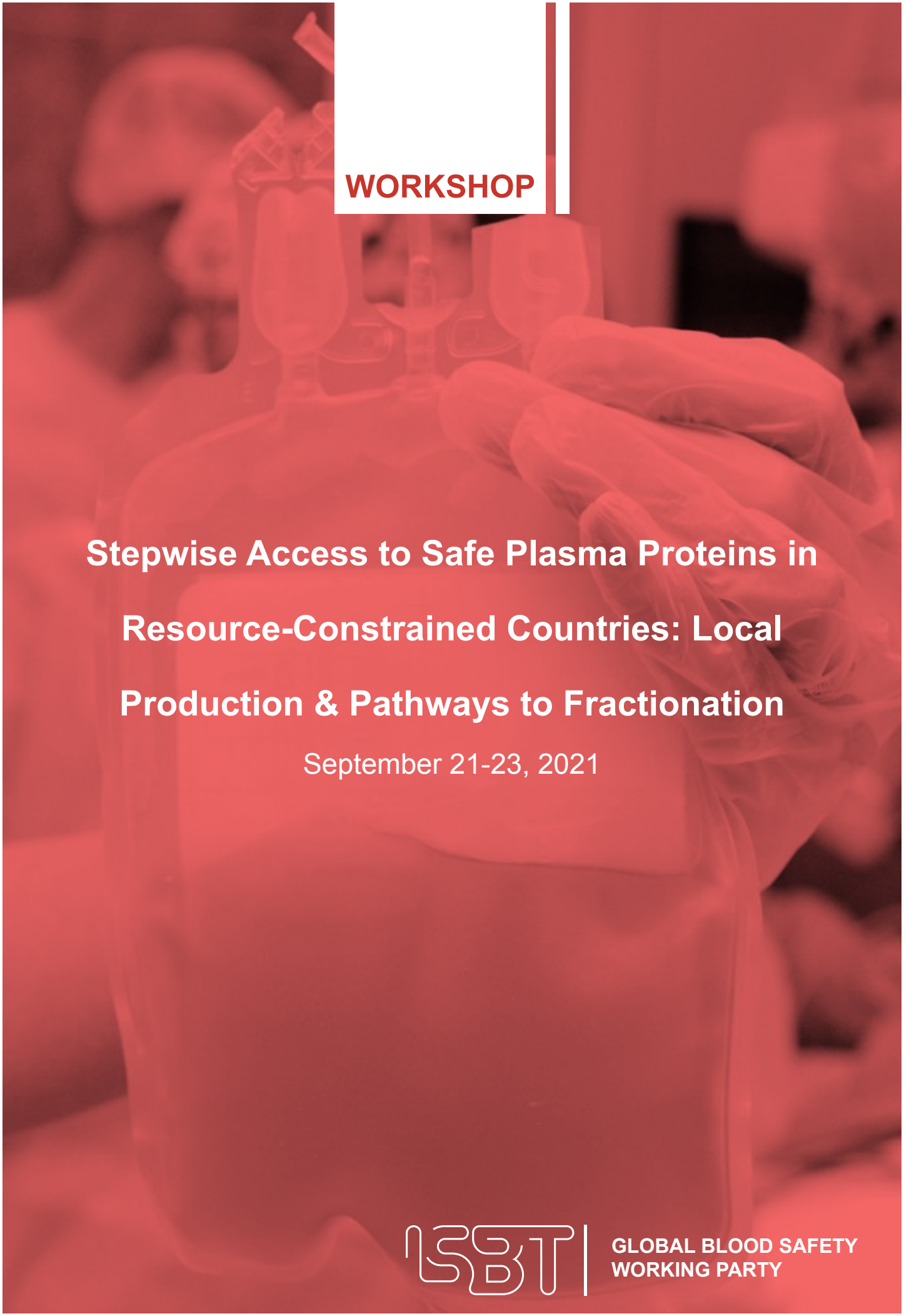


WORKSHOP

Stepwise Access to Safe Plasma Proteins in Resource-Constrained Countries: Local Production & Pathways to Fractionation

September 21-23, 2021

ISBT

GLOBAL BLOOD SAFETY WORKING PARTY

WORKSHOP PROGRAMME

Stepwise access to Safe Plasma Proteins in resource- constrained countries: Local production & pathways to fractionation

Organized by the Working Party for Global Blood Safety of the International Society of Blood Transfusion (ISBT GBS WP)

Day 1. Tuesday, September 21, 2021 (13:00-16:00 CEST)

13:00-13:10 **Introduction of the Workshop:**

Introduction and housekeeping rules: **Martin Smid (The Netherlands - Chair ISBT GBS WP)**

Welcome from ISBT: **Erica Wood (Australia - ISBT President)**

Session 1.1 **Unmet needs for plasma derived medicinal products (PDMP) in low- and middle- income countries**

Moderators: **Cesar Garrido (Venezuela - WFH)** and **Jean-Claude Faber (Luxembourg – ISBT GBS WP)**

13:10-13:30 Coagulation factors (FVIII,VWF, FIX, PCC, fibrinogen, others) - **Saliou Diop (Senegal - WFH)**

13:30-13:50 Immunoglobulins (polyvalent) - **Johan Prévot (Belgium, IPOPI)**

13:50-14:05 Discussion / Q&A

Session 1.2 **Options for fractionation of domestic plasma**

Moderators: **Junping Yu (Geneva - WHO)** and **Thierry Burnouf (Taiwan – ISBT GBS WP)**

14:05-14:25 Wastage of plasma in LMIC - **Yuyun Maryuningsih (Geneva - WHO)**

14:25-14:45 Key steps to improve quality of plasma for further processing - **Vee Armstrong (Australia)**

14:45-15:05 Plasma fractionation technologies: benefits and limitations; technical issues - **Jan Bult (The Netherlands - PPTA)**

15:05-15:25 Oversight of contract plasma fractionation - **Françoise Rossi (France - IPFA)**

15:25-15:45 Country experiences: Thailand - **Narin Kijkriengkraikul (Thailand - Thai Red Cross Society)**, Argentina - **Andrea Corina Zucchi - (Argentina, NU Cordoba)**

15:45-16:00 Discussion / Q&A

Day 2. Wednesday, September 22, 2021 (13:00-16:00 CEST)

Session 2.1 **Options to improve the access to safe plasma protein products in LMCI**

Moderators: **Jay Epstein (USA - ISBT GBS WP)** and **Jean-Claude Faber (Luxembourg – ISBT GBS WP)**

13:00-13:20 Recruitment and retention of safe donors - **Giuliano Grazzini (Italy - FIODS)**

13:20-13:40 Quarantine of plasma as a means to reduce the risk of transfusion-transmitted infection: logistics and feasibility - **Pierre Tiberghien (France - EFS)**

13:40-15:20 Technologies for pathogen reduction of single-donor or mini-pools of plasma, cryoprecipitate, and immunoglobulins: experience from suppliers and users:

- Strategies to move safe plasma products into low resource areas: overview and experience with Riboflavin/UV **Jeffrey Mc Cullough (USA)**
- Psoralen/UVA - **Hans Vermeij (Brazil - Cerus)**
- Methylene blue/light - **Stefan Reichenberg (Germany - Macopharma)**
- Pathogen reduction of COVID-19 convalescent plasma - **Salwa Hindawi (Saudi Arabia - King Abdulaziz University)**
- Mini-pool solvent/detergent treatment of plasma, cryoprecipitate & caprylic acid fractionation of immunoglobulins (VIPS) - **Magdy El-Ekiaby (Egypt - Shabrawishi Hospital)**

14:20-15:40 Viral safety of plasma derived components - **Johannes Blümel (Germany, PEI)**

15:40-16:00 Discussion / Q&A

WORKSHOP PROGRAMME

Day 3. Thursday September 23, 2021 (13:00-16:00 CEST)

Session 3.1 **Scale-up for domestic processing of plasma: technology options, equipment and oversight:**

Moderators: **Micha Nuebling (Germany - PEI)** and **Thierry Burnouf (Taiwan - ISBT GBS WP)**

13:00-13:15 Potential contribution of single-use technologies for processing domestic plasma components - **Prity Bengani-Lutz (USA, Sartorius)**

13:15-13:30 Domestic scalable plasma processing: technological approaches and solutions for LMIC - **Josephine Cheng (Taiwan - Merck Millipore)** and **Jian-Fei Shou (China - Merck Millipore)**

13:30-13:45 Potential contribution of nanofiltration to the virus safety of domestic plasma components **- Tomoko Hongo-Hirasaki (Japan - Asahi Kasei Medical)**

13:45-14:00 SARS-CoV-2 immunoglobulins in India as an example for domestic production of immunoglobulins: Safety, efficacy and quality attributes **- Suma Ray (India - Intas Pharmaceuticals)**

14:00-14:20 Plasma fractionation of animal-derived immunoglobulins in LMIC: lessons to be learned for human plasma IgG production **- Mariángela Vargas (Costa Rica - Instituto Clodomiro Picado)**

14:20-14:40 Regulatory considerations for authorization of plasma processing devices: example of an EU CE marking **- Mohamed Ghönim (Switzerland - QSE Consulting)**

14:40-15:00 Discussion / Q&A

Session 3.2 **The way forward**

Moderators: **Martin Smid (The Netherlands - Chair ISBT GBS WP) and Jay Epstein (USA - ISBT GBS WP)**

15:00-15:20 Models for technology transfer and technical assistance - **Leni von Bonsdorff (Finland - IPFA)**

15:20-16:00 Panel discussion: Lessons learned and next steps**: Yuyun Maryuningsih (WHO), Giuliano Grazzini (FIODS), Cesar Garrido and Salou Diop (WFH), Johan Prévot (IPOPI), Johannes Blümel (PEI), Leni von Bonsdorff, (IPFA), Jan Bult (PPTA)**

16:00 **Closure of the workshop**

Martin Smid, Chair of ISBT GBS Working Party

FOREWORD

Martin Smid (Netherlands, MD Medicine, PhD and MBA) has more than 25 years experience in blood bank management, transfusion medicine and coagulation. He is managing director of Sanquin Consulting Services and the Academic Institute IDTM.

He is chair of the ISBT GBS WP since 2018 and member from the start in 2010. Martin's main responsibilities are international cooperation and knowledge-sharing in international projects and the Management of Transfusion Medicine programme at the Graduate School of Medical Science of the University of Groningen. He is involved in the WHO Global Blood Safety Network and AfSBT Educational Committee and also is an advisor of the Curacao blood bank.

Dear Attendees,

In many Low and Medium Income Countries (LMIC) access of patients to plasma proteins essential for their treatment is still poor. Plasma derived medicinal products that are standard treatment for these patients in high income countries are lacking.

In order to identify and facilitate new avenues of supply the **Global Blood Safety Working Party (GBS WP)** of the International Society of Blood Transfusion (ISBT) has started initiatives from 2017 and published two recommendations on the GBS ISBT website on pathogen inactivated cryoprecipitate and on plasma for fractionation. In December 2020 during the online ISBT congress a session with presentations addressing country experience with alternative solutions was organized.

Recently, WHO has launched a global initiative "**Strategic framework for blood safety and availability 2016–2025**" and published two guidance documents

- **Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma**
- **Guidance on centralization of blood donation testing and processing**

In close consultation with WHO BSP (Blood Safety Programme), the GBS WP of ISBT has worked since the beginning of 2021 to put together a Workshop to "identify pragmatic technical options for stepwise access to safe plasma protein therapies in resource-constrained countries to support implementation of recent WHO guidance on "Increasing Supplies of Plasma-derived Medicinal Products in Low- and Middle

income Countries through Fractionation of Domestic Plasma" and "Centralization of Blood Donation Testing and Processing"

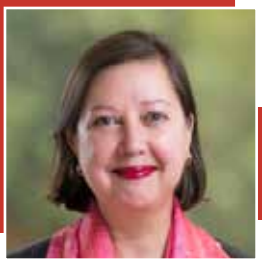
The Workshop is planned to cover a large array of topics:

- Unmet clinical needs in safe plasma protein therapies for treatment of bleeding disorders and immunodeficiencies
- Robust quality and safety criteria of plasma for fractionation and plasma derived products, including coagulation factors and immunoglobulins
- Stepwise measures to avoid wasting recovered plasma and to increase availability of plasma for plasma protein manufacture
- Considerations to implement a contract/toll plasma fractionation program and to address technical and financial issues
- Cost considerations in plasma collection and fractionation
- Interim alternatives to fractionation through local production by blood establishments of safe therapeutic plasma proteins: quarantine/retested plasma; pathogen-reduced plasma, cryopoor plasma, and cryoprecipitate; pathogen-reduced mini-pool plasma products (cryoprecipitate, IgG, and other products)
- Single-use processing for local plasma protein purification and virus inactivation
- Technical solutions from the suppliers of single-use devices for local processing and virus inactivation of plasma, cryoprecipitate, cryoprecipitate-poor plasma and immunoglobulins
- Role of suppliers in training of personnel and local implementation of technologies
- Regulatory considerations for validation of small/medium scale plasma processing.

The organizers of the workshop hope to send to LMIC the necessary stimulus and motivation to consider feasible domestic solutions (either safe local production of plasma proteins or PDMP substitutes needed by patients and/or plasma fractionation options, e.g. contract fractionation) to improve the existing supply shortages and in this way significantly improve treatment possibilities for patients with so far unsatisfied need for PDMPs.

I hope you will find the scientific programme interesting and helping to support new solutions for the benefit of patients in need of plasma proteins in low resource countries.

Thank you and enjoy the Workshop!



Erica Wood, President of ISBT

WELCOME SPEECH

Erica Wood is president of the International Society of Blood Transfusion. She is head of the Transfusion Research Unit at Monash University, and a consultant haematologist at Monash Medical Centre, in Melbourne, Australia. Erica is former president of the International Haemovigilance Network, and a member of the World Health Organization Expert Advisory Panel in Blood Safety. She is a member of Australia's National Haemovigilance Committee, the Therapeutic Goods Administration Advisory Committee on Biologicals, and has served as Chief Examiner in Haematology for the Royal College of Pathologists of Australia.

Dear Attendees,

On behalf of the International Society of Blood Transfusion it is my great pleasure to welcome you to this workshop, organised by the ISBT Working Party for Global Blood Safety, on a very important topic: **improving access to safe plasma protein products in resource-constrained countries for patients who need them**.

As you know, ISBT is an international **community of professionals sharing knowledge to enhance transfusion practice**. We work with many individuals and organisations all around the world, and I am pleased to see so many participating in this workshop – thank you for your contributions!

By bringing together diverse views and expertise on this topic, we can consider the many clinical, technical, regulatory, logistical, and economic issues needed to make progress. In doing so, we will keep a focus on respecting the gifts of donors, the stewardship of national resources, and the needs of patients, and address fundamental scientific, safety, quality and availability issues. This is vital to avoid the wastage of plasma and improve access to care in low and middle-income countries.

Please **get involved with the workshop sessions and discussions** – it's going to be an excellent opportunity to share ideas, hear the latest research, and find solutions together. I thank Martin Smid, GBS Working Party Chair, Thierry Burnouf, GBS Working Party Secretary, and the organising committee – in particular Jay Epstein and Jean-Claude Faber, the ISBT Central Office, and all speakers and supporters, for their efforts to coordinate this meeting. My thanks also to Drs Yuyun Maryuningsih and Junping Yu from WHO for their personal involvement, as well as the World Federation of Hemophilia and IPOPI patient organisations. I am sure it will be a great success!

DAY 1 Tuesday September 21, 2021 (13:00 – 16:00 CEST)

1.1 SESSION

"Unmet needs for plasma derived medicinal products (PDMP) in low- and middle- income countries (LMIC)"

13:10-13:30 Coagulation factors (FVIII, VWF, FIX, PCC, fibrinogen, others)(Saliou Diop, Senegal - WFH)

13:30-13:50 Immunoglobulins (polyvalent) (Johan Prévot, Belgium - IPOPI)

13:50-14:05 Discussion / Q&A

OBJECTIVES OF THE SESSION

The session allows for exchanges of newest available information on the existing treatment situation for patients with **bleeding disorders** and **immune deficiencies** worldwide. Particular emphasis is given to the situation in **LMIC (low- and middle-income countries)** and the focus is on existing problems with safety, availability, accessibility and affordability of therapeutic plasma proteins. Also, trending and extrapolation for coming years of the gaps between need/demand and offer/supply are discussed, allowing for estimation of future situations.

Learning points:

- Coagulations factors and immunoglobulin therapeutic products made from human plasma are safe and essential medicines (many on the WHO Model List of Essential Medicine) used for substitutive therapy in patients with various coagulopathies and immunodeficiencies at global levels.
- While patients in High Income Countries (HIC) receive appropriate treatment, the vast majority of patients in LMIC who have coagulation factor deficiencies or with primary immunodeficiency, that are all treatable by PDMPs, do not have access to safe and sufficient treatment due to global PDMP shortage or high cost.
- Actions must be taken to improve the supply of safe coagulations factors and immunoglobulin therapeutic products in LMIC.
- Patients' organization like the World Federation of Hemophilia (WFH) and the International Patient Organisation for Primary Immunodeficiencies (IPOPI) are advocating urgent global and national (local) efforts to improve the access to safe PDMPs in LMIC

MODERATORS

Cesar Garrido, Venezuela - WFH

Cesar Garrido is president of the World Federation of Hemophilia (WFH). He was born in Caracas, Venezuela and has two sons, one has hemophilia A. In 1996 Cesar became a member of the Venezuelan Association for Hemophilia (AVH) and held a number of roles in that organization. He was part of national programs which increased access to factors, developed outreach and identification campaigns, increased access to education, and set up regional medical workshops for patients with hemophilia. At the international level, he was an Advisory Board member of the International Alliance of Patient Organizations (IAPO) and member of HERO (Haemophilia Experiences, Results and Opportunities). He was also a development manager for a strategic alliance of 27 countries from the Americas that was set up to influence public policies. The WFH has been a big part of his life since 1999: member of the Board of Directors 2002-2010. He has held a number of important roles at the WFH, including chair of the Accreditation Committee, chair of the Hemophilia Organization Twinnings (HOT) Committee, co-chair of Capacity Building Committee, NMO Vice President, and member of the President's Strategic Council.

Jean Claude Faber, Luxembourg - ISBT GB WP

Jean-Claude Faber from Luxembourg is a medical specialist in biological haematology and blood transfusion. He is a member of the Organising Committee of ISBT WP on Global Blood Safety (GBS WP). For the World Health Organisation (WHO) he is a member of the Expert Advisory Panel on Transfusion Medicine since 2010. For the International Haemovigilance Network he was the founding president in 1998. For the Council of Europe (CofE) he was a member of the Group of Experts in Blood Transfusion and Immunohaematology for more than 20 years (1986- 2008) and president of the group for two years (non-renewable term). For the European Commission (EC) he was a national expert in blood transfusion for 20 years (1989-2008) and scientific expert. For the European Blood Alliance (EBA) he served as vice-president 2001-2004. He has worked as a consultant in developing countries for blood systems, blood programmes, blood policies, blood strategies, QMS in blood centres,…: Vietnam, Laos, Nepal, Pakistan, Burkina Faso, Senegal, Ecuador, Nicaragua. For the Luxembourg Association of Haemophiliacs he is the president since 1983.

SPEAKERS

Saliou Diop, Senegal - WFH

Saliou Diop is Professor in Clinical Hematology and Blood transfusion in Cheikh Anta Diop University of Dakar (Senegal). He is also Director of the National Blood Transfusion Center (CNTS) of Senegal. Saliou Diop is currently President of the Senegalese Society of Hematology and Blood Transfusion, and also a member of the Board of Directors of the World Federation of Hemophilia.

Unmet Needs for coagulation factors in LMIC

Blood coagulation is a complex process that involves numerous and essential plasma proteins. The deficit of these proteins can lead to diverse inherited bleeding disorders (IBD) including hemophilia, von Willebrand disease and other rare hemorrhagic diseases. It is recognized that these disorders are present worldwide but only 8 % of the expected cases of IBD are identified in lower income countries, due to lack of awareness, inadequate diagnosis, and unavailability of treatment products.

Regarding access to treatment, 82% of the total FVIII IUs are used by 29% of the population living in Americas and Europe. In the World Federation of Hemophilia (WFH) global survey 2019, mean FVIII usage per capita was 6.01 IU in high income countries versus 0.06 in lower income countries. These identified gaps are responsible for a high morbidity and mortality among patients living in LMIC. Annual bleeding rate was 24 in hemophilia patients living in LIC whereas it was only 4 in high income countries.

The WFH has 147 national Member Organization and aims to improve and sustain care for people with IBD around the world. WFH activities include improving level of knowledge by capacity building and data collection, enhancing advocacy capacities of the different stakeholders, and facilitating access to care by a humanitarian aid program. This program is leading the effort to change this lack of access in LMIC by providing consistent and predictable accesses to treatment for all.

With this program, it was possible to treat more patients for acute bleeds, to realize surgical procedures and to start prophylactic clotting factor replacement therapy for young patients living in LMIC. Furthermore, the humanitarian aid program increases awareness about the need of clotting Factor Concentrates (CFC) availability among stakeholders (governments, physicians, patients). It is designed to take advantage of optimal treatment paradigms and demonstrate further benefits if governments increase support of IBD care and enhance purchase or production of CFCs.

SPEAKERS

Johan Prévot, Belgium - IPOPI

Johan Prévot has worked in the healthcare sector for 20 years in the field of patient advocacy and health policy. He is the Executive Director of the International Patient Organisation for Primary Immunodeficiencies (IPOPI). He is a Board member of the European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune diseases (ERN-RITA), Health First Europe (HFE) and the RE-COMB research programme. He is also a Steering Committee Member of the Platform of Plasma Products Users (PLUS). He previously worked as Director of Health Policy Europe for the Plasma Protein Therapeutics Association (PPTA), a trade association in the field of plasma protein therapies. He has and continues to work closely with other stakeholder organisations sharing common objectives and priorities.

Immunoglobulin Replacement Therapies: Unmet Needs for Plasma Derived Medicinal Products (PDMP) in Low- and Middle- Income Countries (LMIC)

Immunoglobulin (Ig) therapies are currently and have been now for a significant number of years the ‘driving product’ of the plasma derived medicinal products (PDMPs) industry.

The demand for Ig therapies has been growing annually at 6-8% across a broad range of indications with particular growth in secondary immunodeficiency and is not forecasted to decrease much in the years to come.

However, there are still significant disparities in terms of primary immunodeficiency (PID) diagnosis rates and patient access to Ig therapies between regions and sometimes inside the same region.

There is also a significant imbalance in global plasma collection with 65% of this being from the US with a need for more regionally balanced collection to reach global sufficiency in PDMPs.

Progress towards global sufficiency in PDMPs and therefore better access to Ig in LMIC will require collaboration guided by patient needs, donor care, safety of PDMPs and a better understanding of the differences between blood and plasma and their derived therapies.

DAY 1 Tuesday September 21, 2021 (13:00 – 16:00 CEST)

1.2 SESSION

"Options for fractionation of domestic plasma"

14:05-14:25 Wastage of plasma in LMIC (Yuyun Maryuningsih, Geneva-WHO)

14:25-14:45 Key steps to improve quality of plasma for further processing (Vee Armstrong, Australia)

14:45-15:05 Plasma fractionation technologies: benefits and limitations; technical issues (Jan Bult, The Netherlands - PPTA)

15:05-15:25 Oversight of contract plasma fractionation (Françoise Rossi, France - IPFA)

15:25-15:45 Country experiences: Thailand (Narin Kijkriengkraikul - Thailand-Thai Red Cross Society), Argentina (Andrea Corina Zucchi - NU Cordoba)

15:45-16:00 Discussion / Q&A

OBJECTIVES OF THE SESSION

This educational session is intended to take the audience through the various international technical, economic and regulatory requirements that need to be met in LMIC to avoid the substantial wastage of plasma and engage into an industrial plasma fractionation program either through contract/toll fractionation, or by domestic fractionation. The basic starting point for such programs is the capacity to produce a sufficient quantity of quality plasma for fractionation. Information will be provided on current plasma fractionation technologies with some emphasis on quality and safety requirements of modern plasma products. Experiences from two countries that attempted to engage into industrial plasma fractionation program will be shared.

Learning points:

- The processing of whole blood into components in combination with the increasing number of whole blood collection in LMIC to cover the needs for packed red blood cells for clinical use will help to increase volume of recovered plasma.
- Several reasons (technical, logistical, or financial) will be reviewed in this session to understand why the recovered plasma in excess of the need for clinical transfusion is not used for fractionation into PDMPs and is currently wasted.
- A main reason why recovered plasma is wasted in LMIC is linked to an insufficient level of quality or a lack of sufficient regulatory compliance, that is required when plasma is pooled and used for fractionation into licensed medicines (PDMPs).
- The quality and safety criteria of plasma as a starting material used to produce PDMPs are well established in HIC and must be implemented gradually in LMIC to allow its use for fractionation.

- To establish a domestic industrial plasma fractionation program, when the volume of plasma is sufficient, two approaches are possible: domestic fractionation or contract/toll fractionation.
- Establishing a domestic facility is challenging and costly, because plasma fractionation is a complex and highly regulated biotechnology industry combining integrated procedures allowing to purify several PDMPs from the same starting plasma pools and to inactivate or remove pathogens, primarily viruses; in addition, a modern plasma fractionation facility is extremely costly to design, qualify, validate, and operate, and requiring skilled manpower.
- A safer, less capital-demanding, approach to start a plasma fractionation program consists in initiating a contract fractionation or toll fractionation contractual agreement where the domestic plasma is provided to an established licensed plasma fractionator, and PDPM are provided in return following different kinds of contractual mechanisms.

MODERATORS

Thierry Burnouf, Taiwan - ISBT GBS WP

Thierry Burnouf is Vice-Dean, College of Biomedical Engineering and Director, International PhD Program in Biomedical Engineering at Taipei Medical University Taipei, Taiwan. He has a long experience with the plasma fractionation industry and research on therapeutic plasma products purification and virus inactivation. He is the Secretary of the Working Party on Global Blood Safety, Treasurer of the Working Party on “Cellular Therapies”, and member of drafting groups on Covid-19 convalescent plasma and hyperimmune globulin of ISBT. He is an informal consultant to the World Health Organization on quality and safety of plasma products and their access in low- and middle-income countries. He has published over 280 scientific publications on blood products, plasma protein purification and virus reduction treatments, and platelets lysates for cell therapy and regenerative medicine. He serves as editorial board member of several scientific journals including “Platelets”, “Frontiers in Medicine (Haematology)”, “Frontiers in Neuroscience”, “Biologicals”, “Transfusion Clinique et Biologique”, and “Current Nanoscience”.

Junping Yu, Geneva - WHO

Junping Yu is is the Technical officer working for the WHO blood and other products of human origin programme in WHO Headquarters in Geneva, Switzerland. From July 2003 to December 2007 he worked as blood safety specialist in WHO regional office for Western Pacific. Before 2003 he worked in various fields in the Chinese blood transfusion system and was the vice director of Wuhan Blood Centre from 1996 to 2003. He completed his undergraduate and postgraduate educations in the field of cell biology and immunology in universities in China. He holds a master degree in Epidemiology.

SPEAKERS

Yuyun Maryuningsih, Geneva - WHO

Yuyun Siti Maryuningsih Soedarmono is a Medical Doctor with specialization in Transfusion Medicine and a doctorate in Biomedical Sciences from Indonesia. In 2004-2015 she was the Director of the Central Blood Transfusion Service at the Indonesian Red Cross. In 2015-2018 she hold the position of Blood Services Program Coordinator at the Directorate of Primary Health Services within the Ministry of Health of Indonesia. In 2011-2018 she was the Coordinator of the Master Program on Biomedics Specialty in Transfusion Science at Indonesian University. Since October 2018 she is the Team Lead for Blood and other Products of Human Origin, Technical Standard and Specifications Unit, Health Products Policy and Standards Department, WHO Headquarter.

Wastage of plasma in LMIC

WHO Assembly 58.13 and 63.12 Resolutions urge countries to ensure adequate availability of safe and quality blood, blood components and Plasma Derived Medicinal Products (PDMPs). Ensuring a safe, secure, sufficient and ethically obtained supply of PDMPs in low- and middleincome countries (LMIC) is an important public health responsibility. Moreover, increasing collection of plasma for fractionation and better understanding of the plasma manufacturing processes, and its regulations, contributes to sufficiency of PDMPs. PDMPs are critical in the prevention and treatment of serious medical conditions associated with a wide range of inherited and acquired medical disorders and diseases and they have been included into WHO Model List of Essential Medicines.

Supplies of essential PDMPs are inadequate in many LMIC, because most of recovered plasma is not produced or is discarded due to insufficient quality or quantity for industrial fractionation. Multiple reasons explain insufficient plasma quality for industrial fractionation (e.g. fragmented system, absence of regulation, deficient testing, inadequate infrastructure for storage and transport, etc.). Reports suggest that over 9 million liters of plasma collected in LMIC are discarded for lack of acceptability for fractionation and only 50 countries used domestically collected plasma for fractionation through different arrangements. Meanwhile, steady increase in whole blood collection (for RBC needs) may increase volume of wasted plasma.

Given the breadth and scope of the issues and challenges, the WHO guidance in “Increasing supplies of PDMP in LMIC through fractionation of domestic plasma” has been issued in March 2021. The guidance provides a strategic framework to assist Member States in increasing their volume of quality plasma for fractionation. The guidance was developed under the WHO Action

Framework to Advance Universal Access to Safe, Effective and Quality-Assured Blood Products 2020–2023 to advance the objective of “functioning and efficiently managed blood services”. This guidance is complementary to the WHO guidance on centralization of blood donation testing and processing, which assists Member States in deciding whether to centralize blood donation testing and processing and provides practical guidance in that area. Centralization of blood donation processing can play an important role in increasing the availability of quality plasma for fractionation.

SPEAKERS

Vee Armstrong, Australia

Vee Armstrong qualified as a Medical Scientist in London, specialising in Haematology and Blood Group Serology before returning to Zimbabwe to manage a Haematology Laboratory at a large Teaching Hospital in Harare. After emigrating to Australia, she joined the Australian Red Cross Blood Service where she worked for 32 years, initially as Scientist in charge of the Western Australian Virology Laboratory, and then as the State Quality Manager before being appointed the National Quality & Regulatory Affairs Manager. Since leaving the Blood Service, Ms Armstrong has worked as a private Quality and Regulatory Consultant, providing GMP assessments, training and support to customers in Asia in addition to recent participation in a WHO Working Group that developed and published a Guidance on Centralization of blood donation testing and processing.

Key steps to improve quality of plasma for further processing

In resource-constrained countries, limited funding of blood services precludes the acquisition of adequate rapid freezing and storage facilities for large volumes of plasma, and therefore it is common practice for these blood services to have to discard whole blood-derived plasma that is not utilised as transfusible fresh frozen plasma. The volume of discarded plasma can be substantial and translates into a lost opportunity for achieving at least partial if not complete selfsufficiency in plasma-derived medicinal products (PDMPs). Currently, these countries purchase PDMPs at a cost that could be significantly reduced or negated if local plasma was to be fractionated.

As the implementation of quality management systems and good manufacturing practice (GMP) becomes global best practice for blood services, consideration is increasingly being given to utilisation of the discarded plasma for fractionation, either by using an external toll fractionator or an in-country purpose-built fractionator. However, before this can be achieved, its quality must be improved to meet international standards for source plasma.

There are a number of key steps and changes that blood services can take to improve the quality of their plasma. Pre-requisites for these activities are a strong commitment from government agencies, the allocation of additional adequate funding and the implementation of GMP.

The top priority is to procure an adequate number of rapid freezing and storage facilities to ensure that freezing times and storage temperatures can be both achieved and maintained until the plasma can be shipped to the fractionator. Additionally, there are improvements that can be made throughout the manufacturing chain, from donor selection to shipping of the frozen plasma to the fractionator, including the potential introduction of plasmapheresis. These improvements will be discussed in further detail.

SPEAKERS

Jan Bult, The Netherlands - PPTA

Jan Bult was the President & CEO of the Plasma Protein Therapeutics Association for over 2 decades before he retired at the end of 2018 and was appointed to President Emeritus. He is currently active as consultant in the field of plasma protein therapies.

Plasma Fraction Technologies; benefits and limitations; technical issues

The fractionation technology for plasma proteins is more than 75 years old. During World War II, Edwin Cohn was asked to develop a technology to fractionate albumin in for the soldiers on the battlefields. This development was the beginning of a journey that has not come to an end.

The original process to develop different fractionations using a combination of temperature, alcohol concentration, pH, ionic strength and time is still the core of today's fractionation technology.

Many countries do not have a fractionation plant within their borders and are dependent on the import of plasma protein therapies in different degrees. For that reason, some countries may consider to constructing a plant to produce plasma proteins from domestic plasma. Recently the WHO issued a guidance document "Guidance on Increasing Supplies of Plasma-Derived Medicinal Products in Low and Middle-Income Countries Through Fractionation of Domestic Plasma" that provides some practical guidance what steps need two be taken to build a plant.

Once that decision is made, considerations need to be given on various elements that are important for a successful and sustainable fractionation of plasma derived medicinal products. The economics cannot be ignored because building a fractionation plant requires a serious capital investment and technology transfer that will take years before a return can be expected. Short term success is not feasible, it will be a long-term endeavor.

This presentation will investigate the practicalities of today's fractionation technology to assist in making difficult decisions about the product portfolio that can be produced.

SPEAKERS

Françoise Rossi, France - IPFA

Françoise Rossi was trained in Paris, France, as an MD and a Ph.D in Immunology, later with a Master in Medical Ethics. Since 2008, she is Regulatory and Scientific Affair Director at IPFA. In 2003, she joined the Laboratoire français du Fractionnement et des Biotechnologies and today is Head of Regulatory Intelligence. Before, she has been Head of the Plasma-derived and Recombinant Analogous Medicinal Products and Immunology Unit at the French Agency for Safety of Health Products (Afssaps) and operated as such at EMA's BPWP and BWP.

Oversight of contract plasma fractionation

Each country or region needs to ensure its strategic independence in plasma-derived medicinal products (PDMPs) dedicated to their patients. One way to achieve it is to deliver PDMPs made from domestic plasma. As recommended in the newly published WHO guidance on "Increasing supplies of PDMPs in low-and middle-income countries through fractionation of domestic plasma", contract/toll manufacture is the most affordable and early solution to provide PDMPs in a country.

What is contract manufacturing, why is it a best early approach and how can it be achieved? Plasma for fractionation into PDMPs collected as a by-product of different blood components for transfusion or directly through plasmapheresis is manufactured in a contract manufacturing context, by an experienced fractionator, located outside the country which returns the manufactured PDMPs from this plasma.

Other contractual agreements are also possible on a case-by-case basis. Plasma for fractionation should comply with mandatory quality requirements, as PDMPs do with Good Manufacturing Practices. Bringing efforts in blood establishments (BEs) to reach these requirements by implementing quality management systems for both blood & blood components and plasma collection is a win-win situation. When volumes of quality plasma are sufficient to be industrially fractionated, the decision for Contract manufacturing can be made according to a process involving interesting parties, i.e. BEs, local authorities, fractionator, ministry of health, and dedicated funding organisations if needed. PDMPs manufactured in the fractionator plant should also be licensable by the local or regional competent authorities supervising the country.

The mandatory founder document is the Quality Agreement between the BEs Organisation and the fractionator where all quality, technical and contractual conditions are agreed upon. If quality management systems are implemented in all BEs of contiguous coordinated countries to increase the volume of quality plasma for fractionation, the chance to bring PDMPs in these coordinated countries through contract manufacturing will increase to the point that voluntary non-remunerated plasma for fractionation will significantly contribute to the availability of PDMPS in the world.

SPEAKERS

Narin Kijkriengkraikul, Thailand - Thai Red Cross

Narin Kijkriengkraikul is Assistant Director (Production Management) of the National Blood Centre, Thai Red Cross Society. He has gained experience of more than 23 years in blood transfusion services in Thailand for the production management of products related to blood collection bags and blood products. He also participated as a member in the project management steering committee and other committees in establishing the Plasma Fractionation Centre of Thai Red Cross Society (PFC, TRCS) in 2013 until its completion in 2016. At present, he is in charge of managing PFC, TRCS.

Specific local experiences on the development of a domestic plasma fractionation program in Thailand

According to World Health Organization (WHO), ensuring a safe, secure, sufficient and ethically obtained supply of plasma-derived medicinal products (PDMPs) is an important public health responsibility of every national government. Previously in Thailand, PDMPs had to be imported at a high price. The other problems included inequitable access to treatment even for patients meeting full clinical criteria for treatment with PDMPs, frequent shortage of products, and dramatically unpredictable and variable prices. In 2011, the Thai Red Cross Society has taken steps for the establishment of a plasma fractionation plant for fractionating the domestic plasma in order to meet the local demand for three PDMPS: factor VIII concentrate (7,000,000IU/year), intravenous immunoglobulin (IVIG;150,000 grams/year), and albumin (2,000,000 grams/ year).

Initial discussions for a transfer of technology were initiated with a foreign plasma fractionator [Green Cross Corporation (GCC), South Korea]. In 2013, the final agreement was signed between both parties and the plans for the construction of a domestic plasma fractionation facility were initiated. This was followed by phases of qualification and validation, technology transfer, and production batches trials. The clinical studies of the locally-made PDMPs were carried out in university hospitals. The first licensed products were released on the market in 2016, evidencing a quality comparable to that of imported products. The key success factors of this program include: royal support, government support, good diplomatic relationship between Thailand and South Korea, fruitful cooperation among various local health organizations, availability of a local technical expertise and experienced staff, and reliable domestic plasma supply.

This program has successfully created an added value for the surplus plasma in Thailand, and secured the access to PDMPs to local patients at predictable and controlled prices. However, establishing a plasma fractionation facility is very costly and requires complex technology transfers, hence it should be undertaken after a careful assessment and feasibility study taking into account numerous technical and financial factors.

SPEAKERS

Andrea Corina Zucchi, Argentina - University of Cordoba

Andrea Corina Zucchi is Magíster in Quality Engenieering Biochemist and Pharmacist. Specialist in Organizational Productivity. She is the Director of the Biological Raw Material Collection Area at the Hemoderivates Laboratory from the National University of Cordoba, Argentina. Her responsibilities are related to the management of the plasma exchange agreements with plasma supplier centres, and the development and improvement of them.

Fractionation of plasma in South America Region: Hemoderivatives Laboratory´s experience

The Hemoderivatives Laboratory (HL) is a pharmaceutical industry that produces plasma-derived medicinal products (PDMPs). It belongs to the National University of Cordoba (NUC) and is a not for- profit industry. It was established in 1965 with the initial goal to fractionate plasma collected in Argentina. The plasma fractionation contract with domestic blood centers is based on plasma exchange agreements: Argentinian blood centers provide plasma and receive PDMPs in return, as well as equipment or supplies for blood/plasma collection. The plasma fractionation agreements with other countries (Uruguay, Chile, and Paraguay) define that a percentage of the PDMPs produced returns to the country that supplied plasma, and the remaining products are sold by HL to compensate for the fractionation costs. As a result, these countries improve the availability of PDMPs. In Argentina, the possibility to provide equipment and supplies to the blood centers allow to improve the quality of the plasma production processes.

The main difficulties encountered were: a) an insufficient political will for plasma fractionation, b) a lack of compliance of the blood centers operations with the plasma quality requirements for industrial fractionation. The main measures that allowed to improve plasma collection were:

- A Plasma Quality Assurance Program implemented by the HL focusing on the development of compliant plasma collection procedures, and the GMP implementation.
- An organization of the Blood Systems at a national level. The involvement of these stakeholders is essential to achieve the objectives.

In this way, the total volume of plasma collected raised by more than 1000% from 1985 to 2020, reaching about 150.000 kg of plasma fractionated per year. The market covered in Argentina by the local production represents about 40% for Human Serum Albumin and Intravenous Immunoglobulin, as main products. In conclusion, it is essential to implement a long-term program to improve the collection of plasma for fractionation and the availability of PDMPs. This requires the participation of Regulatory Authorities, National Blood Systems, fractionators, and blood centers, to follow-up and achieve sustained progress in plasma fractionation and PDMPs access.

DAY 2 Wednesday September 22, 2021 (13:00 – 16:00 CEST)

2.1 SESSION

"Options to improve access to safe plasma protein products in LMIC"

13:00-13:20 Recruitment and retention of safe Donors (Giuliano Grazzini, Italy-FIODS)

13:20-13:40 Quarantine of plasma as a means to reduce the risk of transfusion-transmitted infection: logistics and feasibility (Pierre Tiberghien, France-EFS)

13:40-15:20 Technologies for pathogen reduction (PR) of single-donor or mini-pools of plasma, cryoprecipitate, and immunoglobulins: experience from suppliers and users:

- Strategies to move safe plasma products into low resource areas: overview and experience with Riboflavin/UV (Jeffrey McCullough, Arizona-USA)
- Psoralen/UVA (Hans Vermeij, Brazil-Cerus)
- Methylene blue/light (Stefan Reichenberg, Germany-Macopharma)
- Pathogen Reduction of Covid-19 Convalescent Plasma (Salwa Hindawi, Saudi Arabia)
- Mini-pool solvent/detergent treatment of plasma, cryoprecipitate & caprylic acid fractionation of immunoglobulins (VIPS) (Magdy El-Ekiaby, Egypt-Shabrawishi Hospital)

15:20-15:40 Viral safety of plasma derived components (Johannes Blümel, Germany-PEI)

15:40-16:00 Discussion/Q&A

OBJECTIVES OF THE SESSION

The session should offer to the audience an opportunity to familiarize with concepts, approaches and technologies which have shown feasibility or are innovative in preparing safe plasma protein products and may offer solutions for existing problems with safety and supply of plasma proteins in LMIC. These may be implemented in selected blood centers with sufficient levels of quality (f.ex. national or larger regional BCs), be applied on locally generated plasma resulting from separation of whole blood collections and lead to local preparation of safe and efficient products for therapies of patients needing either clotting factors or immunoglobulins.

Learning points:

- How donor selection contributes to the safety of the product and health protection of the donor.
- How the risk of products for patients can be reduced by quarantine/retest procedures and pathogen reduction technologies with an overview of different methods.
- Identification of the essential steps related to viral safety of plasma products.

MODERATORS

Jay S. Epstein, USA - ISBT GBS WP

Jay S. Epstein from the US worked at the US FDA for over 30 years where he directed scientific research and regulatory programs for blood products, donor screening tests, and HIV diagnostics. Throughout his FDA career he assisted the Council of Europe and the WHO to advance blood standards and global access to safe blood products. Presently, he leads the COVID-19 response on neutralizing antibodies at the US Department of Health and Human Services. Dr. Epstein trained clinically in Internal Medicine and Infectious Diseases and is author of numerous scientific publications and reviews primarily in the field of blood safety regulation.

Jean-Claude Faber, Luxembourg - ISBT GBS WP

Jean-Claude Faber from Luxembourg is a medical specialist in biological haematology and blood transfusion. He is a member of the Organising Committee of ISBT WP on Global Blood Safety (GBS). For the World Health Organisation (WHO) he is a member of the Expert Advisory Panel on Transfusion Medicine since 2010. For the International Haemovigilance Network he was the founding president in 1998. For the Council of Europe (CofE) he was a member of the Group of Experts in Blood Transfusion and Immunohaematology for more than 20 years (1986- 2008) and president of the group for two years (non-renewable term). For the European Commission (EC) he was a national expert in blood transfusion for 20 years (1989-2008) and scientific expert. For the European Blood Alliance (EBA) he served as vice-president 2001-2004. He has worked as a consultant in developing countries for blood systems, blood programmes, blood policies, blood strategies, QMS in blood centres,…: Vietnam, Laos, Nepal, Pakistan, Burkina Faso, Senegal, Ecuador, Nicaragua. For the Luxembourg Association of Haemophiliacs he is the president since 1983.

SPEAKERS

Giuliano Grazzini, Italy - FIODS

Giuliano Grazzini MD, Hematologist and Transfusion Medicine Specialist. Formerly: deputy director and director of blood banks and transfusion medicine services, director of the Regional Blood Centre of Tuscany (Florence, Italy), director of the National Blood Centre (Rome, Italy) - Italian national blood authority, contract professor of transfusion medicine at the University of Florence (Italy). Author/co-author of 200+ scientific articles, abstracts, book chapters, quality standards manuals, institutional reports. Scopus h-index: 22. Retired from his public appointments in 2015, currently works part-time as scientific and regulatory advisor and voluntarily serves as special counselor to the President of FIODS/IFBDO.

Recruitment and retention of safe blood and plasma donors

Recruitment and retention of voluntary non-remunerated (VNR) blood and plasma donors should aim systematically at maintaining a sufficient blood supply and ensuring that a donor population is healthy, stable, reliable and flexible. In order to pursue these goals, in low- and middle-income countries several factors should be taken into consideration, among which the increasing demand for blood components for transfusion due to progressive medical advancements, unmet needs (including those for plasma-derived medicinal products - PDMPs), the impact of regulation on donor deferral and the limited shelf-life of blood products.

Up-to-date principles of social marketing should be applied to recruitment and retention of blood and plasma donors so as to implement and maintain a culturally and socially sensitive promotion of donation. Blood and plasma donation should be promoted as an inclusive process, encompassing not only individual-level factors but also the expression of socially determined commitments, including social reciprocity. The decision to donate blood and plasma should be sustained less by generic altruistic motives and more by donors' desire to enhance the status of their membership within their own social networks and to maintain the social relationships they trust.

In the perspective of a stepwise access to safe PMDPs through the implementation of full utilization of recovered plasma, the introduction of plasmapheresis and fractionation of domestic plasma, sensitization and education of donors on the specific value of plasma and its products is of paramount importance and should be based on the recognition of human plasma as a critical regional, national and global resource.

Policies for the recruitment and retention of donors and programs of social marketing aimed at creating a solid and positive culture of VNR donation as a normal part of a healthy lifestyle should take into consideration the potentially high value of blood donor organizations, as well as all the fundamental elements to protect donors' health and rights.

SPEAKERS

Pierre Tiberghien, France - EFS

Pierre Tiberghien is a medical doctor, holds also a Ph.D. and was a clinical hematologist at the Besançon University Hospital, France until 2009, He headed the Bourgogne France-Comté Etablissement Français du Sang (EFS) blood transfusion establishment before taking up the position of EFS deputy CEO, head of medicine and research and qualified person from 2009 to 2017. He is currently senior advisor for European and international medical and scientific affairs at EFS. Professor of medicine at the Université of Franche- Comté, He teaches immunology and transfusion medicine. His main research focus is on immunotherapy as well as on safety and efficacy of blood products. He is President of the European Blood Alliance since January 1st, 2020.

Quarantine of plasma as a means to reduce the risk of transfusion-transmitted infection: logistics and feasibility. A perspective from France

Pierre Tiberghien[1,2], Thibaud Bocquet[1], Stéphane Bégué[1]

[1]Etablissement Français du Sang, La Plaine St Denis, France

[2]Université de Franche-Comté, Besançon, France

Prevention of transfusion-transmitted infections includes donor selection, post-donation information, donor testing, product leucodepletion, pathogen reduction as well as, when feasible, product quarantine. If infectious markers at a second donation are non-reactive, thus confirming that the previous donation did not occur during the window period of a transfusion-relevant infection, the quarantined plasma is released for transfusion.

In France, 90% of plasma for transfusion (maintained frozen at < 25 °C) for transfusion undergo a > 60 days quarantine (10% undergo pathogen reduction). The quarantine plasma (QP) will be released for transfusion if a following donation between day (d) 61 and d160 exhibits negative infectious markers as well. In the presence of such marker(s), the QP is destroyed. In the absence of a timely donation, the QP is oriented towards fractionation. A successful quarantine is achieved for 45% (whole blood) to 65% (apheresis) donations with PQ and is highly dependent on the ability to win the loyalty of repeat donors and adapted donations facilities. Measures to ensure a foolproof process include rigorous product information and traceability, all manufacturing steps under one integrated information technology infrastructure, as well as robust freezing and monitoring capacities.

In 2020, ≈ 212 000 QP units from whole blood (87 %) or apheresis (13%) were issued. Frequency of QP donations with a following donation positive for an infectious marker (HIV, HBV, HCV, HTLV, Syphilis) is <0,002%. Considering testing sensitivities and resulting window periods, the estimated infectious residual risk addressed by the quarantine process in France is very low.

Overall, plasma quarantine will mitigate the risk associated with a donation occurring during an infectious window period. Overall efficiency will depend on the ability to engage with donors who undergo timely repeat donations, availability of a robust manufacturing infrastructure, screening tests sensitivity (determining window period length) and donor infectious epidemiology and destination of plasma for which successful quarantine is unconfirmed.

SPEAKERS

Jeffrey Mc Cullough, USA - Professor Emeritus

Jeffrey Mc Cullough has extensive experience in both hospital transfusion service and blood centers. He has published more that 350 articles and his own book Transfusion Medicine now in its fifth edition.
He was the editor of the journal Transfusion for 15 years, has served on many advisory committees, has extensive international experience and was the founding president of the US National Marrow Donor Program.

Experience with Riboflavin/UV Plasma

Steps to provide the safest possible blood involve those related to the donor and to laboratory testing. Use of all volunteer donors is crucial for safe blood. Questioning potential donors about behaviors that might put them at risk for transmitting infection has a large positive impact on improving blood safety. While laboratory testing is valuable, there are many infectious agents for which we do not have tests. Testing is reactive and accept that some patients may be harmed before mitigation can be implemented. Thus treating the unit of blood to minimize the chance of infection is also a very valuable step in blood safety.

The riboflavin UV light system can be used to treat plasma or platelets and also to prepare cryoprecipitate. The process of establishing this technology in a blood center is straightforward and involves consideration of facilities, environment, power, space, equipment, staffing, training and establishing a quality control program. Riboflavin UV treated fresh frozen plasma has coagulation factor levels nearly the same as untreated plasma and well above the levels need for clinical effectiveness as reported in clinical investigations. Cryoprecipitate can be prepared from riboflavin/UV plasma. Riboflavin UV cryoprecipitate has levels of factor VIII, fibrinogen and vWF well above the EU requirements. Company support for implementation and operation of this system is available in low resource areas.

Ongoing support for quality operation can be provided.

SPEAKERS

Hans Vermeij, The Netherlands - Cerus

Hans Vermeij has an educational background is Biochemistry and later he specialized in Quality, Environment, Safety and Health. Started his career at the Blood Bank Rotterdam, The Netherlands, in 1982 and build his blood banking experience through different positions and responsibilities in the blood bank over 24 years. Currently he is supporting Cerus customers all over the world implementing new techniques and technologies in combination with INTERCEPT Pathogen Reduction.

Psoralen/UVA

Pathogen reduction (PR) is rapidly becoming the standard of care in many countries to addressthe infectious risk associated with the transfusion of blood components, mostly platelet concentrates and plasma.

Pathogen reduction technologies (PRT) for red blood cells are in development and limited options are currently available for whole blood treatment. PRT have been implemented heterogeneously across geographies depending on regulatory approvals and commercial availability but are increasingly being used.

This presentation will provide an overview on PRT global use, will focus on the experience with routine use of PRT to increase platelet and plasma components safety and availability while maintaining hemostatic efficacy. Examples will be provided to illustrate the role of PRT to enhance blood safety and continuity in various contexts and the rationale for inclusion of PRT in preparedness programs for business continuity in the light of scarce resources, decline in blood-donations and emerging threats. PRT not only allows for the production of safer ‘standard’ blood components but in addition novel derivatives can now be produced. This presentation will focus on new PRT applications to produce cryoprecipitate (CP) for the replacement of coagulation factor concentrates and cryo-poor plasma (CPP) for specific indications. Production methods for better affordability will be explored. A method was developed to produce safer CP and CPP through efficient utilization of whole blood collections for increased blood availability.

The INTERCEPT™ Blood System (Cerus Corporation, Concord, CA) utilizing amotosalen and UVA light, allows for the production of PRCP and PRCCP from minipools of ABO-matched previously frozen INTERCEPT plasma units. Levels of Fibrinogen, factor FVIII and albumin content measured demonstrated the quality of these products. A pathway for low- and middle-income countries to attain increased blood safety and affordable self-reliance will be explained and supported by real life examples of success stories.

SPEAKERS

Stefan Reichenberg, Germany - Macopharma

Stefan Reichenberg studied biology in Germany and graduated with a doctorate in 1999. He's working in Macopharma since 2001, first as a Project Manager in the Transfusion department, and from 2011 as Scientific Marketing Manager. Since 2012, he is Senior Medical Manager for global Macopharma. During this time, he published more than a dozen articles related to his main area of interest, THERAFLEX MB-Plasma.

Pathogen reduction (PR) of single-donor plasma: THERAFLEX MB-Plasma

Pathogen reduction in single-donor plasma using the THERAFLEX MB-Plasma technology is in use for more than 20 years in abt. 15 countries worldwide. Several million units have been treated and transfused. The system has an excellent safety profile, with a rate of serious adverse reactions of 0.5/10,000 units, shown in a prospective hemovigilance study. The significant number of units transfused up to date and the large accumulated experience, make this incidence consistent enough to conclude or consider that a substantial change will not occur in time.

The process can be implemented for a wide variety of throughputs. The minimum requirements comprise standard blood bank laboratory conditions including a stable power supply and can be used with both apheresis-derived and whole blood-derived plasma.

Macopharma supports implementation and offers training through an extensive subsidiary and distributor network online as well as on-site. The support also includes maintenance and technical assistance. The most recent analysis of its performance has shown a very low rate of defects and claims per million units. Besides, it has demonstrated its power to reduce pathogens on many enveloped and some non-enveloped viruses (i.e., Parvovirus B19).

Implementation and successful routine usage in some LMIC have been done.

SPEAKERS

Salwa Hindawi, Saudi Arabia - University of Jeddah

Salwa Hindawi is Professor in Haematology and Transfusion Medicine at King Abdulaziz University Jeddah, Saudi Arabia. She had her MRCPath in Haematology 1999 and Certificate in Transfusion Medicine2000 and FRCPath on 2007. She is president of Saudi Thalassemia & Sickle Cell Anemia Society and Chief Scientific Officer of Saudi Society of Transfusion Medicine.

Pathogen reduction of COVID-19 convalescent plasma

Convalescent plasma (CP) is often the first, and for a certain time, only potential option, to treat a newly emerging disease and protect against infection. The key hypothesis is that convalescent individuals, formerly infected with an emerging pathogen, develop neutralizing antibodies. During the global COVID-19 pandemic, COVID-19 convalescent plasma (CCP) is currently collected from donors with high neutralization titers and used for treatment in early stages of disease as well as for the immunization of immunocompromised patients who cannot be vaccinated.

The major concern transfusing CCP is the transmission of blood-borne pathogens like HIV, HBV and HCV; other known and unknown pathogens are also of concern. Since CP donors are likely to be first time donors, and there is no time for quarantine to reduce the likelihood of a potential window period transmission and to mitigate that risk, pathogen reduction (PR) treatment may be an interesting option to provide an additional layer of safety. On one side the PR-treatment should be effective against all pathogens of concern, on the other side it should not negatively impact the CCP neutralizing efficacy (NA).

There are currently three commercially available technologies for the PR-treatment of plasma: amotosalen/UVA (AS), riboflavin/UVB (RB) and methylene blue/visible light (MB). Different levels of broadness and effectiveness against blood borne pathogens of concern were published and claimed by manufacturers. Regarding SARS-COV-2 as current potential pathogen of concern (despite blood transmissibility was not demonstrated) effective inactivation was shown with AS and RB, for the closely related SARS-CoV-1 with AS and MB.

We recently demonstrated the efficient inactivation of a local clinical SARS-CoV-2 isolate in human plasma with amotosalen/UVA pathogen Reduction (PR) process uses a photochemical reaction to crosslink nucleic acids, resulting in the inhibition of cell and pathogen replication and transcription.

The first data regarding the impact of PR on the neutralizing activity of CP was published with Ebola Virus convalescent plasma (EBOV-CP), showing no significant reduction of neutralizing activity post AS-treatment. In vitro studies reported no significant impact of AS and RB on the NA of CCP. The neutralizing antibodies were measured in CCP before and after PR technique is applied in study done by our group comparing between two different pathogen inactivation methods. Results and challenges will be discussed. In conclusion, PR has the potential to increase the safety of CCP. There may be differences in PR-technology broadness of effectiveness and impact on CCP antibody quantity, which need to be considered when adopting PR.

SPEAKERS

Magdy El-Ekiaby, Egypt - Shabrawishi Hospital

Magdy El Ekiaby is a Hematologist and Transfusion Consultant by practice. He is the Director of Shabrawishi Blood Transfusion and International Hemophilia Treatment Center, Cairo, Egypt. He was also a WFH Board of Directors Member 2010-2020 and member of the ISBT WP TTIDs (Transfusion Transmissible Infectious Diseases) organizing committee 2012-2020.

Mini-pool solvent/treatment of plasma, cryoprecipitate & caprylic acid fractionation of immunoglobulins (VIPS)

Background: Plasma Derived Medicinal Products (PDMP) is considered on the WHO List of Essential Medicines (LEM). The products include coagulation factors and immunoglobulins which are used to treat a variety of inherited and acquired coagulation and immunological disorders. Unfortunately the access to such products is limited in medium and low income countries (MLIC). The current model of plasma fractionation industry as well as recombinant protein industry is so far unable to fill in this gap of supply.

New approach to improve access to safe alternatives to PDMP: The solution depends on miniature of Plasma Fractionation industry to a scale that can be adapted to National Blood Transfusion Centers (NBTC) in LMICs.

The solution: Development of a series of CE marked sterile medical devices with the aim to pool plasma or cryoprecipitate in mini-pools (pool sized ranges from 4 – 7 Liters), to produce coagulation factors and IVIG. The products are regulated under blood bank regulations when using the CE marked Medical Devices. Final products can have a dose label of the following plasma proteins; FVIII, VWF, Fibrinogen, FXIII as well as IVIG. Clinical Experience Mini Pool Plasma Products: Pharmacokinetic studies for Mini-Pool FVIII and IVIG showed similar half life, clearance rate and safety similar to PD CFCs. It also showed similar product efficacy when compared to PDMPs.

Conclusion: Mini Pool Plasma Fractionation is developed in a form of CE Marked medical devices which can enable National Blood Transfusion Centers to produce safe alternatives for CFCs and IVIG at an affordable cost. It also improves the utilization of recovered plasma in these countries and reduces the discard of this valuable resource.

SPEAKERS

Johannes Blümel, Germany - PEI

Johannes Blümel is leading the virus safety section at the Paul-Ehrlich-Institut, Langen. He is dealing with assessment of virus safety and TSE safety of blood products and recombinant DNA products such as monoclonal antibodies for clinical trials and marketing authorization. He participates as expert in EMA-Biologics Working Party (BWP) and EDQM TSE-certification procedure. Further, he is working in several research projects on virus inactivation and virus removal.

Viral safety of plasma derived components

Viral safety of plasma proteins relies on complementary measures such as selection of donors, testing for specific agents, and methods virus inactivation/removal. Robust methods for virus inactivation/removal such as solvent/detergent treatment or pasteurization have been successfully applied against blood-transmitted viruses such as HIV, HBV, HCV.

While there is no single inactivation/removal methods that reliably clears all kinds of viruses, a combination of methods offers a high degree of safety against a wide range of potential contaminants including even unknown or unexpected viruses. This presentation will discuss the various methods for virus inactivation/removal with respect to their range of affects viruses as well as to critical process parameters.

Considering that individual inactivation steps could be overwhelmed by highly viremic donations it seems preferable to apply virus inactivation towards pooled/homogeneous materials rather than to pool single-units that have been treated for virus inactivation.

DAY 3 Thursday September 23, 2021 (13:00 – 16:00 CEST)

3.1 SESSION

"Scale-up for domestic processing of plasma: technology options"

13:00-14:00 Technical solutions from the suppliers of single-use equipment for local processing and virus reduction of plasma, cryoprecipitate, cryoprecipitate-poor plasma and immunoglobulins:

- Potential contribution of single-use technologies for processing domestic plasma components. (Prity Bengani-Lutz, USA - Sartorius)
- Domestic scalable plasma processing: technological approaches and solutions for LMIC (Josephine Cheng, Taiwan, and Jian Fei Shou, China - Merck Millipore)
- Potential contribution of nanofiltration to the virus safety of domestic plasma components (Tomoko Hongo-Hirasaki, Japan - Asahi Kasei Medical)
- SARS-CoV-2 immunoglobulins in India as an example for domestic production of immunoglobulins: Safety, efficacy and quality attributes (Suma Ray, India - Intas Pharmaceuticals)

14:00-14:20 Plasma fractionation of animal-derived immunoglobulins in LMIC: lessons to be learned for human plasma IgG production (Mariángela Vargas, Costa Rica - Inst. Clodomiro Picado)

14:20-14:40 Regulatory considerations for authorization of plasma processing devices: example of an EU CE marking (Mohamed Ghönim, Switzerland - QSE Consulting)

14:40-15:00 Discussion / Q&A

OBJECTIVES OF THE SESSION

In line with Chapter 9 "**Stepwise approach to domestic manufacture of plasma, plasma components and immune globulin concentrates with enhanced virus safety**" of the "**WHO Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma**", this session is intended to increase the awareness on concrete technical solutions (e.g. single-use devices, equipment) available from industry suppliers to consider, as a step-wise approach, implementation of small-scale plasma processing methods allowing to prepare virus-safe plasma products such as Factor VIII/von Willebrand factor/fibrinogen and immunoglobulins. Such an approach should be regarded as an intermediate means to improve safe plasma product supply and avoid wastage of recovered plasma at domestic level in LMIC. This ramp-up phase can be used to get local stakeholders get more familiar with issues associated with plasma processing, and is a strategy to help training operators. Concrete examples of production of human plasma derived immunoglobulins in LMIC will be presented, based on the production of anti-SARS-CoV-2 IgG in India. A presentation on how the small-scale production of therapeutic antivenom immunoglobulins is achieved in LMIC will also be given as a concrete reference for what can be achieved for fractionation of human plasma into IgG.

Learning points:

- Suppliers to the plasma fractionation and biotech industry have developed pragmatic and scalable processing technologies, sometimes single-use, for protein purification and virus inactivation or removal that can fit the needs of LMIC seeking to perform mini- or small-scale domestic processing of plasma into safe plasma protein therapeutic fractions.
- Those suppliers can play an important role in establishing some processing technologies and in training local operators, and in providing regulatory files useful for local regulatory approval of locally-produced plasma protein products in LMIC.
- One manufacturer in India provides one example for the domestic implementation of a production technology of plasma derived immunoglobulins (anti-COVID-19 hyperimmune globulins) involving precipitation, chromatography, transmembrane filtration, and nanofiltration, thereby demonstrating a technical feasibility under particular circumstances.
- The production of animal plasma derived antivenoms immunoglobulins, which is currently mostly conducted in LMIC, provides a pragmatic example of a local production of plasma-derived therapeutic immunoglobulins using production technologies, quality control and quality assurance approaches, and regulatory requirements in many points comparable to that of human plasma-derived immunoglobulins.
- The regulatory requirements for the approval of medical devices, that can be used for virus inactivation and protein purification

MODERATORS

Micha Nuebling, Germany - PEI

Micha Nuebling from Germany is a doctor in biology. He got his PhD in 1990 PhD in biology with virology as background. He was a scientist at the PEI (Paul-Ehrlich-Institut, Langen, Germany) from 1990 to 2014 with involvement in public health measures safety of blood and blood products on national and European levels. He was the group lead “blood and related biologiocals” at WHO from 2015 to 2018. Since 2018, he is the head of the division “Major Policy Issues” at the PEI.

Thierry Burnouf, Taiwan - ISBT GBS WP

Thierry Burnouf is Vice-Dean, College of Biomedical Engineering and Director, International PhD Program in Biomedical Engineering at Taipei Medical University Taipei, Taiwan. He is the Secretary of the WP on Global Blood Safety, Treasurer of the WP on “Cellular Therapies”, and member of drafting groups on Covid-19 convalescent plasma and hyperimmune globulin of ISBT. **(Full bio on page 10)**

SPEAKERS

Prity Bengani-Lutz, USA - Sartorius Stedim Biotech

Prity Bengani-Lutz is a Market Entry Strategy Manager at Sartorius. She has several years of experience in bioprocessing industry both as an end user as well as a technology provider focused on upstream and downstream solutions for protein based therapeutics. She is based in Massachusetts, USA.

Potential contribution of single-use technologies for processing domestic plasma components

Prity Bengani-Lutz, Priyanka Gupta, Ganesh Kumar / Sartorius Stedim Biotech

Global need for plasma and plasma-derived therapies is growing rapidly, especially for autoimmune inflammatory diseases, and remain strong to treat immunodeficiencies and coagulopathies. In addition, the recent massive use of plasma-based passive immunotherapy to treat Covid-19 has increased the demand even further, including in low- and middle-income countries (LMIC) where many patients with immunodeficiency or coagulation factor deficiencies do not still receive appropriate and safe treatments due to global product shortage. Two thirds of the world's plasma come from the United States, while a large quantity of plasma goes to waste each year in LMIC, due to the cost of a traditional industrial plasma fractionation facility, and lack of skilled manpower resources, suitable process, and technical and regulatory knowledge. Therefore, there is a great need for pragmatic scalable solutions to help bridge step by step the gap in LMIC.

Single use technologies are rapidly gaining momentum to address these challenges and can therefore be regarded as a practical approach to ease plasma processing into safe protein fractions in LMIC. Single use solutions increase flexibility and efficiency, lower contamination risk and cost and at the same time greatly simplify scale-up and process implementation which leads to accelerated timelines. In this presentation, we will discuss scalable single use solutions for processing, purification and virus removal that can be of value for domestic plasma processing.

A case study will be presented on the selection and implementation of scalable, single use solutions for purification of IVIG from human blood plasma. This study highlights the capabilities of high performance, prepacked CIMmultus® monolithic columns featuring large flow-through channels. With capacities exceeding those of resin-based columns, monolithic columns can provide substantial technical advantages for blood and plasma processing, including for implementation in LMIC.

SPEAKERS

Josephine Cheng, Taiwan - (APAC) Merck-Millipore

Josephine Cheng is the Senior Consultant responsible for Core Modalities Bioprocessing Strategy APAC, where she looks closely into customer and market insights specifically in the plasma & vaccine industry, supports strategy development, and fosters customer collaborations. She has held various regional roles in the technical and marketing field, led successful projects, and drove business development in the plasma and vaccine space. Josephine holds both Bachelor's and Master degrees in Bio-resources & Agriculture from the National Taiwan University with focus on protein expression/ purification/monoclonal antibodies preparation.

Jianfei Shou, China - (TASS) Merck-Millipore

Jianfei Shou currently is Senior MSAT Manager. He leads Integrated Platform team to supports activities covering process and system design, scale-up, implementation, and troubleshooting, as well as customer training. Jianfei Shou joined Millipore in 2008 as Process Development Scientist for downstream process in South China. He has been an invited speaker at various technical conferences, has authored for sterile filtration guideline for SFDA and has also published several books and papers about bioprocessing. Jianfei Shou holds a master's degree in Molecular Biology from Sun Yat-sen University.

Domestic scalable plasma processing: technological approaches and solutions for LMIC

Plasma-derived immunoglobulin (IgGs) are essential medicines that are in worldwide shortage, especially in low-and-middle-income countries (LMIC). A good strategy to look at an optimized readily scalable manufacturing process could help to support the local supply and self-sufficiency concept. This presentation aims to examine possible ways to facilitate a domestic scalable plasma protein purification process, utilizing a case study from public-private collaboration, with novel combinations of processing technologies implementable on different plasma feedstock to achieve a safe IgG end product. The process steps include chromatography, clarification and sterile filtrations, single-pass ultrafiltration, virus inactivation, anti-A/B affinity chromatography, and anion exchange chromatography, all in a flow-through mode operation, optimizing various steps in the purification process.

These process steps allow to obtain a purified IgG with >99% purity, virus inactivated, depleted of anti-A and anti-B isoagglutinins and free of in vitro thrombogenic markers.

In addition, with the incorporation of single-use technologies, we would like to propose possible pragmatic solutions for obtaining safe plasma, safe cryoprecipitate, and safe IgGs, in a scalable way, therefore potentially contributing to help meet the PDMP demands in LMIC using available quality domestic plasma.

The presentation will also highlight the various levels of technical assistance and training that can be provided to support the introduction and regulatory approval of plasma processing technologies in LMIC as a means to help fill the gap in plasma protein product quality and supply.

SPEAKERS

Tomoko Hongo-Hirasaki, Japan - Bioprocess Division, Asahi Kasei Medical

Tomoko Hongo-Hirasaki has worked with Planova virus removal filters for over 20 years. She obtained her Ph.D. of Pharmaceutical Science from Kyushu University for a study of the separation mechanisms of biopolymers on cellulose porous membranes. She specializes in virus evaluation, colloid science, membrane science and biophysics of proteins. She is the lead expert of Evaluation and Analysis in Virus Filtration in the Bioprocess Division as advanced professional system in Asahi Kasei. Her research has focused on virus filtration mechanisms, viral clearance study design, design space studies for virus filtration and the characterization of virus removal membranes. Now she is in charge of global scientific activity and leading scientific publication.

Potential contribution of nanofiltration to the virus safety of domestic plasma components

After the launch of the world first dedicated virus removal filter “Planova” in 1989, and over 30 years history, nanofiltration has contributed to the virus safety of industrial plasma derived medicinal products and has been recognized for almost the last two decades as the most robust virus removal methods by the plasma fractionation industry and in international regulatory guidance. The historical experience gained in the application of nanofiltration by the plasma fractionation industry may benefit now the virus safety of therapeutic plasma fractions made in LMIC.

Nanofiltration, using single-use filters for the targeted removal of viruses of different sizes (i.e., small, medium and large size viruses) is a virus reduction method applicable to various types of plasma products (IVIG, coagulation factors, etc.) and has been implemented in manufacturing process of a wide range of industrial plasma products globally. Nanofiltration is a reliable process that is largely predictable and demonstrated to remove various known and emerging viruses, including HIV, HBV, HCV, Zika virus, West Nile virus, Dengue virus, etc.) based on a size exclusion mechanism.

Nanofiltration filters are available with different surface area (such as 0.01 to 1 m2) making scalability a straightforward process for implementation from mini-pools to large-scale batches of plasma fractions. The experience developed over the years by our technical support teams in optimizing the performance and establishment of nanofiltration processes for various protein fractions can be made available, through experienced/scientific knowledge sharing, to help stepby- step initiatives for manufacture of domestic plasma components, such as immunoglobulins, factor VIII, and factor IX, in LMIC.

This presentation will introduce, based on our concrete experience, practical points to consider in the introduction of a nanofiltration process in the manufacture of plasma-derived products in LMIC, and present the range of technical assistance that our company can provide for process implementation and validation.

SPEAKERS

Suma Ray, India - Intas Pharmaceuticals

Suma Ray is the Sr Vice President and Head for Plasma Operations at the Plasma Fractionation Centre of Intas Pharmaceuticals, Ahmedabad, India. Prior to assuming this responsibility, she has worked at various capacities in global roles at Sartorius Stedim Biotech and Biocon, India. She has varied expertise in Plasma derived therapeutics, viral vaccines as well as different recombinant therapeutic antibodies. Dr. Ray holds a PhD degree from ´All India Institute of Medical Sciences`, New Delhi, followed by post doctorate fellowships from `Stanford University School of Medicine´ and ´University of Virginia` and has to her credit several publications in the areas of Hematology, Virology and Oncology in peer reviewed journals.

SARS CoV-2 Immunoglobulin- a reference for production of normal Immunoglobulin in India: Safety, Efficacy & Quality attributes

Economic production of human plasma derivatives makes a serious contribution towards improving the quality of life as these products are mostly used for critically ill patients. India with a population of more than 1.3 billion, needs more of such products with assurance of quality and safety and affordable pricing to meet the daily demands of the otherwise starved market.

In order to facilitate this, the Indian fractionation industry is gearing up to speed by integrating the latest technology platforms in order to deliver improved processes with safe and quality products with high yields and improved efficacy.

During the pandemic, Intas Pharmaceuticals took the initiative to collect convalescent plasma from blood banks in India approved by the DCGI office of the Goverment of India for the manufacturing of purified and virus inactivated/removed Covid Hyperimmunoglobulin to serve the country under the Corporate Social Responsibility (CSR) initiative.

The SARS-CoV-2 hyper immunoglobulin, purified from pools of hundreds of litres of virus tested convalescent plasma using standard purification techniques including orthogonal virus inactivation/removal methods, was found to be safe, well-tolerated and efficient against SARSCoV-2 virus infection. The quality attributes of the final product have met all the regulatory requirements for normal human immunoglobulin as seen globally.

The possibility to develop and implement this production process at such a short time span, during the pandemic, illustrates the technical capability of the manufacturer to develop, validate, implement and operate globally accepted technologies for the manufacture of licensed PDMPs from domestic plasma resources.

SPEAKERS

Mariangela Vargas, Costa Rica - Instituto Clodomiro Picado

Mariangela Vargas is a researcher at the Technological Development Department of Instituto Clodomiro Picado in Costa Rica. This institute belongs to the University of Costa Rica, and its main goal is to solve the problematic associated to snakebite envenomation. She is part of a research group that has impacted positively on improvement of antivenoms quality, the development of new biotechnological products, and in the pre-clinical evaluation of immunobiological products.

Plasma fractionation of animal-derived immunoglobulins in LMIC: lessons to be learned for human plasma IgG production

Instituto Clodomiro Picado (ICP, University of Costa Rica) is a public institution, with over 50 years of experience in research and development and fractionation of various snake antivenoms immunoglobulins from immunized horse plasma.

Snakebite envenomation represents a public health issue, mainly in LMIC-tropical and subtropical countries worldwide, and the parenteral administration of antivenom immunoglobulins is the only scientifically validated therapy for the treatment of these envenomations. Antivenom immunoglobulins, like several human plasma derived products, are on the WHO list of Essential Medicines. The development and domestic manufacture of high quality antivenom immunoglobulins is essential to guarantee that envenomated patients have sufficient access to products with reliable quality, safety and efficacy.

Snake antivenoms are polyclonal immunoglobulin preparations obtained from the fractionation of plasma of animals, usually horses, immunized with snake venoms. As is the case for human plasma fractionation, industrial production of antivenom immunoglobulins is a complex and multidisciplinary good manufacturing process, that comprises a careful selection of healthy horse plasma “donors”; collection, quality control and storage of plasma; pooling of plasma and its fractionation into antivenom immunoglobulins, by dedicated purification steps to remove unwanted protein contaminants and provide virus safety; formulation and stabilization; filling into final containers; and quality control of in process and final products. Due to similarities with human plasma fractionation, both industries share experiences providing feedback of mutual benefit.

In this regard, we present the ICP experience, as a leading low- and middle-income country (LMIC) manufacturer of antivenom immunoglobulins that benefit many countries in Central America, the Caribbean, South America and sub-Saharan Africa. Also, we address our experience in the development of a new technology for human plasma fractionation, initially conceived for the fractionation of

hyperimmune equine plasma. The overall manufacture system, and its challenges and difficulties are discussed, including technical, financial, regulatory and distribution issues.

The experience developed by several LMIC in the fractionation of antivenoms immunoglobulins demonstrate the feasibility of a domestic production of plasma-derived biologicals that may provide a roadmap for the supply of human plasma fractions in LMIC and fill the gap with highincome countries in product supply and quality.

SPEAKERS

Mohamed Ghönim, Switzerland - QSE

Mohamed Ghönim is the Regulatory Affair Director at QSE, Switzerland, with 20 years' experience. Ghonim supported national competent authorities, and several notified bodies as lead auditor and technical expert in several medical scope including blood transfusion.

Regulatory considerations for authorization of plasma processing devices "Pathogen Inactivation"

Pathogen Inactivation Medical Device [PIMD] undergoes a sophisticated pathway from the design phase to clinical use; manufacturers of PIMD must prepare a complete set of objective evidence related to Performance, Safety, and Efficacy [PS&E] to a Notified Body [NB], and National Regulatory Authority [NRA].

Manufacturers presume compliance for such devices either as an integrated set including Chemical Compound [CC] or approve the device, and Chemical separately. Notified body [NB] assesses the device to ensure Performance, Safety, and efficacy [PS&E].

NB must plan a periodical on-site audit; eventually, NB certifies the product and keep monitoring periodically. NB process takes [1-2] years to certify such devices based on old medical device directive 93/42/EEC [MDD]; this timeline is being doubled [2-4 years] following the introduction of the medical device regulation 2017/745 [MDR] which became effective on May 26th, 2021. This complication led to the fact that [PIMD] became costly, time-consuming and entails an immense regulatory knowledge base along all PIMD's interested parties [NRAs, NB, and Manufacturers]. These complications cause/continue to cause a limited availability of [PIMD] worldwide, especially in constrained-resources countries.

In this presentation, we will elucidate a harmonized pragmatic approach to enhance/accelerate authorization unequivocally, without compromising Performance, Safety, and efficacy [PS&E]. We will also discuss the procedures how low- and Middle-Income countries can approve PIMD aiming at the virus inactivation of essential mini-pool plasma-derived fractions like cryoprecipitate and immunoglobulins.

DAY 3 Thursday September 23, 2021 (13:00 – 16:00 CEST)

3.2 SESSION "They way forward"

15:00-15:20 Models for technology transfer and technical assistance (Leni von Bonsdorff, Finland - IPFA)

15:20-16:00 Panel discussion: Lessons learned and next steps:

- Yuyun Maryuningsih - WHO
- Giuliano Grazzini - FIODS
- Cesar Garrido and Salou Diop - WFH
- Johan Prévot- IPOPI
- Johannes Blümel-PEI
- Leni von Bonsdorff - IPFA
- Jan Bult - PPTA

OBJECTIVES OF THE SESSION

This session is intended to focus on concrete next steps that can be taken in LMIC to prepare virus-safe plasma protein products including cryoprecipitate (as a source of FactorVIII/von Willebrand factor/fibrinogen) and immunoglobulins. Such an approach should be regarded as an intermediate strategy to improve access to safe plasma products and to avoid wastage of recovered plasma while ramping up toward fractionation of quality assured plasma. This phase of development can be used to familiarize stakeholders withthe issues associated with plasma collection and processing, and to help train operators. Possibilities for technology transfer by established fractionators will be presented.

Learning points:

- Possible models for technological assistance and technology transfer of fractionators for their counter-parts in LMIC to improve the production and availability of PDMP will be presented.

MODERATORS

Martin Smid, The Netherlands - ISBT GBS WP

Martin Smid (Netherlands, MD Medicine, PhD and MBA) has more than 25 years experience in blood bank management, transfusion medicine and coagulation. He is managing director of Sanquin Consulting Services and the Academic Institute IDTM.

He is chair of the ISBT GBS WP since 2018 and member from the start in 2010. In recent years the position of the WP became was a main issue, now it is settled the focus needs to shift to visibility of availability and safety of the blood supply globally for ISBT members and to ways how to improve the situation in limited resource countries. Martin's main responsibilities are international cooperation and knowledge sharing in international projects and the Management of Transfusion Medicine programme at the Graduate School of Medical Science of the University of Groningen. He is involved in the WHO Global Blood Safety Network and AfSBT Educational Committee and also is an advisor of the Curacao blood bank.

Jay S. Epstein, USA - ISBT GBS WP

Jay S. Epstein from the US worked at the US FDA for over 30 years where he directed scientific research and regulatory programs for blood products, donor screening tests, and HIV diagnostics. Throughout his FDA career he assisted the Council of Europe and the WHO to advance blood standards and global access to safe blood products. Presently, he leads the COVID-19 response on neutralizing antibodies at the US Department of Health and Human Services. Dr. Epstein trained clinically in Internal Medicine and Infectious Diseases and is author of numerous scientific publications and reviews primarily in the field of blood safety regulation.

SPEAKERS

Leni von Bonsdorff, The Netherlands - IPFA

Leni von Bonsdorff is the Executive Director of the International Plasma and Fractionation Association (IPFA). She has over 30 years' experience of plasma derived medicinal products and has held executive positions at Sanquin in Finland and worked with R&D at the Finnish Red Cross Blood Service. Her doctoral degree in technology relates to research on purification and clinical use of a novel plasma product.

Models for technology transfer and technical assistance

To set up full scale manufacturing of plasma derived medical products PDMPs, there needs to be a basic understanding of the clinical needs in the market, how to handle the market for new products, sufficient surplus of qualified plasma as well as sufficient funding and technical knowledge and skills to run a pharmaceutical facility. In addition, a long-term view on how to build and retain a sustainable business is of importance. The importance of a supporting government as well as suitable national regulation cannot be overlooked. When all these elements are in place, there are different ways to start up a full scale fractionation and technical assistance can be provided through different routes. For the actual manufacturing facility specialized engineering consulting is available. For the manufacturing technology, the process can be developed by the company itself, but many times the licensing of the technology offers a quicker route. The management of the new establishment should have knowledge and understanding in all areas of the value chain of manufacturing and supply of PDMPS even if parts of the business is outsourced.

PANEL DISCUSSION

Yuyun Maryuningsih - WHO; Giuliano Grazzini - FIODS; Cesar Garrido and Salou Diop - WFH; Johan Prévot - IPOPI; Johannes Blümel - PEI; Leni von Bonsdorff - IPFA; Jan Bult - PPTA

The lessons learned throughout the workshop will be discussed from the perspective of diverse stakeholders with a goal to develop recommendations on next steps. The panel members will offer their views on needs for further education, potential pilot projects on a national or local level and opportunities for additional cooperation amongst stakeholders.

Remaining questions raised during the Workshop will be discussed along the line of the following fundamental questions:

1. **Local preparation of plasma protein products:**
   - What are the best approaches for locally made virally-safe cryoprecipitate or immunoglobulins to be licensed in an LMIC?
   - How can you endorse the use of cryoprecipitate, even pathogen-reduced, or virallyinactivated, in LMIC while concentrates are used as standard of care in high-income countries? Are there two standards of treatment?
   - How to guarantee that locally made small-scale products can be as safe as imported products? Which minimum standards and control mechanisms should be put in place for patients' safety and to promote confidence in using such products?
   - What level of regulatory oversight is needed for clinical evaluation of locally produced plasma proteins?
   - What would be needed in terms of education and training and by whom?

2. **Fractionation of domestic plasma:**
   - Is it reasonable for a LMIC to initiate a plasma fractionation program while modern therapies increasingly rely on recombinant products and gene therapy?
   - Is it economically viable to consider a small-scale plasma processing facility?
   - WHO already has initiated actions to help improve the collection of plasma (and blood components) in LMIC. How can the WHO assist in anyway in the establishment of a domestic plasma fractionation program?
   - Is there a document that applies to the critical points that GMP inspectors should consider when licensing a small-scale domestic facility? Does a document exists based on the experience from antivenom immunoglobulins that can be used?
   - Can established plasma fractionators provide at-cost training on plasma fractionation technologies to operators from LMIC?
   - What would be needed in terms of education and training and by whom?

3. **Next steps to move forward with supply in LMIC :**
   - With what we know from the workshop what actions can be taken as next steps and how?