WHO International Standard
The 3rd International Standard for Low Molecular Weight Heparin
NIBSC code: 11/176
Instructions for use
(Version 1.0, Dated 27/06/2013)

1. INTENDED USE
The 3rd International Standard for Low Molecular Weight Heparin, consists of ampoules, coded 11/176, containing aliquots of a freeze-dried material prepared from porcine mucosa. This preparation was established as the 3rd International Standard for Low Molecular Weight Heparin by the Expert Committee on Biological Standardisation of the World Health Organisation in 2012. It is intended for anti-Xa and anti-IIa potency estimation of low molecular weight heparin.

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 22 laboratories from 13 countries against the 2nd International Standard for Low Molecular Weight Heparin (01/608). Anti-Xa and anti-IIa chromogenic methods were used in the study. Twenty-two laboratories performed anti-Xa assays (100 assays in total) and anti-IIa assays (80 assays in total). The following potencies were assigned based on the geometric mean of all the valid assay results:

- 1068 International Units of anti-Xa activity per ampoule
- 342 International Units of anti-IIa activity per 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 +/- 0.1%.

4. CONTENTS
Country of origin of biological material: France

The mean weight of liquid content of 879 check weight ampoules was 1.0068g, with a coefficient of variation of 0.097%. The mean weight of the freeze-dried plug was 9.22mg, with a coefficient of variation of 1.39%. The mean residual moisture was 3.41%.

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
DIIN 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 of distilled water.

Low molecular weight heparin is reasonably stable and aliquots of the reconstituted solution, at a suitable concentration (eg 100 anti-Xa IU/mL) could be stored frozen at –40°C or below for up to 6 months. Once reconstituted, diluted and/or aliquoted, users should determine the stability of the material according to their own method of preparation, storage and 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. 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 amended. Accelerated degradation studies for this preparation have, to date shown no loss in activity.

9. REFERENCES
N/A

10. ACKNOWLEDGEMENTS
All participants in the international collaborative study. We are also grateful to the following manufacturers for their kind donation of low molecular weight heparin samples, two of which were used as candidates for the collaborative study:

- Leo Pharmaceutical Products Ltd
- Laboratoires Rovi SA
- Opocrin SpA
- Sanofi Aventis
- Pfizer
- Glaxo Smith Kline

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

<table>
<thead>
<tr>
<th>Physical and Chemical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance: White freeze-dried solid</td>
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<tr>
<td>Corrosive: No</td>
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<tr>
<td>Stable: Yes</td>
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<tr>
<td>Oxidising: No</td>
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<tr>
<td>Hygroscopic: Yes</td>
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<tr>
<td>Irritant: Yes</td>
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<tr>
<td>Flammable: No</td>
</tr>
<tr>
<td>Handling: See caution, Section 2</td>
</tr>
<tr>
<td>Other (specify): Contains material of porcine origin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicological properties</th>
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</thead>
<tbody>
<tr>
<td>Effects of inhalation: Not established, avoid inhalation</td>
</tr>
<tr>
<td>Effects of ingestion: Not established, avoid ingestion</td>
</tr>
<tr>
<td>Effects of skin absorption: Not established, avoid contact with skin</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Country of origin for customs purposes*: United Kingdom</th>
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<tbody>
<tr>
<td>* 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.</td>
</tr>
</tbody>
</table>

Net weight: 9.22 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.