



121st Blood Products Advisory Committee Meeting

Tommy Douglas Conference Center
Silver Spring, MD

November 22, 2019

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Considerations for Cold Stored Platelets Intended for Transfusion

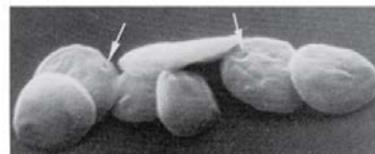


Introduction

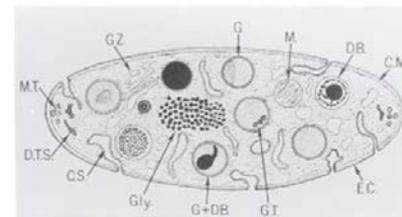
- FDA is seeking advice from the Committee to advance the safe, effective, and efficient development of cold stored platelets (CSP)
- The Committee will hear presentations discussing available data on CSP, including characterization and functional testing, clinical studies, and their potential role in clinical care
- The Committee is asked to consider the available evidence and provide advice on studies needed to support the use of CSP intended for transfusion and stored beyond 3 days

Platelets

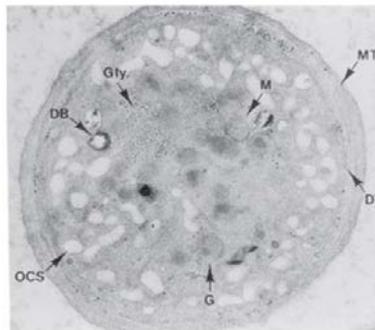
- Important role in normal hemostasis and control of bleeding
- Platelets are transfused to:
 - Prevent bleeding in patients with thrombocytopenia
 - Treat active bleeding
 - Treat patients with dysfunctional platelets



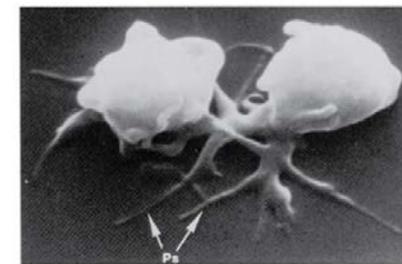
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Williams Hematology, 7th ed, 2006

Platelets for transfusion

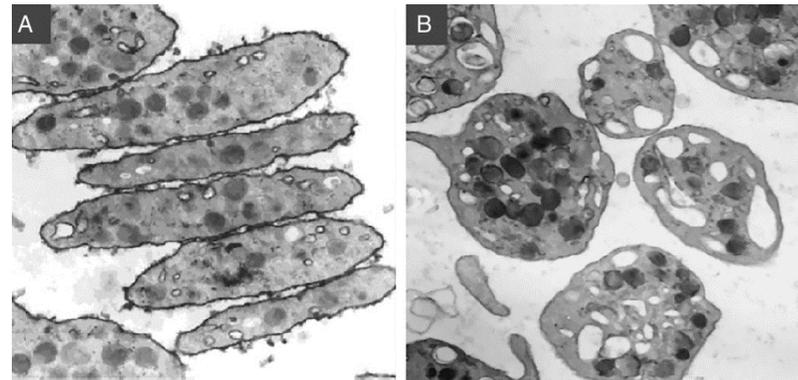
- Are collected by apheresis or prepared from whole blood
- Can be stored in plasma with or without platelet additive solution
- May undergo additional modification (e.g. pathogen reduction)



Image Source: *Clinical Guide to Transfusion*. Canadian Blood Services. Available from: <https://professionaleducation.blood.ca/en/transfusion/guide-clinique/platelet-transfusion-alloimmunization-and-management-platelet>

Platelets for transfusion

- Conventional platelets are stored at room temperature (20-24°C) for up to 5 or 7 days
- For room-temperature platelets (RTP), agitation facilitates oxygen utilization and helps to maintain morphology, function, and pH
- Physiologic and biochemical changes occur during storage (“storage lesion”)



Escolar, G. and J. McCullough, Platelet in vitro assays: their correspondence with their in vivo hemostatic potential. *Transfusion*, 2019.

Cold stored platelets (CSP)

- Platelets can also be stored at 1 to 6°C [21 CFR 640.24 (d)(2)]
- Although studies showed decreased circulatory recovery and survival when compared to RTP, CSP were commonly used prior to the 1970s
- Storage was historically limited to 72 hours from time of collection
- Agitation is optional [21 CFR 640.25(a)]

Regulatory History of CSP

- **1974:** Preamble to proposed rule (39 FR 2008) concerning Additional Standards for Platelet Concentrates included the following:
 - “Platelets stored at 20-24°C exhibit a longer posttransfusion survival time”
 - “Platelets stored between 1-6°C which, on the other hand, appear to be more potent during the initial stages of producing hemostasis”
 - “the Commissioner proposes that a licensed manufacturer may store the product at either temperature”

Regulatory History of CSP

- **1975:** Regulations finalized (40 FR 4304), and included cold storage of platelets with a dating period of 72 hours
- **1982:** Final rule (47 FR 49019) reduces dating period for CSP to 48 hours
- **1985:** Final rule (50 FR 4134) revises product names and restores dating period for CSP to 72 hours

Regulatory History of CSP

- **2007:** Final rule (72 FR 45887) changed dating period regulations to allow for flexible dating periods depending on the type of collecting, processing, and storage system used
 - For CSP: up to 72 hours or as specified in the directions for use
- **2016:** Final rule (81 FR 26691) amended regulations for consistency with updated practices in the biological product industry
 - All platelets outside room temperature: dating period is as specified by the instructions for use (21 CFR 610.53(b))

Cold stored platelets

- Given the prevalence of platelet transfusion for prophylaxis in thrombocytopenic patients, the decreased circulatory recovery and shorter survival of CSP led to a shift to RTP
- Attributes of cold storage
 - No agitation (slowed metabolism)
 - Limits bacterial growth
 - Potential for longer storage period

In vitro characterization of CSP

- Cold induced changes in platelet physiology (“Cold storage lesion”)
 - Physical characteristics
 - Biochemical/metabolic status
 - Platelet activation
 - Physiologic responses
- Hemostatic function
 - Aggregometry
 - Viscoelastic testing

Clinical studies with CSP

- Limited, but sometimes conflicting studies in 1970s showed CSP may better correct bleeding times in aspirin-treated healthy volunteers or thrombocytopenic subjects (Becker et al. 1973, Valeri 1974, Slichter and Harker 1976)
- Recent studies have examined CSP circulation in healthy volunteers, and CSP function in cardiac surgery patients (Stolla et al. 2018, Strandenes et al. 2018)
- Additional CSP studies have been proposed to determine safety and efficacy of CSP after different storage durations (Krachey et al. 2018)



Regulatory considerations for CSP

- While FDA regulations permit storage at 1 to 6°C, commonly used blood collection, processing, and storage systems do not include cold storage of platelets in their instructions for use
- To comply with applicable regulations, blood establishments have requested approval of exceptions or alternative procedures (21 CFR 640.120)
- Approval of a variance is based on data showing that the alternate process ensures the safety, purity, potency, and effectiveness of the blood component or blood product
- Requests for a variance include specific circumstances and may require submission of supporting data unique to the circumstance

Variations

- **2015:** FDA granted a variance to a blood establishment that allows storage of CSP without agitation for up to 3 days for use in the resuscitation of actively bleeding patients
- **2019:** FDA granted a variance to the Dept. of the Army that allows storage of CSP for up to 14 days for the treatment of active bleeding when conventional platelets are unavailable or their use not practical

Points to Consider

- The design of clinical studies to evaluate the safety and efficacy of CSP stored beyond 3 days
- The predictive value of *in vitro* studies on clinical efficacy and safety
- The impact of differences in product manufacturing variables (e.g. collection platform, storage medium, pathogen reduction) on the quality and efficacy of the product
- The benefit:risk profile of CSP, considering reduced circulation, potential adverse events, and intended patient population

Agenda

- Introduction to Topic
 - Carlos H. Villa, M.D., Ph.D., OBRR/CBER/FDA
- Platelet Transfusion in Clinical Medicine
 - Darrell Triulzi, M.D., University of Pittsburgh
- Introduction to *in vitro* Characterization of Platelets and Regulatory Approaches to Evaluation of Platelet Products
 - Monique Gelderman, Ph.D., OBRR/CBER/FDA
- *In vitro*, preclinical, and *in vivo* Recovery and Survival Studies of Cold Stored Platelets
 - Moritz Stolla, M.D., Ph.D., Bloodworks Northwest
- Break

Agenda

- Clinical Trial of Cold Stored Platelets in Cardiac Surgery
 - Geir Strandenes, M.D., Norwegian Armed Forces Medical Services
- Blood Establishment Considerations for Cold Stored Platelets
 - James Stubbs, M.D., Mayo Clinic
- Role of Cold Stored Platelets in Clinical Care in the General Population
 - Donald Jenkins, M.D., University of Texas San Antonio Health
- Lunch

Agenda

- Evaluation of Cold Stored Platelet Function and Military Experience with Cold Stored Platelets
 - COL Andrew Cap, M.D., Ph.D., U.S. Army Institute for Surgical Research
- A Proposed Clinical Trial to Evaluate the Efficacy of Cold Stored Platelets in Surgical Patients and Potential Endpoints for Cold Stored Platelets Clinical Studies
 - Philip Spinella, M.D., Washington University
- Break
- Open Public Hearing
- Open Committee Discussion

Questions to the committee

1. Please comment on the available data on cold stored platelets, including discussion of knowledge gaps and potential need for preclinical or clinical studies, with respect to the following:
 - a. Length of storage beyond 3 days
 - b. Indications for use (such as treatment of active bleeding)
 - c. Differences in collection platforms and storage media
 - d. Pathogen reduction

Questions to the committee

2. Please comment on the design of any additional clinical studies needed to evaluate the safety and hemostatic efficacy of cold stored platelets to support their widespread use in the United States