Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
4th International Standard for Blood Coagulation Factors II, VII, IX, X, Plasma
NIBSC code: 09/172
Instructions for use
(Version 3.0, Dated 24/02/2016)

1. INTENDED USE

The 4th International Standard for Blood Coagulation Factors II, VII, IX, X, Plasma, consists of ampoules, coded 09/172, containing approximately 1 ml aliquots of normal human plasma, freeze dried. This preparation was established in 2010 as the 4th International Standard for Blood Coagulation Factors II, VII, IX, X, Plasma by the Expert Committee on Biological Standardization of the World Health Organization, and is intended for use as a primary reference standard for calibration of factors II, VII, IX and X functional activity in plasma samples. Details of collaborative study is described in WHO/BS/10.2145 and is available from WHO (http://www.who.int/biologicals/expert_committee/BS_2145_Gray_II_VII_IX_X_Plasma_ECBS_EG.pdf)

This preparation was further established in 2015 for Blood Coagulation Factor IX antigen in plasma by the Expert Committee on Biological Standardation of the World Health Organisation, and is intended for use as the primary reference standard for the calibration of factor IX antigen in plasma samples only. Local validation of this reference standard is required for Factor IX antigen measurement in therapeutic concentrates. Details of collaborative study is described in WHO/BS/2015.2261 and is available from the WHO (http://www.who.int/biologicals/expert_committee/BS2261_Establishment_Factor_IX_5th_WHO_IS.pdf).

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. UNITAGE

The Standard was calibrated by 29 laboratories in 14 countries against the 3rd IS for Blood Coagulation Factors II, VII, IX, X,, Plasma, 99/826, using functional assays. It has been assigned with the following potencies:

Factor II:	0.89 IU/ampoule
Factor VII:	0.99 IU/ampoule
Factor IX:	0.86 IU/ampoule
Factor X:	0.89 IU/ampoule

The standard was calibrated by 14 laboratories against normal plasma pools for factor IX antigen. It has been assigned the following value:

Factor IX antigen: 0.90 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 +/- 0.20%.

4. CONTENTS

Country of origin of biological material: United Kingdom.
Plasma from 85 donors, collected in CPD-adenine from the National Blood and Transfusion Service was buffered with HEPES to 0.05 M, pooled and distributed in 1ml quantities into ampoules, then filled and freeze dried under conditions used for International Biological Standards(1). Each individual donation was tested and found negative for anti-HIV 1/2, HBsAg and anti-hepatitis C.

5. STORAGE

Unopened ampoules should be stored in the dark at or below –20°C.
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
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 distilled or deionised water.
For functional activity of FII, VII, IX and X, studies have shown the reconstituted standard to be stable for upto 2 hours when kept on melting ice, it is recommended that assays using this standard are carried out as soon as possible after reconstitution.
For FIX antigen, the standard was stable upto 4 hours after reconstitution and kept on melting ice.

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 if the WHO not to assign expiry dates to its reference materials.

Preliminary accelerated degradation studies, involving potency estimation of ampoules stored at elevated temperatures against ampoules stored at below -150°C, have shown minimal loss of activity. Estimation of % predicted loss for amopules stored at -20°C is less than 0.1% for all measured factors. These studies shown that when stored at -20°C 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.

9. REFERENCES

1.Campbell P J. J Biol Standardisation 1974, 2, 259 - 267.

10. ACKNOWLEDGEMENTS

All participants in the International collaborative study and the support of the FVIII/FIX Sub-committee of the Interntional Society on Thrombosis and Haemostasis/ Scietnific and Standardisation Committee.

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WHO International Laboratory for Biological Standards,
UK Official Medicines Control Laboratory

World Health Organization

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:	No	Oxidising:	No
Hygroscopic:	Yes	Irritant:	Unknown
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: 0.103 g
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_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.

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