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This letter is provided in response to a request from the Director of Health Products Policy and Standards on the subject: Input and comments from the WHO Technical Departments, 25th Expert Committee on Selection and Use of Essential Medicines.

The input and comments provided by the Blood and Other Products of Human Origin Team refer to the WHO international survey on the availability and clinical use of cryoprecipitates conducted in November 2024, discussion with and feedback received from BTT's stakeholders.

The discussion has been conducted, followed by inputs received by BTT, which were also shared with the EML Secretariat. These inputs came from the following sources:

- The International Society of Blood Transfusion (ISBT), a Non-State Actor in official relations with the WHO
- The WHO Advisory Group for Blood Regulation, Availability and Safety (AG-BRAS)

Another input received by BTT came from:

- The Shanghai Blood Centre, China, which serves as a WHO Collaborating Centre for Blood

Unfortunately, we did not receive input from the following WHO Collaborating Centres on Blood:

1. Health Sciences Authority – Singapore: The institution explained that it does not treat patients, and therefore could not contribute.
2. Etablissement français du sang (EFS) – France: EFS noted that, following the reorganization of blood transfusion services in France in 1993, expertise in hemophilia management now resides in hospitals, and not within EFS itself.
3. Paul Ehrlich Institute – Germany: The institute expressed concern over a potential conflict of interest in providing medical advice, given its role as a licensing authority.
4. Korean Red Cross – Republic of Korea: No response was received from this institution.

Here is BTT's response:

**A.12 - Emicizumab**

In alignment with the discussion and input received from the ISBT and AG-BRAS, and input from the Shanghai Blood Centre, the BTT supports the independent listing of emicizumab as a distinct "square box" entry under Section 10.2 (Medicines Affecting Coagulation) of both the EML and EMLc. The reason is that emicizumab has demonstrated favourable efficacy and cost-effectiveness.

**A.23 - Recombinant Clotting Factor Concentrates (rCFCs)**

In alignment with the discussion and input from the ISBT and AG-BRAS, as well as input from the Shanghai Blood Centre, the BTT supports the inclusion of recombinant FVIII (rFVIII) and recombinant FIX (rFIX) as individual medicines within the "square box" listings under Section 10.2 (Medicines Affecting Coagulation).

**C.1 - Cryoprecipitate (PR and Non-PR) & Plasma-Derived Clotting Factors**

Non-Pathogen-Reduced Cryoprecipitate ("Cryo")

In alignment with the results of the WHO international survey on the availability and clinical use of cryoprecipitates conducted in November 2024, where both high-income countries (HICs) and low-to middle-income countries (LMICs) continue to produce and use non PR Cryoprecipitate; discussion and input from the ISBT and AG-BRAS, as well as input from the Shanghai Blood Centre, the BTT proposes to retain non-pathogen-reduced cryoprecipitate (Cryo) in both the EML and EMLc under the “Blood and Blood Components”. This recommendation is consistent with the continued listing of other non-pathogen-reduced blood components, including whole blood, plasma, platelets, and red blood cells. BTT emphasizes that strict TTIs blood screening should be applied during the production of Non-PR Cryoprecipitate, and other blood components, to reduce TTIs risks.

Pathogen-Reduced Cryoprecipitate (PR Cryo) & Hemophilia A/VWD

Based on the results of the WHO international survey on the availability and clinical use of cryoprecipitates conducted in November 2024, pathogen-reduced cryoprecipitate (PR-Cryo) continues to play a critical role in ensuring treatment accessibility for acute bleeding conditions, where recombinant / plasma-derived products are unavailable. Therefore, the BTT proposes that the use of PR-Cryo should not be limited to non-hemophilia indications.

Transfer of Plasma-Derived FVIII and FIX to the Core List

In alignment with discussion and input from the ISBT and AG-BRAS, and input from the Shanghai Blood Centre, the BTT supports the reclassification of plasma-derived FVIII and FIX from the Complementary List to the Core List.

Removal of FIX Complex as a Therapeutic Alternative

In alignment with discussion and input from the ISBT and AG-BRAS, and input from the Shanghai Blood Centre, the BTT supports the removal of FIX Complex as a therapeutic alternative due to the risk of thrombosis

For reference, we hereby attach the report of the WHO international survey on the availability and clinical use of cryoprecipitates conducted in November 2024.

Thank you,

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# Report of an international survey on the availability and clinical use of cryoprecipitates

## Introduction

The World Health Organization (WHO) conducted an international survey in 2024 to identify countries' production and need of cryoprecipitates for the treatment of bleeding conditions, including inherited clotting disorders in relation to World Bank Income (WBI) levels. A questionnaire was distributed to all member countries through the WHO regional offices. The survey was undertaken to help inform pending decision-making about the inclusion in 2023 of cryoprecipitate, pathogen-reduced, and cryoprecipitate (not pathogen-reduced) as a therapeutic alternative, in Section 11.1 (Blood and blood components) of the Model Lists of Essential Medicines (EMLs) for adults and for children.[1] Those listings were added on the recommendation of WHO's Expert Committee on Selection and Use of Essential Medicines. Nevertheless, almost immediately, WHO was asked to remove cryoprecipitate (not pathogen-reduced) from the EMLs. The argument was made that the risks and limitations involved with using cryoprecipitate (not pathogen-reduced) make it unacceptable for treating inherited clotting disorders, Hemophilia A, and von Willebrand Disease compared with existing industrially manufactured products.[2,3] Conversely, advocates responded that globally unmet patient needs continue to justify listing of cryoprecipitate (not pathogen-reduced) along with cryoprecipitate, pathogen-reduced as essential medicines for these and other bleeding indications since preferred products are not sufficiently available and affordable, especially in many low- and middle-income countries (LMICs).[4,5] A WHO determination whether to retain the listings will affect the 24$^{th}$ (2025) EMLs.

## Background

Cryoprecipitate is a component prepared from fresh frozen plasma by re-suspending the precipitate formed during controlled thawing (+2 to +6 °C) in 10–20 ml of plasma supernatant. Cryoprecipitate contains about half of the Factor VIII and fibrinogen from the donated whole

blood-derived plasma unit: e.g. Factor VIII: 80–100 IU/unit; fibrinogen: 150–300 mg/unit. It is usually supplied as a single donor unit or a bag of 4–6 donor units pooled.[6,7]

Cryoprecipitate may be used as an alternative to Factor VIII concentrate in the treatment of inherited deficiencies, i.e. of Von Willebrand Factor (von Willebrand's disease) and Factor VIII (hemophilia A), **only** if recombinant or pathogen-inactivated factor concentrates are unavailable. It can also be used as a source of Factor XIII. Furthermore, it may be used as a source of fibrinogen in patients with acquired coagulopathies: for example, disseminated intravascular coagulation (DIC), and critical bleeding requiring massive transfusion.[6,7]

Pathogen-reduced cryoprecipitate, or Cryo-PR, is a class of products created by incorporating pathogen-reduction technology during the preparation of cryoprecipitate. The starting material for Cryo-PR can be a single unit of plasma separated from whole blood, a pool of such units, a single unit or pool of units obtained through apheresis, or a pool of cryoprecipitates. Various pathogen reduction technologies can be used to treat plasma products, including heat treatment[8] and chemical incubation that disrupt the viral lipid envelope[9,10] or nucleic acids, sometimes with activation by ultraviolet light.[11-14]

Whenever possible, cryoprecipitate should be administered using ABO-compatible products. After thawing, it should be infused promptly through a standard blood administration set. Cryoprecipitate must be infused within 6 hours of thawing and 4 hours of pooling.[6,7] According to the Global Database on Blood Safety,[15] the number of cryoprecipitate transfusions increased by 17% across 112 countries between 2013 and 2018. Within the WHO regions, "cryoprecipitate transfused increased by 17% in 112 countries between 2013 and 2018. Across WHO regions, the Americas, Europe, Africa and the Eastern Mediterranean reported an increase at rates of 10%, 32%, 46% and 73%, respectively. The Western Pacific and South-East Asia reported a decrease at rates of 10% and 4%, respectively."

Although recombinant and plasma-derived clotting factor concentrates (CFCs), which are industrially manufactured, are the preferred treatments for inherited bleeding disorders, access to these products remains a significant challenge in low- and middle-income countries (LMICs).[16-18]

A key barrier to the global availability of CFCs is the insufficient supply of plasma that meets internationally recognized standards for fractionation.[19] Additionally, in the absence of organized procurement agreements, the costs of industrially manufactured products typically limit their availability in LMICs.

The WHO has acknowledged the global importance of access to industrially produced recombinant and plasma-derived plasma proteins. The WHO's *Guidance on Increasing Supplies of Plasma-Derived Medicinal Products in Low- and Middle-Income Countries Through Fractionation of Domestic Plasma*[19] recognizes the local preparation of Cryo-PR as part of a phased approach to meeting patient needs for clotting factor concentrates. This stepwise strategy for improving access to safe plasma proteins, particularly clotting factors and immune globulins, reflects the understanding that it requires time and significant financial investment to achieve a sufficient volume of quality-assured domestic plasma for industrial fractionation. Local production of safe plasma-derived proteins can enhance access to essential clotting factors and immune globulins, supplementing available industrial supplies while fostering improvements in the collection and processing of blood components.[19]

**Development and dissemination of the survey**

The Blood and Other Products of Human Origin Team (BTT), serving as the WHO focal point for blood safety and blood products, disseminated a survey questionnaire focused on the production of cryoprecipitate, pathogen-reduced cryoprecipitate (including methods for pathogen reduction), and clotting factor concentrate (CFC). The survey also asked whether Nucleic Acid Testing (NAT) for HIV, HBV, and HCV was performed on blood collected for preparation of cryoprecipitate, the clinical indications for use of these products, as well as opinions whether the supplies of CFC and recombinant products are sufficient to meet the needs of patients (the survey in English is attached). The questionnaire was distributed to the WHO Advisory Group for Blood Regulation, Availability, and Safety (AG BRAS) and the Working Party for Global Blood Safety of the International Society of Blood Transfusion (ISBT) for their feedback and input.

Once the survey questionnaire was finalized, it was translated into Arabic, Chinese, French, Russian, and Spanish. To run the survey, the Assistant Director-General issued a memo to the Regional Directors, requesting them to distribute it to all Member States through the WHO Representative at the country level.

The period to fill in the survey was from 8 October to 30 November 2024. Responses were sent directly to BTT for compilation, reconciliation and analysis.

**Survey results**

The term “countries” was defined to include territories as individual countries. After removing duplicate reports and combining multiple submissions from single countries (or territories) into unitary responses, a total of 51 “countries” responded to the survey.

Responses were received from 25 high-income countries (HICs) and 26 low- and middle-income countries (LMICs). By WHO region, these encompassed 8 countries in Africa, 9 in the Americas, 4 in the Eastern Mediterranean, 16 in Europe, 7 in South-Eastern Asia, and 7 in the Western Pacific.

Thirty-six out of 51 countries reported that "blood establishments or hospitals in their country produce cryoprecipitate." By World Bank economic grouping (ref), 17 of these countries are HICs, representing 68% (17/25) of reporting HICs, while 19 are LMICs, accounting for 73% (19/26) of reporting LMICs. All countries reported use of nucleic acid testing for donations of blood used to prepare cryoprecipitates.

Six out of 51 countries (three HICs: Honduras, United States of America, and Poland; and three LMICs: Egypt, Thailand, and China (partially)) reported that "blood establishments or hospitals in their countries produce pathogen-reduced cryoprecipitates." The pathogen-reduction technologies mentioned include the "Intercept Blood System (Cerus)," "Mini-Pool Solvent Detergent and microbial filtered cryoprecipitate," "Heat-treated dried cryoprecipitate," "Theraflex MB Plasma (with methylene blue)," and "Intercept (with amotosalen hydrochloride)" as well as "Methylene Blue Photochemistry."

Among 36 countries (17 HIC, 19 LMIC) reporting production of “native” or non-pathogen-reduced cryoprecipitate, 20 reported that the products are used for “inherited bleeding disorders (e.g., Hemophilia A, Von Willebrand Disease, Fibrinogen deficiencies, FXIII deficiency)”, 21 reported use for “maternal bleeding”, and 30 reported uses for “Other bleeding conditions (e.g., related to surgery, trauma)”.

Further categorization of these results by economic groups is shown in Table I. Among the 17 HICs, 41% (7/17) reported that the products are used for “Inherited bleeding disorders”, 71% (12/17) reported use for “maternal bleeding”, and 94% (16/17) reported use for “Other bleeding conditions (e.g., related to surgery, trauma).” Among the 19 LMICs, 68% (13/19) reported that the products are used for “Inherited bleeding disorders”, 47% (9/19) reported use for “maternal bleeding”, 11% (2/19) reported use for “Other bleeding conditions (e.g., related to surgery, trauma)”.

Among the 6 countries reporting production of Cryo-PR, 3 reported that the products are used for “Inherited bleeding disorders”, 3 reported use for “maternal bleeding”, and 5 reported use for “other bleeding conditions (e.g., related to surgery, trauma)”.

To the question of “products for the treatment of inherited bleeding disorders other than Cryoprecipitate?” (multiple answers possible), 38 of 51 responding countries reported “Commercially imported Clotting factor concentrates (CFC), 16 reported “CFC obtained through contract plasma fractionation”, 6 reported “ Domestically fractionated CFC”, 15 reported “donated products CFC”, 31 reported “recombinant products: [Products analogous to Clotting factor concentrates]”, 22 reported “recombinant products: [Recombinant bi-specific FVIII mimetic antibodies]”, 37 reported “Fresh frozen plasma (FFP)”, 3 reported “ others”. Further categorization of these results by economic groups is shown in Table II.

Regarding opinions on sufficiency of products, 21 of 51 countries indicated that “supplies of Clotting factor concentrates and Recombinant products [are] sufficient to meet the needs of patients with inherited bleeding disorders without the use of Cryoprecipitates”. By economic

grouping, 72% (18/25) HICs gave positive responses while 12% (3/26) LMICs reported positive responses.

Regarding opinions on continued need for cryoprecipitates, 29 of 51 reported that "Cryoprecipitates [are] still needed in your country to treat patients with bleeding disorders". By economic grouping: 44% (11/25) HICs expressed the opinion that Cryoprecipitates are still needed while 72% (18/26) LMICs stated that cryoprecipitates are still needed.

**Conclusion**

Although the responses to the survey were limited statistically, representing only 30% (25/83) of HICs and 19% (26/134) of LMICs categorized by WBI, the patterns seen in the country reports provide insight on global availability and use of cryoprecipitates and sufficiency of access to industrially manufactured products for inherited bleeding disorders (IBDs). It is evident that cryoprecipitate that is not pathogen-reduced remains commonly in use in HICs as well as LMICs, though typically prepared from blood donations that were tested for HIV, HBV and HCV by NAT. The patterns of clinical use appear to differ by WBI group with a higher percentage of LMICs compared with HICs reporting use to treat IBDs and a much lower percentage of LMICs reporting use of cryoprecipitates to treat maternal and other bleeding conditions. These findings correlated with the greater proportion of use of industrially manufactured products to treat IBDs in HICs versus LMICs, presumably reflecting better access to these known preferred products. Lower use of cryoprecipitates in LMICs compared with HICs to treat maternal and other bleeding conditions suggests insufficiency of cryoprecipitates in LMICs given that their use in massive hemorrhage (including maternal bleeding and trauma) is recognized clinically as a standard of care. Production of Cryo-PR appears limited globally, but was reported by both some LMICs and HICs suggesting a common underlying desire to provide a safer product than native cryoprecipitate despite the added costs and complexity of preparation. A variety of pathogen-reduction technologies are in use, predominantly including methods that can be performed locally in blood establishments.

In conclusion, the survey results indicate that both high-income countries (HICs) and low- and middle-income countries (LMICs) continue to produce native cryoprecipitate, which remains in

use for treating inherited bleeding disorders (hemophilia A, and VWD), maternal bleeding, and other bleeding conditions. Access to clotting factor concentrates and their recombinant analogues remains insufficient, not only in LMICs but also in some HICs.

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**Table I: Uses of "Native" Cryoprecipitate[a] Reported in 2024 by 36 out of 51 Countries**

| **Number of reporting countries** | **Global (36)** | | **HIC (17)** | | **LMIC (19)** | |
|---|---|---|---|---|---|---|
| **Clinical Use** | No. | % | No. | % | No. | % |
| **Inherited bleeding disorders** | 20 | 56% | 7 | 41% | 13 | 68% |
| **Maternal bleeding** | 21 | 58% | 12 | 71% | 9 | 47% |
| **Other bleeding conditions (related to surgery, trauma)** | 30 | 83% | 16 | 94% | 2 | 11% |

[a]"Native" cryoprecipitate means cryoprecipitate (not pathogen-reduced) as listed in the EMLs

**Table II: Use of Products Other than Cryoprecipitate for Treatment of Inherited Bleeding Disorders**

| Number of Reporting Countries | Global (51) | | HIC (25) | | LMIC (26) | |
|---|---|---|---|---|---|---|
| **Source of products** | No. | % | No. | % | No. | % |
| **Commercially imported Clotting factor concentrates (CFC)** | 38 | 75% | 24 | 96% | 14 | 54% |
| **CFC obtained through contract plasma fractionation** | 16 | 31% | 12 | 48% | 4 | 15% |
| **Domestically fractionated CFC** | 6 | 12% | 3 | 12% | 3 | 12% |
| **Donated products CFC** | 15 | 29% | 2 | 8% | 13 | 50% |
| **Recombinant products: [Products analogous to Clotting factor concentrates]** | 31 | 61% | 19 | 76% | 12 | 46% |
| **Recombinant products: [Recombinant bi-specific FVIII mimetic antibodies]** | 22 | 43% | 15 | 60% | 7 | 27% |
| **Fresh frozen plasma (FFP)** | 37 | 73% | 14 | 56% | 23 | 88% |
| **Other products** | 3 | 6% | 3 | 12% | 0 | 0% |