

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”**

Additional copies are available from:
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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
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[Note: Page numbering may vary for documents distributed electronically.]

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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”**

GENERAL INFORMATION

I. BACKGROUND

In the Federal Register of July 8, 1997 (62 FR 36558), the Food and Drug Administration (FDA) announced the availability of Revised Form FDA 356h, “Application to Market a New Drug, Biologic, or an Antibiotic for Human Use.”^{3, 5} This document provides guidance on the completion of this form and the content and format of the Chemistry, Manufacturing, and Controls (CMC) section and the Establishment Description section of a License Application for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture. For these products, FDA is now implementing the BLA (revised Form FDA 356h) and will accept biologics license applications instead of two separate license application submissions, the product license application (PLA) and the establishment license application (ELA).

This document finalizes the draft guidance entitled “Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and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 Form FDA 356h, ‘Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use,’” that was announced in the Federal Register of July 10, 1998 (63 FR 37401).

Key points:

- This guidance is a list of what a new applicant should submit in support of an application to become a U.S. licensed manufacturer of human blood and blood components.
- This guidance may also be used by the holder of a U.S. license for human blood and blood components who wishes to supplement their Biologics License Application [see 21 CFR 601.12 and other FDA published guidance documents]. Only information directly related to the supplement should be submitted. Throughout this guidance document

^{*} This document represents FDA’s current thinking on the content and format of the Chemistry, Manufacturing and Controls and Establishment Description information for human blood and blood components intended for transfusion or for further manufacture. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

comments have been included which may guide applicants in the proper filing of a supplement to their Biologics License Application.

- Current holders of an Establishment License and Product License(s) will not be required to resubmit information already on file with FDA. When such information is relevant to a supplement, it can be referenced by the original submission date and/or FDA assigned Reference Number. The applicant should be certain that the referenced material is up-to-date.
- This guidance does not detail specific review criteria for license applications and supplements.
- The Form FDA 356h should be used with all submissions to FDA regarding a Biologics License including supplements for review and approval [21 CFR 601.12(b) and (c)], annual reports [21 CFR 601.12(d)], label changes for review and approval [21 CFR 601.12(f)] and notifications [e.g., change in Authorized Officials or new mailing address].
- Not all parts of this document will be applicable to all manufacturers. This document, associated references, and the Division of Blood Applications, Blood and Plasma Branch (phone: 301/827-3543), may be consulted when preparing a submission.

II. DEFINITIONS

acquisition – An *acquisition* is the purchase of a facility previously operated under one U.S. License by a new applicant or an applicant holding a different U.S. License. The acquired facility will no longer be connected to the original U.S. License. The first license will either be revoked or supplemented to delete the facility. The existing license application for the legal entity acquiring the facility will be supplemented to include the manufacture of product at the acquired facility. Before the elimination of establishment location licensing, this was previously referred to as a “rollover.”

amendment – An *amendment* is the submission of information to a pending license application or a pending supplement, to revise or modify the application or supplement as originally submitted [21 CFR 600.3(ff)]. Any pending supplement (a BLA supplement which has not received FDA approval) or pending application can have additional information submitted to be included in the review. Each addition of information is an amendment to the application or supplement.

applicant – An *applicant* is any legal person or entity who has submitted an application to manufacture a product subject to licensure under section 351 of the Public Health Service Act. The applicant assumes responsibility for compliance with the applicable product and establishment standards. Also see *manufacturer*.

authorized official – An *authorized official* is a person or persons appointed by the applicant to correspond with FDA. Authorized officials can initiate a BLA or a supplement to a BLA, discuss applications and supplements with FDA representatives and provide additional information in support of a BLA.¹

BLA – Biologics License Application – The single license application proposed to replace both the Establishment License Application (ELA) and the Product License Application (PLA).¹⁰

BLA number – In the future the license application tracking system will change from the currently assigned reference number to a BLA number. The BLA number will be a permanent tracking number for a particular product application. A BLA number will be assigned to each product application sent to FDA for review. The BLA number will look like: “BL1234.”

Manufacturers of blood and blood components will receive a single BLA number that will be assigned to the group of generally recognized human-derived products; e.g., Whole Blood, Red Blood Cells, Plasma, Platelets and Cryoprecipitated AHF (Anti-Hemophilic Factor).

If a licensed applicant wishes to manufacture additional generally recognized products, or to change an already approved manufacturing Standard Operating Procedure(s) (SOP), the application will be a supplement to the original BLA. FDA will assign a supplement number which expands on the root BLA number. The BLA supplement number will look like: “BL1234.XXX.”

Should an applicant develop a novel product, or a novel use for an existing product, it may be assigned a unique BLA number.

broker – A person or entity who arranges the sale or re-sale of blood and blood components, frequently intended for manufacturing use under a short supply agreement. Short supply agreements are between the licensed manufacturer of the final product and the facility which recovers the plasma, not with brokers. If a broker takes custody (stores or manipulates) blood or blood components, the broker must register with FDA [21 CFR 607].

CBER – Center for Biologics Evaluation and Research, one of FDA’s five centers.

CFR – Code of Federal Regulations.

contractor – Any person or entity, not the applicant, who performs part or all of the manufacturing of the licensed product as a service to the applicant. The applicant assures the contractor’s compliance with the applicable product and establishment standards. Both the applicant and the contractor will be legally responsible for the work performed by the contractor.

distributor – Selling agent or *distributor* means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license [21 CFR 600.3(aa)].

human blood and blood components intended for transfusion or for further

manufacture – For the purposes of this document, this generic phrase will refer to generally recognized human-derived products manufactured by licensed blood banks and source plasma centers. More specifically, this would include products for which safety and efficacy have been demonstrated in an FDA approved license application and the approval grouped the product with other “traditional” blood products; i.e. whole blood, red blood cells, platelets, plasma, Cryoprecipitated AHF or source leukocytes.

in-process controls – The analytical or process controls used during the various stages of manufacturing and processing. These control procedures are established to monitor the output and to validate the performance of those manufacturing processes that may cause variability in the characteristics of in-process material and the final product. In-process controls are often called Quality Control (QC).

license number – A *U.S. license number* is issued by CBER to an applicant upon approval of the applicant’s first BLA. The U.S. license number, which must appear on the product label, (21 CFR 610.60, 610.61) was formerly known as the establishment license number. Those who currently have an approved PLA and ELA will maintain the same license number; no additional application will be necessary.

manufacture – *Manufacture* means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer [21 CFR 600.3(u)].

manufacturer – *Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act; “Manufacturer” also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards [21 CFR 600.3(t)].

manufacturing, divided – *Divided manufacturing* is an arrangement in which two or more manufacturers, each registered with FDA in accordance with 21 CFR parts 207 & 607 and licensed to manufacture a specific biological product in its entirety, participate jointly in the manufacture of the product.⁴

manufacturing, shared – *Shared manufacturing* is an arrangement in which two or more manufacturers are licensed for different aspects of the manufacturing of a product. Neither applicant is licensed for all aspects of the manufacturing. Each manufacturer has an approved Biologics License Application for its part of the manufacturing process. Each participant in a shared manufacturing arrangement should be responsible for significant product manufacturing steps which result in the preparation of an identifiable, stabilized intermediate or end product.⁴

merger – Union of two or more licensed manufacturers to form a new legal entity. A new U.S. license number will be issued to the new entity.

novel product – A *novel product* is a product for which safety and efficacy have not been demonstrated in an FDA approved license application.

short supply – Permits shipment of unlicensed source material from licensed or unlicensed collection facilities to licensed fractionators. The unlicensed collection facility must be registered with FDA [21 CFR 207, 601.22 and 607]. These activities require oversight by the licensed final manufacturer. The licensed manufacturer reports periodically to FDA regarding production specifications and suppliers of the short supply material.

SOP – Standard Operating Procedure(s).

supplement – A *supplement* is a request to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application [21 CFR 600.3(gg)]. An applicant who has received FDA approval for an original BLA submission is licensed to produce the product as presented in the application. Future changes which require FDA review and approval [21 CFR 601.12] should be submitted to FDA as a supplement. Each supplement is assigned a number which uses the BLA number as a root. The number will appear as in the following example: “BL1234.002.” Any amendments submitted to a pending supplement should refer to the supplement number.

III. DIRECTIONS FOR COMPLETING FORM FDA 356h

The following instructions are to assist manufacturers of blood and blood components in the completion of the Form FDA 356h. These instructions are not intended for manufacturers of other biological products.

A. When to use

The Form FDA 356h should be included with each submission to FDA relating to a Biologics License Application. It is the “cover sheet” which allows proper identification, routing and filing of the attached information. FDA continues to encourage applicants to use a cover letter to introduce and summarize the application.

Submit the form with each:

1. Original application submission
2. Supplement to an approved application
3. Amendment to a pending supplement or to a pending application
4. Annual report
5. New or revised labeling
6. Resubmission
7. Notification

B. Submission recommendations

All submission materials should be sent to CBER as a single package and should include:

1. Original copy of all submission materials.
If the submission includes changes to materials which have previously been submitted to FDA, please annotate the changes and reference the previous submission. Any clearly evident method of annotation can be used; e.g., with a highlight marker, bold print, italic print or with brackets in the page margins.
2. For original applications or supplements to an existing Biologics License, send one duplicate copy of the original submission materials.
 - a) Clearly mark as “COPY.”
 - b) If the original has been specially annotated to demarcate the items which have been changed since an earlier submission, the copy should also be annotated.
3. For annual reports send an original and two copies.
4. When new or revised labels are part of the submission they should be submitted detached from the original and duplicates mentioned in sections III.B.1 and III.B.2 above. Specific submission recommendations are discussed under Item #2, Labeling, on the back of the Form FDA 356h (later in this document).

Labels need not be submitted when a previously approved label or *Circular of Information* is being used without change. Instead, FDA assigned “Label Review Number” of the previously approved label should be referenced.

C. Detailed instructions – front of Form FDA 356h

Any information which will not fit in the allotted space on the form should be included in attached documents.

The information boxes on the front of the Form FDA 356h are numbered in Figure 1 to correspond with the detailed instructions included in this document.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>		Form Approved OMB No. 0910-0338 Expiration Date: April 30, 2000 See OMB Statement on page 2.
		FOR FDA USE ONLY
		APPLICATION NUMBER (1)
APPLICANT INFORMATION		
NAME OF APPLICANT (2)		DATE OF SUBMISSION (3)
TELEPHONE NO. (Include Area Code) (4)		FACSIMILE (FAX) Number (Include Area Code) (5)
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): (6)		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE (7)
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) (8)		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) (9)	PROPRIETARY NAME (trade name) IF ANY (10)	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) (11)	CDCE NAME (if any) (12)	
DOSAGE FORM (13)	STRENGTHS: (14)	ROUTE OF ADMINISTRATION: (15)
[PROPOSED] INDICATION(S) FOR USE: (16)		
APPLICATION INFORMATION		
APPLICATION TYPE (check one) (17) <input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507 (18)		
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug (19) Holder of Approved Application		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION (20) <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
REASON FOR SUBMISSION (21)		
PROPOSED MARKETING STATUS (check one) (22) <input type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED (23)	THIS APPLICATION (24) <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	
ESTABLISHMENT INFORMATION		
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. (25)		
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) (26)		

FORM FDA 356h (7/97)

PAGE 1

EF

Figure 1: Form FDA 356h (front)

Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use

C. Detailed Instructions – Front of Form FDA 356h *continued*

- (1) For FDA use only. Do not write in this block.
- (2) The name of the legal entity or person to whom the license will be issued.
 - An applicant who is licensed for more than one product should use exactly the same name on all FDA 356h forms submitted.
 - The name should be the proper legal name of the corporation or person who is the applicant. A copy of the certificate of incorporation is not necessary.
 - Applicant authorized officials should be designated in the establishment description section (item #15 on the back of Form FDA 356h).
- (3) The date that the submission materials are completed and forwarded to FDA.
- (4) The phone number(s) of the applicant. Include the country code for foreign manufacturers.
- (5) The facsimile number of the applicant. Include the country code for foreign manufacturers.
- (6) The applicant's full address (number, street, city, state, zip code of the headquarters location) should be listed. Include the country for non-U.S. manufacturers.

Applicants with a previously issued U.S. license number (formerly also known as the establishment license number) should record the number.

- (7) If applicable, list the name, full address, phone number and facsimile number for the applicant's authorized U.S. agent. Complete this box only if the applicant is a foreign manufacturer who has authorized a U.S. agent to speak on its behalf on all matters related to FDA licensure and review.
- (8) For first time applicants, the BLA number will be assigned at the time of application submission. First time applicants should leave this field blank.

Current holders of approved ELA and PLA licenses will be assigned their BLA number when FDA receives the first supplement under the new BLA system. Licensed applicants who have not yet been assigned a BLA number should leave this field blank.

Licensed applicants who have their assigned BLA number should list it here.

If materials are being submitted in support of a pending BLA supplement such as a resubmission in response to a Complete Response Letter, record the BLA supplement number in this field. These materials are amendments to the supplement.

In the rare event that an application is for a novel blood product which has been addressed in another protocol (e.g., Investigational New Drug (IND)), list FDA tracking number for the related submission.

- (9) through (10) – Not Applicable – these boxes do not apply to routine blood products. Complete these boxes only if the application is for a novel blood product.
- (11) Provide the name of the product or products affected by this application as it will appear on the product label.
- (12) through (15) Not Applicable – these boxes do not apply to routine blood products. Complete these boxes only if the application is for a novel blood product.
- (16) For products intended for **transfusion**, the indications for use should be included in the *Circular of Information* submitted with the product labeling. Complete this box only if new indications for use, not previously included in a FDA approved *Circular of Information*, are proposed.

For products intended for **further manufacture**, indicate either “for manufacture into injectable products” and/or “for manufacture into non-injectable products.”

- (17) Check the box for Biologics License Application.
- (18) and (19) Not Applicable – these boxes do not apply to routine blood products. Complete these boxes only if the application is for a novel blood product.
- (20) Blood and blood product applicants should check only one of the following:
- **Original Application** – the inaugural application submitted by the applicant or a new application for a novel product not previously submitted for license. This will only include products for which a new BLA number will be assigned. For manufacturers of blood and blood components, check this box only when submitting an application for a novel blood product or if this will be the first license application for routine blood products.
 - **Amendment to a Pending Application** – additional materials submitted for an application or supplement already under FDA review. Additional materials may be submitted based on further data gathering, such as QC material, or on FDA written or verbal requests.
 - **Resubmission** – Submission of:
 - ◇ A complete response to an FDA complete response letter.
 - ◇ An application for a product which was previously withdrawn by the applicant.
 - ◇ An application for a product which previously received a “refusal to file” action from FDA.

- **Presubmission** – Information submitted prior to the submission of a complete new application, usually in preparation for an applicant / FDA presubmission conference.
- **Annual Report** – Check this box if the form is being used as a cover sheet for the annual report required under 21 CFR 601.12(d).
- **Establishment Description Supplement** – Check if this submission is exclusively to report changes related to the Establishment Description section (item #15 on the back of Form FDA 356h). This may include such issues as:
 - ◊ A change in the establishment being reported as required under 21 CFR 601.12(b) or (c).
 - ◊ A change in license holder (applicant).
- **SUPAC Supplement** – Not Applicable: The Scale Up and Post Approval Changes option does not apply to blood and blood components.
- **Efficacy Supplement** – Not Applicable: This option does not apply to previously approved blood and blood components. Efficacy information would have to be provided for the first time submission of a novel product.
- **Labeling Supplement** – New or changed labeling for a previously approved product as required under 21 CFR 314.70 and 601.12. (Should also include Form FDA 2567.) This box is checked when labeling is the only reason for the supplement. Labels may also be submitted in support of a current application; check item #2 on the back of Form FDA 356h.
- **Chemistry, Manufacturing and Controls Supplement** – Submission of manufacturing change to an approved BLA (item #4.A. on the back of Form FDA 356h). This may include such issues as:
 - ◊ Request to manufacture an additional product covered neither by the original BLA nor by an already approved supplement to the BLA.
 - ◊ Request to manufacture approved products at an additional facility or facilities.
 - ◊ A change to manufacturing protocols being reported as required under 21 CFR 601.12(b) or (c).
- **Other** – Any submission not covered above, such as the submission of data as agreed in post approval commitments or notifications regarding your Biologics License Application about which FDA must be notified, but does not “review and approve.” Please note the reason for the submission in the next block. For example, issues which might be included in this category:
 - ◊ A change in Authorized Official.
 - ◊ Shipment of viral marker reactive product.

- (21) This section, and the recommended cover letter, should contain a brief explanation of the reason for the submission, for example “response to complete response letter of 3/10/98” or “revised *Circular of Information* consistent with new Leukocyte Reduction Guidance.”

If the submission is a change to an approved application, per the requirements of 21 CFR 601.12, the following abbreviations may be used:

- PAS Prior Approval Supplement
- CBE30 Supplement – Changes Being Effected in 30 Days
- CBE Supplement – Changes Being Effected
- AR Annual Report

- (22) If the product is intended for transfusion, check “prescription product (Rx).” If the product is for further manufacturing, no box should be checked.
- (23) Identify the number of volumes, including electronic media, contained in the original copy of this submission. Most submissions from blood manufacturers are contained in a single volume. A volume is a bound set of data, such as a notebook. There may be multiple volumes of data in a copy.
- (24) At this time most blood bank submissions will be “paper.”

FDA is eager to work with applicants who can make submissions in an electronic format. FDA has published guidance regarding the general considerations of electronic submissions.¹¹ Manufacturers of blood and blood components who have read the available guidance and wish to submit using an electronic format should contact the Division of Blood Applications. An Electronic Submissions Coordinator, along with a Consumer Safety Officer, will work with the applicant.

- (25) Provide the requested information for each facility included in, or affected by, the submission. Include the following information for each facility: name, address, telephone number, registration number, and the name of a contact person. The DMF (Drug Master File) number is not applicable for blood components. Explain which manufacturing steps or type of testing are performed at each facility. Indicate if each facility is currently prepared for inspection or when it will be ready.

Please note that the complete establishment description is requested under item #15 on the back of Form FDA 356h. Establishment information relevant to the submission may be reported either here or under item #15.

Information which has been previously reported and is still up-to-date need not be reported again. For information which is unchanged since an earlier submission, such as a BLA supplement or an Annual Report, reference the earlier submission by date and/or FDA tracking number.

- (26) If the SOP or data related to this application have previously been submitted to FDA, list FDA tracking number(s) here. This may be a BLA number, a BLA supplement number, or a previous reference number assigned to an Establishment or Product License Application (ELA or PLA).
- Since blood and blood components will be licensed under a single BLA for each applicant, often there will be no data to be recorded in this box.
 - If this application is being submitted for review using a previously approved comparability protocol [21 CFR 601.12(e)], note “COMPARABILITY PROTOCOL” and list the BLA supplement number of the approved protocol.
 - If the application is for a novel blood product, list all filings (e.g., BLA, IND, NDA, PMA, 510(k), IDE, BMF and DMF) referenced in the current application.

D. Detailed instruction – back of Form FDA 356h

The information boxes on the back of the Form FDA 356h are numbered on the original form. The detailed instructions included in this document are numbered to correspond with the numbering on the form or the titles in the box.

Items 1 through 19 constitute a check list that should be used to indicate which types of information are included with the submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order of the inclusion of those sections in the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index.

The CFR references on the Form FDA 356h are provided for most items to clarify what information should be submitted.

Item #1 – Index

An index should be provided near the front of the submission which shows the organization and order of the contents. For blood or blood component submissions which are concise and uncomplicated, the index requirement may be satisfied by the cover letter.

Item #2 – Labeling

Check this box if labeling is included in the submission. Each label submitted for review should be submitted with:

1. One original and one copy of each label. These may be printer’s proofs or final labels.
2. Each label set (original + copy) should be accompanied by a single Form FDA 2567, “Transmittal of Labels and Circulars,” completed and signed by an authorized official.
3. Labels and the Form FDA 2567 should be detached from the rest of the submission.

4. If the *Circular of Information*, or other labeling which accompanies the product, is new or revised, send one copy with its own Form FDA 2567.

If a label has been previously approved and is to be used without change, do not submit for another review. Instead, reference the label review number which identifies the previously approved label.

A standard base label that is used for more than one product may be submitted for review of changes involving an address, or viral marker testing on Source Plasma labels. Individual labels should be submitted when new products are collected or manufactured, including the collection of Source Plasma from donors with pre-existing disease associated antibodies, Red Blood Cell antibodies, or Human Leukocyte Antigen antibodies.

Item #3 – Summary

Original applications should include a summary sufficient for the reader to obtain a good general understanding of the data and information in the application. Supplements filed under the requirements of 21 CFR 601.12 do not require a summary; however, a summary in the cover letter is useful.

Item #4.A. – Chemistry section / Chemistry, manufacturing and controls information (CMC)

The submission requirements for this section are discussed in detail in “Part I” below.

Item #4.B. – Chemistry section / Samples

Ship product samples to FDA only when requested by FDA. Even if it is known that FDA will require samples, ship only after shipping arrangements have been discussed with an FDA official.

Item #4.C. – Chemistry section / Methods validation package

Item #5 – Nonclinical pharmacology and toxicology section

Item #6 – Human pharmacokinetics and bioavailability section

Items #4.C. to #6 are not applicable for most blood and blood component submissions, but may be required when submitting an application for a novel product.

Item #7 – Clinical Microbiology

This section is not applicable for most blood and blood component submissions, but may be required when submitting an application for a novel product. Microbiology data may be required to demonstrate sterility of product in the CMC section – see the discussions about individual products.

Item #8 – Clinical data section

Item #9 – Safety update report

Item #10 – Statistical section

Item #11 – Case report tabulations

Item #12 – Case report forms

Item #13 – Patent information on any patent which claims the drug

Item #14 – A patent certification with respect to any patent which claims the drug

Items #8 to #14 are not applicable for most blood and blood component submissions, but may be required when submitting an application for a novel product.

Item #15 – Establishment description

The submission requirements for this section are discussed in detail in “Part II” below.

Item #16 – Debarment certification

Section 306(k) of the Food, Drug and Cosmetic Act prohibits the use of the services of any individual who has been debarred according to the provisions of the Act. Applicants must provide a statement with a new application for a Biologics License that no debarred individuals have worked or will work for the applicant or have provided services in support of the application. This may be provided in a separate attachment, or can be an additional paragraph in the cover letter. The debarment list is available at http://www.fda.gov/ora/compliance_ref/debar/default.htm. The statement should be signed by the applicant or an authorized official.¹²

Although the debarment certification statement is not required for supplements, the requirements of the Act still apply; that is, the applicant must not use in any capacity the services of any debarred persons.

Item #17 – Field copy certification

Item #18 – User Fee Cover Sheet

Items #17 and #18 are not applicable for most blood and blood component submissions, but may be required when submitting an application for a novel product.

Item #19 – Other (Specify)

Use this item to indicate that you have included materials in the application not clearly belonging to one of the above categories. Describe the item here, or in your index.

Signature –

The form should be signed and dated by an agent or official authorized by the applicant to represent the applicant to FDA. The authorized official’s typed name, title, address and phone number should be provided in the areas indicated. This information will be used by FDA for future contacts regarding the submission. The signer indicates agreement with the “Certification” statement on the form.

PART I – CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

Item 4.A. on the back of the Form FDA 356h

I. PRODUCTS INCLUDED IN “BLOOD & BLOOD COMPONENTS” BLA

The CMC section will include detailed information regarding the manufacture of each licensed product in the applicant’s facility or facilities.

The following list of traditional blood and blood component products may be applied for and will be approved under a single BLA.

- A. Whole Blood
- B. Red Blood Cells
- C. Plasma
 - 1. Plasma
 - 2. Fresh Frozen Plasma
 - 3. Source Plasma – can be licensed as a stand-alone product, without first being licensed for Plasma.
- D. Platelets
- E. Cryoprecipitated AHF
- F. Source Leukocytes

Many variables will combine to define a specific licensed product. A listing of some of the possible variables would include anticoagulant, dating period, instrumentation, container type, special manufacturing device (separation chambers or filters), intended product use, product specifications, storage requirements and donor source. These many variations combine to make a comprehensive list of licensed products well beyond the scope of this document. Since variations exist for every possible product, the approval letter(s) from CBER must be read carefully to determine exactly what product(s) the applicant has been approved to manufacture and ship.

II. MANUFACTURING PROCEDURES COMMON TO MULTIPLE TRANSFUSION COMPONENTS

The following processes may be applied to more than one product. For each product included in a submission, the applicant should identify all of the processes used to manufacture the final product. The supporting documentation submitted in the CMC section for each product should include the SOP and labeling as described elsewhere in this document. Additional useful process-specific information to report in the CMC section is described below.

A. Irradiation^{2,8}

1. Two months' irradiation logs which include each product for which approval is requested.
2. Dosimetry reports
 - a) Annual for Cesium-37
 - b) Biannually for Cobalt-60

B. Leukocyte reduction⁹

1. Include related SOP (e.g., use of sterile connecting device).
2. Identify system used (e.g., filter manufacturer, filter name and model number).
3. Identify when filtration is performed (i.e., during initial 8 hour hold or after units have been refrigerated).
4. Descriptions of all the methods used for in-process controls (e.g., leukocyte counts) including frequency of testing, acceptance criteria and required follow-up when criteria are not met (e.g., product labeling, product disposition, problem investigation).
5. Quality Control (QC) records for at least 2 months (4 units per month or 1% of total monthly production, whichever is greater, for each methodology).

C. Divided product

1. Include related SOP (e.g., use of sterile connecting device).

D. Washed product

1. Include related SOP (e.g., use of the sterile connecting device).
2. Identify the washing system (instrument, soft-goods) used.
3. Provide detailed descriptions of all the methods used for in-process controls (e.g., red blood cell recovery, minimum acceptable level for residual total protein, etc.), including acceptance criteria and required follow-up when criteria are not met.
4. Submit sterility data for ten units of washed red blood cells. If not performed in-house, submit the name and address of the Clinical Laboratory Improvement Act of 1988 (CLIA) approved laboratory performing the testing. If the laboratory is registered with FDA, provide the registration number. The applicant should include a statement that the contract laboratory 1) is using a sterility testing protocol which has been reviewed and accepted by the applicant, 2) is using a program which has been included in the applicant's Quality Assurance (QA) plan, and 3) is prepared to

permit FDA inspection. It is unnecessary to send copies of original agreements or supporting letters from the contract laboratory.

E. Frozen / deglycerolized, rejuvenated, frozen rejuvenated, rejuvenated deglycerolized

1. Submissions for multiple products may occur sequentially or simultaneously. For example, if an applicant is already approved to manufacture Red Blood Cells Frozen, the BLA may be supplemented to include Red Blood Cells Frozen Rejuvenated. Alternatively, if the applicant is not yet licensed for Red Blood Cells Frozen the submission may include data for both products simultaneously. License approval for a product will not be granted until precursory product(s) are approved.
2. Provide detailed descriptions of all the methods used for in-process controls (e.g. glycerol removal, determination of free hemoglobin, red blood cell recovery), including acceptance criteria and required follow-up when criteria are not met.
3. Completed examples of all records and logs used.
4. Sterility data for 10 units of frozen, deglycerolized and/or rejuvenated blood or for 10 lots of red blood cells for immunization. If not performed in-house, submit the name and address of the CLIA approved laboratory performing the testing. If the laboratory is registered with FDA, provide the registration number. The applicant should include a statement that the contract laboratory 1) is using a sterility testing protocol which has been reviewed and accepted by the applicant, 2) is using a program which has been included in the applicant's QA plan, and 3) is prepared to permit FDA inspection. It is unnecessary to send copies of original agreements or supporting letters from the contract laboratory.

III. SUPPORTING DOCUMENTATION

All submissions should include appropriate SOP, labels and supplementary information defined in other FDA documents. The supporting documentation should demonstrate that the proposed manufacturing is in compliance with the law, the regulations and consistent with FDA guidance and recommendations.

Information unchanged from previously approved supplements need not be submitted again. Instead, the information may be referenced by the BLA Supplement identification number. If it contributes to the clarity of the submission, previously submitted information should be included rather than referenced.

A. SOP (Standard Operating Procedure(s))

New SOP or SOP with substantive revisions as well as all associated forms or information pamphlets, on any of the following topics, should be forwarded to CBER for review and approval:

1. Donor suitability, including donor deferral.
2. Blood collection and processing, including:
 - a) Arm preparation;
 - b) Sample collection; and
 - c) List of tests performed, including method used.
(Do not submit testing SOP, except as noted in product specific information found in other documents.)
3. High risk behavior questions / AIDS information.
4. Donor history forms (including informed consent).
5. Blood and blood component manufacturing for licensed products only:
 - a) Submit the SOP for the manufacturing steps in product production.
 - b) For in-process control testing (QC testing), submit a list of tests performed, including the method used.
(Do not submit testing SOP, except as noted in product specific information found in other documents.)
6. Quarantine and disposition of unsuitable product.

Indicate the source of all SOP included in your submission; e.g., internally developed, obtained from another licensed establishment or from a proprietary organization.

If an SOP change is in response to an FDA Memorandum or Guidance, follow the instructions in the Memorandum or Guidance for reporting the change to FDA.

B. Additional Supporting Documentation

In the future FDA intends to publish additional guidance regarding unique supporting documentation for specific products and the specific review criteria used by CBER. Until such additional guidance is published, use of the CFR, FDA Memoranda, FDA Guidance, FDA Points to Consider and previously published review checklists⁷ should provide sufficient information for the preparation of a complete submission.

IV. MANUFACTURING AGREEMENTS

A. Contractors

The applicant assures that all steps performed by contractor(s) comply with the applicable product and establishment standards for manufacturing or testing performed in support of manufacturing. Both the applicant and the contractor will be legally responsible for the work performed by the contractor.

1. Which contracts to report

Use the following examples as a guide to determine which contracts to report.

- a) Do report new, change in, or addition of, contractors for services such as:
- (1) Outside testing facilities performing:
 - (a) Routine serological and infectious disease testing related to product labeling (tests of record).
 - (b) Confirmatory testing used for donor re-entry decisions.
 - (c) In-process controls (product QC testing) such as leukocyte counts, platelet counts and sterility.
 - (d) Confirmatory testing used only for donor counseling.
 - (2) Irradiation.
 - (3) Product collection such as apheresis services.
 - (4) Off-site storage of blood and blood components under the control of the applicant.
 - (5) Staffing services for personnel directly involved in manufacturing such as donor screening and blood collection.
 - (6) Suppliers of Red Blood Cell (RBC) for immunization programs.
- b) Do not report contractors for services such as:
- (1) Hazardous waste disposal.
 - (2) Common carriers and delivery.
 - (3) Equipment service and maintenance.
 - (4) Housekeeping.
 - (5) Donor emergency transport or treatment.

2. List contractor(s)

Provide a list of contractors. Include:

- a) Legal name of the contractor
- b) Address
- c) Name of contact person
- d) FDA registration number (when available)
- e) Contract summary (described below)

3. FDA registration of contractors

Except for specific examples listed below, each facility that collects, manufactures, stores, tests, provides red blood cells for immunization, labels and/or distributes any portion of the manufactured product must be registered with FDA [21 CFR 607.21 and 607.3(d)]. While registration is not required for all contractors, all contractors performing a manufacturing step in support of a U.S. license are subject to inspection by FDA.

FDA registration is neither required nor recommended for the following:

- a) Contractors which provide off-site storage and/or shipping of product need not register unless the contractor's duties include manufacturing functions such as culling product which tested positive for infectious disease markers, filling, testing, labeling or packaging.
- b) In-process control testing (e.g., leukocyte counts, platelet counts and sterility testing) may be performed in either a registered or an unregistered laboratory. Unregistered laboratories should be CLIA approved.
- c) Confirmatory testing used only for donor counseling may be performed in either a registered or an unregistered laboratory. Unregistered laboratories should be CLIA approved.

4. Contract summary or summaries

For each contract, summarize the terms of the contract. It is not necessary to include the actual contract; neither is it necessary to include confidential business information, such as fees and volume discounts. Include:

- a) A precise listing and description of the services provided, such as the tests or the manufacturing steps performed.
- b) A description of the product shipped to the contract facility.
- c) A description of the responsibilities of each participant, including the supervision and control exercised by the license applicant, for operations performed at the contract facility. Through an outline, diagram and/or narrative, explain how the contracted activities are integrated into the applicant's manufacturing process.
- d) A brief summary of the applicant's SOP for periodically assessing the contract facility's compliance with applicable product and establishment standards and current Good Manufacturing Practice (cGMP). The applicant should state when the most recent assessment occurred.

B. Cooperative manufacturing agreements – shared or divided

Since cooperative manufacturing is performed under the manufacturing licenses of all the participants, each participant holds approvals under their individual license.

1. List each participating manufacturer.
2. Provide a detailed description of contractual agreements. Especially specify the particulars of manufacturing responsibilities. Section IV.A.4 above may be used as a guide for the minimum information which should be submitted.
3. Through an outline, diagram and/or narrative, explain how these facilities function in the applicant's manufacturing process.
4. Submit labels for FDA review and approval.

PART II – ESTABLISHMENT DESCRIPTION SECTION

Item 15 on the back of the Form FDA 356h

It is FDA's goal to understand the applicant's organizational structure and function well enough to make competent judgments about the ability to produce a quality product in conformance with the law, the regulations and current good manufacturing practices. Contemporary standards for quality manufacturing increasingly focus on issues related to the organization, lines of communication and quality assurance oversight. FDA intends to move toward oversight of manufacturing systems and the applicant's ability to manage those systems in place of the continued review of the details included in SOP, training programs, validation and QC records.

Establishment description information should be included in a first-time BLA submission.

Those who are already licensed may submit information such as that described under "Description of Manufacturing Organization" as part of their first annual report after publication of this guidance document. Other information, such as that described under "Major Equipment," should only be submitted as applicable in support of an individual submission.

Once establishment description information has been submitted, an applicant need not submit the information again unless it has changed. Hence, BLA supplements can refer to the most recent submission of still-current establishment description information. The date and/or FDA-assigned tracking number for the document in which the information was last reported should be included in the submission. If it contributes to the clarity of the submission, previously submitted information may be included rather than referenced.

Send changes in authorized officials and mailing address to FDA when they occur.

I. ORGANIZATION AND PERSONNEL

A. Description of Manufacturing Organization

Summarize the general characteristics of the organization. Provide an organizational diagram showing reporting authorities, complete with descriptive job titles. The diagram should be sufficient for someone unfamiliar with your organization to recognize the interrelationships of the major functional units.

B. Authorized Officials

List of authorized officials¹ – those authorized by the applicant to initiate a BLA or BLA supplement and to discuss licensure and regulatory issues with FDA representatives. The list should include for each authorized official:

1. Name;
2. Title;
3. Mailing address and location (The location is only necessary when the individual's office is different than the mailing address.);

4. Phone number (include country code if applicable); and
5. Facsimile number (include country code if applicable).

II. PHYSICAL PLANT AND MAJOR EQUIPMENT

A. Physical Plant

Do not submit this information with the application. Physical plant information will be reviewed upon inspection for compliance with the CFR [21 CFR 211 & 606] and with cGMP.

B. Major Equipment (if applicable to the submission)

In a table, list major equipment used in the manufacture of blood and blood components. Include number of units, model numbers, version numbers, a description of the equipment used and pertinent notes; e.g., special chambers used on apheresis equipment.

1. Equipment listed should include, but not necessarily be limited to:
 - a) Computer system (central processing unit) and associated software (manufacturer, product name, version number)
 - b) Apheresis equipment
 - c) Blood irradiators
 - d) Sterile connecting devices
 - e) Infectious disease testing instrumentation
 - f) Self-contained mobile collection units
2. Equipment which should not be included are:
 - a) Computer peripherals such as printers, label printers, terminals
 - b) Personal Computer (PC) based systems such as word processors and spread sheets
 - c) Laboratory testing equipment other than infectious disease testing instrumentation
 - d) General laboratory centrifuges
 - e) Refrigerators, freezers or other temperature and humidity controlled storage systems

III. QUALITY ASSURANCE

FDA has described its recommendations for the Quality Assurance functions in a guidance document.⁶ Depending on the size and organization of the applicant's manufacturing operation, the make-up of the staff performing these duties can vary greatly and still successfully accomplish the recommended QA functions. Provide a summary of your QA program [21 CFR 211.22(a)]. The summary need not be extensive, but should address the following topics when applicable to your operations:

A. Reporting responsibility

- Who performs the QA functions and how these functions are integrated into the manufacturing process.
- To whom the QA unit, those performing QA functions, reports.
- The QA unit's position and relationship in the general organizational structure relative to other organizational units.

B. Oversight

The facets of the manufacturing process which are included in the QA unit's oversight, such as those directly under the applicant's control, contracted processes, materials and supplies, laboratory testing for tests of record, and laboratory testing for in-process controls.

C. Authorities

Authority to act, to report or to recommend.

D. Training and assessment of personnel

The QA unit's role in performing or reviewing the training and assessment of personnel in all aspects of the manufacturing process.

E. Competency evaluation

The QA unit's activity in performing or reviewing competency evaluations of personnel in all aspects of the manufacturing process.

F. Proficiency testing

The QA unit's activity in performing or reviewing proficiency evaluations of personnel in all aspects of the manufacturing process.

G. Systems validation

- The general requirements and/or recommendations for system validation.
- How the QA unit monitors conformance with its validation requirements and/or recommendations.

H. Problem investigation and resolution

- The system for collecting problem reports.
- The approach to problem analysis and trend analysis.
- The plan to ascertain the effectiveness of implemented changes and corrections.

I. Audits

- The system for designing audits and collecting data.
- The approach to analyzing audit data.
- The plan to ascertain the effectiveness of implemented changes and corrections.

IV. MERGERS AND ACQUISITIONS

A. Merger

A merger of two or more licensed manufacturers results in the formation of a new legal entity which will require the issuance of a new U.S. License. The new U.S. License holder should provide statements which address the following issues: the managerial structure, reporting responsibilities, QA oversight, any changes to the physical plant or equipment and/or manufacturing procedures. Hence, a merger application would need to include the establishment description information described above (Part II).

Unless the participants in the merger were using matched manufacturing SOP, the information described in the CMC section (Part I) should also be included in the merger submission.

B. Acquisition

1. An acquisition occurs when one U.S. License holder purchases a facility that was previously operating under a different U.S. License. The license of the previous U.S. license holder will be revised to delete the facility and the license of the U.S. License holder acquiring the facility will be supplemented to include the acquired facility.

The U.S. License holder acquiring the facility should include a statement that describes how the new facility will be incorporated into their manufacturing organization. The following issues should be addressed: SOP to be used at new facility, changes in staff or equipment, disposition of product remaining at the facility which was collected under the previous U.S. License, responsibility for donor deferral and look-back procedures for testing done under the previous U.S. license, and any change in contracting facilities (e.g., outside testing laboratory). That is, the supplement sent to FDA would include elements described in both the CMC section (Part I) and the establishment descriptions section (Part II) of this document.

2. An acquisition may also occur when an applicant who currently holds no U.S. License purchases a facility that was previously operated under a U.S. License, but does not purchase the entire license. The license of the previous U.S. license holder will be revised to delete the facility and the new owner must apply to be licensed as a new applicant. All of the information recommended in this guidance document should be included in support of the application.

PART III – REFERENCES

1. Federal Register, 10/15/97, 62 FR 53536, Final Rule: Revision of the Requirements for a Responsible Head for Biological Establishments.
2. Memorandum: Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products, July 22, 1993.
3. Federal Register, 7/8/97, 62 FR 36558, Revised Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use; Availability.
4. Federal Register, 11/25/92, 57 FR 55545, FDA’s Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics.
5. Guidance for Industry: Changes to an Approved Application: Biological Products, July, 1997. (July, 24, 1997, 62 FR 39904)
6. Guideline for Quality Assurance in Blood Establishments, July 11, 1995. (July 14, 1995, 60 FR 36290)
7. Workshop for Licensing Blood Establishments, January 30 & 31, 1995, Sponsored by FDA, CBER.
8. Guidance for Industry: Gamma Irradiation of Blood and Blood Components: A Pilot Program for Licensing, December, 1998. (January 27, 1999, 64 FR 4118)
9. Memorandum to All Registered Blood Establishments, “Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products,” May 29, 1996.
10. Federal Register, 7/31/98, 63 FR 40858, Proposed Rule: Biological Products Regulated by Section 351 of the Public Health Service Act; Implementation of Biologics License; Elimination of Establishment License and Product License.
11. Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations, January, 1999. (January 28, 1999, 64 FR 4433)
12. Guidance for Industry (Draft Guidance): Submitting Debarment Certification Statements, September, 1998. (December 2, 1998, 63 FR 53060)

APPENDIX A

Form FDA 356h

Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use

Including standard instructions

<http://www.fda.gov/opacom/morechoices/fdaforms/CBER.html>

Updated October 2005 to revise link to Form FDA 356h only