WHO International Standard
5th International Standard For Unfractionatd 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-IIa 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
1.0082 (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. 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 manufacturers 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. 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 Industrieparken, 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:
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
14. MATERIAL SAFETY SHEET
Classification in accordance with Directive 2000/54/EC, Regulation (EC) No 1272/2008: Not applicable or not classified

<table>
<thead>
<tr>
<th>Physical and Chemical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance: Freeze dried solid</td>
</tr>
<tr>
<td>Stable: Yes</td>
</tr>
<tr>
<td>Hygroscopic: Yes</td>
</tr>
<tr>
<td>Flammable: No</td>
</tr>
<tr>
<td>Other (specify):</td>
</tr>
</tbody>
</table>

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: No
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.