

Update from the ISBT Working Party for Global Blood Safety (WP GBS)

Jay S. Epstein, MD
Chairman, WP GBS

IPFA/PEI 29th International Workshop on Surveillance
and Screening for Blood Borne Pathogens

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Mission of the WP GBS

- The mission of the WP GBS is to promote advancements to the availability, quality and safety of blood and blood products in low resource settings by using available knowledge to develop solutions that fit those environments.
 - The WP GBS was founded in 2010 in the spirit of the prior WHO Global Collaboration for Blood Safety (2000-2008)
 - WP GBS has 47 members from 20 countries, with a nine member organizing committee that includes five regional representatives
 - WP GBS presently has working groups in three areas:
 - Cryoprecipitate and plasma for fractionation
 - Voluntary versus replacement donation
 - Harmonization of regulations and standards

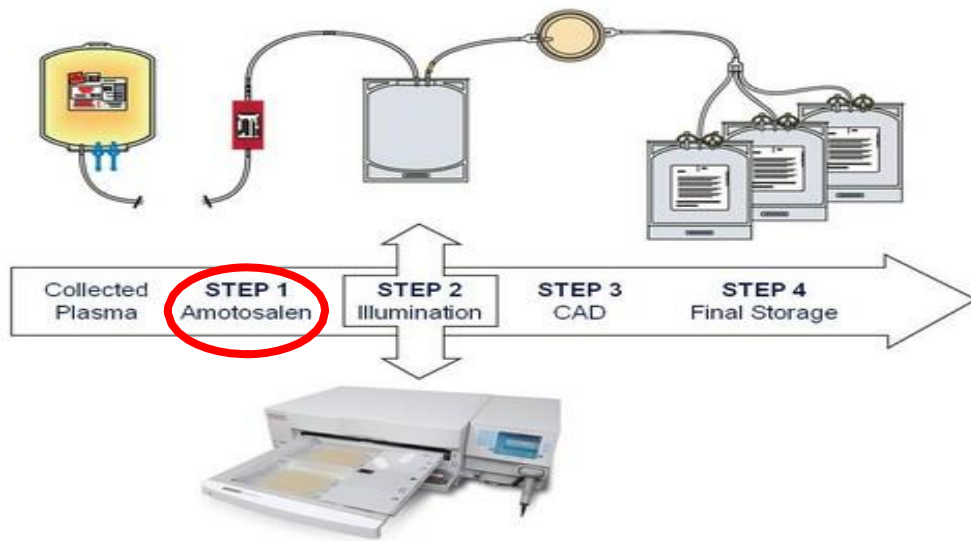
Activities of the WP GBS aligned with the WHO “Achilles Project” - I

- WHO established the “Achilles Project” in 2009 to improve access to plasma-derived medicinal products (PDMPs) in low- and middle- income countries by reducing plasma wastage and improving quality of plasma, but progress waned in recent years.
- WP GBS Subgroup on Cryoprecipitate and Plasma for Fractionation worked since 2017 to improve global access to clotting factors and immune globulins, including two publications on preparation and use of pathogen-reduced cryoprecipitate.
- Alignment of the work of the WP GBS with the Achilles Project was realized with revitalization of the Achilles project under a new WHO “Action Framework” for blood products published in 2020.

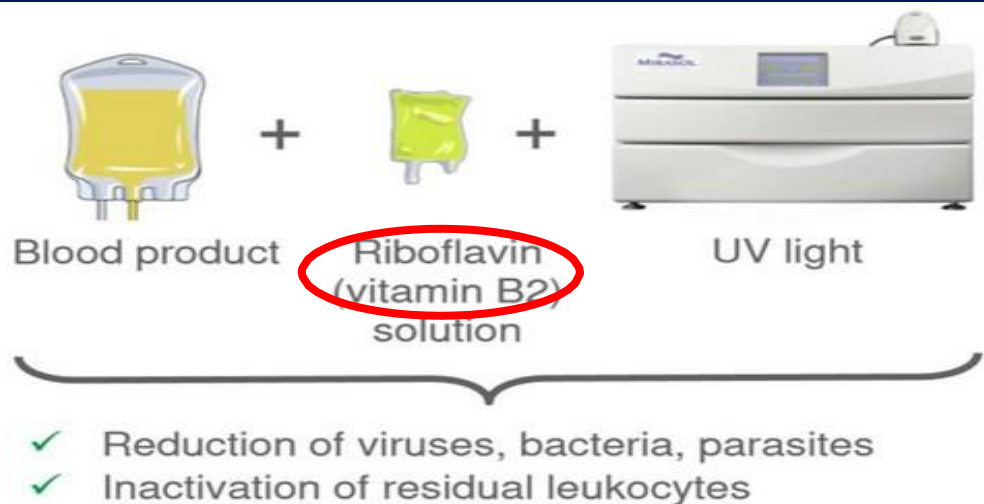
Activities of the WP GBS aligned with the WHO “Achilles Project”- II

- In 2021, WHO published “Guidance on Increasing Supplies of Plasma-Derived Medicinal Products in Low- and Middle-Income Countries through Fractionation of Domestic Plasma” with support from members of WP GBS.
- The WHO guidance recognized a stepwise approach of local small-scale production of safe plasma proteins to progressively increase the quality, safety and volume of domestic plasma suitable for fractionation.
- In September 2021, the WP GBS subgroup organized an online ISBT workshop on “Stepwise access to safe plasma proteins in resource-constrained countries” to identify pragmatic technical options for implementing a stepwise approach. Ca. 400 persons, mostly from LMIC attended daily.
- Plasma quality and pathogen reduction in preparation of small scale products including cryoprecipitate and immune globulin is fundamental to this strategy.

Available PR technologies for FFP and/or Cryo



INTERCEPT® by Cerus:
Approved for **FFP&PLT (&Cryo)**



MIRASOL® by TerumoBCT: approved for **FFP&PLT (has been used for WB)**



CRYO-SD/F® by VIPS:
approved for **cryoprecipitate&plasma**

THERAFLEX® by Macopharma
approved for plasma (using MB methylene blue)

Application to WHO to include Pathogen-Reduced Cryoprecipitate (Cryo-PR) on the Model Lists of Essential Medicines for adults and children (EML/EMLc)

- The WP GBS submitted an application to the WHO EML Secretariat on 16 December 2022 as a co-applicant with the WHO Group on Blood and other Products of Human Origin (BTT).
- The application was considered by the WHO Expert Committee on Selection and Use of Essential Medicines in April 2023 in a closed session.
- Final action by the WHO is pending.

Rationale for Inclusion of Cryo-PR on the EML/EMLc - I

- There is an unmet global need for clotting factors that can be partially addressed through local preparation of safe plasma proteins.
- Local production of safe plasma proteins can supplement the available supplies of preferred industrially manufactured products while promoting quality advancements in collection and processing of blood components.
- Cryo-PR is a safer source of fibrinogen, FVIII, vWF, and FXIII than non-pathogen-reduced cryoprecipitate wherever the latter product is used.

Rationale for Inclusion of Cryo-PR on the EML/EMLc - II

- For acute bleeding, Cryo-PR may serve as an alternative product to industrially manufactured concentrates of fibrinogen, FVIII, vWF and FXIII when those products are unavailable or unaffordable.
- Labeling of Cryo-PR with concentrations of clotting factors in standard units permits dosing to be based on clinical guidelines that exist for non-pathogen-reduced cryoprecipitate.
- Cryo-PR products using various technologies have been authorized by regulators in Thailand (dry heating), UK (Methylene Blue), US (psoralen-UV) and Egypt (Solvent/Detergent).

Establishment of the International Coalition for Safe Plasma Proteins (ICSPP) - I

- The ICSPP was established in October 2022 on a recommendation of the September 2021 ISBT Workshop on Stepwise Access to Safe Plasma Proteins in Resource-Constrained Countries in which the founding members participated.

<https://www.isbtweb.org/resource/launch-of-the-international-coalition-for-safe-plasma-proteins-icspp.html>

- The voting members (FIODS, IPOPI, ISBT, WFH) and non-voting members (IPFA, PPTA) of ICSPP agreed to collaborate to advance improvements in the supply of safe plasma protein products in resource-constrained countries.

Establishment of the International Coalition for Safe Plasma Proteins (ICSPP) - II

- The ICSPP is chaired by the ISBT through the WP GBS and operates in cooperation with WHO under a Memorandum of Understanding with ISBT.
- The member organizations represent, at the global level, blood and plasma donors, patients with bleeding disorders or immunodeficiencies, blood establishments, and plasma fractionators.
- WHO/BTT members (Yuyun Maryuningsih and Junping Yu) represent WHO in collaborative activities under the MOU.

Members of the ICSPS Steering Committee

- ISBT/WP GBS
 - Jenny White/Thierry Burnouf, Jay Epstein, Jean-Claude Faber, Martin Smid
- International Federation of Blood Donor Organizations
 - Giuliano Grazzini, Gianfranco Massaro
- International Patient Organisation for Primary Immunodeficiencies
 - Martine Pergent, Johan Prévot, Leire Solis
- World Federation of Hemophilia
 - Alain Bauman, César Garrido, David Page
- International Plasma and Fractionation Association
 - Leni von Bonsdorff, Robert Perry
- Plasma Protein Therapeutics Association
 - Sonia Balboni, Joshua Penrod

Goals of the ICSPP

- Support introduction in low- and middle-income countries (LMIC) of technologies for preparation of safe plasma protein products
- Provide situationally tailored approaches toward plasma fractionation
- Facilitate implementation and sustainability of these advancements
- Empower LMIC to progressively alleviate existing supply gaps and shortages of safe plasma protein products
- Promote collaboration toward these ends amongst relevant public and/or private organizations, including public-private-partnerships

Major Strategic Objectives of the ICSP

- Preparation in existing blood establishments of safe plasma protein products with use of small-scale methods that include pathogen-reduction
- Technology transfer from plasma fractionators to assure suitability of domestic plasma for fractionation with potential for national fractionation
- Contract fractionation of domestic plasma in a facility abroad
- National plasma fractionation if feasible and cost-efficient
- Assistance from manufacturers of medical devices and disposables to enable local preparation of pathogen reduced plasma protein products
- Strengthening of national blood systems under Competent National Authorities, with adoption of Good Manufacturing Practices in Blood Establishments, hospital-based Blood Banks, and other relevant parts of the blood system

ICSPP Model Projects

- Local small-scale production of Cryo-PR
 - Feasible at major blood establishments with appropriate infrastructure and ability to achieve compliance with Good Manufacturing Practices
- Local small-scale preparation of pathogen reduced immune globulin
 - Feasible at major blood establishments where quality assured surplus recovered plasma and/or cryoprecipitate-poor plasma can be prepared; promote use of apheresis plasma
- Fractionation of domestic plasma under contract abroad with an established fractionator (contract/toll fractionation)
 - Feasible where a sufficient and sustainable volume of quality assured plasma (50K L/ year) can be generated on a national or regional scale in a coordinated system

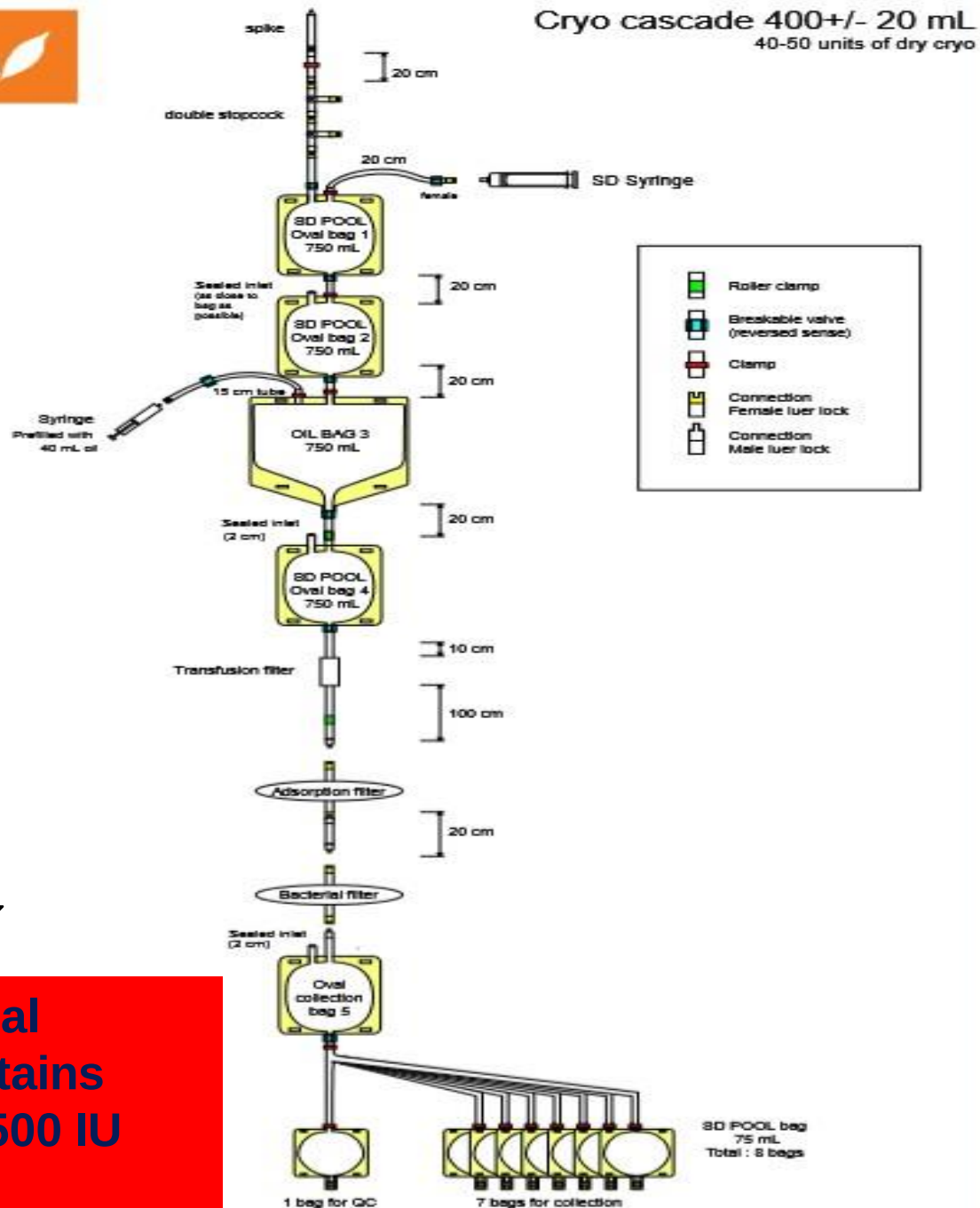
Minimal Criteria for Initiation of ICSP Model Projects

- Unmet need for safe plasma proteins
 - Evidence that clotting factors and immune globulin are locally unavailable or unaffordable
 - Changes to improve access to PDMPs are unrealistic in the near term
- Sufficient maturity level at the project site:
 - Adequate infrastructure and level of quality management to ensure that locally produced plasma protein products are safe and effective
 - Use of regulatorily authorized pathogen reduction devices and systems of preparation
- National support for project implementation
- Local champion
 - A committed, knowledgeable and well-connected person with the necessary authority to coordinate and implement the project

ICSPP Project at the National Blood Transfusion Center (NBTC) in Dakar, Senegal - I

Product Manufacturing:

- Preparation of Cryo-PR (phase 1) using technology selected by NBTC, Dakar: V.I.P.S. Solvent Detergent Virus Inactivation kits (V.I.P.S., Colombier, Switzerland)
- Planned duration of 6 months with 2 production days per week
- Four pools of 30-35 plasma depleted cryoprecipitates to be virus inactivated and sterile filtered per production day to yield 8 bags of Cryo-PR each containing ca. 3,500 IU FVIII:C
 - Overall, 150 cryoprecipitate pools will be processed yielding ca. 450,000 IU of FVIII and VWF and ca. 750 g of fibrinogen



Each final bag contains up to 3,500 IU FVIII:C

Pool 30-35 low-plasma cryos

***Add solvent-detergent SD:
TnBP & Triton X45***

Mix carefully 2x

Add oil

Remove/extract SD with oil

Pass through absorption filter

«Sterilize» with bacterial filter

Dispense into smaller portions

ICSPP Project at the National Blood Transfusion Center (NBTC) in Dakar, Senegal - II

Clinical Study of Cryo-PR

- In the absence of commercial clotting factors, acutely bleeding patients with hemophilia A, von Willebrand Disease and massive peripartum or traumatic hemorrhage will be treated with Cryo-PR
- Treated patients will be enrolled in observational clinical studies including coagulation assays, FVIII inhibitors, and serology for TTIDs

Plan for Production of Pathogen Reduced IG

- Cryo-poor plasma will be frozen for preparation of pathogen reduced IG in phase 2. (V.I.P.S technology exists for small scale IG preparation with caprylate inactivation that models plasma fractionation)

Progress of the ICSP Project in Dakar, Senegal - I

- Situation Analysis for the NBTS, Dakar - completed October, 2022
 - Experienced auditor used “PIC/S Good Practice Guidelines for Blood Establishments and Hospital Blood Banks, PE 005-4, June 2021” as the international reference standard
- Developmental Action Plan completed December 2022
- Capacity building on Good Manufacturing Practices (GMP) for blood establishments is ongoing
 - Virtual GMP training organized by WHO/BTT conducted February 27 to March 2, 2023 (training provided to participants from 24 Francophone countries including Senegal)
- Technology transfer & validation of Cryo-PR preparation
 - V.I.P.S., Colombier, Switzerland is donating devices for the project
 - In June/July 2023 V.I.P.S will provide operators with training at Shabrawishi Hospital in Cairo, Egypt and at NBTS Dakar, Senegal

Progress of the ICSP Project in Dakar, Senegal - II

Ongoing:

- Capacity building for the national blood regulatory authority
 - The WHO unit on Regulatory System Strengthening is engaged with the medicines authority in Senegal and will provide training on blood regulation using the Global Benchmarking Tool (Version 6 Plus Blood)
- Enhancement of safe donor recruitment
 - FIODS will assist the blood donor organization in Senegal to support the project

Pending:

- Informing patients with bleeding disorders & patient interest groups
- Training health care providers (physicians, nurses, hospitals)
- Communicating with blood/plasma donors & donor organizations
- Actions & metrics to ensure sustainability after the project ends
- Final evaluation after closure of the project

Summary - I

- Access to safe plasma proteins in low-resource settings can be improved through local production of pathogen-reduced cryoprecipitate and immune globulin
 - This approach also promotes adoption of GMP in blood establishments and increases the volume of quality assured plasma suitable for eventual fractionation
- In support of this approach:
 - ISBT/WP GBS sponsored a 2021 workshop on stepwise access to safe plasma proteins in resource-constrained countries that resulted in an international collaboration
 - WHO/BTT and ISBT/WP GBS applied to WHO for recognition of pathogen-reduced cryoprecipitate as an essential medicine

Summary - II

- FIODS, IPFA, IPOPI, ISBT, PPTA and WFH have formed the International Collaboration for Safe Plasma Proteins (ICSPP) to promote global access to safe plasma protein products in close cooperation with WHO
 - A pilot project on local production of pathogen-reduced cryoprecipitate and immune globulin is in progress at NBTS in Dakar, Senegal
 - Additional ICSPP projects are under active consideration

References

WHO Action Framework to Advance Universal Access to Safe, Effective and Quality-Assured Blood Products 2020–2023. Geneva: World Health Organization
(<https://www.who.int/publications/i/item/9789240000384>)

WHO Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma
(<https://apps.who.int/iris/handle/10665/340171>)

Thierry Burnouf, Jay Epstein, Jean-Claude Faber, Claude Tayou Tagny, Daniel Somuah, W Martin Smid. Rationale for supporting stepwise access to safe plasma proteins through local production in low- and middle-income countries: A commentary of an international workshop. *Biologicals*. 2022 Sep;79:27-30.
(<https://doi.org/10.1016/j.biologicals.2022.08.003>)

El Ekiaby M, Burnouf T, Goubran H, Radosevich M, El Ekiaby A. Role of the mini-pool cryoprecipitate technology for cost-saving and guarantee of local Factor VIII, Von Willebrand Factor and Fibrinogen product supply: Egypt experience. *Ann Blood* 2018;3:22. doi: 10.21037/aob.2018.02.07

Thank You!