Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
6th International Standard for Unfractionated Heparin
NIBSC code: 07/328
Instructions for use
(Version 2.0, Dated 12/07/2013)

1. INTENDED USE

The 6th International Standard for Unfractionated Heparin, consists of ampoules, coded 07/328, containing aliquots of freeze-dried heparin prepared from porcine mucosa. This preparation was established as the 6th International Standard for Unfractionated Heparin, by the Expert Committee on Biological Standardisation of the World Health Organisation in 2009, with labelled potency of 2145 IU/ampoule.

2. CAUTION

This preparation is not for administration to humans or animals in the human food chain.

The material is not of human or bovine origin. 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 calibrated by 33 laboratories in 18 countries against the 5th International Standard for Unfractionated Heparin (97/578). Twelve different methods were employed in the study: anti-Xa chromogenic assay using purified antithrombin, anti-IIa chromogenic assay using purified antithrombin, anti-Xa chromogenic assay using human plasma, anti-IIa chromogenic assay using human plasma, anti-Xa clotting assay, activated partial thromboplastin time (APTT), the European Pharmacopoeial (EP) assay, the United States Pharmacopoeial (USP) sheep plasma assay*, the Chinese Pharmacopoeial (CP) assay, the Japanese Pharmacopoeial (JP) assay, Thrombin Time and Prothrombinase induced clotting time. A total of 690 assays were carried out. The potency of 2145 IU/ampoule was assigned by taking the geometric mean of all the valid assay results. The details of the collaborative study is documented in WHO/BS 09.2124.

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 ±0.12%.

*The USP sheep plasma assay was the official USP potency assay for Heparin Sodium and Heparin Calcium until the end of September 2009. The current USP potency assay for Heparin Sodium and Heparin Calcium is an anti-IIa chromogenic assay using purified antithrombin and 9 participants carried out this current USP anti-IIa chromogenic assay.

4. CONTENTS

Country of origin of biological material: USA.
The bulk starting material consisted of a single batch of porcine mucosal sodium heparin. 275.0 g of dried powder were dissolved in 26 L of sterile distilled water. The solution was distributed at room temperature into 24,000 ampoules, coded 07/328. The contents of the ampoules were then freeze-dried under conditions normally used for international biological standards (1).

The mean weight of the liquid content of 99 checkweight samples was 1.0050g, with coefficient of variation 0.12%. The mean weights of the freeze dried plug was 10.7 ± 0.39 mg (mean of 6 estimates).

5. STORAGE

Unopened ampoules should be stored at ot 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 as directed, taking care to ensure that all material is in the lower part of the ampoule. Reconstitue with 1.0 ml of distilled water. Heparin is very stable and aliquots of the reconstituted solution, at a suitable concentration (eg 10 IU/ml) could be stored frozen at - 40°C or below for subsequent use. Storage of 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 an expiry date to their international reference materials. They remain valid with the assigned potency and status until withdrawn or ammended.

Accelerated degradation studies, which involves potency estimation of ampoules stored at elevated temperatures relative to ampolues stored at -150°C, have shown that the 6th International Standard is very stable in unopened ampoules stored at –20°C. No loss of activity was observed even when the material has been stored at +45°C for 5 years. The accelerated degradation study and real time monitoring will continue for the lifetime of the standard.

9. REFERENCES

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

10. ACKNOWLEDGEMENTS

All participants in the international collaborative study and the support of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. We are also grateful to the following manufacturers for their kind donation of heparin samples:

Leo Pharmaceutical Products Ltd, 55 Industriparken, DK-2750 Ballerup, Denmark

Scientific Protein Laboratories, 700 E Main Street, Waunakee, 53597-0158 USA

Bioiberica, SA, Plaza Francesc Macià , 7 Barcelona 08029 , Spain

Opocrin SPA, 3, V. Pacinotti 41043 Corlo di Formaigine (MO), Italy

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

NV Organon (Schering-Plough), P O Box 20 5340 BH Oss, Kloosterstraat 6 5349 AB Oss, The Netherlands

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: White freeze-dried solid		Corrosive:	No
Stable:	Yes	Oxidising:	No
Hygroscopic:	Yes	Irritant:	Yes
Flammable:	No	Handling:	See caution, Section 2
Other (specify):	Contains material of porcine 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: 10.7 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.