

CHAPTER 5 BLOOD, PLASMA, AND CELLULAR BLOOD COMPONENTS

INTRODUCTION

This chapter of the Guideline provides recommendations to Sponsors of Requests for Revision for new monographs for blood, plasma, and cellular blood components. For blood and plasma-*derived* products, which are usually proteins drawn from natural sources or produced by biotechnological processes, please see Chapter 2 of this Guideline. This chapter focuses on blood, plasma and cellular blood components (hereafter products). Prior to 2000, monographs for these products were abbreviated, containing Packaging and Storage, Expiration Date, and Labeling statements, with references to 21 *CFR* 600–680 for Description. In 2000 USP’s Council of Experts elected to develop “full-length monographs” for these products. With this decision, USP now provides manufacturers, practitioners, and patients with more complete information to ensure acceptable quality, purity, and potency parameters for blood, blood components, and blood products.

A Request for Revision to create a new USP monograph for these product types should include name, description, definition, other requirements (packaging and storage, labeling, and USP Reference Standards), and the product specification. The specification should include universal tests and may include specific tests as well. In some instances, one or more of the universal tests may not be applicable to these products. Specific tests should be included when they have an impact on the quality of the product for release and/or compendial testing. Taken as a whole, a specification should be stability indicating, using either one or more procedures for quantitation that are stability indicating, or a procedure for quantitation that is not stability indicating with an accompanying stability-indicating procedure for impurity testing.

WHY USP MONOGRAPHS?

- a) US manufacturers of blood and blood components are encouraged to develop *USP–NF* monographs for their products as a means of providing support in developing a uniform international standard for each product and in turn taking a leadership role in the process.
- b) In many cases, the tests, procedures, and acceptance criteria and other information in monographs published in other pharmacopeias do not completely conform to those contained in the biological license approved by FDA.
- c) Although *USP–NF* contains monographs for articles legally marketed in the US, its standards are recognized in numerous countries. Monographs in *USP–NF* can help US manufacturers minimize regulatory impact on global distribution of their products.

d) The designation of “USP” in conjunction with the official title or elsewhere on the label of an article indicates that a monograph for the article is contained within *USP*, and the article purports to comply with all applicable *USP* standards.

e) Public standards for blood and blood products help ensure consistent and appropriate quality.

In addition to recommendations in this chapter, a blood or blood product monograph must also conform to the requirements discussed in the *General Notices and Requirements* chapter of *USP–NF*.

BLOOD, BLOOD COMPONENTS, AND BLOOD PRODUCTS

Blood is a complex mixture of plasma (the liquid component), white blood cells, red blood cells, and platelets. Plasma is 90 percent water and constitutes about 55 percent of blood volume. Plasma can be fractionated or separated into derivatives/products. These include albumin (the chief protein constituent), fibrinogen (responsible in part, for the clotting of blood), globulins (including antibodies), and other clotting factors.

Name Sponsors submitting a Request for Revision for a *USP* blood, plasma, or cellular blood component monograph should provide a proposed proper name (for additional information see 21 *CFR* 640). This name should uniquely identify and differentiate the product from similar products. Additional differentiation can be achieved by including 1) the method of preparation, e.g., Platelets, Pheresis, which specifies a specific method of preparation, or 2) intended use of the component, e.g., Source Plasma.

Definition The Request for Revision should contain the product’s Definition, indicating the specific fractionation method(s) used to prepare the component. If the method(s) involves the selective removal of a component, the (minimum) permissible amount of the depleted component should be indicated in the Request for Revision.

Packaging and Storage The Request for Revision should indicate the type of container to be used for the blood, plasma, or cellular blood component. It should also indicate the storage temperature, using the temperature definitions under *General Notices and Requirements* (see also 21 *CFR* 610.53). If necessary, it should also indicate a requirement to protect from light and freezing.

OTHER REQUIREMENTS

Expiration Date The establishment of an expiration date should be based upon stability data that have received appropriate regulatory evaluation and approval (see 21 *CFR* 610.53).

Labeling The Request for Revision should provide labeling information conforming to guidance provided in 21 *CFR* 610.60 and 606.61 and the American Association of Blood Banks’ *Circular of Information for the Use of Human Blood and Blood Components*.

This labeling information should include instructions for use, storage temperatures, recommended dose, route of administration, and expiration date (day and time, if applicable). The labeling should also indicate the donor category (paid or volunteer and autologous, if applicable), ABO group, and Rh type, if applicable. For multiple-dose containers, the individual dose should also be provided. Cautionary statements, such as “avoid freezing” or “avoid exposure to light” should be included in the labeling, where appropriate. The Request for Revision should indicate preservative(s) and anticoagulants used, as necessary. If an antibiotic is present, its name and amount per dose should be provided. When applicable, chemical method(s) used to inactivate microorganisms or virus should be indicated in labeling.

REFERENCE STANDARDS

The Request for Revision should indicate which monograph tests require an official USP Reference Standard(s). When a USP Reference Standard is not available, manufacturers should use available standards from FDA’s Center for Biologics Evaluation and Research (CBER) or World Health Organization reference standards. Procedural standards to determine the suitability of tests and assays, when appropriate, should be included. The source of reference standards, including official USP Reference Standards, should be included within the test protocol and clearly identified.

SPECIFICATIONS

Although USP develops monographs that are as comprehensive as possible, USP recognizes that some information needed in a Request for Revision may be proprietary. When proprietary information is provided and so identified, USP treats this information confidentially (see *USP Document Disclosure Policy* available at <http://www.usp.org/aboutUSP/governance/policies/documentDisclosure.html>). Nonetheless, procedures in the specification should be sufficiently detailed so that any competent analyst with the appropriate equipment and reagents may conduct the analysis. Where this is not the case, the general technique and acceptance criteria should be provided in the Definition (see above).

The Request for Revision must include validation data for each procedure, as appropriate (see General Chapter *Validation of Compendial Methods* <1225>). For validation not covered by <1225> (e.g., bioassay, serological procedures), reliance on ICH, CBER, or another guideline may be appropriate.¹ The Request for Revision should indicate the document followed for validation.

Identification The Identification test usually includes multiple procedures (also see 21 *CFR* 610.14). These procedures should adequately identify the blood, plasma, or cellular blood component. Procedures used to establish the product’s group and type, where applicable, should be indicated in the labeling. These can rely on physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods,

immunological, molecular biological, or other procedures. The primary goal is to unambiguously differentiate the product from any other related product.

Visual Inspection When applicable, the Request for Revision should include visual inspection of the product during storage and prior to use.

Impurities Test Products may contain residual components, e.g., red blood cells. If platelets are the product, they may contain leukocytes. These are to be regarded as impurities. The Request for Revision should contain a validated procedure (e.g., residual white cell count using a hemocytometer) with acceptance criteria (limits) for these impurities.

Infectious Disease Agents Tests To minimize transmission of infectious diseases, the Request for Revision should contain information/guidelines for tests conducted on source blood to test for the presence of infectious disease agents using FDA-approved and -licensed commercially available test kits and/or nucleic acid assays. Currently FDA mandates (21 *CFR* 610.40) testing of source blood for syphilis, hepatitis B virus, hepatitis C virus, human T-cell virus (HTLV) Type I and Type II, and HIV.

Red Cell Antigens Test If relevant (e.g., whole blood and red blood cells), the Request for Revision should indicate testing for unexpected red cell antigens, using FDA-approved and licensed commercially available test kits.

ASSAY

For Assay, the Request for Revision may measure potency using either an in vitro or in vivo procedure. This test should include reference to an official USP Reference Standard for the product, if applicable. In some instances (e.g., blood or red blood cells) a laboratory measurement may suffice for Assay (e.g., hemoglobin content). The Assay may also rely at times on physicochemical procedures such as HPLC, electrophoresis, colorimetric methods, or cell-count procedures, e.g. platelet or leukocyte counts. When commercially available kits are used, they should be qualified for suitability using an official USP Reference Standard, if available.

SPECIFIC TESTS

Specific tests in addition to the ones described above may be included to better describe and control the potency, quality, and purity of a blood, plasma, and cellular blood components. Reference should be made to appropriate General Chapters, where applicable. If the procedure is not included in a General Chapter, the Request for Revision should include complete validation data (see General Chapter *Validation of Compendial Methods* <1225>).

Sterility Test An injectable blood, plasma, or cellular blood component (recovered plasma, source leukocytes, and source plasma) can also be intended for use in further

manufacturing into noninjectable products and should comply with General Chapter *Sterility Tests* <71> if the label of the product claims it as sterile. When a Sterility test is not included for a product claimed as sterile, the Sponsor should provide justification. The Request for Revision should indicate if the Membrane Filtration Method or the Direct Transfer Method is used. The Direct Transfer Method is used if the Membrane Filtration Method is not applicable.

Bacterial Endotoxins Test or Pyrogen Test The Request for Revision should include the procedure to be used for the Bacterial Endotoxins test (see General Chapter *Bacterial Endotoxins Test* <85>) when the label of the product claims it to be pyrogen free. Different procedures may use different acceptance criteria depending on the type of product. The limit is expressed per dose and is calculated based on the maximum dose injected per kg of body weight per hour. When the Bacterial Endotoxins test cannot be validated or the regulatory requirement indicates otherwise, the procedure to test for pyrogens should be employed (see General Chapter *Pyrogen Test* <151>)

Container–Closure Test The Request for Revision for products should document that the container–closure test maintains integrity (see General Chapter *Sterility Tests* <71>).

Particulate Matter Test Injectable blood, plasma, and cellular blood components must meet the limits set forth under General Chapter *Particulate Matter in Injections* <788>.