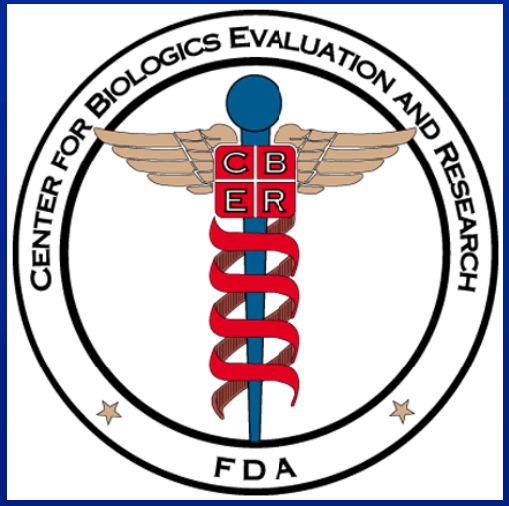

The Biologics License Application (BLA)

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CBER

Presentation Outline

- Application contents
- Application review process
  - Desk review
  - Pre-license inspection
- Approval process

BLA Approval or License Issuance

21 CFR 601.2: BLA approval or issuance of license constitutes a determination that the establishment and product meet applicable requirements to ensure the continued safety, purity and potency of products

When to Submit Application

- **21 CFR 607.21: Register facility within 5 days**
  - **Products may only be distributed *intrastate***

- **21 CFR 600.21 and 601.2**

  AFTER:
  - **Manufacturing has started**
  - **Personnel have been trained**
  - **Operations and processes have been validated**
  - **Ensuring manufacturing operations are in compliance**

BLA Content

- Cover Letter
- Form FDA 3674
- Form FDA 2830
- Form FDA 2567
  - Labels
  - Circular of Information
- Form FDA 356h
- Chemistry, Manufacturing and Controls (CMC)
- Establishment Description

Cover Letter Content

21 CFR 601.2: Include a detailed description of the operations and manufacturing methods.

For example:

- **Summary of BLA content**
- **Applicant's name and address**
- **Product names and processes**
- **Locations, addresses, registration numbers:**
  - **Manufacturing sites: testing facilities, collection and processing sites**
  - **Contract facilities**
- **Date manufacturing began**

FDA Forms

- **Form FDA 3674: Certification of Compliance**
- **Form FDA 2830: Blood Establishment Registration and Product Listing**
- **Form FDA 2567: Transmittal of Labels and Circulars**
- **Form FDA 356h: Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use**

Forms Page Link:

http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

CMC Information

- Table of Contents
- Standard Operating Procedures (SOPs)
- Validation Summary
- Quality Control (QC)
- Records

CMC: SOPs
21 CFR 606.100

- **Donor suitability**
  - Medical history criteria
  - Donor qualifying tests
  - Donor notification and deferral
  - Adverse events
- **Blood collection**
  - Arm preparation
  - Method for relating product back to donor
  - Method for measuring the quantity of blood removed from the donor (RBC loss)

CMC: SOPs (cont.)
21 CFR 606.100

- **Manufacturing**
  - Methods of component preparation
  - Tests and repeat tests performed
  - Labeling process
  - Storage, shipping, dating period requirements
  - Equipment maintenance and calibration
  - QC of product, reagents and supplies
  - Failure investigations

CMC: SOPs (cont.)

- 21 CFR 606.40(a)(4) and (6): Quarantine
- 21 CFR 606.100
  - Disposition of unsuitable products
  - Record review prior to product release and distribution
  - Look back process
  - Final disposition of products

CMC: Considerations for Validation and QC

- **21 CFR 601.2: Demonstrate that you are manufacturing product that meets requirements for safety, purity and potency**
- **Validation summary that includes:**
  - **Procedure outline**
  - **Expected outcome**
  - **Results summary**
  - **Failure investigation**
  - **Approval signatures**

CMC: Considerations for Validation and QC (cont.)

- Approved applications have typically contained two consecutive months of QC
- Examples: Products
  - Platelets
  - Cryoprecipitated AHF
- Examples: Processes
  - Leuko-reduction
  - Irradiation

CMC: Records
21 CFR 606.160(a)

- Documentation occurs concurrently with manufacturing steps
- Trace significant steps
- Legible and indelible
- Provide a complete history of work
- Identify
  - Dates
  - Personnel
  - Test results and interpretation of test results
  - Lot numbers of supplies/reagents used for final product

CMC: Records
21 CFR 606.160(b)

- Donor records
- Processing records
- Storage and distribution records
- QC records
- General records
  - Maintenance records for equipment
  - Supplies and reagents

Establishment Description

- Organization chart
- Authorized Officials
- Major equipment
- Manufacturing agreements
- Quality Assurance unit

Authorized Official(s)

- Name
- Title
- Mailing address
- Phone number
- Facsimile number

Major Equipment

- List
  - Manufacturer, Model, Version
- Examples
  - Computer systems
  - Automated collection systems
  - Irradiators
  - Sterile connecting devices
  - Infectious disease testing instrumentation or methodology

Contractor Information

- Legal name
- Address
- If applicable, FDA registration number, U.S. License Number, CLIA number
- Summary of contract
  - Services provided
  - Responsibilities of each party
  - Assessment of compliance

QA Unit

- QA authority
- QA oversight
  - Personnel assessment
  - Equipment
  - Quality control
  - Product release
  - Records management
- Problem investigations
- Audits

Application Review Process
Desk Review of Application

- **Review for completeness and accuracy**
  - **Manufacturing consistent with regulations and product standards**
- **Resources used during FDA review**
  - **Code of Federal Regulations**
  - **Guidance documents**
  - **Device Operator's Manuals**
  - **Package Inserts for reagents and supplies**
  - **Published scientific literature**
  - **Precedent reviews**

Application Review Process Pre-License Facility Inspection

- **Pre-announced inspection**
  - **21 CFR 600.22: FDA investigates methods of collecting, processing, testing, and storing to ensure consistency with regulations and cGMPs and**
  - **FDA reviews records**
- **Applicant responds to inspectional observations**

Approval Process

- **Office of Blood Research and Review (OBRR) requests that Office of Compliance and Biologics Quality (OCBQ) complete a compliance evaluation of applicant**
- **OBRR prepares approval letter**

License Approval

- **Approvals are specific**
  - **Site**
  - **Product**
  - **Method/product characteristics**

- **Allows**
  - **License number on licensed products**
  - **Interstate distribution of licensed products**

License Approval (cont.)

- **Approval letter states**
  - **U.S. License Number**
  - **Product expiration dates and storage temperatures**
  - **Approved products**
  - **Manufacturing sites**
  - **Instructions to submit final product labels**

Licensure Responsibilities

- 21 CFR 607.20: Maintain current and correct registration and product listing information
- 21 CFR 606: Comply with FDA regulations on cGMPs (including BPD and fatality reporting)
- 21 CFR 601.12: Notify CBER of any changes to the approved license, including contractor changes
- 21 CFR 600.21: Facility may be FDA inspected every 2 years

References

- **Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" May 1999**

Link:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm

Questions - Contact us!

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