IPFA Yogyakarta 02.03.2017

"Local preparation of cryoprecipitate-pathogen reduced in developing countries" (Local Cryo-PR in LDI)

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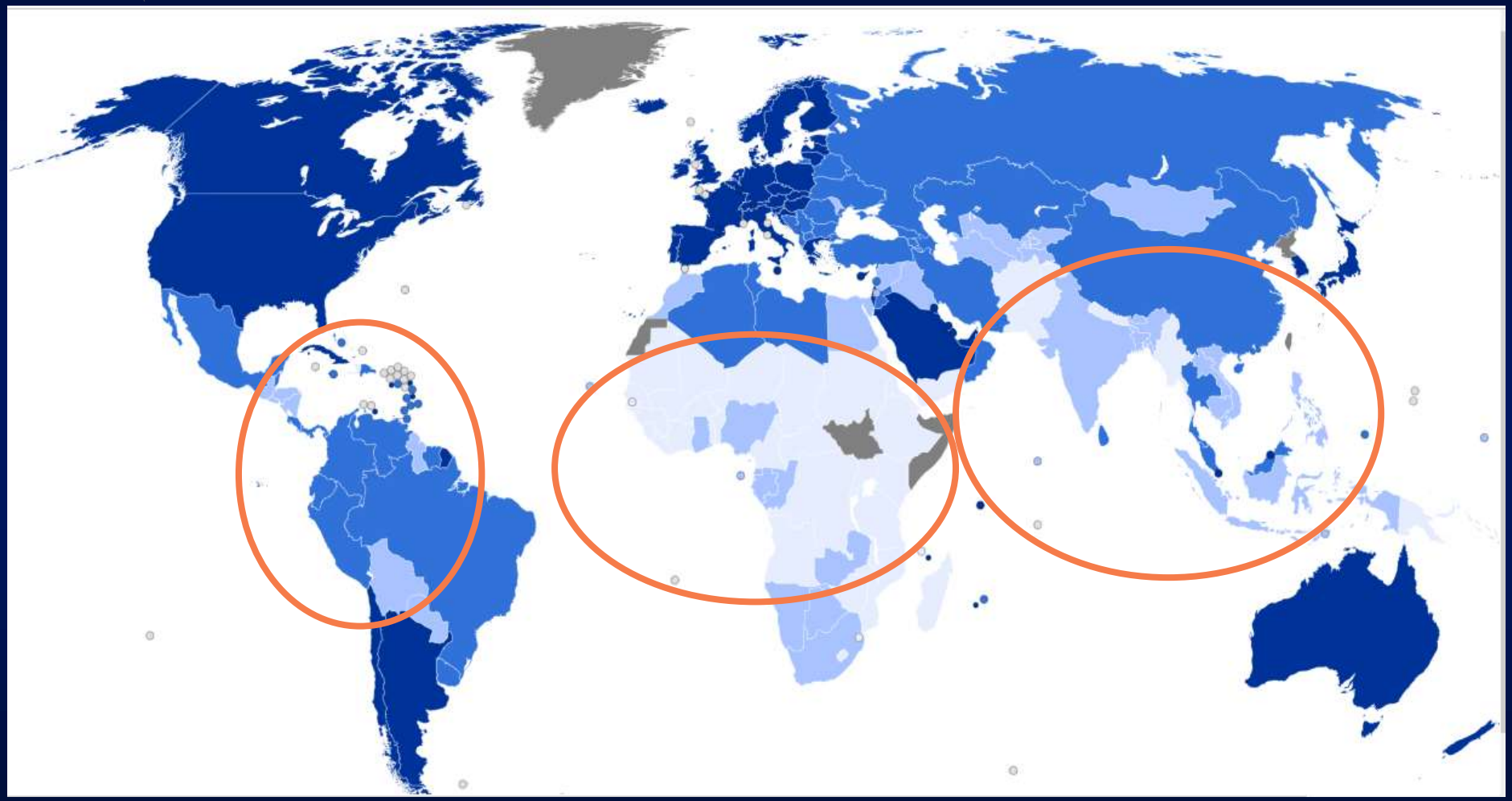
No conflict of interest in the context of Cryo-PR.

HDI = UN Human Development Index



Developing countries → low HDI (LDI) with score < 0,600

World Federation of Haemophilia (WFH) Congress 2016

PWH: worldwide 175000 known, largely underdiagnosed

For other bleeding disorders (VWD, fibrinogen depletion/ dysfunction): numbers unknown.

Treatment: holistic approach using clotting factor concentrates (CFC), managed/supervised by CCC

75-80% of all PWH have ***no*** access to ***any*** form of treatment – ***unchanged*** for past 20 years (at least)

Past experience has shown that **clotting factor concentrates (CFC) cannot solve the problems in LDI,** if they are used as the sole means in the treatment of patients with bleeding disorders.

Toll fractionation may be, in the best of the cases, an additional source of CFC for some LDI.

Recent developments

In the past, **WFH** (World Federation of Hemophilia) has recommended the use of **CFC** and assisted increasingly with **products donated by industry**. The supply situation in LDI has remained catastrophic.

Recently, significant developments have occurred :

1. **blood systems** (blood centers) in many LDI have improved;
2. novel **technologies for pathogen reduction (PR)** of blood components are now available (amotosalen, riboflavin, SD,…).

In some LDI, local preparation of pathogen-reduced cryoprecipitate has been introduced and **Cryo-PR has proven to be a safe and effective therapeutic** for patients with bleeding disorders, at an affordable cost.

A **global initiative** is needed to promote **local preparation of Cryo-PR in LDI** and to facilitate implementation & sustainablility.

Local safe&effective products from **existing blood centres** in LDI

Whole blood donations

Centrifugation of whole blood

Separation of different blood layers for BC production

Release of finished blood components

Additional step: pathogen reduction (viral inactivation)

Comprehensive and global initiative

Recently, **WFH** has been invited to take the **lead in a worldwide movement** on local preparation of safe products to treat patients with bleeding disorders in LDI and to **collaborate with *international* partnering organizations:**

a. WHO
b. ISBT (and possibly others)

and ***national* stakeholders in developing countries**:

1. competent authorities
2. blood suppliers (blood centres and blood services)
3. patient organisations (WFH NMOs) and possibly others.

This global initiative comprises **6 core interventions**, supported by **additional flanking activities.**

Comprehensive and global initiative for "Local Cryo-PR in LDI"

The 6 core interventions in the worldwide initiative:

1. WFH to revisit/review/revise/update policies, strategies, recommendations and guidelines on "anti-hemophilic" therapies (with particular attention and focus on LDI);
2. WFH to give a high(er) priority to local preparation of pathogen reduced-cryoprecipitate in developing countries
3. WFH to advocate for Local Cryo-PR in LDI;
4. WFH to run a pilot project on Local Cryo-PR in LDI;
5. WFH to establish an expansion programme for Local Cryo-PR;
6. WFH to support activities for implementation & sustainability of Local Cryo-PR in LDI,

supported by several **additional flanking activities.**

Prop. Initiative "Local Cryo-PR in LDI": schematic overview

WFH takes the lead in the initiative for local preparation of products to treat bleeding disorders in developing countries (LDI)

- Revisit/review/revise/update policies, strategies recommendations, guidelines,… of WFH on "antihemophilic" therapy in LDI

  → *internal process within WFH (EB, TPSSA)*

- *Prioritize "Local Cryo-PR" in LDI*
- *Advocate for "Local Cryo-PR" in LDI*
- *Run a pilot project on "Local Cryo-PR" in LDI*
- *Establish an expansion programme for "Local Cryo-PR" in LDI*
- *Support LDI in their activities for "Local Cryo-PR"*

"Local Cryo-PR" in LDI results in (additional) supply of safe &effective products to treat bleeding disorders

WFH policies: CFC! …and Cryo-PR?

"WFH's strongly held view is that the ***principles of management*** of hemophilia are ***the same all over the world".***

Basically, this recommendation is agreed and accepted.

Nonetheless, WFH recognises that ***"one size does not fit all".*** Therefore, an exception to this statement is made by WFH when it comes to "treatment dosage" (dual set of doses).

Taking into account the disastrous situation in developing countries, it is suggested that a similar adaptation is urgently made when it comes to "therapeutic products" (dual set of products): ***CFCs should be used, if available. Otherwise, Cryo-PR should be recommended by WFH.***

Treatment protocols:

- *Malmœ protocol (50 IU/kg BW/3x week)*

vs.

- *Dutch protocol (25 IU/kg BW/2x week):*

→ *Identical results in terms of number of bleedings*

vs.

- *"Low dose" protocol (Egypt, Algeria,...)*

  10 IU/kg/2x week; if breakthrough bleedings- doses to be increased

→ *Acceptable results in terms of bleedings*

WFH policies: CFC! …and Cryo-PR?

The revised recommendations should be ***stratified according to jurisdictions***, ranging from countries with highly developed health care systems to those where health care is still severely hampered.

A ***distinction between the developed world and the developing countries*** needs to be made for management/ treatment of patients with bleeding disorders … at least temporarily, during ***an intermediate phase.***

This is particularly true when it comes to therapeutic products: CFC alone cannot solve the unacceptable situation of treatment availability in developing countries, but ***Cryo-PR has the potential to alleviate it.***

"Anti-hemophilic" products and inhibitors

F.VIII products come with a serious problem: **inhibitor** formation.

Clotting factor concentrates (CFC) should not bring "more bad than good" to developing countries:

1. 25-35% of PUPs are developing an inhibitor with F.VIII CFC (*SIPPET NEJM, 2016*), recombinant CFC being more likely to trigger an INH than plasma-derived;
2. majority of products donated by industry are recombinant CFC
3. the incidence of INH induced by r-CFC may be as high as 50% if PUPs are treated for the 1st time, while being in "immunological storm" (trauma, emergencies, massive bleeds)
4. patients in LDIs forming an INH are very likely to be "lost".

On the other hand, the incidence of inhibitors is low when using **cryoprecipitate** (probably some 5%).

SIPPET= Survey of Inhibitors in Plasma-Product Exposed Toddlers

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A

F. Peyvandi, P.M. Mannucci, I. Garagiola, A. El-Beshlawy, M. Elalfy, V. Ramanan, P. Eshghi, S. Hanagavadi, R. Varadarajan, M. Karimi, M.V. Manglani, C. Ross, G. Young, T. Seth, S. Apte, D.M. Nayak, E. Santagostino, M.E. Mancuso, A.C. Sandoval Gonzalez, J.N. Mahlangu, S. Bonanad Boix, M. Cerqueira, N.P. Ewing, C. Male, T. Owaidah, V. Soto Arellano, N.L. Kobrinsky, S. Majumdar, R. Perez Garrido, A. Sachdeva, M. Simpson, M. Thomas, E. Zanon, B. Antmen, K. Kavakli, M.J. Manco-Johnson, M. Martinez, E. Marzouka, M.G. Mazzucconi, D. Neme, A. Palomo Bravo, R. Paredes Aguilera, A. Prezotti, K. Schmitt, B.M. Wicklund, B. Zulfikar, and F.R. Rosendaal

ABSTRACT

BACKGROUND

The development of neutralizing anti–factor VIII alloantibodies (inhibitors) in patients with severe hemophilia A may depend on the concentrate used for replacement therapy.

METHODS

We conducted a randomized trial to assess the incidence of factor VIII inhibitors among patients treated with plasma-derived factor VIII containing von Willebrand factor or recombinant factor VIII. Patients who met the eligibility criteria (male sex, age <6 years, severe hemophilia A, and no previous treatment with any factor VIII concentrate or only minimal treatment with blood components) were included from 42 sites.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Peyvandi at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, and Department of Pathophysiology and Transplantation, University of Milan, Via Pace 9, 20122 Milan, Italy, or at flora.peyvandi@unimi.it.

"anti-hemophilic" products and economics

- The **costs** for industrially-manufactured **CFC** vary significantly from one country to another: 1 IU of F.VIII concentrate may cost as low as 0,35 USD but also as much as 1 (to 2) USD,depending amongst others on whether it is a plasma-derived or a recombinant medicinal product.

- The **costs** for **Cryo-PR** are relatively low (for SD/F some 0,07 USD per IU F.VIII) as native cryo can be produced locally in the blood center and then subject to viral inactivation. Its low cost is linked to the fact that premises, equipment and staff involved are anyway in place for preparation of blood components from whole blood donations.

Taking into account inhibitors and costs, the "overall" balance is very much in favor of Cryo-PR.

Prop. Initiative "Local Cryo-PR in LDI": schematic overview

WFH takes the lead in the initiative for local preparation of products to treat bleeding disorders in developing countries (LDI)

- *Revisit/review/revise/update policies, strategies recommendations, guidelines,… of WFH on "antihemophilic" therapy in LDI*

Give high priority to "Local Cryo-PR" in LDI

→ *internal process within WFH (EB, TPSSA)*

- *Advocate for "Local Cryo-PR" in LDI*
- *Run a pilot project on "Local Cryo-PR" in LDI*
- *Establish an expansion programme for "Local Cryo-PR" in LDI*
- *Support LDI in their activities for "Local Cryo-PR"*

"Local Cryo-PR" in LDI results in (additional) supply of safe &effective products to treat bleeding disorders

Product donation: the benefits and the problems

WFH has been stating in the past that "improving access to safe and effective products" is to be reached **"through advocacy and product donation"** (as mentioned in WFH Annual Report 2015).

WFH's goal is "Treatment for All": this cannot be achieved through CFC alone (donated or purchased) - additional interventions are vital in developing countries and autonomous, local production of safe and effective hemostatic products in existing blood centers in LDIs can contribute significantly to improve product supply and reduce shortage.

CFC (recombinant or plasma-derived) have some **serious drawbacks (high inhibitor formation in PUPs, costs).**

Donations of CFC have additional risks: they create ***dependency*** from a few donating companies and they are ***not "risk managed" interventions*** as donations may be discontinued or not prolonged.

Therefore, WFH should give high priority to "Local Cryo-PR".

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- *Prioritize "Local Cryo-PR" in LDI*
- Advocate for "Local Cryo-PR" in LDI → *in collaboration with WHO, ISBT and WFH NMOs*
- *Run a pilot project on "Local Cryo-PR" in LDI*
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- *Prioritize "Local Cryo-PR" in LDI*
- *Advocate for "Local Cryo-PR" in LDI*
- Run a pilot project on Local Cryo-PR in LDI

  → *in 6 pilot sites BTCs in Africa, Asia, Latin America; feasibility & implementation; in cooperation with ISBT & selected BS in hHDI*
- *Establish an expansion programme for "Local Cryo-PR" in LDI*
- *Support LDI in their activities for "Local Cryo-PR"*

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Logical Framework for the **Pilot Project**

On January 31, 2017: research grant application with WFH amounting 50 000 USD

Local Preparation of Cryoprecipitate-Pathogen Reduced in selected blood centres in developing countries» (LP of Cryo-PR in LDIs)

INTERVENTION LOGIC	OBJECTIVELY VERIFIABLE INDICATORS (OVI)	MEANS AND SOURCES OF VERIFICATION (MSV)	HYPOTHESES (H), PREREQUISITE CONDITIONS (CP) AND RISKS (R)
GLOBAL OBJECTIVE			
Contribute to improvement of medical treatment of patients with bleeding disorders, especially in developing countries			
SPECIFIC OBJECTIVE			**Contributing to the global objective**
Facilitate introducing, implementing and maintaining local preparation of hemostatic products for the treatment of patients with bleeding disorders in selected blood centres in the developing world, especially the local preparation (LP) of cryoprecipitate-pathogen reduced (Cryo-PR)	- Quality: all selected blood centres are in compliance with Good Manufacturing Practices (GMP) - Safety: all selected blood centres produce all cryoprecipitates using a validated pathogen reduction technique before release - Supply and Availability: all	- Quality: Audits conducted by teams set up by WFH in collaboration with partners - Safety: Monthly statistics by selected blood centres and periodic reports by WFH - Supply and Availability: Monthly statistics by selected blood centres and periodic reports by WFH	- Commitment of the Health Authorities responsible for the selected blood centres to support local preparation of products for patients with bleeding disorders (Cryo-PR) (CP) - National Blood Policy updated for LP of Cryo-PR (CP) - Regulatory Agency to authorize use of technologies for Cryo-PR (CP)

Logical Framework for the **Pilot Project:**
Financial aspects

As premises, equipment and staff are already in place, the **budgets** needed to support the pilot sites are covering essentially:

1. ***training and education*** (of BE staff, but also of clinicians to use the local products);
2. ***quality management and work flows*** (adjustments);
3. ***personnel*** (additional, if needed);
4. ***material*** (kits for the "viral inactivation" of locally prepared Cryo-PR) - this position will have the highest price tag. A decision on the technology for Cryo-PR to be used in the Pilot Project is pending: 1 device approved by Authorities, 2 more candidates.

VIPS®

SD Cryoprecipitate Kit

CE mark of medical devices

ZERTIFIKAT

Nr.: TÜV-A-MT-1/09/Q070

TÜV AUSTRIA

Vollständiges Qualitätssicherungssystems - *Full quality assurance system*
93/42/EWG Anhang II Abschnitt 3 – *93/42/EEC Annex II section 3*

Hersteller / *Manufacturer*:

V.I.P.S. SA
Viral Inactivated Plasma Systems SA
Avenue de la Gare 26
2013 Colombier, Switzerland

Produktkategorie / *Product category*:

Virus-inaktivierungs Produkt für Plasma und Kryopräzipitat (-)
Virus-inactivation product for plasma and cryoprecipitate (-)

Dieses Zertifikat gilt nur für Produkte und Fertigungsstätten die im Anhang zum Zertifikat angeführt sind. - *This certificate is valid for products and facilities listed in annex to certificate only.*

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Bericht Nr. / *Report No.*: 09MT0200WRO

CE 0408

Erstausstellung / *First issue*: 13.07.2009

Datum der Ausstellung / *Date of issue*: 13.07.2009

Zertifizierungsbeauftragter / *Certification representative*: Dipl.-Ing. Michael Pölzleitner

Ende der Gültigkeit / *End of validity*: 02.03.2014

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ZERTIFIKAT

Nr.: TÜV-A-MT-1/09/Q070

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Product category:

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Virus-inactivation product for plasma and cryoprecipitate (-)

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CE
0408

Free Sales Certificate

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FREE SALES CERTIFICATE

Nr.: FSC-2010-13180 valid until: 19 July 2013

The SWISS AGENCY FOR THERAPEUTIC PRODUCTS certifies herewith, that medical devices are regulated in Switzerland under the Federal Law on Medicinal Products and Medical Devices (Law on Therapeutic Products) of 15 December 2000 in force since 1 January 2002 and the Medical Devices Ordinance of 17 October 2001 in force since 1 January 2002.

The following medical device(s) meets (meet) the legal requirements set out in the Swiss Medical Devices Ordinance and which incorporates the Medical Devices Directives of the European Community:

Product category: Virus-Inactivation Product for Plasma and Cryoprecipitate
Products:
- **V.I.P.S. Single-Use Processing System for SD Virus Inactivation of Cryoprecipitate**
- **V.I.P.S. Single-Use Processing System for SD Virus Inactivation of Plasma**
- **V.I.P.S. Single-Use Processing System for SD Virus Inactivation of Cryoprecipitate and Plasma**

Therefore, the firm V.I.P.S. SA VIRAL INACTIVATED PLASMA SYSTEMS SA, Avenue de la Gare 26, CH-2013 Colombier, Switzerland,

in conformity with the laws of Switzerland is authorized to develop, manufacture and sell on the Swiss market and to export into any country the medical device(s) above-mentioned.

This certificate is valid until 19 July 2013

Bern, 20 July 2010

Swiss Agency for Therapeutic Products
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FREE SALES CERTIFICATE

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Products:
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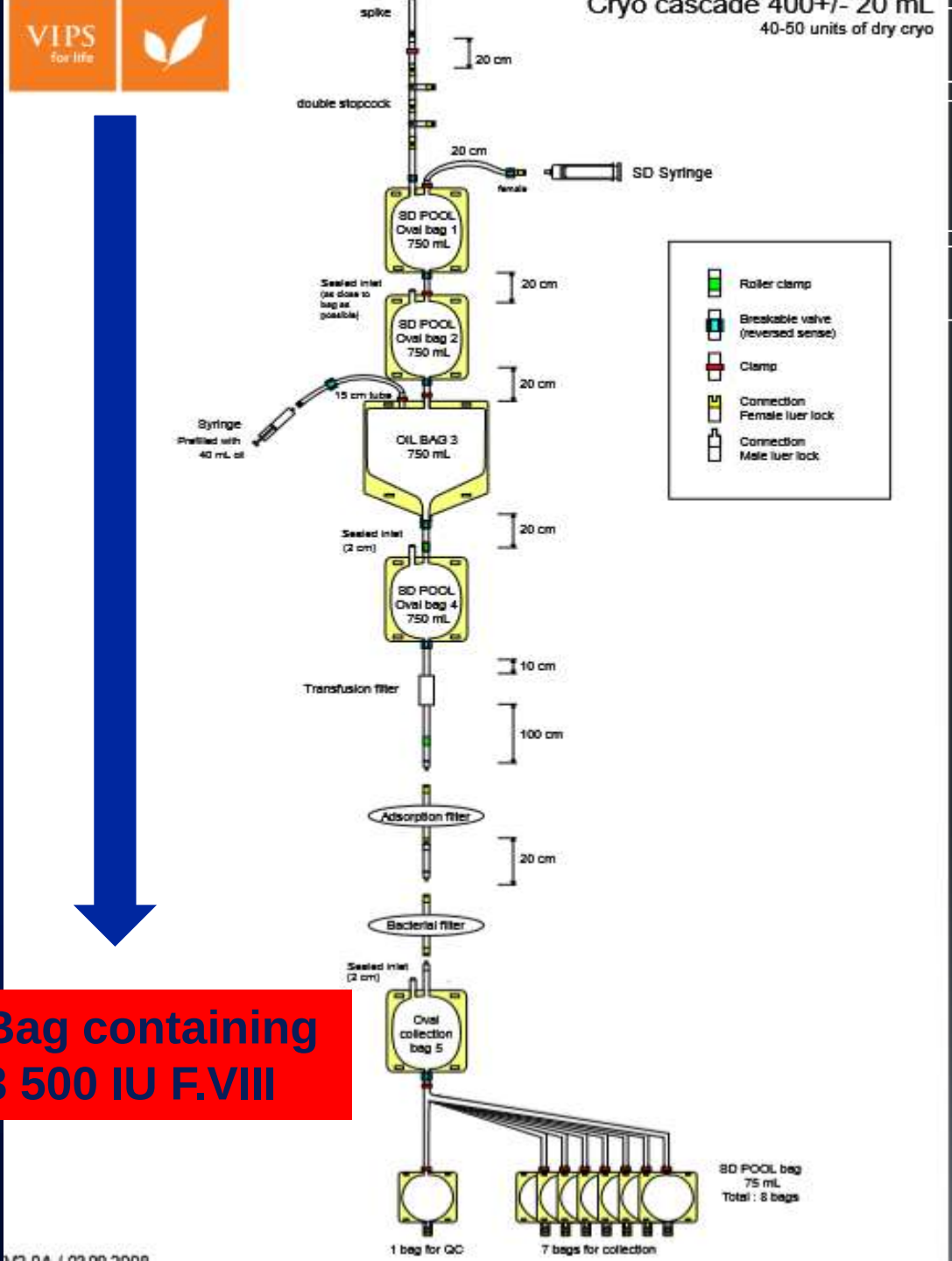
- **V.I.P.S. Single-Use Processing System for SD Virus Inactivation of Cryoprecipitate and Plasma**



Bag containing 3 500 IU F.VIII

Pool 30-35 native «dry» cryos

Add solvent-detergent SD: TnBP and Triton X45

Mix carefully 2x

Add oil

Remove/extract SD with oil

Pass through absorption filter

«Sterilize» with bacterial filter

Condition in smaller portions

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- *Revisit/review/revise/update policies, strategies recommendations, guidelines,… of WFH on "antihemophilic" therapy in LDI*
- *Prioritize "Local Cryo-PR" in LDI*
- *Advocate for "Local Cryo-PR" in LDI*
- *Run a pilot project on "Local Cryo-PR" in LDI*
- Establish an expansion programme for "Local Cryo-PR" in LDI → *in collaboration with WHO (HQ&RO):Global Forum, Regional Consultations, WS, Network of CC*
- *Support LDI in their activities for "Local Cryo-PR"*

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- *Establish an expansion programme for "Local Cryo-PR" in LDI*
- Support LDI in their activities "Local Cryo-PR"
  → *WFH to set up a specific programme and dedicate a regular budget line*

"Local Cryo-PR" in LDI results in (additional) supply of safe &effective products to treat bleeding disorders

Roles of NMOs of WFH

NMOs in LDI have to play an important role in strengthening both arms of the blood system: production and usage of blood products.

NMOs in developing countries need to advocate for:

1. building on existing national blood systems (integrating local preparation of Cryo-PR)
2. improving blood policies, extending their coverage to Cryo-PR;
3. incorporating additional safe blood products into national blood programmes;
4. facilitating local preparation of hemostatic products safeguarded by PR-technologies through reviewed national blood plans, quality manuals, standards&guidelines.

NMOs also should promote the usage of local Cryo-PR, with bleeding patients, prescribing physicians and hospital blood banks.

Prop. Initiative "Local Cryo-PR in LDI": schematic overview

In addition, flanking interventions to support the 6 "core" interventions:

- **Twinning** programmes between blood centers (→ *in cooperation with BS in developed countries*)
- **Research** on new technologies for Local Cryo-PR (→ *in cooperation with ISBT and industry*)
- **Training** Programmes (→ *using WHO's worldwide Network of Collaborating Centers*)
- **Lobbying** programmes (→ *with&for NMOs in LDI*),…
- **IEQAS** for therapeutic products (→ *WHO's worldwide Network of Collaborating Centers or twinned BCs*)

Conclusions

The global initiative on Local Cryo-PR in LDI is meant to be **additional to other activities of WFH (factor concentrate donations and contract fractionation of plasma, where feasible).** Local Cryo-PR in LDI should be seen as **complementing temporarily existing activities**, resulting in (additional) supply of safe and effective products to treat patients with bleeding disorders.

Taking into account the experience from the past, it cannot be denied that **availability, accessibility and affordability of appropriate "anti-hemophilic" treatment remain unsolved problems in LDI.** Despite WFH's activities to alleviate the critical situation of patients with bleeding disorders in LDI, the problems are not solved effectively.

Therefore innovative approaches are needed and the the proposal to WFH for a lead initiative in ***Local Cryo-PR in LDI has the potential to improve the existing unacceptable situation.***

Final considerations

- The existing situation in the treatment of patients with bleeding disorders in developing countries must change.
- Recent developments offer a treatment option with Cryo-PR if CFC are not available: 1. improvement in the blood sector in most developing countries 2. availability of new technologies (Cryo-PR).
- A global&comprehensive initiative should involve WFH, WHO, ISBT, WFH NMOs (and possibly others) and it is needed to bring "Local Cryo-PR" into developing countries.
- If implemented at a larger scale in LDI, ***local preparation of Cryo-PR*** *can significantly improve quality&safety, supply, availability, accessibility&affordability of hemostatic products* ***for patients with hemophilia A, Willebrand disease and fibrinogen depletion in developing countries,*** *thus benefiting patients in a desperate situation and allowing them to survive.*