



WHO International Standard
WHO 3rd International Standard von Willebrand Factor
Concentrate
NIBSC code: 18/248
Instructions for use
(Version 1.0, Dated 13/06/2022)

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1. INTENDED USE

The WHO 3rd International Standard (IS) for von Willebrand Factor, Concentrate was established by the Expert Committee on Biological Standardisation of the World Health Organisation in October 2021. The preparation consists of glass sealed ampoules (coded 18/248) containing 1 ml aliquots of von Willebrand factor concentrate, freeze-dried. The WHO 3rd IS 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 WHO 3rd IS has assigned values for the following analytes:

von Willebrand factor: antigen - VWF:Ag
von Willebrand factor: ristocetin cofactor - VWF:RCo
von Willebrand factor: collagen binding - VWF:CB
VWF binding to recGPIb - ristocetin-dependent - VWF:GPIbR
VWF binding to recGPIb - gain-of-function mutant - VWF:GPIbM

Further details on the preparation and the collaborative study can be found in the WHO document WHO/BS/2021.2408.

2. CAUTION

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. This preparation is not for administration to humans or animals

3. UNITAGE

Value assignment of the WHO 3rd IS was based on an international collaborative study involving 48 laboratories in 22 different countries

The following assigned values of the WHO 3rd IS were determined by assays relative to the WHO 2nd IS VWF Concentrate (09/182):

VWF:Ag 12.0 International Units per ampoule
VWF:RCo 8.7 International Units per ampoule
VWF:CB 9.8 International Units per ampoule

The following assigned values of the WHO 3rd IS were determined by assays relative to the WHO 6th IS FVIII/VWF Plasma and International Reference Reagent for GPIbR and GPIbM methods (07/316):

VWF:GPIbR 8.6 International Units per ampoule
VWF:GPIbM 7.3 International Units per ampoule

Value assignment for VWF:GPIbR and VWF:GPIbM to the WHO 6th IS FVIII/VWF was achieved by adopting the VWF:RCo value on the 6th IS, which also now serves as the International Reference Reagent for the VWF:GPIbM and VWF:GPIbR methods [1]. VWF:GPIbM and VWF:GPIbR are seen as alternatives to VWF:RCo

in the estimation of GPIbA binding/platelet binding. Internationally agreed nomenclature for the new methods distinguishes them from the conventional ristocetin cofactor method (VWF:RCo), and identifies when binding to recombinant GPIbA is ristocetin-dependent (VWF:GPIbR) or relies on a "gain-of-function" mutant of GPIbA for ristocetin-independent binding (VWF:GPIbM) [2]. The values assigned to the WHO 3rd IS VWF Concentrate for VWF:RCo, VWF:GPIbR and VWF:GPIbM are only valid for the specified assay method. Measurement of therapeutic concentrate products should be performed relative to the relevant assigned value on the 3rd IS.

4. CONTENTS

Country of origin of biological material: United Kingdom.
The WHO 3rd IS was prepared at the National Institute for Biological Standards and Control from VWF Concentrate product used for therapy. The formulated product was kept at 4 °C throughout distribution into 20,000 glass ampoules and then freeze-dried under conditions used for international biological standards [3]. The mean liquid filling weight based on 217 check-weight ampoules was 1.0067 g with a coefficient of variation of 0.12%. Estimates of residual moisture after freeze-drying gave a mean value of 0.10%.

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. 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

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 WHO 3rd IS by adding 1.0 ml of distilled or deionised water, using gentle shaking, then transfer the contents to a plastic tube. Although studies have shown the reconstituted standard to be stable for up to 4 hours when stored on melting ice it is recommended that assays should be carried out as soon as possible once reconstitution is complete. The use of frozen aliquots of the WHO 3rd IS is not recommended.

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. It is the policy of WHO not to assign an expiry date to their international reference materials and they remain valid with the assigned potency until withdrawn or amended. Predictions on long term stability are made by monitoring ampoules stored under accelerated degradation conditions over time.

9. REFERENCES



- Hubbard AR, Haberichter SL, SSC Subcommittee on VWF, ISTH. Establishment of an International Reference Reagent for standardization of von Willebrand factor binding to recombinant glycoprotein Ib (VWF:GPIbM and VWF:GPIbR): Official Communication of the SSC. J Thromb Haemost. 2019;17(6):1003-5.
- Bodo I, Eikenboom J, Montgomery R, Patzke J, Schneppenheim R, Di Paola J, Factor SW. Platelet-dependent von Willebrand factor activity. Nomenclature and methodology: communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis. 2015;13(7):1345-50.
- Campbell PJ. Procedures used for the production of biological standards and reference preparations. Journal of Biological Standardization (1974) 2, 259-267.

10. ACKNOWLEDGEMENTS

The manufacturers for supplying candidate materials (Laboratoires Français de Fractionnement et des Biotechnologies (LFB), Lille, France; Octapharma Pharmazeutika Produktionsges.m.b.H., Vienna, Austria; and Baxter AG (Takeda), Vienna, Austria); to the participants in the collaborative study and to the SSC/ISTH sub-committee on von Willebrand factor.

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: 0.015 g
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_1nter_biolefstandardsrev2004.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.