WHO International Standard
7th International Standard Factor VIII Concentrate
NIBSC code: 99/678
Instructions for use
(Version 5.0, Dated 01/04/2008)

1. INTENDED USE
The 7th International Standard for Blood Coagulation Factor VIII:C, Concentrate, consists of ampoules, coded 99/678, containing aliquots of a freeze-dried concentrate of plasma derived Factor VIII, formulated with human albumin. This preparation was established by the Expert Committee on Biological Standardization of the World Health Organization in November 2003. This standard is primarily intended to be used to calibrate secondary and/or in-house working Factor VIII concentrate standards.

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. The concentrate standard was prepared from pooled therapeutic concentrates which were manufactured from pools of human plasma in which every donation was tested and found negative for HBsAg, anti-HIV 1 & 2, and anti-hepatitis C antibodies; in addition, the plasma pools were tested and found negative for hepatitis C RNA (NAT testing). The therapeutic concentrates had also undergone a virus inactivation procedure. The concentrate standard contains human albumin, clinical grade, which was also prepared from pools of human plasma in which every donation was tested and found negative for HBsAg, anti-HIV 1 and 2, and anti-hepatitis C antibodies.

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. UNITAGE
The 7th International Standard was calibrated in an international collaborative study involving 38 laboratories in 21 countries. A potency of 2186pmol/L was determined.

11.0 INTERNATIONAL UNITS per ampoule

has been assigned. This figure is based on comparison with the 5th & 6th International Standard for Factor VIII Concentrate, the Mega 1 Factor VIII Concentrate and Ph. Eur. BRP Batch 2 Factor VIII Concentrate, using one-stage and chromogenic assays.

4. CONTENTS
Country of origin of biological material: United Kingdom
The 7th International Standard for Blood Coagulation Factor VIII:C, Concentrate, consists of a freeze-dried plasma derived FVIII concentrate formulated with clinical grade human albumin.

In 2000, the bulk freeze-dried material was reconstituted in sterile distilled H2O and diluted to approximately 5.2 litres in Tris buffer, pH 7.4, containing: 50 mM Tris, 150 mM NaCl, 1 mM CaCl2, 1% (w/v) trehalose and 1% (w/v) human albumin (clinical grade) and other proprietary excipients. It was then distributed at 4°C into ampoules, coded 99/678 and the contents of the ampoules were freeze-dried under the conditions normally used for international biological standards1. The mean content of 74 ampoules before freeze-drying was 1.0111g (range 1.0039-1.0124g, cv 0.12%) and the mean moisture content of 3 ampoules after freeze-drying and secondary desiccation was 0.059%.

5. STORAGE
Unopened ampoules should be stored at -20°C. After reconstitution, any unused material must be discarded, not frozen for later use. 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. Various types of ampoule breaker are available commercially. To open the ampoule, tap the ampoule gently to collect material at the bottom (labelled) end and follow manufactures instructions provided with the ampoule breaker.

7. USE OF MATERIAL
The total contents of the ampoule should be reconstituted at room temperature with 1 ml distilled water, dissolved by gentle swirling to avoid froth and transferred immediately to a suitable plastic tube. No attempt should be made to weigh out any portion of the freeze-dried material. The reconstituted Standard is stable for up to 2 hours at room temperature.

N.B. When using this standard to calibrate other concentrates, both standard and test concentrates MUST be pre-diluted in FVIII deficient plasma, either haemophilic plasma, or artificially depleted plasma containing normal levels of VWF, before making the assay dilutions. Assay dilution buffers should contain 1% albumin, preferably clinical grade.

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.

Accelerated degradation studies have shown that this standard is extremely stable both when stored at -20°C and at mailing temperatures. Predicted loss of FVIII activity when stored at -20°C was below 0.001% per year.

NIBSC follows the policy of WHO with respect to its reference materials.

9. REFERENCES

10. ACKNOWLEDGEMENTS
The contributions of all the participants in the study are gratefully acknowledged. We are grateful to donors for the supply of concentrates for the study. In addition we express our sincere thanks to our colleagues at the FDA/CBER and EDQM for all their help with the study.

11. FURTHER INFORMATION
Further information can be obtained as follows:
This material: enquiries@nibsc.org
WHO Biological Standards:
http://www.who.int/biologicals/en/
JCTLM Higher order reference materials:
http://www.bipm.org/en/committees/jc/jctlm/
Derivation of International Units:
http://www.nibsc.org/standardisation/international_standards.aspx
Ordering standards from NIBSC:
http://www.nibsc.org/products/ordering.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></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance: Freeze dried powder</td>
<td>Corrosive: No</td>
</tr>
<tr>
<td>Stable: Yes</td>
<td>Oxidising: No</td>
</tr>
<tr>
<td>Hygroscopic: Yes</td>
<td>Irritant: No</td>
</tr>
<tr>
<td>Flammable: Yes</td>
<td>Handling: See Caution (Section 2)</td>
</tr>
<tr>
<td>Other (specify): Contains material of human origin</td>
<td></td>
</tr>
</tbody>
</table>

Toxicological properties
Effects of inhalation: Not established, avoid inhalation
Effects of ingestion: Not established, avoid ingestion
Effects of skin absorption: Not established, avoid contact with skin

Suggested First Aid
Inhalation: Seek medical advice
Ingestion: Seek medical advice
Contact with eyes: Wash with copious amounts of water. Seek medical advice
Contact with skin: Wash thoroughly with water.

Action on Spillage and Method of Disposal
Spillage of ampoule contents should be taken up with absorbent material wetted with an appropriate disinfectant. Rinse area with an appropriate disinfectant followed by water. Absorbent materials used to treat spillage should be treated as biological waste.

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.

Unless expressly stated otherwise by NIBSC, NIBSC’s Standard Terms and Conditions for the Supply of Materials (available at http://www.nibsc.org/About_Us/Terms_and_Conditions.aspx or upon request by the Recipient) (“Conditions”) apply to the exclusion of all other terms and are hereby incorporated into this document by reference. The Recipient’s attention is drawn in particular to the provisions of clause 11 of the Conditions.

16. INFORMATION FOR CUSTOMS USE ONLY

| Country of origin for customs purposes*: United Kingdom |
* Defined as the country where the goods have been produced and/or sufficiently processed to be classed as originating from the country of supply, for example a change of state such as freeze-drying. |
| Net weight: 0.04g |
| Toxicity Statement: Non-toxic |
| 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_efstandardsrev2004.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.