels)
    • Base label – ISBT requirements
Validation Plan / Pre- BLA Meeting

• Level 2 Documents
  – Labeling
    • Base label 610.60
      – Proper name of the product
      – Name, address and license number
      – Lot number – or other lot identification – use the DIN number (So anything that is prepared from that lot number is considered same lot number)
      – Expiration date
      – Preservative
      – Amount of product
      – Rx
    • Partial label
      – Proper name
      – Lot number or other lot identification (DIN)
      – Name of manufacturer- name and address
Validation Plan / Pre-BLA Meeting

• Level 2 Documents
  • Equipment
    – Evaluate based on manufacturing need and intended use
    – Qualified
    – Cleaned and maintained
    – Manufacturer recommendation- PM, Calibration
    – Identified within the production records
    – Records and documentation
  • Validation
    – Key Elements
      » Plan
      » Approval
      » Acceptance criteria
    – Assay
    – Process
Validation Plan / Pre-BLA Meeting

• Level Documents
  • Assay validation - Level II document
  • Each individual validation and procedure is your level III document
    − Sterility
    − IDM
    − Hemoglobin
  − CBC (Cord sample)
  − CD34
  − Viability
  − ABO
  − HLA
  − CFU

Safety

Potency/Purity

Identity
Validation Plan / Pre- BLA Meeting

• Level 2 Documents
  • Assay validation plan with acceptable criteria and meet the “compendium” requirements as defined in the guidance documents
  • Requirements
    – Accuracy
    – Precision
    – Linearity or Reportable range
    – Sensitivity – Limit of detection (LOD)
Validation Plan / Pre-BLA Meeting

• Level 2 Documents
  – Occurrence Management System
    • Adverse Event - biologics - form 3500A
      – Outcomes that are both serious and unexpected that result in outcomes
        ◆ Death
        ◆ Life – threatening adverse experience
        ◆ Prolongation of existing hospitalization
    • Biologic Product Deviation (report) - form 3486
      – Product deviations form cGMP, applicable standards or established specifications that may affect the safety, purity and potency
      – Of a distributed product
      – Testing, processing, packaging, labeling, storage or distribution
      – FDA inspection during that process and if they find something they track to the BPDR
Validation Plan / Pre- BLA Meeting

• Level 2 Documents
  • Environmental monitoring
    – What is required
    – Biological Safety Cabinet vs Clean room
    – Cleaning supplies used
  • Bioburden
    – Use both a dynamic and a static for the initial validation
    – Monitor on a regular basis
    – Contamination
      » Take the equipment out of use and clean
      » Re-assess for bioburden levels
      » Acceptable limit of less than 3 CFU

- SOP is provided
VALIDATION PLAN AND THE PRE-BLA MEETING
Validation Plan / Pre-BLA Meeting

Audit  -->  Outcomes  -->  Quality Indicators

Collection  -->  Transport  -->  Testing  -->  Stability  -->  Thawing

Cord Blood

Recruiting Eligibility  -->  Processing  -->  Environment  -->  Distribution  -->  Supplies
Validation Plan / Pre-BLA Meeting

- Validation plan and on your way to the BLA
  - Guidance lists what you need to validate
    - Cord Blood Collection
      - Sterile
      - Viable
        » Determine your time frame for processing to retain the viability
      - Average and range for your volume and TNC
        » Determine your time frame for processing to retain the viability
    - Cord Blood Processing
      - Sterile
      - Viable
      - Recovery
      - TNC and CD34
      - HCT
Validation Plan / Pre- BLA Meeting

• Validation plan and your way to the BLA
  – Guidance lists what you need to validate

• Storage- holding the HCT/P for future processing and/or distribution
  – Actual storage of the cord blood unit and the continuous monitoring of that storage environment
    » From the time of collection to transport to laboratory
    » Storage at collection site/ laboratory before and during processing
    » Storage in the LN2 – vapor or actual liquid
    » Vapor storage - the validation should include the length of time before the cords are exposed to warmer temperatures
    » Include the overwrap process component
Validation Plan / Pre- BLA Meeting

• Validation plan and your way to the BLA
  – Guidance lists what you need to validate
    • Shipping
      – Temperature maintained within the shipper
      – Tracking
    • Thawing- need to establish a acceptable range
      – Viability
      – Recovery percentage
Validation Plan / Pre- BLA Meeting

- Validation plan and on your way to the BLA
  - Guidance lists the required SOP
  - Flow diagram that outlines each process starting with recruitment and the corresponding SOPs as listed in the guidance document
    - Collection
      » Maternal screening
      » Donor eligibility

- Physical Screening
  - MRQ
  - MHQ

- Infectious Disease Testing

- Additional Medical Chart Review

- Post donation information

- Donor Eligibility Screening and Testing
Validation Plan / Pre-BLA Meeting

- Validation plan and your way to the BLA
  - Guidance lists the required SOP
    - Flow diagram that outlines each process starting with recruitment and the corresponding SOPs as listed in the guidance document
      - Collection
        » Maternal screening
        » Donor eligibility
        » Notification of moms
        » Positive Identification or a way of linking the patient demographics with the DIN number
      - Collection
      - Storage
      - Transport back to the processing laboratory
Validation Plan / Pre-BLA Meeting

- Validation plan and your way to the BLA
  - Guidance lists the required SOP
    - Flow diagram that outlines each process starting with recruitment and the corresponding SOPs as listed in the guidance document
      - Processing
        » Manufacturing process
        » Storage
        » Lot release
      - Selection
        » Registry listing
      - Shipping and Handling
        » Shipping
        » Thawing
        » Emergency product
BLA – Form FDA 356h

BLA

- 4-page document with instructions attached

  » http://www.forms.gov/bgfPortal/docDetails.do?dId=3496
## Application Information

**Applicant Name:**
San Diego Medical Bank

**Telephone:**
16032812

**Facsimile:**
192.20.234

**Address:**
San Diego, Calif. 92108

**Principal Investigator:**

**Address:**

**Telephone:**

**Facsimile:**

**Address:**

**Telephone:**

**Facsimile:**

## Product Description

- **New Drug or NUEO Applicant Number:**
- **Generic Application Number:**
- **Active Pharmaceutical Ingredient:**
- **International Nonproprietary Name:**
- **Trade Name:**
- **Proprietary Name (Drug):**
- **Proprietary Name (Brand):**

## Application Information

- **Form Type:** FDA 356h
- **Application Form:**
- **Application Date:**

## Application Description

- **Application Type:**
- **Approval Category:**
- **Type of Submissions:**
- **Initial Approval:**
- **Subsequent Approval:**
- **Approval Date:**
- **Effective Date:**

## Establishment Information

- **Establishment Name:**
- **Address:**
- **Telephone:**
- **Facsimile:**
- **Number of Volunteers:**
- **Type of Establishment:**
- **Location:**
- **Occupational Health:**
- **Inspections:**
- **Inspection Dates:**
- **Inspection Results:**
- **Inspection Notes:**

## Additional Information

- **Investigational Use:**
- **Study Information:**
- **Study Design:**
- **Study Population:**
- **Study Site:**
- **Study Outcome:**
- **Study Duration:**
- **Study Sponsor:**
- **Study Sponsor Contact:**

## Functional Information

- **Function:**
- **Description:**
- **System:**
- **Institution:**
- **Address:**
- **Telephone:**
- **Facsimile:**
- **Number:**
- **Type:**
- **Location:**
- **Function:**
- **System:**
- **Institution:**
- **Address:**
- **Telephone:**
- **Facsimile:**
- **Number:**
- **Type:**
- **Location:**
- **Function:**
- **System:**
- **Institution:**
- **Address:**
- **Telephone:**
- **Facsimile:**
- **Number:**
- **Type:**
- **Location:**

## Additional Notes

- **Notes:**
- **Comments:**
- **Questions:**
- **References:**
- **Attachments:**

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**Foundation for the Accreditation of Cellular Therapy**

**Page 1 of 4**
This application contains the following items: (Check all that apply).

1. IND
2. General Drug Approval
3. Surveys
4. Summary
5. Chemistry
6. Clinical Pharmacology
7. Clinical Bioavailability
8. Clinical Safety
9. Statistical
10. Case Report
11. Consent
12. Patient Information
13. Establishment Description
14. Assay Certification
15. Patient Certification
16. User Guide
17. Financial Information
18. Certification

CERTIFICATION
I agree that the information on this application and any other information provided by the applicant, including the identity of the applicant, is true, complete, and accurate, and that the applicant is authorized to apply for an IND. I agree to notify the Food and Drug Administration of any changes in the information provided in this application, and to provide any additional information requested by the Food and Drug Administration.

SIGNED FOR REPRESENTATION: [Name]
Title: [Title]
Date: [Date]

Public reporting burden for this collection of information is estimated to average 4 hour per respondent. If you have comments regarding the accuracy of the time estimate, please send your comments to the Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Clinical Pharmacology, 10th Floor, 5600 Fishers Lane, Rockville, MD 20857.

[Form FDA 356h (10/06)] PAGE 2 OF 4
APPLICATION INFORMATION

PRODUCT DESCRIPTION

• Established name
  – Hematopoietic Progenitor Cells, Cord HPC-C

• Indications for use
  – Intended for hematological reconstitution in patients with defined diseases as listed and in the summary

APPLICATION DESCRIPTION

• Application type
  – BLA

• Type of Submission
  – Original application

REASON FOR SUBMISSION

• New application for biologic license

PROPOSED MARKETING STATUS

• PRESCRIPTION PRODUCT (RX)

ESTABLISHMENT INFORMATION

• Locations
• Ready for Inspection

CROSS REFERENCES

• IND- (NMDP)
Biologics License Application- pg 2

• Page 2

• Application contains
  – Index
  – Summary
  – Chemistry Section
    • A. Chemistry, manufacturing and control information
    • C. Methods validation package

• Certification
Biologics License Application- BLA

- Cover letter
  - Introduce the bank and your product
- Index ( #1 on page 2 of the BLA)
  - Index outlining what is in the submission package
- Draft label
- Summary ( #3 on page 2 of the BLA)
  - Summary of the information submitted in the application
  - Product and application description
Biologics License Application- BLA

– Index
• Cover letter
• Draft label
• Form FDA356h- Summary
• Chemistry, Manufacturing and Controls (CMC)
• Validation Summary Data
• Facility Description
• Other
Biologics License Application- BLA

- Summary section
  - In enough detail that the reader may gain a good understanding of the data and information
  - Discuss all aspects of the application
  - Synthesize the information into a well-structured and unified document
  - Data should be submitted in a tabular or graphic form
Biologics License Application- BLA

– CMC section

A. HPC-C Description and Characteristics
   – Table on page 9 of the Guidance document
   – Describe the test and the expected results for your product specifications

B. Manufacturer(s)

1. Identification – list
   – Name and address
   – All licenses / registration (CLIA, FDA)
     » Manufacturer (Cord Blood Bank)
     » All collection sites
     » Laboratory performing testing
Biologics License Application - BLA

– CMC section

B. Manufacturer

1. Identification of all Manufacturer(s)

2. Floor diagram
   a) Narrative Description

3. Contamination procedure
   a) Aseptic technique
   b) Help to identify or prevent
Biologics License Application - BLA

CMC section

C. Methods of Manufacturing

1. SOPS
2. Validation
3. Flow Charts
   1. Visual representation
   2. List your in-process controls
   3. Test performed at each step
   4. Time limits

4. Microbiology
   • Use pre-sterilized – one time use – than you just need to describe it
   • Sterilize in house – than you will need to submit validation

5. Control of Aseptic
   1. Describe your bioburden monitoring and sterility testing
Biologics License Application- BLA

CMC section

D. Container Closure System

Describe your bag
Describe the over wrap

E. Method Validation

1. IDM
   a) List all the tests, manufacturer, IVD status

2. Other Test Methods
   a) Describe your test methods for all the tests performed for the safety, purity, potency and identity
Biologics License Application- BLA

– CMC section

F. Labeling
   ➢ Include your labels

G. Environment Assessment
   ➢ Based on the regulation- it is a categorical exclusion
Thank you for joining us today.

- Join us for the upcoming inspection and accreditation workshops:
  - Cellular Therapy
    - February 16, 2011 in Honolulu, Hawaii at BMT Tandem Meetings
    - May 18, 2011 in Rotterdam, the Netherlands at ISCT Annual Meeting
  - Cellular Therapy Collection
    - May 31, 2011 in Scottsdale, Arizona at ASFA Annual Meeting
  - Cord Blood
    - June 12, 2011 in San Francisco, CA
Evaluations and Continuing Education Credit

- Continuing education credits can be purchased via the online FACT store at www.factwebsite.org
  - All inspectors can obtain CME/CNE certificates free of charge
  - Program and bank personnel requesting CME/CNE credit can purchase credit for 20 USD
- Evaluations will be distributed to participants not wishing to receive CME/CNE credit
QUESTION AND ANSWER SESSION