Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
2nd INTERNATIONAL STANDARD FOR FIBRINOGEN CONCENTRATE
NIBSC code: 09/242
Instructions for use
(Version 1.0, Dated 03/01/2013)

1. INTENDED USE

The 2nd International Standard for Fibrinogen Concentrate, consists of ampoules, coded 09/242, containing aliquots of a freeze-dried concentrate of fibrinogen prepared from human plasma. This preparation was established by the Expert Committee on Biological Standardization of the World Health Organization in October 2012, with labelled contents for Clottable Protein and Total Protein. Details of the preparation and value assignment are available in the document WHO/BS/2012.2208, (available from WHO). This standard is primarily intended to be used to calibrate secondary and/or in-house working fibrinogen 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. 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

Value assignment to this standard was carried out in an international collaborative study involving 27 laboratories in 12 countries. Value assignment for Clottable Protein was based on subsequent protein determination methods following clot removal (CLOTr) and for Total Protein based on standard protein determination methods.

The assigned potencies are:

Clottable Protein - 10.9 mg/ampoule
Total Protein - 15.0 mg/ampoule

These figures are based on assays relative to the 1st International Standard for Fibrinogen Concentrate (98/614). Please note that the assigned value for Clottable Protein did not include estimates from Clauss assays. Use of Clauss assays for estimation of Clottable Protein in fibrinogen concentrates should be validated locally.

4. CONTENTS

Country of origin of biological material: United Kingdom.
The 2nd International Standard for Fibrinogen Concentrate (coded 09/242), contains freeze-dried (1 mL) aliquots of fibrinogen concentrate.

The raw material was a plasma-derived fibrinogen concentrate, prepared using precipitation and chromatography methods. Manufacturing of this product also included 2 viral inactivation steps, solvent detergent treatment and heat treatment at 80°C for 72 hours. After reconstitution, the concentrate material was pooled and formulated in the following buffer: 40mM Tri-Sodium Citrate.$2H_2O$, 20mM Tris-HCl, 3% sucrose (w/v), 4mM L-arginine-HCl (pH 7.3). The formulated material was filled and freeze-dried in sealed glass ampoules at NIBSC, under conditions required for International Standards (Campbell, 1974). One ml of this material was dispensed into each of approximately 10,000 ampoules. The mean filling weight was 1.0093 g (range 1.0015 g to 1.0135 g) and the coefficient of variation (CV) was 0.27% based on 468 check-weight samples. Mean residual moisture after freeze-drying was 0.39% (CV 19.3%, n=12) and mean oxygen headspace was 0.11% (CV 55.2%, n=12).

5. STORAGE

Unopened ampoules should be stored at -20ºC. 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.
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

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. The reconstituted Standard is stable for up to 3 hours at room temperature.

8. STABILITY

Reference materials are held at NIBSC within assured, temperature-controlled storage facilities and they should be stored on receipt as indicated on the label. It is the policy of WHO not to assign an expiry date to their international reference materials. Accelerated degradation studies have indicated that this material is suitably stable, when stored at -20ºC or below, for the assigned values to remain valid until the material is withdrawn or replaced. These studies have also shown that the material is suitably stable for shipment at ambient temperature without any effect on the assigned values. Users who have data supporting any deterioration in the characteristics of any reference preparation are encouraged to contact NIBSC.

9. REFERENCES

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 our colleagues in the Standards Division for ampouling and processing the candidate and trial preparations and for the dispatch of collaborative study samples to participants. We are grateful to Baxter Healthcare (Austria) and BPL (UK) for their kind donation of materials for the study. We further like to thank the ISTH/SSC Factor XIII and Fibrinogen Subcommittee for their support.

National Institute for Biological Standards and Control,
Potters Bar, Hertfordshire, EN6 3QG. T +44 (0)1707 641000, nibsc.org
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:	Yes	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: 0.08g
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_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.

National Institute for Biological Standards and Control,
Potters Bar, Hertfordshire, EN6 3QG. T +44 (0)1707 641000, nibsc.org
WHO International Laboratory for Biological Standards,
UK Official Medicines Control Laboratory

World Health Organization