Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
2nd International Standard For Protein C, Plasma, Human
NIBSC code: 02/342
Instructions for use
(Version 5.0, Dated 05/08/2016)

1. INTENDED USE

The 2nd International Standard for Protein C, Plasma, Human, consists of ampoules, coded 02/342, containing approximately 1 mL aliquots of normal human plasma, freeze-dried. This preparation was established in October 2006 as the 2nd International Standard for Protein C, Plasma, Human by the Expert Committee on Biological Standardization (ECBS) of the World Health Organization.

The ECBS report is available from the WHO (www.who.int/biologicals). Document number: WHO/BS/2045.

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 assayed in an international collaborative study involving 20 laboratories from 10 countries against the 1st International Standard for Protein C, Plasma, Human, 86/622. The following potency was assigned based on the geometric mean of all the valid assay results:

Function: 0.85 IU/ampoule; Antigen: 0.84 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 +/- 0.06 %.

4. CONTENTS

Country of origin of biological material: United Kingdom.
The WHO 2nd IS was prepared from a plasma pool derived from 26 normal healthy donors (United Kingdom Blood Service, North London Blood Transfusion Centre). Blood was collected using conventional venepuncture into CPD-adenine anticoagulant at a nominal ratio of 63 ml anticoagulant to 450 ml whole blood. The donations underwent leuko-filtration followed by two centrifugation steps after which the plasma was frozen rapidly and stored at -70^{o}C until the day of ampoule filling. Individual donations were tested and found negative for HBsAg, antibodies to HIV-1 and -2 and antibodies to HCV. The donations were also tested as mini-pools and found negative for the presence of HCV RNA using a PCR technique.

On the morning of the fill the plasma units were thawed in a waterbath at 37^{o}C and pooled. Glycine and a buffering agent HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid) and were added to the pooled plasma at a final concentration of 1 % w:v and 40 mmol/L respectively.

The pooled plasma was kept at 4 ^{o}C throughout distribution into approximately 5,000 ampoules, then freeze-dried and secondary desiccated according to the requirements for International Biological Standards (1). The coefficient of variation for the liquid fill was 0.06 %. The final freeze-dried material has a mean dry weight of 0.08 g and mean residual moisture of 0.09 %.

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
To reconstitute, allow ampoules to warm to room temperature. Open ampoule following direction given in section 6 of this Instruction for Use, 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. Transfer the reconstituted Standard to a plastic tube and keep on melting ice. Under these conditions the Standard has been found to be sufficiently stable to be used over a four hour period. Storage of the reconstituted Standard under different conditions must be validated locally by users.

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 expiry dates to international reference materials.

Accelerated degradation studies, which involves potency estimation of ampoules stored at elevated temperatures relative to ampoules stored at below -150°C, have indicated that the standard is very stable, when stored at -20°C or below. Predicted loss over one year whilst stored at -20°C is less than 0.01% for all measured parameters. These studies have shown that the assigned values will remain valid until the material is withdrawn or replaced.

Users who have data supporting any deterioration in the characteristics of any reference preparation are encouraged to contact NIBSC.

9. REFERENCES

Campbell PJ (1974) J Biol Standardization, 2, 249-267

10. ACKNOWLEDGEMENTS

The participants of the study

The support of the Plasma Coagulation Inhibitors subcommittee of the SSC of the ISTH

11. FURTHER INFORMATION

Further information can be obtained as follows;

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

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 HUMAN MATERIAL
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: ~80 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.