WHO International Standard
1st International Standard for Factor XI, Plasma, Human
NIBSC code: 04/102
Instructions for use
(Version 3.0, Dated 10/02/2014)

1. INTENDED USE
The 1st International Standard for Factor XI, Plasma, Human consists of ampoules, coded 04/102, containing approximately 1 mL aliquots of normal human plasma, freeze-dried. This preparation was established in 2005 as the 1st International Standard for Factor XI, Plasma, Human by the Expert Committee on Biological Standardization (ECBS) of the World Health Organization.

The ECBS report is available from the WHO (www.who.int/biologicals).

Document number: WHO/BS/05.2017

2. CAUTION
This preparation is not for administration to humans or animals in the human food chain.

The preparation contains material of human origin, and either the final product or the source materials, from which it is derived, have been tested and found negative for HBsAg, anti-HIV and HCV RNA. As with all materials of biological origin, this preparation should be regarded as potentially hazardous to health. It should be used and discarded according to your own laboratory’s safety procedures. Such safety procedures should include the wearing of protective gloves and avoiding the generation of aerosols. Care should be exercised in opening ampoules or vials, to avoid cuts.

3. UNTAGE
The standard was assayed in an international collaborative study involving 27 laboratories from 11 countries against locally collected fresh normal plasma pools (no of pools = 42; no of donors = 351) and frozen plasma pools (no of pools = 4; no of donors > 2000). Comparison of results from fresh and respective frozen normal plasma pools showed no significant differences between estimates from fresh and frozen plasma pools. The following potency was therefore assigned based on the geometric mean of all the valid assay results against both fresh and frozen pools:

Functional Activity: 0.86 IU/ampoule

Uncertainty: the assigned unitage does not carry an uncertainty associated with its calibration. The uncertainty may therefore be considered to be the variance of the ampoule content and was determined to be +/- 0.25%.

4. CONTENTS
Country of origin of biological material: United Kingdom.
The WHO 1st IS for Factor XI, Plasma, Human was prepared from a plasma pool derived from 19 normal healthy donors (United Kingdom Blood Service, North London Blood Transfusion Centre). Blood was collected using conventional venepuncture into CPD-adenine anticoagulant at a nominal ratio of 63 ml anticoagulant to 450 ml whole blood. The donations underwent leuko-filtration followed by two centrifugation steps after which the plasma was frozen rapidly and stored at -70 ºC until the day of ampoule filling. Individual donations were tested and found negative for HBsAg, antibodies to HIV-1 and -2 and antibodies to HCV. The donations were also tested as mini-pools and found negative for the presence of HCV RNA using a PCR technique.

On the morning of the fill the plasma units were thawed in a waterbath at 37 ºC and pooled. Glycine and a buffering agent HEPES (N-[2-Hydroxyethyl]piperazine-N’-[2-ethanesulfonic acid) were added to the pooled plasma at a final concentration of 1 % w/v and 40 mmol/L respectively. To avoid activation of FXI, polyethylene vessels were used for storage and transport of the pooled plasma. The pooled plasma was also maintained at room temperature after thawing and throughout filling of the material into siliconised glass ampoules.

Activation status of the WHO IS: The non-activated partial thromboplastin time (NAPTT) is known to be sensitive to activated clotting factor especially factor XIa and so it was used to assess the activation status of the finished product. The long mean clotting time of 298s (n = 6; sd ± 22s) for 04/102 indicates the samples to be relatively unactivated.

5. STORAGE
Unopened ampoules should be stored in the dark at or below -20 ºC. Please note: because of the inherent stability of lyophilized material, NIBSC may ship these materials at ambient temperature.

6. DIRECTIONS FOR OPENING
DIN ampoules have an ‘easy-open’ coloured stress point, where the narrow ampoule stem joins the wider ampoule body. Tap the ampoule gently to collect the material at the bottom (labeled) end. Ensure that the disposable ampoule safety breaker provided is pushed down on the stem of the ampoule and against the shoulder of the ampoule body. Hold the body of the ampoule in one hand and the disposable ampoule breaker covering the ampoule stem between the thumb and first finger of the other hand. Apply a bending force to open the ampoule at the coloured stress point, primarily using the hand holding the plastic collar.

Care should be taken to avoid cuts and project glass fragments that might enter the eyes, for example, by the use of suitable gloves and an eye shield. Take care that no material is lost from the ampoule and no glass falls into the ampoule. Within the ampoule is dry nitrogen gas at slightly less than atmospheric pressure. A new disposable ampoule breaker is provided with each DIN ampoule.

7. USE OF MATERIAL
No attempt should be made to weigh out any portion of the freeze-dried material prior to reconstitution.

Allow ampoules to warm to room temperature. Open ampoule, taking care to ensure that all material is in the lower part, and reconstitute with 1.0 mL of distilled water. After reconstitution please store the material as indicated in section 8 (On Bench Stability).

8. STABILITY
Reference materials are held at NIBSC within assured, temperature-controlled storage facilities. Reference Materials should be stored on receipt as indicated on the label.

NIBSC follows the policy of WHO with respect to its reference material. It is the policy of WHO not to assign expiry dates to international reference materials. They remain valid with the assigned potency and status until withdrawn or amended.

Accelerated degradation study, which involves potency estimation of ampoules stored at elevated temperatures relative to ampoules stored at below -150 ºC, has indicated that the Standard is stable when stored at below -20 ºC or below; a predicted loss of less than 0.01% per year. The study was carried out in one laboratory (NIBSC), using a one-stage assay based on the APTT. The predicted loss for samples stored at +20 ºC is 0.9% per year and this supports the shipment of ampoules at ambient temperature. These studies have shown that when stored at -20 ºC or below the assigned values remain valid until the material is replaced or withdrawn.

Users who have data supporting any deterioration in the characteristics of any reference preparation are encouraged to contact NIBSC.

On Bench Stability: It is recommended that assays are to be performed as soon as possible after reconstitution. The stability of coagulation
factors in plasma standards, after reconstitution, is mainly affected by two components - the surface of the container and the storage temperature. Unlike other WHO IS for blood coagulation factors it is recommended that upon reconstitution, the standard should either be transferred to a plastic tube or retained in the siliconised ampoule at room temperature (15 - 22 °C) in order to prevent cold activation of FXI. Results from NIBSC indicated no significant change in FXI clotting activity when the reconstituted material was stored at room temperature in the siliconised ampoules for over 2 hours. However, users will be advised that local validation will be necessary if the reconstituted standard is stored under different conditions.

The use of frozen aliquots of the Proposed WHO International Standard cannot be recommended since the effect of freezing and thawing, under local conditions, on the FXI activity is unpredictable.

9. REFERENCES

10. ACKNOWLEDGEMENTS
The participants of the study

The support of the Plasma Coagulation Inhibitors subcommittee of the SSC of the ISTH

11. FURTHER INFORMATION
Further information can be obtained as follows;
This material: enquiries@nibsc.org
WHO Biological Standards: http://www.who.int/biologicals/en/
Derivation of International Units: http://www.nibsc.org/standardisation/international_standards.aspx
NIBSC Terms & Conditions: http://www.nibsc.org/terms_and_conditions.aspx

12. CUSTOMER FEEDBACK
Customers are encouraged to provide feedback on the suitability or use of the material provided or other aspects of our service. Please send any comments to enquiries@nibsc.org

13. CITATION
In all publications, including data sheets, in which this material is referenced, it is important that the preparation's title, its status, the NIBSC code number, and the name and address of NIBSC are cited and cited correctly.

14. MATERIAL SAFETY SHEET
Classification in accordance with Directive 2000/54/EC, Regulation (EC) No 1272/2008: Not applicable or not classified

<table>
<thead>
<tr>
<th>Physical and Chemical properties</th>
<th>Corrosive: No</th>
<th>Oxidising: No</th>
<th>Irritant: Yes</th>
<th>Handling: See caution, Section 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance: Freeze dried powder</td>
<td>Yes</td>
<td>No</td>
<td>Hygroscopic: No</td>
<td>Flammable: No</td>
</tr>
<tr>
<td>Stable</td>
<td></td>
<td></td>
<td></td>
<td>Other (specify): Contains material of human origin</td>
</tr>
</tbody>
</table>

15. LIABILITY AND LOSS
In the event that this document is translated into another language, the English language version shall prevail in the event of any inconsistencies between the documents.

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16. INFORMATION FOR CUSTOMS USE ONLY
Country of origin for customs purposes*: United Kingdom
Net weight: ~100mg
Toxicity Statement: Toxicity not assessed
Veterinary certificate or other statement if applicable: Attached: No

17. CERTIFICATE OF ANALYSIS
NIBSC does not provide a Certificate of Analysis for WHO Biological Reference Materials because they are internationally recognised primary reference materials fully described in the instructions for use. The reference materials are established according to the WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards http://www.who.int/bloodproducts/publications/TRS932Annex2_Inter_biol_refstandardsrev2004.pdf (revised 2004). They are officially endorsed by the WHO Expert Committee on Biological Standardization (ECBS) based on the report of the international collaborative study which established their suitability for the intended use.