

Considerations for the Development of Dried Plasma Products Intended for Transfusion

Guidance for Industry

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are providing recommendations 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 plasma¹ 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. This guidance finalizes the draft guidance of the same title dated October 2018.

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

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.

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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 room temperature up to 24 hours after phlebotomy (PF24RT24) 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. Armed 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 enhanced testing methods and pathogen reduction technologies, interest in the development of dried plasma products reemerged. More recent clinical studies have demonstrated promising efficacy and safety of dried plasma, particularly in military applications, and dried plasma products are available for limited use in Germany, South Africa, and France (Ref. 3).

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 or 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 product manufacturing are subject to the testing requirements for relevant transfusion-transmitted infections (RTTI) in 21 CFR 610.40. Manufacture of a dried plasma product may occur prior to completion of RTTI testing. However, testing for RTTI must be completed, and the results must be nonreactive, before distribution of the finished dried plasma product (21 CFR 630.30). Manufacturers preparing dried plasma from pooled donations should consider additional measures to reduce infectious disease transmission risks. Examples of such measures may include viral inactivation or manufacture from input plasma treated with an FDA-approved pathogen reduction technology.

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4. Development of dried plasma products that can be administered irrespective of the ABO group of the recipient offers operational advantages and may decrease the risk of transfusion of ABO incompatible units, especially in urgent clinical settings. Manufacturers should consider the use of input plasma from AB donors or A donors with low anti-B titers.
5. For products that can be administered irrespective of the ABO group of the recipients, FDA recommends documentation of the anti-A and anti-B antibody titers of the input plasma (in accordance with the ABO blood groups included in the pools), and the methods used for measuring the titer levels.
6. For development of ABO-group-specific products, early discussion with FDA is recommended.

B. Manufacturing and Product Quality

1. Carefully consider the design, validation, and documentation of the steps involved in the manufacturing process, including the controls used to maintain product quality. These steps include input plasma selection (which may include donor selection, donation testing, and plasma collection procedures), pathogen reduction (if applicable), pre-drying treatment (freezing, for instance), process for thawing of frozen input plasma, storage conditions, characterization of antibody titers (if applicable), time elapsed prior to drying, and the drying process. Processing steps should be performed under aseptic conditions.
2. Submit characterization data of the final reconstituted plasma product intended for transfusion, including a paired comparison to the input plasma, to demonstrate the effects of the manufacturing process on the quality of plasma. Characterization studies should be discussed in advance with FDA and should, in general, assess the following properties:
 - a. Activities of pro-coagulant and anti-coagulant proteins in the reconstituted plasma, including but may not be limited to the following tests:
 - 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

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- d. Characterization of particles to determine the impact of the drying process and storage conditions, and to assist in establishing the proper reconstitution time.
3. Develop a written stability testing program to determine the appropriate storage conditions and expiration dates (21 CFR 211.166). If applicable, stability data should include information on transport conditions, and on short and long-term temperature excursions from labeled storage conditions, including exposure to freezing and high temperatures.
4. The written stability testing program must include testing of dried plasma products immediately after reconstitution (21 CFR 211.166(a)(5)) and at the end of the proposed timeframe between reconstitution and administration of product. Studies should be performed to support the stability of the product at various time points following reconstitution. The post-reconstitution stability studies that support the expiration date should be described in the labeling.

C. Packaging and Reconstitution

1. Although dried plasma products have been effectively lyophilized/dried in glass containers, 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., battlefields, remote locations, and other austere settings) and where risks of glass breakage are likely to increase.
2. Given the unique characteristics of dried plasma products (volume, electrolyte content, pH), and the possibility of their use in the field or emergency settings, FDA suggests that manufacturers consider assembling a packaging kit that includes all the materials needed for reconstitution, including the appropriate volume of diluent, as well as instructions for reconstitution and use. Distribution of the product as a complete package enhances safety by minimizing reconstitution errors and ensures 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, with no need for special equipment.

D. Clinical Studies

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

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2. For indications where conventional plasma (such as FFP or PF24) is unavailable or impractical for use, FDA recommends conducting safety and coagulation factor recovery studies 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 additional units of reconstituted dried plasma or conventional plasma (as control). Additional studies may be recommended. 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 studies, FDA recommends the conduct of coagulation testing, and the determination of factor levels in the subjects 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, additional adequate and well-controlled clinical studies would likely be necessary and should be discussed in advance with FDA.

E. Regulatory Pathway for Marketing of Devices for the 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, devices intended for the manufacture of dried plasma will likely be considered class III medical devices subject to premarket approval (PMA) requirements (21 CFR Part 814).³
2. Manufacturers seeking approval to market a device 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. Data should be provided which demonstrate your device consistently produces a plasma product that meets established quality specifications.

³As 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.

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3. Considerations regarding input plasma, manufacturing and product quality, packaging, reconstitution, and clinical studies, as described earlier in this guidance, also apply to devices used for the manufacture of dried plasma and their output. 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/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics>

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/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products>

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VI. REFERENCES

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