Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
The 1st International Standard for Protein C, Concentrate, Human
NIBSC code: 04/252
Instructions for use
(Version 2.0, Dated 12/07/2013)

1. INTENDED USE

The 1st International Standard for Protein C, Concentrate, Human, consists of ampoules, coded 04/252, containing aliquots of a freeze-dried concentrate prepared from human plasma. This preparation was established as the 1st International Standard for Protein C, Concentrate, Human, by the Expert Committee on Biological Standardisation of the World Health Organisation in 2007. The ECBS report is available from the WHO (www.who.int/biologicals); document number: WHO/BS/07.2067. This standard is intended for use in the estimation of functional chromogenic activity and antigenic content of protein C concentrates.

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 value assigned in an international collaborative study involving 20 laboratories from 10 countries against the 2nd International Standard for Protein C, Plasma, Human, 02/342. The following potency was assigned based on the geometric mean of all the valid assay results:

Functional (chromogenic assay only) : 15.0 IU/ampoule
Antigenic: 14.5 IU/ampoule

NOTE: This standard has not been assigned with a functional activity by clotting assays and therefore should not be used for calibration of protein C activity by clot based methods.

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 +/- 0.32 %.

4. CONTENTS

Country of origin of biological material: Germany.

One aliquot (50,000 U, ~100 ml) of plasma derived human protein C concentrate was thawed at 37°C and was further diluted with approximately 3.5 litres of 0.05M Tris, 0.15M NaCl, pH 7.4 containing 2 mg/ml trehalose and 5 mg/ml human albumin. The solution was distributed at 4°C into 3500 ampoules, coded 04/252. The mean weight of liquid content of 44 check weight ampoules was 1.0081g, with limits of 1.0037 - 1.0273g (coefficient of variation 0.32%). The contents of the ampoules were then freeze-dried under the conditions normally used for international biological standards (Campbell PJ, 1974).

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 water. Stand for 10 minutes at room temperature to allow complete disssolution of the material before use. The reconstituted standard should be transferred to a plastic tube and stored on melting ice. The reconstituted Standard should be used as soon as possible, preferably within 4 hours of reconstitution.

8. STABILITY

Reference materials are held at NIBSC within assured, temperature-controlled storage facilities and should be stored on receipt as indicated on the label. Once reconstituted, diluted or aliquoted, users should determine the stability of the material according to their own method of preparation, storage and use.

NIBSC follows the policy of the WHO with respect to its reference materials. It is the policy of WHO not to assign an expiry date to their international reference materials. They remain valid with the assigned potency and status until withdrawn or amended.

Stability of this standard has been assessed in an accelerated degradation study which involves the potency estimation of ampoules stored at elevated temperatures relative to ampoules stored at -150ºC. The study was carried out in one laboratory (NIBSC), using a chromogenic assay with Protac® activation for functional activity and ELISA assay for antigen activity. Potency assessment after 7 years of storage at elevated temperatures showed that at -20°C there was no loss of activity. The predicted loss at +20°C is less than 0.6% for all measured parameters which supports shipping of the Standard at ambient temperatures. The accelerated degradation study and real time monitoring will continue for the lifetime of the standard.

9. REFERENCES

Campbell PJ. Procedures used for the production of biological standards and reference preparations. J Biol Standardisation. 1974, 2, 259-267.

10. ACKNOWLEDGEMENTS

We would like to acknowledge the donation of the protein C concentrate by Baxter AG (Vienna, Austria), the participants of the study, the support of the Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.

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:

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

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: white freeze-dred 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 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: 0.03g per ampoule
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.