Considerations for the Development of Dried Plasma Products Intended for Transfusion

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
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I. INTRODUCTION

This guidance is intended to assist manufacturers, sponsors, and applicants developing dried plasma products intended for transfusion in order to facilitate the availability of safe and effective dried plasma[1] products in the United States (U.S.). This guidance provides considerations for the successful development and licensing of dried plasma products and for the approval of devices used to manufacture dried plasma. The guidance includes recommendations on optimal sources of input plasma[2]; manufacturing and product quality, including product characterization; packaging and reconstitution; clinical studies; and device submissions.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Plasma is a critical component of early transfusion therapy in the management of traumatic hemorrhage (Ref. 1). Plasma can replenish various coagulation proteins that are consumed during the coagulopathy that may accompany traumatic injury (Ref. 2). Because plasma products intended for transfusion such as fresh frozen plasma (FFP), plasma frozen within 24 hours after phlebotomy (PF24), and plasma frozen within 24 hours after phlebotomy held at

[1] For the purposes of this guidance, "dried plasma" means dried (e.g. lyophilized, spray-dried) plasma that is intended for transfusion following reconstitution.

[2] For the purposes of this guidance, "input plasma" describes plasma used as the starting material for the preparation of the dried plasma product or used as the input into a device intended for the preparation of a dried plasma product. Recommendations regarding use of Plasma (as defined in 21 CFR Part 640, Subpart D) or Source Plasma (as defined in 21 CFR 640, Subpart G) as input plasma appear in section III.A of this guidance.

room temperature up to 24 hours after phlebotomy (PF24, RT24) are stored frozen, these products need to be thawed prior to transfusion. This limits or prevents the use of plasma in settings where freezers and other support equipment are unavailable (e.g. battlefields, remote locations, and other austere settings), and may lead to delayed administration. Dried plasma (such as freeze-dried or spray-dried plasma) offers the potential to address these challenges by providing a product that is stable at ambient temperatures, and which can be rapidly reconstituted and transfused.

The potential benefits of dried plasma were recognized long ago, and dried plasma products were used by U.S. forces during WWII (Ref. 3). However, further development and use of dried plasma was generally discontinued in the U.S. in large part because of infectious disease transmission risks (Ref. 4). As mitigation of infectious disease transmission risks improved, including improved testing methods and pathogen reduction technologies, interest in the development of dried plasma products reemerged.

III. CONSIDERATIONS FOR PRODUCT DEVELOPMENT

A. Considerations Regarding Input Plasma

1. Plasma donors are subject to the donor eligibility requirements set forth in 21 CFR 630.10 and 630.15.

2. The dried plasma product should be manufactured from a licensed single donor plasma product intended for transfusion (such as FFP or PF24) or from pools of these products. While Source Plasma (21 CFR Part 640, Subpart G) may also be considered in the manufacture of dried plasma, it is recommended that manufacturers considering the use of Source Plasma discuss this with FDA in advance of product development (section V of this document).

3. Blood and blood components, including plasma, intended for transfusion or for use in manufacturing a product are subject to the testing requirements for relevant transfusion-transmitted infections in 21 CFR 610.40. Manufacturers preparing dried plasma from pooled donations should consider additional measures to reduce infectious disease transmission risks. Examples may include viral inactivation (e.g., solvent/detergent treatment), or manufacture from input plasma treated with an FDA-approved pathogen reduction device.

4. FDA recommends the development of a dried plasma product that can be administered independent of the ABO type of the recipients (“universal” type). Manufacturers should consider the use of input plasma from AB donors or A donors with low anti-B titers, either as individual units or manufactured from

5. pools of multiple units. FDA recommends documentation of the anti-B and anti-A antibody titers of the input plasma, in accordance with the ABO blood types included in the pools.

6. While development of ABO-type-specific dried plasma products may be considered, use of a non-universal product introduces additional safety challenges, particularly in settings where blood establishments or transfusion services are unavailable. For development of ABO-type-specific products, early discussion with FDA is recommended to help ensure effective risk mitigation strategies.

B. Manufacturing and Product Quality

1. Sponsors should carefully consider the design, validation, and documentation of all steps involved in the manufacturing process as well as the controls needed to maintain product quality during manufacturing. This includes donor selection and testing, plasma collection, process for thawing of input plasma, pathogen reduction (if included in the process), all aseptic processing steps including pre-drying treatment (freezing for instance), storage conditions, characterization of antibody titers (if applicable), time elapsed prior to drying, drying process, and characterization of the solubilized final product in comparison to the plasma input into the process.

2. FDA recommends applicants submit characterization data of the final reconstituted plasma product intended for transfusion to demonstrate the effects of the manufacturing process on the quality of plasma. Proposed characterization studies should be discussed in advance with FDA. In general, the characterization studies should assess the following properties:

    a. Activities of pro-coagulant and anti-coagulant proteins in the reconstituted plasma. Among other tests, the following should be performed:

        i. Prothrombin time (PT) or international normalized ratio (INR)
        ii. Activated partial thromboplastin time (aPTT)
        iii. Activity of heat-labile proteins (e.g. Factor V, Factor VIII)
        iv. Activity of anticoagulant proteins (e.g. Protein S, Protein C)
        v. Antigen and activity of large coagulation proteins prone to aggregation and degradation (e.g. fibrinogen, von Willebrand factor)
        vi. Markers of coagulation activation (e.g. thrombin-antithrombin complexes, fibrin degradation products)

    b. Residual moisture content of the dried plasma product
    c. pH of the reconstituted plasma
    d. Presence of particles (protein complexes and aggregates) in the reconstituted plasma at the time of transfusion

3. Characterization studies should be performed on paired plasma samples, i.e., plasma before the drying process and after dried plasma reconstitution. Ideally, these samples should be tested in parallel, and compared to a range of the same proteins and activities of interest obtained with a licensed plasma product intended for transfusion.

4. FDA recommends that dried plasma products be stable at room temperature prior to reconstitution. Manufacturers of dried plasma products must have a written stability testing program, and the results of such testing must be used in determining appropriate storage conditions and expiration dates (21 CFR 211.166). If relevant to the intended use, stability data should include information on transport conditions, as well as information regarding both short- and long-term temperature excursions from room temperature, including exposure to freezing and extremely high temperatures.

5. The written stability testing program must include, among other things, testing of dried plasma products at the time of dispensing (as directed in the labeling) as well as after reconstitution (21 CFR 211.166(a)(5)). Studies should be performed to support the stability of the product at various times following reconstitution. The post-reconstitution stability to support expiration dating should be described in the labeling.

6. Dried plasma products are subject to the sterility requirements outlined in 21 CFR 610.12, unless such products meet the criteria for exceptions outlined in 21 CFR 610.12(h). We recommend further discussions with FDA regarding the specific requirements for your product.

C. Packaging and Reconstitution

1. Although dried plasma products have been effectively lyophilized/dried in glass vials, FDA recommends breakage-resistant alternatives supporting lyophilization/drying. One advantage of dried plasma is its ability to be used in settings where the use of conventional plasma is not practical (e.g., austere settings, such as battlefields and remote locations) and where risks of glass breakage are likely to increase.

2. Given the unique nature of dried plasma products (volume, electrolyte content, pH, in combination with the possible use in field or emergency settings), FDA suggests that manufacturers consider a packaging kit that includes all the materials needed for reconstitution, including the appropriate volume of diluent, as well as specific instructions for use. Distribution of the product as a complete package is likely to enhance safety by minimizing errors upon reconstitution and to ensure rapid time-to-transfusion, a major advantage of dried plasma products.

3. The time to reconstitute a dried plasma product may vary. FDA suggests that products be able to be fully reconstituted within five minutes given their likely use in urgent medical situations. FDA also suggests the development of dried plasma products that may be reconstituted by the simple addition of diluent, or at most, with gentle swirling of the product, and that no special equipment be needed to facilitate the process.

D. Clinical Studies

1. Clinical studies necessary to support approval will vary depending on the indication(s) sought, as well as the degree of clinical experience with the product.

2. For indications where conventional plasma (such as FFP or PF24) is unavailable or impractical for use, FDA recommends conducting a coagulation factor recovery and safety study in healthy subjects, following thorough *in vitro* product characterization. Autologous plasma may be used, provided the processing is conducted in a manner identical to that of the ultimate product, except for pooling. The initial safety cohort should receive one unit of the reconstituted dried plasma product, and optimally, subsequent cohorts should be randomized to receive two to three units of conventional plasma or reconstituted dried plasma. Adverse events must be recorded for all enrolled subjects and reported to FDA when required under 21 CFR Part 312 or 812. As part of the randomized study, FDA recommends that samples be obtained for coagulation testing and the determination of factor levels prior to and following the administration of both conventional plasma and reconstituted dried plasma.

3. To expand the indications for use of dried plasma to situations where conventional plasma (such as FFP or PF24) is available, FDA recommends the conduct of an additional adequate and well-controlled clinical study or studies, to be discussed in advance with FDA.

E. Devices for Manufacturing of Dried Plasma

1. In general, based on the device risks and the regulatory requirements necessary to provide a reasonable assurance of its safety and effectiveness, FDA expects that devices intended for the manufacture of dried plasma will be considered class III medical devices subject to premarket approval (PMA) requirements (21 CFR Part 814)[3].

[3]As additional experience with devices used to manufacture dried plasma is obtained, FDA will consider whether reclassification of such devices is appropriate, including whether the de novo pathway is appropriate for such devices.

2. Manufacturers seeking approval for devices to be used for the manufacture of dried plasma should include, as part of the device for which they are seeking approval, the necessary equipment with precise specifications for a blood establishment to process the dried plasma product, except for that which is likely to be standard equipment in a blood establishment (e.g. sterile connecting devices, storage freezers, water baths). Validation and product characterization data on the dried plasma, performed as recommended in this guidance, should be provided using a consistent and pre-specified final device configuration. The category of input plasma (e.g. FFP, PF24) unique to the device should be specified.

3. Considerations regarding input plasma, manufacturing and product quality, packaging and reconstitution, and clinical studies, as described in this guidance, are also relevant to devices to be used for the manufacture of dried plasma and the outputs of such devices. Manufacturers seeking marketing approval for such devices should generally submit clinical data to demonstrate that the dried plasma manufactured with the device is safe and effective.

IV. EXPEDITED PROGRAMS

There are several expedited programs that may be available to sponsors of dried plasma products intended to address unmet medical needs in the treatment of serious or life-threatening conditions. Further information on these programs is available in a separate guidance document[4].

V. COMMUNICATION WITH FDA

FDA recommends communication with the Office of Blood Research and Review (OBRR) early in product development, before submission of an investigational new drug application (IND) (21 CFR Part 312) or investigational device exemption (IDE) (21 CFR Part 812) application. There are different meeting types that can be used for such discussions, depending on the stage of product development and the issues to be considered. These include Q-subs (pre-submission meetings for devices), pre-IND meetings, and, earlier in development, INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings.[5] Contact OBRR with any questions regarding the appropriate meeting type.

[4] Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014, https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

[5] Going forward, INTERACT meetings will serve in place of pre-pre-IND meetings. For additional information about INTERACT meetings, please see https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

VII. REFERENCES

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