Alternative Procedures for the Manufacture of Cold-Stored Platelets Intended for the Treatment of Active Bleeding when Conventional Platelets Are Not Available or Their Use Is Not Practical

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Guidance for Industry

This guidance is for immediate implementation.

This guidance is being implemented in accordance with 21 CFR 10.115(g)(2) without prior public comment because the Food and Drug Administration has determined that prior public participation for this guidance is not feasible or appropriate. This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

Alternative Procedures for Cold-Stored Platelets Intended for the Treatment of Active Bleeding when Conventional Platelets Are Not Available or Their Use Is Not Practical

Guidance for Industry

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

FDA (we) is issuing this guidance to provide a notice of exceptions and alternatives to certain requirements in Title 21 of the Code of Federal Regulations (CFR) regarding blood and blood components. This notice is being issued under 21 CFR 640.120(b) to respond to a public health need and address the urgent and immediate need for platelets for the treatment of active bleeding when conventional platelets are not available, or their use is not practical. Maintaining platelet availability in the face of logistical challenges (e.g., in military, prehospital, or austere settings) or other threats to blood availability (e.g., mass casualty events or public health emergencies) is critical to assure that platelets are available to patients with active bleeding.

Additionally, the guidance provides recommendations to blood establishments for the manufacture and labeling of cold-stored platelets (CSP). The guidance also discusses the need for additional data on the efficacy of CSP, in particular, to address whether their use is supported when conventional platelets are available, and their use is practical.

For the purposes of this guidance, conventional platelets include all platelets (as defined in 21 CFR 640.20) intended for transfusion and stored at 20 to 24°C. Conventional platelets are also referred to as room-temperature platelets (RTP). Platelets stored continuously at 1 to 6°C within a specified time after collection are referred to in this guidance as CSP.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency'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 Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Platelet Transfusions

Platelets have a critical role in normal hemostasis and control of bleeding. Platelet transfusions are used to treat patients with thrombocytopenia, dysfunctional platelet disorders (congenital, metabolic, or medication-induced), or active platelet-related bleeding, or for patients at serious risk of bleeding (i.e., prophylactic use) (Ref. 1). Platelets for transfusion may be manufactured from whole blood collections or collected by plateletpheresis (21 CFR 640.20(b)). In the United States (U.S.), most plateletsare collected by plateletpheresis and stored continuously at 20 to 24°C (see 21 CFR 640.24(d)(1)). The dating period (expiration date) for platelets with a storage temperature between 20 and 24°C is 5 days from the date of collection, unless a different dating period is specified in the instructions for use by the blood collection, processing and storage system approved or cleared for such use by FDA (21 CFR 610.53(b)). In the U.S., the current maximum dating period for platelets with a storage temperature between 20 and 24°C is up to 7 days in the FDA-cleared or approved storage containers. Thus, platelets may be stored at 20 to 24°C for a period of up to 7 days, depending on the bacterial risk control strategy (Ref. 2), and the blood collection, processing and storage system approved or cleared for such use by FDA (21 CFR 610.53(b)). Despite efforts to maintain an adequate inventory of platelets stored at room temperature, in circumstances involving logistical challenges or other threats to blood availability, there remains an unmet need for platelets for the treatment of active bleeding in both pre-hospital and hospital settings. At the November 2019 meeting of the Blood Products Advisory Committee (BPAC), presenters and public comments described rural and military settings where platelets were not available for treatment of acute bleeding, as well as logistical challenges in mainting platelet availability in the pre-hospital setting, including short potential storage duration, and need for agitation (Ref. 3). Considering the hemostatic properties and potential logistical advantages of CSP that could address these challenges, there is a renewed interest in clinical use of CSP (see section II.C. of this guidance).

B. Regulatory History of CSP

Regulatory standards for platelets established in 1975 (40 FR 4304) included cold storage of platelets at 1 to 6°C, with a dating period of 72 hours.[1] Although CSP were commonly used in the 1970s, investigators at that time observed that room-temperature storage of platelets resulted in higher recovery and longer survival in circulation in transfused patients (Refs. 4-6). In subsequent decades, given the predominant use of prophylactic platelet transfusion to maintain adequate circulating platelets and reduce the risk of spontaneous bleeding in patients who develop thrombocytopenia following chemotherapy or hematopoietic stem cell transplantation, platelets were stored almost exclusively at 20 to 24°C.

[1] See Additional Standards for Platelet Concentrate (Human), and Whole Blood (Human), January 29, 1975; 40 FR 4300, at 4304; https://archives.federalregister.gov/issue_slice/1975/1/29/4298-4308.pdf#page=3.

The dating period of platelets stored outside 20 to 24°C is defined as specified in the instructions for use by the blood collection, processing and storage system approved or cleared for such use by FDA (21 CFR 610.53(b)). Additionally, supplies and reagents used in the collection, processing, compatability testing, storage, and distribution of blood and blood components must be used in a manner consistent with instructions provided by the manufacturer (21 CFR 606.65(e)). However, currently, there are no blood collection, processing and storage systems cleared or approved by FDA for storage of platelets at temperatures other than 20 to 24°C. Consequently, the manufacture of CSP by blood establishments is contingent upon issuance of exceptions or alternative procedures to 21 CFR 610.53(b), 21 CFR 606.65(e). Further, exceptions or alternatives to the quality control testing requirements requirements in 21 CFR 640.25(b)(1) and 21 CFR 640.25(b)(3) are necessary to assure the availability of platelets, as discussed in more detail in section II.E. of this guidance. FDA has issued alternative procedures in response to requests from individual blood establishments under 21 CFR 640.120(a) to manufacture CSP (Ref. 7).

C. Available Data on Quality and Use of CSP

While use of RTP became standard practice, researchers continued to perform *in vitro* studies to assess the effects of cold storage on platelet viability, activation, metabolism, and hemostatic function (Refs. 8-10). These studies demonstrated that CSP have different physiologic properties compared to RTP (Refs. 10-13). In summary, CSP have an "activated" profile, and, in some studies, CSP have demonstrated greater aggregation responses to agonists, higher clot strength in viscoelastic testing, and improved adhesion under flow when compared to RTP of similar storage age, especially beyond 5 days of storage (Refs. 14-19). CSP may be more prone to aggregate formation during storage compared to RTP, and aggregation may be influenced by use of platelet additive solution, method of platelet preparation, and bedside filtration (Refs. 20-22). Studies have also shown that cold storage inhibits growth of several bacterial strains in platelets (Ref. 23).

The *in vitro* data prompted renewed interest in the use of CSP, especially in settings of trauma and massive bleeding (Refs. 24-26), because CSP potentially have longer dating periods than RTP and do not require the use of continuous agitation during storage (21 CFR 640.25(a)). Although the *in vitro* results suggest that CSP may have better preservation of hemostatic activity when compared to RTP with similar storage duration, well-controlled clinical studies examining their use remain limited (Ref. 27). Studies published in the 1970s demonstrated that CSP prepared from whole blood showed improved pH and aggregability following up to 72 hours of storage, but their circulation and recovery *in vivo* were impaired compared to similarly prepared RTP (Ref. 6). In thrombocytopenic patients and in healthy volunteer subjects pre-treated with aspirin, some studies found that CSP demonstrated better correction of bleeding time (Refs. 6 and 28), while another study found either no measurable improvement, or only transient improvement, in bleeding time with CSP transfusion, whereas fresh platelets or RTP were largely able to correct bleeding times (Ref. 4). More recent studies have confirmed the reduction in circulatory recovery and survival of CSP compared to RTP (Ref. 29),

with a continuous decline in platelet recovery from 5 to 20 days of storage, and with platelet survival reaching its lowest level at 10 days (Ref. 30).

To assess the efficacy of CSP in the treatment of bleeding, investigators in Norway conducted a two-stage pilot study in patients undergoing complex cardiac surgery comparing apheresis CSP to similarly prepared RTP (Ref. 31). The first stage of the trial compared CSP to RTP in a two-armed randomized study, with 25 subjects per arm, and both components stored up to 7 days in platelet additive solution (PAS). In the first stage, there was no significant difference in the median chest drain output between the study arms. In the second stage, a single-arm study was performed in 15 subjects with CSP stored 8 to 14 days, and similar median chest drain output was observed. No significant differences were observed between CSP and RTP in other outcomes such as number of transfused units of red cells, plasma, and platelets, platelet function testing, thromboembolic events, intensive care unit stay, and mortality. The authors concluded that the pilot trial supported the feasibility of CSP stored for up to 14 days. In a different study of CSP and RTP transfused to healthy volunteers after receiving anti-platelet medications (clopidogrel and acetylsalicylic acid (ASA)) (Ref. 32), CSP showed differences in *in vitro* testing when compared to RTP. Although both CSP and RTP showed an immediate ASA-reversing effect after transfusion, the effect was shorter-lived in recipients of CSP compared to RTP. Clopidogrel-reversing effects were not observed for either CSP or RTP, similar to other recent reports (Ref. 33). The U.S. Department of Defense (DoD) also reported on CSP use in the military, with 48 patients transfused with CSP stored for up to 10 days (Ref. 34).

The *in vitro* and clinical data on CSP were the topic of a November 2019 BPAC meeting (Ref. 35). During this meeting, presenters shared most of the clinical and in vitro data summarized above with the committee. In addition, investigators shared their clinical experience with use of CSP under a variance that allowed for 3 day storage, including an obervational study comparing trauma patients transfused with RTP to those transfused with CSP (20 subjects per arm). These investigators described that while laboratory measures and clinical outcomes appeared similar between the groups, there were high rates of wastage with CSP, largely owing to expiration, and, to a lesser extent, aggregate formation. Researchers from DoD also shared an observational study of 161 patients tranfused with only RTP compared to 94 patients transfused with CSP and RTP, and one patient transfused with only CSP, when the CSP had been stored for up to 14 days. This comparison found no significant differences in rates of thromboembolic events, sepsis, or mortality when adjusting for injury severity.

D. The Need for Additional Studies on CSP

At the November 2019 meeting of the BPAC (Ref. 35), the committee also recognized the need for additional data to support indications for use of CSP where conventional platelets are an available alternative. FDA is also not aware of well-controlled clinical studies supporting use of CSP for prevention of bleeding (prophylactic transfusion). An adaptive trial design in the setting of cardiac surgery, previously described in published literature (Ref. 36), was proposed and discussed at BPAC (Ref. 35) and is currently

underway. (See, e.g., Ref. 37; the ongoing nature of this study has also been disclosed on participating sites' websites.) Additional studies of CSP manufactured using different procedures and devices, for example CSP prepared from platelets manufactured using pathogen-reduction devices or CSP prepared from Whole-Blood-derived platelets, would provide additional information. Sponsors and investigators planning such studies to support regulatory submissions for CSP are encouraged to contact FDA to discuss applicable regulatory pathways.

FDA also expects that the use of CSP manufactured under the alternative procedures and recommendations described in this guidance will generate real-world evidence to further inform regulatory decision-making on the storage conditions and dating periods for devices used in the manufacture of CSP. The use of standardized product labeling for CSP using the International Society of Blood Transfusion (ISBT) format (as recommended in section IV.E. of this guidance) has the potential to facilitate future data collection using surveillance infrastructure such as the FDA/CBER Biologics Effectiveness and Safety Initiative (BEST).

FDA will continue to assess the available data on the use of CSP to determine whether changes to the alternative procedures and recommendations described in this guidance are appropriate.

E. Regulatory Considerations

Under 21 CFR 640.120(b), to respond to a public health need, the Director of CBER may issue a notice of exception or alternative to any requirement in subchapter F of chapter I of title 21 of the CFR (21 CFR parts 600-680) regarding blood, blood components, or blood products, if a variance under this section is necessary to assure that blood, blood components, or blood products will be available in a specified location or locations to address an urgent and immediate need for blood, blood components, or blood products or to provide for appropriate donor screening and testing.

A variance under 21 CFR 640.120(b) is necessary to assure that platelets will be available to treat active bleeding when conventional platelets are not available, or their use is not practical, to address the urgent and immediate need for platelets. Accordingly, section III. of this guidance provides a notice of exceptions or alternatives under 21 CFR 640.120(b) to the following regulations:

- Section 21 CFR 610.53(b), which defines the dating period for platelets stored at temperatures other than 20 to 24ºC as specified in the instructions for use of the blood collection, processing, and storage system approved or cleared for such use by FDA, and

- section 21 CFR 606.65(e) which specifies that supplies and reagents used in the collection, processing, compatability testing, storage, and distribution of blood and blood components must be used in a manner consistent with instructions provided by the manufacturer. This means that blood establishments must follow

the instructions for use provided by the device manufacturer for the blood collection, processing, and storage system.

Exceptions or alternatives to these requirements are necessary for the manufacture of CSP because the blood collection, processing and storage systems currently cleared or approved by FDA are not intended for platelet storage at temperatures other than 20 to 24°C.

In addition, section III. of this guidance provides a notice of exceptions or alternatives to certain quality control testing requirements for the manufacture of CSP, specifically:

- section 21 CFR 640.25(b)(1), regarding testing for platelet count at the end of the storage period, and

- section 21 CFR 640.25(b)(3), regarding measurement of actual plasma volume at the end of the storage period.

The platelet count and plasma volume of platelets are routinely measured at the time of collection to determine collection yields. A platelet count and plasma volume of CSP at the end of storage may not provide meaningful information due to aggregates formed during storage (Ref. 20) and FDA anticipates that requiring such testing would limit the availability of CSP. Exceptions or alternatives to these requirements are necessary to assure the availability of platelets.

III. NOTICE OF EXCEPTIONS OR ALTERNATIVES

To address the urgent and immediate need for platelets in the U.S., the Director of CBER is issuing the following exceptions and alternatives under 21 CFR 640.120(b):

- Sections 21 CFR 610.53(b) and 21 CFR 606.65(e): The Director of CBER is issuing alternative procedures to 21 CFR 610.53(b) and 21 CFR 606.65(e) to permit the storage of apheresis platelets at 1 to 6°C for up to 14 days from the date of collection, when such apheresis platelets are intended for the treatment of active bleeding when conventional platelets are not available or their use is not practical.

- Sections 21 CFR 640.25(b)(1) and 21 CFR 640.25(b)(3): The Director of CBER is issuing exceptions to the requirements in 21 CFR 640.25(b)(1) and 21 CFR 640.25(b)(3), regarding testing for platelet count and measurement of actual plasma volume, for the manufacture of apheresis platelets stored at 1 to 6°C for up to 14 days from the date of collection, and intended to treat active bleeding when conventional platelets are not available or their use is not practical.

Blood establishments may adopt the above-listed exceptions and alternatives without submitting a request to FDA under 21 CFR 640.120(a). Licensed establishments must report changes to their approved application in accordance with 21 CFR 601.12 as discussed in section V. of this guidance.

IV. RECOMMENDATIONS AND CONSIDERATIONS FOR THE MANUFACTURE OF COLD-STORED PLATELETS

Blood establishments that manufacture CSP must comply with all requirements that apply to platelets collected by automated methods, except for the alternative procedures and exceptions under 21 CFR 640.120(b) described in section III. of this guidance. Notably, collection of apheresis platelets and further processing (such as leukocyte reduction or pathogen reduction) must be performed in accordance with the device manufacturer's instructions for use (21 CFR 606.65(e)), except for their instructions for the platelet storage temperature and dating period.

A. Manufacture of Apheresis CSP and Storage Conditions

1. Blood establishments should prepare CSP from apheresis platelets suspended in 100% plasma or an FDA-approved PAS.

2. Blood establishments must place CSP that have not been treated with an FDA-approved pathogen reduction device at 1 to 6°C no later than 4 hours from the end of collection to assure that the risk of bacterial contamination is adequately controlled (21 CFR 606.145(a)), see section IV.B. of this guidance.

3. Blood establishments should place pathogen-reduced apheresis CSP in cold storage at 1 to 6°C no later than 4 hours after completion of the pathogen reduction process.

4. Blood establishments must continuously store CSP at a temperature of 1 to 6°C (21 CFR 640.24(d)(2)), must maintain CSP at a temperature of 1 to 10°C during shipment (21 CFR 600.15(a)), and should not return CSP placed in room-temperature conditions back into cold-stored inventory or relabel CSP as RTP.

5. For CSP stored at a temperature of 1 to 6°C for a period of up to 14 days, agitation is optional (21 CFR 640.25(a)).

B. Control of Bacterial Contamination of Platelets

1. Cold storage of apheresis platelets as described in this guidance is an adequate and appropriate method to assure that the risk of bacterial contamination is adequately controlled (21 CFR 606.145(a)). However, blood establishments may consider implementing additional measures described in the FDA guidance, titled "*Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion"* (Ref. 2).

2. Blood establishments must not release CSP, or any other component prepared from the same collection procedure, for transfusion if the platelets are identified as bacterially contaminated (21 CFR 606.145 (b) and (c)).

C. Process Validation

1. Blood establishments must conduct process validation to assure that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics (21 CFR 211.100). We recommend that blood establishments validate the CSP manufacturing process using a binomial distribution statistical sampling plan to demonstrate with 95% confidence that greater than 75% of the platelets stored at 1-6° C maintain a pH not less than 6.2 at the end of the storage period of up to 14 days. The blood establishment should test consecutively manufactured platelet components at each manufacturing location at the end of the storage period. Testing approaches consistent with this recommendation include:

    - test 11 platelet components with no failures, or
    - test 18 platelet components with 1 allowable failure, or
    - test 24 platelet components with 2 allowable failures

    Note that you may combine platelet components prepared from all approved collection types (e.g., single/doubles/triples) and collection devices.

D. Quality Control Testing

Blood establishments must conduct monthly pH quality control (QC) testing on CSP, and that testing must be performed in accordance with the QC statistical sampling plan as described in the firm's written procedures (21 CFR 640.25 (b)(2), 21 CFR 211.160(b), and 21 CFR 211.165(c)). The number of CSP components included in the overall monthly QC testing plan should represent the proportion of CSP in the total platelet inventory. For example, if 20% of your total platelet inventory is CSP, you should include that proportion of CSP in your monthly QC platelet testing plan.

E. Container Labels

1. Blood establishments must label CSP in accordance with 21 CFR 606.121.

2. We recommend the use of a uniform container label for CSP. In particular, we recommend you use the International Society of Blood Transfusion (ISBT) 128 format specified in the U.S. Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128 for container labels.

F. Circular of Information

Blood establishments must provide adequate directions for use of CSP in the Circular of Information (21 CFR 606.122). We recommend including the following statements and information:

a. "CSP are intended for the treatment of active bleeding when conventional platelets are not available, or their use is not practical."

b. "CSP must be stored continuously at 1-6°C to control the risk of bacterial contamination for up to 14 days" (section IV.B. of this guidance).

c. "Transfusion services should establish procedures for examining CSP for visible aggregates before transfusion."

V. REPORTING IMPLEMENTATION OF MANUFACTURING AND LABELING CHANGES

Blood establishments that manufacture licensed blood components must report changes to their approved Biologics License Application in accordance with 21 CFR 601.12.

For establishments already licensed to manufacture apheresis platelets or Whole Blood-derived platelets, the manufacture of CSP is considered to have a moderate potential to adversely affect the identity, strength, quality, purity, or potency of the product as it may relate to the safety or effectiveness of the product. Therefore, you must report this change to your approved application to FDA as a Supplement - CBE30 in accordance with 21 CFR 601.12(c).

We recommend that you include the following in your CBE30 submission:

a. Form FDA 356h, "Application to Market a New or Abbreviated New Drug or Biologic for Human Use".

b. Cover letter describing the contents of the supplement and a description of the CSP manufacturing process.

c. Address and registration number(s) of the facility/facilities that will manufacture CSP, including quality control testing and storage at 1-6 °C.

d. Standard operating procedures, if changes to previously approved procedures have been made or new procedures created to describe the manufacturing process for CSP.

e. Summary of results of the validation study performed at each manufacturing facility to show that a pH of ≥ 6.2 is maintained throughout the storage period.

f. Container labels.

g. Amended Circular of Information.

Unlicensed blood establishments are not required to report this change to FDA.

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