WHO International Standard
5th International Standard For Unfractionated Heparin,
(established 1998)
NIBSC code: 97/578
Instructions for use
(Version 4.0, Dated 01/04/2008)

1. INTENDED USE
   The 5th International Standard for Unfractionated heparin, consists of
   ampoules, coded 97/578, containing aliquots of a freeze-dried material
   prepared from porcine mucosa. This preparation was established as the
   5th International Standard for Unfractionated Heparin, by the Expert
   Committee on Biological Standardisation of the World Health Organisation
   in 1998, with labelled potency of 2031 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.

3. UNITAGE
   The standard was calibrated by 24 laboratories in 14 countries against the
   4th International Standard for Unfractionated Heparin (82/502). Seven
   different methods were employed in the study: anti-Xa chromogenic
   assay, anti-Ilia chromogenic assay, activated partial thromboplastin time
   (APTT), Heptest, the European Pharmacopoeia (EP) assay, the United
   State Pharmacopoeia (USP) assay and the Japanese Pharmacopoeia
   (JP) assay. A total of 184 assays were carried out. The potency of 2031
   IU/ampoule was assigned by taking the geometric mean of all the valid
   assay results.

   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 ±0.07%

4. CONTENTS
   Country of origin of biological material: Denmark.
   The bulk starting material consisted of a single batch or porcine mucosal
   sodium heparin. 50.05 g of dried powder were dissolved with 5000 ml of
   sterile distilled water. The solution was distributed at 4°C into 5000
   ampoules, coded 97/578. The contents of the ampoules were them
   freeze-dried under conditions normally used for international biological
   standards.

   The mean weight of the liquid content of 99 checkweight samples was
   1.0063g, with the limits 1.0034 – 1.0092 (coefficient of variation 0.07%).
   The mean weights of the freeze dried plug was 8.85 ± 0.16mg (mean of
   25 estimates)

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.
   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

   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. 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.

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
   Accelerated degradation studies have shown that the 5th 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 6 months.

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. We are also grateful
    to the following manufacturers for their kind donation of heparin samples, two
    of which were used as candidates for the collaborative study:
    Diosynth bv, 5340 BH Oss, The Netherlands
    Crinos Industria Farmacobiologica SpA, 22079 Villa Guardia, Como, Italy
    Laboratori Derivati Organici, SS 31 bis Trino, Italy
    Leo Pharmaceutical Products Ltd, 55 Industriparken, DK-2750 Ballerup,
    Denmark
    Pharmacia & Upjohn, 160 Industrial Drive, Franklin, Ohio 45005, USA
    Scientific Protein Laboratories, 700 E Main Street, Waunakee, USA
    New Zealand Pharmaceuticals Ltd, Palmerston North 5330, Linton, New
    Zealand

11. FURTHER INFORMATION
    Further information can be obtained as follows; This material: enquiries@nibsc.org
    WHO Biological Standards:
    WHO Biological Standards:
    http://www.who.int/biologicals/en/
    http://www.who.int/biologicals/en/
    JCTLM Higher order reference materials:
    JCTLM Higher order reference materials:
    http://www.bipm.org/en/committees/jc/jctlm/
    http://www.bipm.org/en/committees/jc/jctlm/
    Derivation of International Units:
    Derivation of International Units:
    http://www.nibsc.org/standardisation/international_standards.aspx
    http://www.nibsc.org/standardisation/international_standards.aspx
    Ordering standards from NIBSC:
    Ordering standards from NIBSC:
    http://www.nibsc.org/products/ordering.aspx
    http://www.nibsc.org/products/ordering.aspx
    NIBSC Terms & Conditions:
    NIBSC Terms & Conditions:
    http://www.nibsc.org/terms_and_conditions.aspx
    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 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 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: 8.85mg
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_biol_efstandardsrev2004.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.