Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
3rd International Standard for Protein S, Plasma
NIBSC code: 22/202
Instructions for use
(Version 1.0, Dated 14/12/2023)

This material is not for in vitro diagnostic use

1. INTENDED USE

The 3rd International Standard for Protein S, Plasma, Human consists of ampoules (code-labelled 22/202) containing 1 ml freeze-dried pooled human plasma. This standard has been assigned potencies for free and total Protein S antigen and for Protein S function.

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 3rd International Standard was calibrated in an international collaborative study involving 21 laboratories for Free Protein S Antigen, Total Protein S Antigen and Protein S Function by assay against the 2nd International Standard (03/228). The standard was established by the WHO Expert Commeitte on Biological Standardisation in October 2023. Details of the collaborative study are avaliable in the WHO document WHO/BS/2023.2460.
The following values have been assigned to the 3rd Internaional Standard:

Protein S function:	0.71 IU per ampoule
Free Protein S antigen:	0.83 IU per ampoule
Total Proteins S antigen:	0.88 IU per ampoule

Uncertainty: The International Unit of 22/202 is assgned without uncertainty. The uncertainty of the ampoule content of 22/202 may be considered to be the coefficient of variation of the ampoule filling, which was determined to be 0.13%

4. CONTENTS

Country of origin of biological material: United Kingdom.
The 3rd International Standard was prepared in September 2022 by the pooling of plasma collected from 30 normal healthy donors. Blood was collected into CPD-adenine anticoagulant into plastic packs, at a ratio of 450 ml to 63 ml anticoagulant. Each donation underwent leuko-filtration and was double spun before storage at -70°C. The units were thawed in a 37°C water bath and pooled on the day of filling. THe final pool was buffered by the addition of HEPES (N-[2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid]) to a final concentration of 40 mmol/L and Glycine to a final concentration of 1% w/v with the plasma diluted by 10%.

Distribution into Ampoules

The pooled plasma was kept at 4°C throughout distribution into approximately 8,000 ampoules, then freeze-dried acording to the requirements for International Biological Standards (1). The cofficient of variation for the liquid fill was 0.13% and the fill weight was 1.1078 (range 1.1000 to 1.1150 g) to correct for the dilution by HEPES/Glycine buffer. The final content of the freeze-dried material has a mean dry weight of 0.099g and mean residual moisture of 0.42%

5. STORAGE

Unopend ampoules should be stored at -20°C or below.
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 ampoules to warm to room temperature. Reconstitute the total contents with 1.0 ml of distilled water and allow to stand for 10 minutes at room temperture and aid reconstitution by regular gentle shaking/swirling. Transfer the reconstituted contents to a plastic tube and keep on melting ice. Under these conditions the stanadrd has been found to be sufficiently stable for use over a 4 hour period, however it is recommended to use the material immediately once reconstituted.
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 the WHO not to assign expiry dates to International Reference materials. They remain valid with the assigned potency and status until wthdrawn or amended.

Accelerated degradation studies, which involve potency estimation of ampoules stored at elevated temperatures relative to ampoules stored at -70°C or below, have shown that the material is very stable in unopened ampoules stored at -20°C. Predicted loss over one year whlst stored at -20°C is less than 0.1%.

9. REFERENCES

1. Campbell PJ (1974) J Biol Standardisation, 2 249-267

10. ACKNOWLEDGEMENTS

The efforts of the participants in the collaborative study, the members of the Physiologic Anticoagulate and Thrombophilia sub-committee of the International Society of Thrombosis and Haemostasis and the staff of the Centre for Biological Reference Materials (NIBSC) are gratefully acknowledged

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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: Solid		Corrosive:	No
Stable:	Yes	Oxidising:	No
Hygroscopic:	Yes	Irritant:	No
Flammable:	No	Handling: See caution, Section 2	
Other (specify):	Contains material of human origine		
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: 99 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.