WHO International Standard

1st INTERNATIONAL STANDARD VON WILLEBRAND FACTOR, CONCENTRATE
NIBSC code: 00/514

Instructions for use
(Version 3.0, Dated 17/03/2008)

1. INTENDED USE
The 1st International Standard (IS) for von Willebrand Factor, Concentrate was established by the Expert Committee on Biological Standardisation of the World Health Organisation in November 2001. The preparation consists of ampoules (coded 00/514) containing 1 ml aliquots of von Willebrand Factor concentrate, freeze-dried. The 1st International Standard is intended to be used for the estimation of von Willebrand Factor in therapeutic concentrates via the calibration of working standards, such as manufacturers "in house" standards. The 1st International Standard is calibrated for the following parameters:

von Willebrand Factor: Ristocetin Cofactor- VWF:RCo
von Willebrand Factor: Antigen - VWF:Ag

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 assigned values of the standard were determined by comparison against the 4th IS Factor VIII/von Willebrand Factor, Plasma (97/586) in an international collaborative study involving 26 laboratories in 9 countries. The overall mean values assigned to each ampoule of the 1st IS von Willebrand Factor Concentrate are as follows:

VWF:RCo 9.4 International Units per ampoule
VWF:Ag 11.0 International Units per ampoule

4. CONTENTS
Country of origin of biological material: United Kingdom.

The International Standard was prepared at the National Institute for Biological Standards and Control from VWF Concentrate product used for therapy. The reconstituted product was kept at 4 °C throughout distribution into 5,000 ampoules and then freeze-dried under conditions used for international biological standards (1). The mean liquid filling weight of 68 checkweight ampoules was 1.0050 g (range 1.0034 - 1.0076 g) with a coefficient of variation of 0.08 %. Estimates of residual moisture after freeze-drying and secondary desiccation gave a mean value of 1.32 %.

5. STORAGE
Unopened ampoules should be stored in the dark at -20 °C or below.

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 projectile 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. Dissolve the contents of each ampoule of the standard by adding 1.0 ml of distilled water, using gentle shaking, then transfer the contents to a plastic tube. It is recommended that assays should be carried out as soon as possible once reconstitution is complete. VWF:RCo measurements should only be made using freshly reconstituted standard. The use of frozen aliquots for subsequent measurements of VWF:Ag should be validated by the user.

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 materials.

9. REFERENCES

10. ACKNOWLEDGEMENTS
Are made to Dr Andrew C Chang (CBER/FDA, USA) and Dr Claudine Mazurier (LFB, Lille, France on behalf of the SSC/ISTH von Willebrand Factor sub-committee) for help with the organisation of the calibration exercise; to the manufacturers of the two candidates included in the international calibration exercise (Aventis Behring, Marburg, Germany; Laboratoire Français du Fractionnement et des Biotechnologies, Lille, France) and to all of the participants in the collaborative 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>
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<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: No</td>
<td>Handling: See caution, Section 2</td>
</tr>
<tr>
<td>Other (specify): n</td>
<td></td>
</tr>
</tbody>
</table>

Toxicological properties

| Effects of inhalation: | Not established, avoid inhalation |
| Effects of ingestion: | Avoid ingestion |
| Effects of skin absorption: | 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 |
| 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.