
Human Platelet Lysate requirements for cell therapy expansion in support of clinical trials

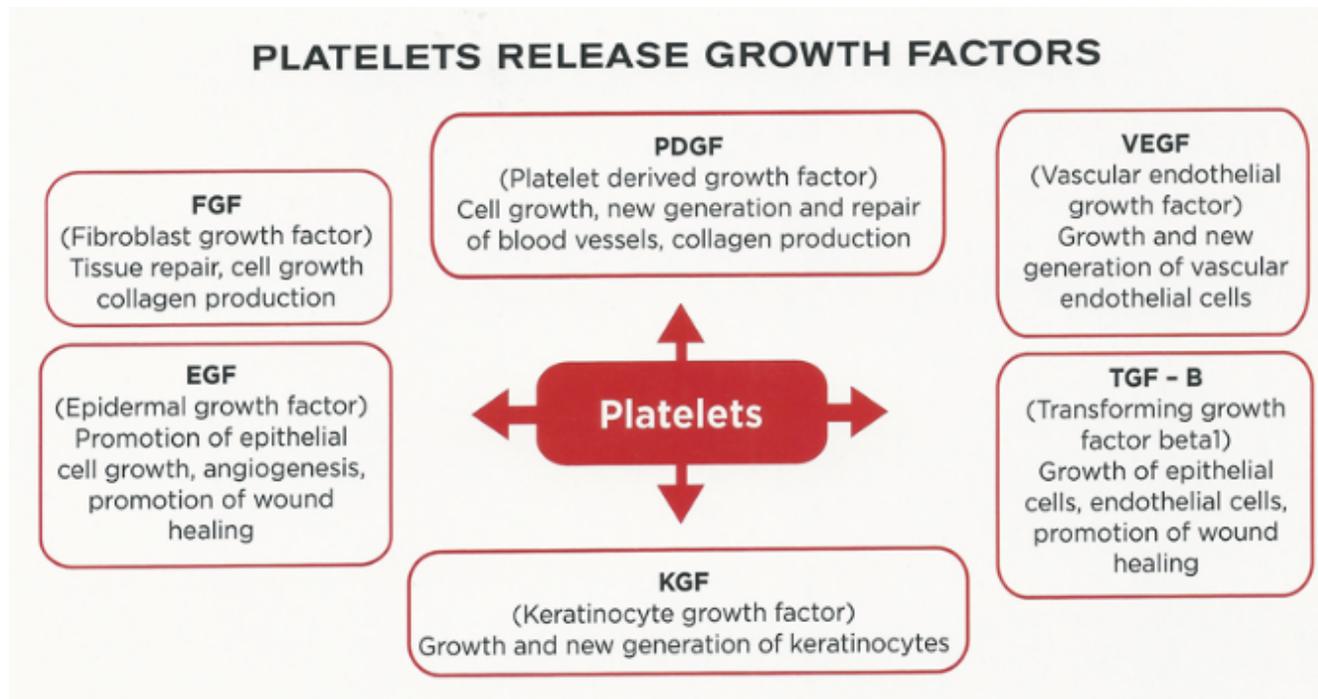
Robert Tressler, San Diego Blood Bank

The Issue

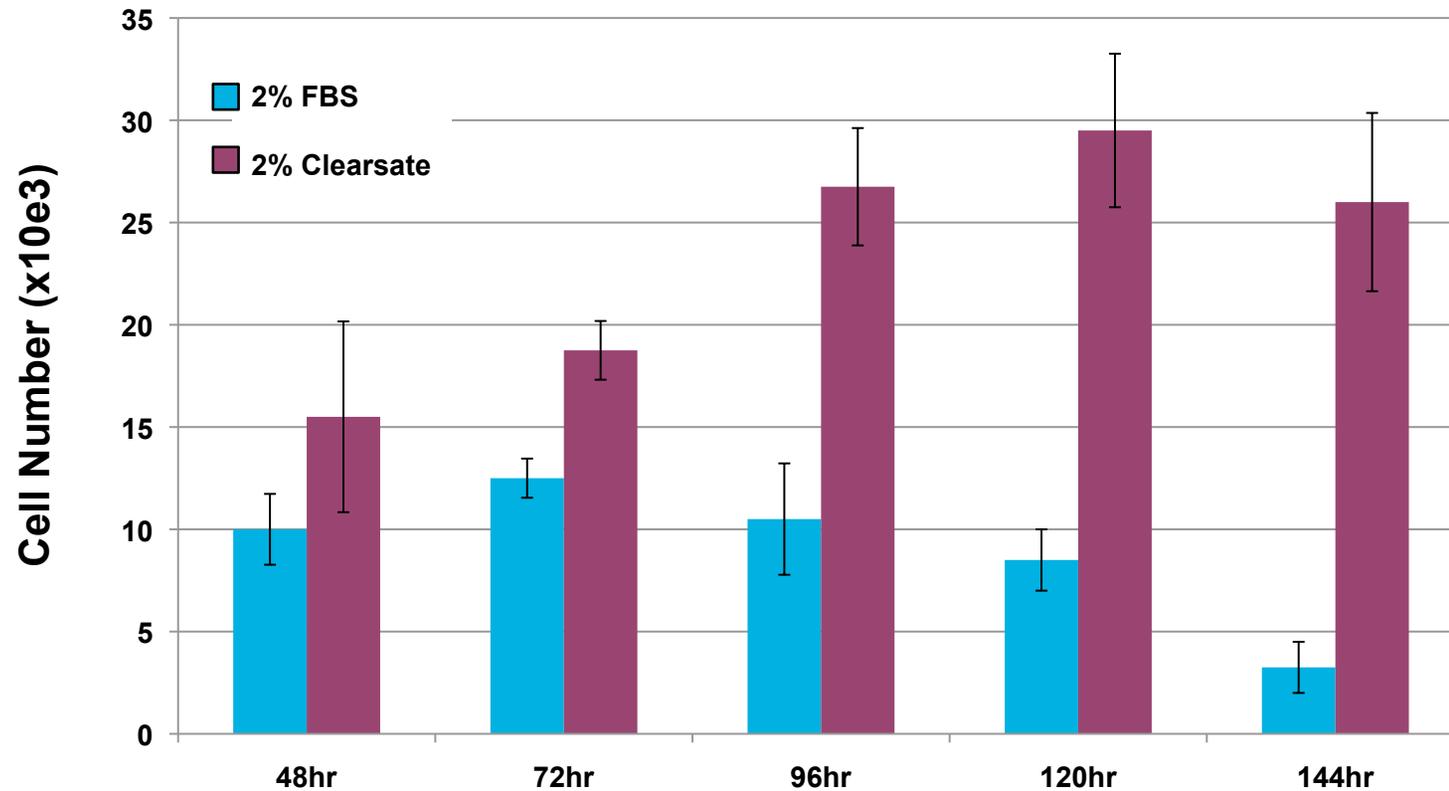
- cGMP manufacture of cell therapies needs to avoid the use non-human animal supplements.
 - Current options:
 - Defined media
 - Limited utility to date
 - AB serum
 - Not optimal for culture of some cells
 - Supply concerns
 - Human platelet lysate (HpL)
 - Extensive literature demonstrating utility of HpL for cell culture
 - Multiple companies/organizations marketing or developing HpL product formulations
 - » There is variability in manufacture of HpL
 - » Establishing a minimum set of criteria for HpL production/ characterization is needed

Why platelets?

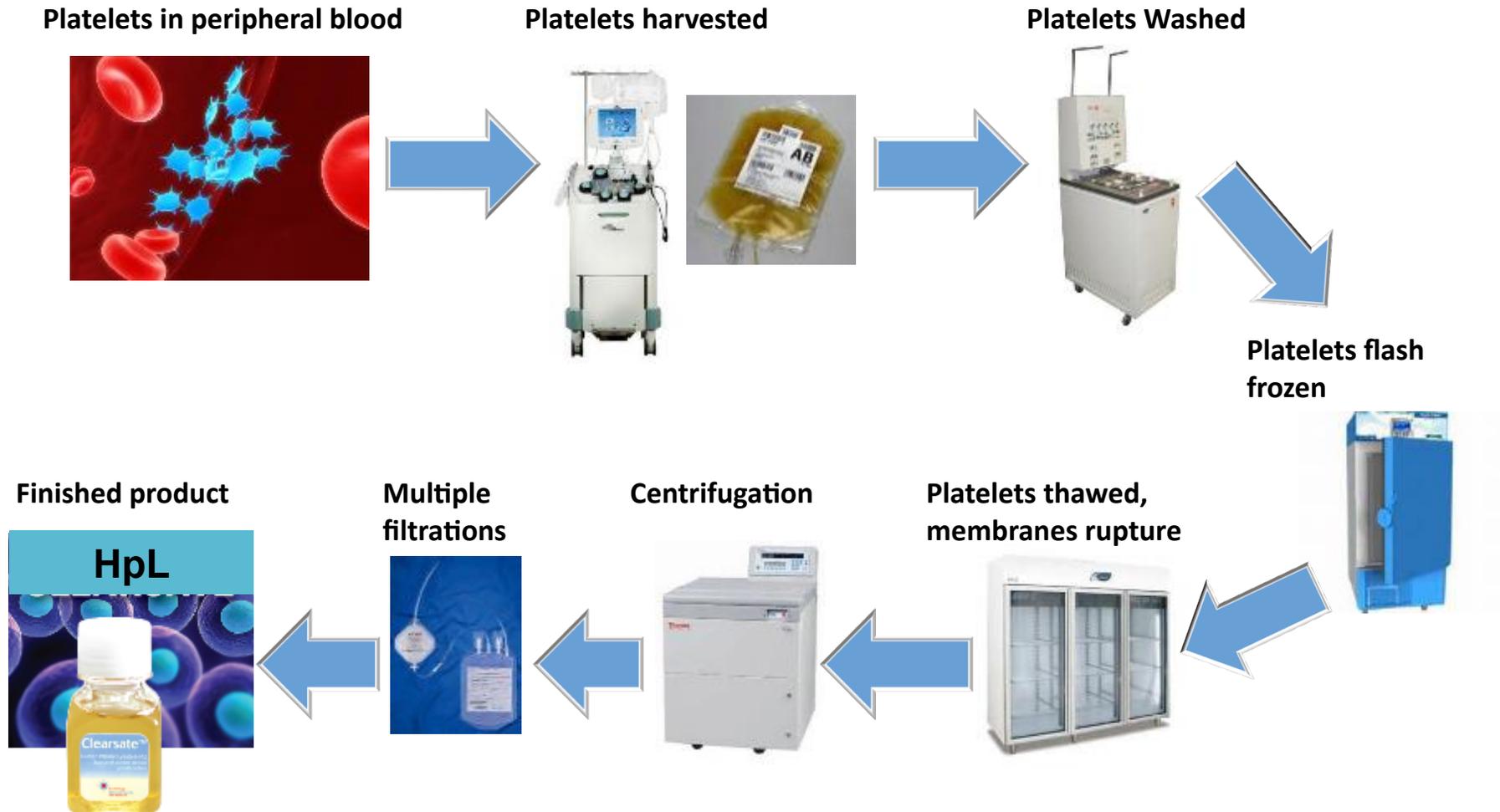
- The growth factors contained within platelets are key factors for tissue repair and regeneration, vital to inducing cells to grow rapidly, but not abnormally in the body.



HpL VS FBS Effect On CB MSC Proliferation

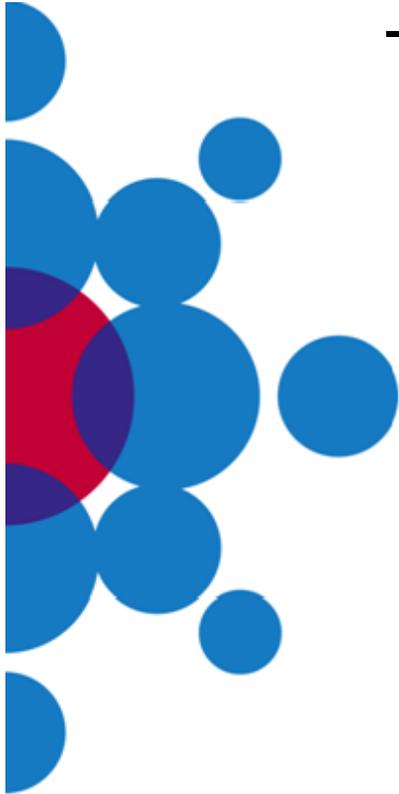


General Manufacturing Scheme for HpL

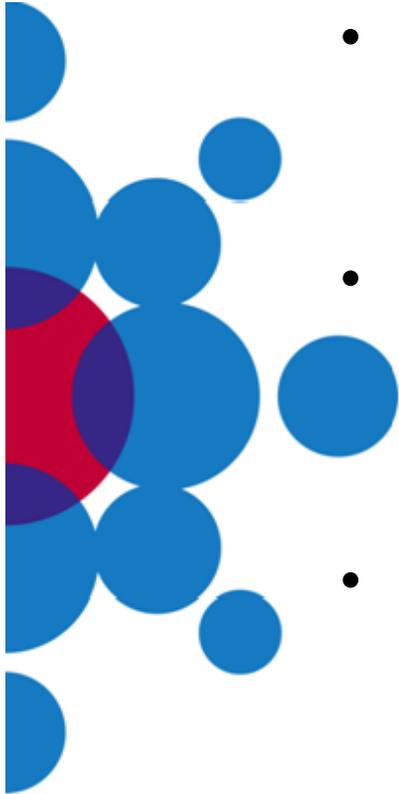


HpL Starting Material

- Typically expired platelets collected for transfusion are used as starting material
 - Collected at accredited (AABB, FACT) facilities with that follow State and CFR guidelines for clinical blood products
 - The appropriate consent must be obtained from donors prior to collection and use
 - IDM and sterility tested prior to release for manufacture of HpL
 - Assures a consistent, safe, traceable starting material with QA/QC oversight
 - Need to finalize how “old” can expired platelets can be and still be acceptable for use



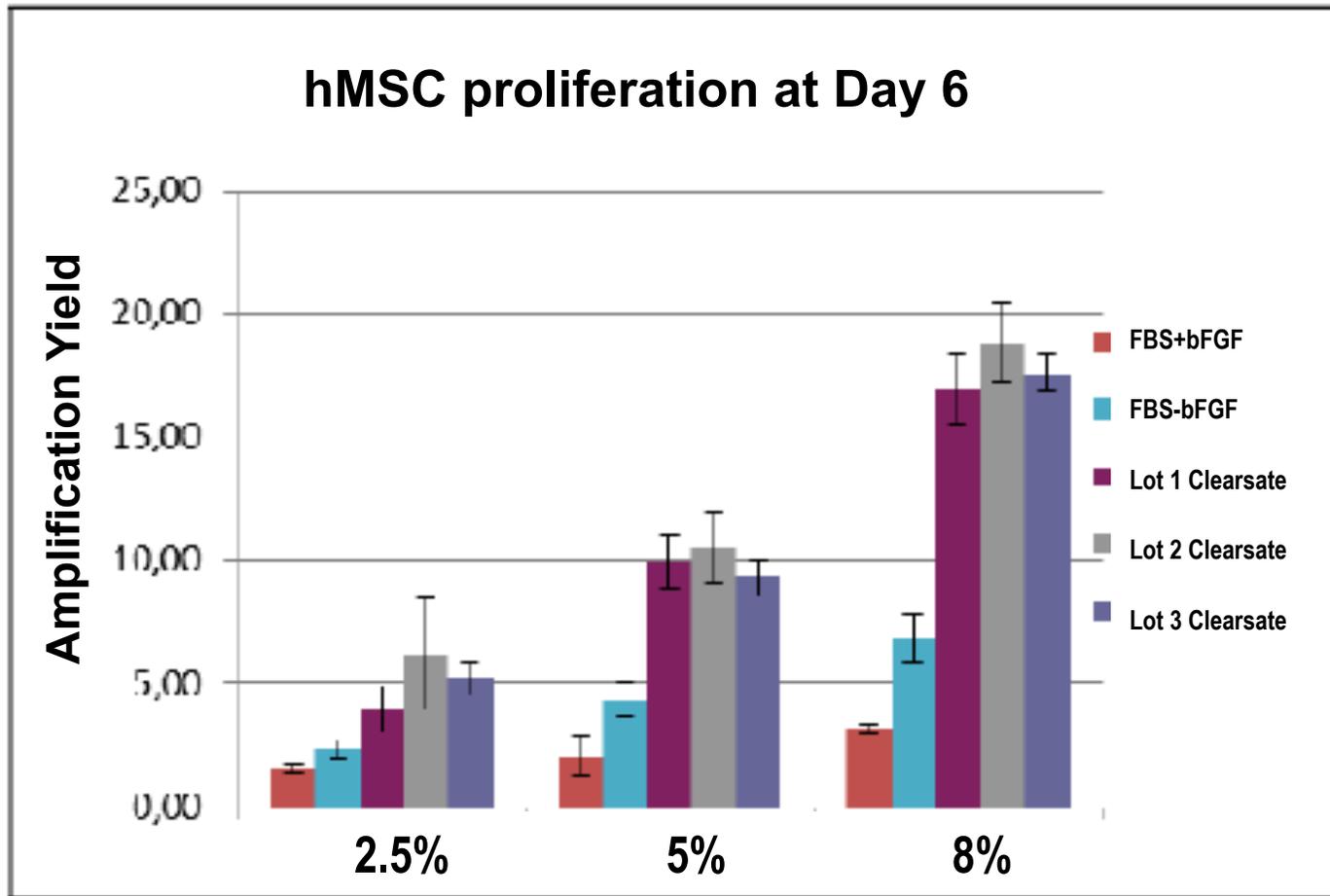
HpL Production Process



- Standardization of policies and procedures for HpL manufacturing processes assure production of a safe, consistent HpL product
- Manufacturing processes should be cGMP compliant, with Quality oversight
 - Environment, equipment, personnel, manufacturing supplies
 - Monitoring, validation, training, qualification
- Implementing these practices for HpL production is a key support for cGMP manufacture of the final cell therapy product



Lot to Lot Consistency Assessment



Product Characterization

- A Certificate of Analysis (CoA) should be included with each HpL manufacturing lot

- Additives*
- Lot number
- Protein concentration
- Endotoxin
- IDM
- Mycoplasma
- Sterility
- Expiration Date

*if used, for heparin, porcine source may be an issue

Certificate of Analysis and Release

Product: Clearstate™ (Human Platelet Lysate) from saline washed Human Platelets, GMP process, no non-Human biologicals or anti-coagulants added.

- Clearstate™ produced by: **San Diego Blood Bank**
- Lot Number: DIN _____
- Clearstate™ Storage Conditions: ≤ -20°C
- Not for transfusion into humans
Not for Human or Animal Consumption

All human platelet units, prior to selection for Clearstate™ production, were tested and found to be negative or non-reactive for the following (each unit of platelets used in each lot can be individually traced to the test results for the specific unit):

Platelets Used To Manufacture Clearstate Tested For:
Antibody Detection (Unexpected antibodies to red cells)
Human Immunodeficiency Virus (HIV) 1 & 2 plus O
Hepatitis B Virus
Hepatitis C Virus
Human T-Lymphotropic Virus Types I and II
Treponema pallidum (Syphilis)
Trypanosoma cruzi (Chagas)
West Nile Virus (WNV)
Zika Virus (ZIKV)
Bacterial Contamination
Mycoplasma
Endotoxin

Final Lysate Product:

- | | | | |
|---|---------------|-----------------------|----------------|
| • Sterility Tested: Bacterial/Fungal, aerobic & anaerobic | METHOD | SPECIFICATION* | RESULT* |
| | BacTec FX | N | N |

*All batches of Human Platelet Lysate have been sterile filtered and sterility tested and found to be N = Negative/Non-reactive prior to release. Sterility testing performed at San Diego Blood Bank.

Quality Assurance/Compliance Department Review and Lot Release

The above lot number tested using the methods listed has been found negative or non-reactive and is approved for release.

Signature _____

Printed Name and Title _____

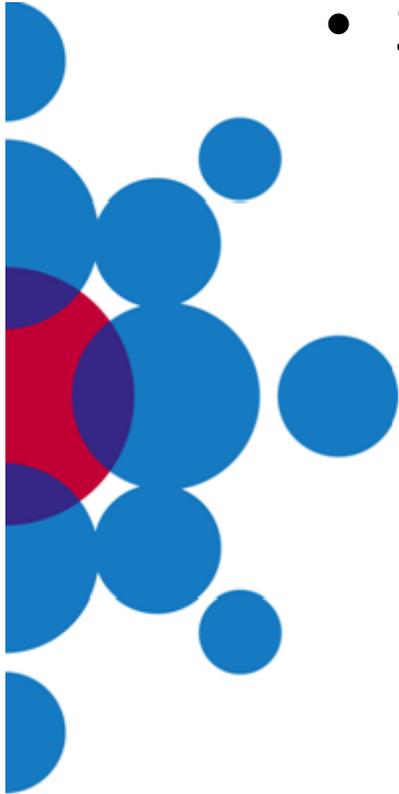
Release Date _____



San Diego
Blood Bank

HpL Product Characterization

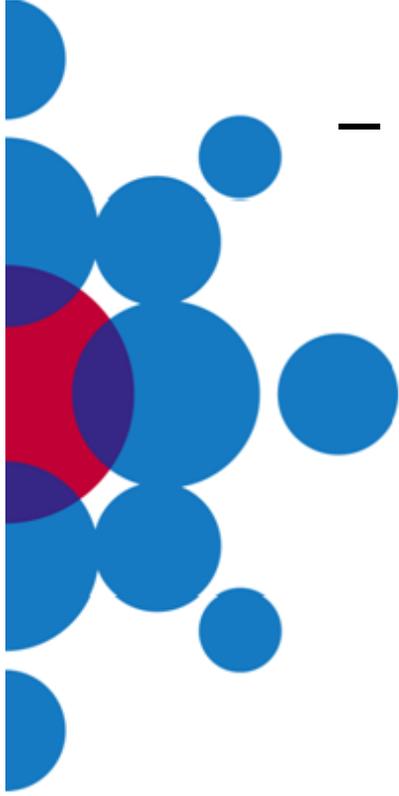
- Stability
 - A stability plan may be needed to determine shelf life of HpL products for a specific storage condition
 - -20 or -80 C storage conditions
 - Stability may be assessed with an in vitro cell proliferation potency assay
 - May need to use FBS standard or develop an HpL reference lot as comparator



Potency Assessment

- Used to support stability studies
- Used for HpL lot release criteria
 - Potential cell types to be screened:
 - MSCs, HSCs, other
 - Cell counts taken at multiple time points
 - Data compared to a reference standard

HpL Quality Control and Assurance

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- QA/QC oversight is a key aspect of HpL production to support cGMP cell therapy manufacture
 - Release of expired platelets as starting material for HpL manufacturing
 - Manufacturing standardization to assure safety and lot-to-lot consistency of the product

Suggestions for FDA to Consider

- A draft guidance for sourcing platelets that are the starting material for HpL production
 - Transfusion-grade Platelets sourced from cGMP facilities with appropriate accreditations, Consent and Quality oversight
 - Assures safety and consistency of starting material, typically expired platelet product and still acceptable for HpL manufacture
 - A cGMP compliant HpL manufacturing process preferred with Quality program oversight supporting environmental, equipment, personnel and materials management
 - A CoA with each manufacturing lot of HpL having the minimum criteria listed below:
 - Sterility, protein concentration, IDM, endotoxin, mycoplasma, lot number, expiration date, additives (if used)
 - Optional: Growth factor(s) content, potency assay results
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