



WHO International Standard
8th INTERNATIONAL STANDARD FACTOR VIII CONCENTRATE
NIBSC code: 07/350
Instructions for use
(Version 1.0, Dated 14/01/2010)

1. INTENDED USE

The WHO 8th International Standard for Blood Coagulation Factor VIII:C, Concentrate, consists of glass ampoules, coded 07/350, 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 October 2009 and details of the preparation and value assignment are available in document WHO/BS/09.2117. 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 as well as the pools were 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 WHO 8th International Standard was calibrated in an international collaborative study involving 38 laboratories in 17 countries. A potency of

9.4 INTERNATIONAL UNITS (IU) per ampoule

has been assigned. This figure is based on comparison with the 7th International Standard for Factor VIII Concentrate and the Ph. Eur. BRP Batch 3/Mega 2 US Factor VIII Concentrate standard, using one-stage and chromogenic assays.

4. CONTENTS

Country of origin of biological material: United Kingdom
The WHO 8th International Standard for Blood Coagulation Factor VIII:C, Concentrate, consists of a freeze-dried plasma derived FVIII concentrate formulated with clinical grade human albumin and was prepared at the National Institute for Biological Standards and Control in March 2008.

The concentrate freeze-dried material was reconstituted in sterile distilled H₂O and diluted to approximately 20 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 glass ampoules, coded 07/350 and the contents of the ampoules were freeze-dried under the conditions normally used for international biological standards¹. The mean content of 624 ampoules before freeze-drying was 1.0054g (range 1.0015-1.0100g) and the coefficient of variation was 0.16%. Estimates of residual moisture after freeze-drying gave a mean value of 0.46% (n=12). Estimates of oxygen in the headspace gave a mean value of 0.44% (n=11).

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. Although studies have shown the reconstituted standard to be stable for up to 3 hours when kept on melting ice, it is recommended that assays of FVIII:C be carried out as soon as possible after reconstitution.

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 0.01% per year.

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

9. REFERENCES

1. Campbell P J. "Procedures used for the production of biological standards and reference preparations." J Biol Standardization, 1974, 2, 259-267.

10. ACKNOWLEDGEMENTS

The contributions of all the participants in the study are gratefully acknowledged. We are grateful to all donors (Baxter Healthcare, Bayer Healthcare, CSL Behring, Grifols and Talecris Plasma Resources) 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

Physical and Chemical properties	
Physical appearance: Freeze dried powder	Corrosive: No
Stable: Yes	Oxidising: No
Hygroscopic: Yes	Irritant: No
Flammable: No	Handling: See Caution (Section 2)
Other (specify):	Contains material of human origin
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.