Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO Reference Reagent
Activated Blood Coagulation Factor X (FXa), Human
NIBSC code: 15/102
Instructions for use
(Version 1.0, Dated 23/11/2017)

1. INTENDED USE

The WHO Reference Reagent for Activated Blood Coagulation Factor X (FXa) (15/102) was established by the Expert Committee on Biological Standardisation of the World Health Organisation in October 2017, and a report of the collaborative study is available from WHO, reference number WHO/BS/2017.2324

The intended use of this preparation is to standardise FXa potency measurements in therapeutic APCC (activated prothrombin complex concentrate) products. The reference reagent may also be investigated to standardise FXa measurements for other theraputic products, or to standardise the biological activity of FXa inhibitors. The outcome of any investigation may inform the nature of a future collaborative study to establish 15/102 as a WHO International Standard for FXa.

A potency of 6.7 units/ampoule was assigned in a collaborative study, based on chromogenic assays relative to the Non-WHO Reference Material for Blood Coagulation Factor Xa (75/595), a bovine preparation of FXa. Using a chromogenic method ensured continuity of the Factor Xa unit of activity between 75/595 and 15/102; clotting assay methods will however require additional calibration by the end user due to the discrepancy between bovine and human factor Xa.

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 assigned potency of this preparation is 6.7 units/ampoule

4. CONTENTS

Country of origin of biological material: United Kingdom.
The bulk material used to prepare the reference reagent for FXa was donated by one manufacturer as a frozen concentrate of human plasma-derived factor X, activated using Russell's viper venom-factor X activator (RVV-X) and purified by affinity chromatography using Benzamidine-Sepharose. The material was thawed and diluted to a final concentration of 7 units/ml (based on local potency estimates) in 20 mM Hepes buffer (pH 7.4), 10 mg/ml human serum albumin, 5 mg/ml trehalose and 150 mM NaCl. A total of 11739 5 ml DIN ampoules were filled with 1 ml aliquots of the diluted material, with a mean filling weight of 1.009 g (cv = 0.13%). Freeze-drying was done following WHO procedures to product ampoules with a mean dry weight of0.0299 g (cv = 3.37%) and a residual moisture of 0.205% (cv = 43.85%).

5. STORAGE

Upon receipt 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 the ampoule to reach ambient temperature before opening and reconstitute with 1.0 ml distilled or deionised water.

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 their assigned potency until withdrawn or amended.

Predictions on long term stability are made by monitoring ampoules stored under accelerated degradation conditions over time.

Based on the results of a stability test it is advised that ampoules are stored on wet ice following reconstitution, and assays should be completed as soon as possible and within 4 hours.

9. REFERENCES

A report of the collaborative study to calibrate the standard is availbale from WHO, reference number WHO/BS/2017.2324

10. ACKNOWLEDGEMENTS

We are grateful to Shire (Austria) for the donation of the starting material; to the collaborative study participants; and to the Control of Anticoagulation Subcommittee of the Standardization and Scientific Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH).

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.

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

World Health Organization

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: Solid		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: 29.9 mg
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.