WHO International Standard
2nd INTERNATIONAL STANDARD FOR FIBRINOGEN
CONCENTRATE
NIBSC code: 09/242
Instructions for use
(Version 1.0, Dated 03/01/2013)

1. INTENDED USE
The 2nd International Standard for Fibrinogen Concentrate, consists of
ampoules, coded 09/242, containing aliquots of a freeze-dried concentrate
of fibrinogen prepared from human plasma. This preparation was
established by the Expert Committee on Biological Standardization of the
World Health Organization in October 2012, with labelled contents for
Clottable Protein and Total Protein. Details of the preparation and value
assignment are available in the document WHO/BS/2012.2208, (available from WHO). This standard is primarily intended to be used to
validate secondary and/or in-house working fibrinogen concentrate
standards.

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
Value assignment to this standard was carried out in an international
collaborative study involving 27 laboratories in 12 countries. Value
assignment for Clottable Protein was based on subsequent protein
determination methods following clot removal (CLOTr) and for Total
Protein based on standard protein determination methods.

The assigned potencies are:

Clottable Protein - 10.9 mg/ampoule
Total Protein - 15.0 mg/ampoule

These figures are based on assays relative to the 1st International
Standard for Fibrinogen Concentrate (96/614). Please note that the
assigned value for Clottable Protein did not include estimates from Clauss
assays. Use of Clauss assays for estimation of Clottable Protein in
fibrinogen concentrates should be validated locally.

4. CONTENTS
Country of origin of biological material: United Kingdom.
The 2nd International Standard for Fibrinogen Concentrate (coded 09/242),
contains freeze-dried (1 mL) aliquots of fibrinogen concentrate.

The raw material was a plasma-derived fibrinogen concentrate, prepared
using precipitation and chromatography methods. Manufacturing of this
product also included 2 viral inactivation steps, solvent detergent
 treatment and heat treatment at 80°C for 72 hours. After reconstitution,
the concentrate material was pooled and formulated in the following
buffer: 40mM Tr-Sodium Citrate, 2.0H2O, 20mM Tris-HCl, 5% sucrose (w/v),
4mM L-arginine-HCl (pH 7.3).
The formulated material was filled and
freeze-dried in sealed glass ampoules at NIBSC, under conditions
required for International Standards (Campbell, 1974). One ml of this
material was dispensed into each of approximately 10,000 ampoules. The
mean filling weight was 1.0093 g (range 1.0015 g to 1.0135 g) and the

coefficient of variation (CV) was 0.27% based on 468 check-weight samples.
Mean residual moisture after freeze-drying was 0.39% (CV 19.3%, n=12)
and mean oxygen headspace was 0.11% (CV 55.2%, n=12).

5. STORAGE
Unopened ampoules should be stored at -20°C. After reconstitution, any
unused material must be discarded, not frozen for later use.
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

The total contents of the ampoule should be reconstituted at room
temperature with 1 ml distilled water, dissolved by gentle swirling to avoid
foth and transferred immediately to a suitable plastic tube. The
reconstituted Standard is stable for up to 3 hours at room temperature.

8. STABILITY
Reference materials are held at NIBSC within assured, temperature-
controlled storage facilities and they should be stored on receipt as
indicated on the label. It is the policy of WHO not to assign an expiry
date to their international reference materials. Accelerated degradation
studies have indicated that this material is suitably stable, when stored at
-20°C or below, for the assigned values to remain valid until the material
is withdrawn or replaced. These studies have also shown that the
material is suitably stable for shipment at ambient temperature without
any effect on the assigned values. Users who have data supporting any
deterioration in the characteristics of any reference preparation are
encouraged to contact NIBSC.

9. REFERENCES
Campbell P J. Procedures used for the production of biological standards and

10. ACKNOWLEDGEMENTS
The contributions of all the participants in the study are gratefully
acknowledged. We are grateful to our colleagues in the Standards Division
for ampling and processing the candidate and trial preparations and for
the dispatch of collaborative study samples to participants. We are grateful
to Baxter Healthcare (Austria) and BPL (UK) for their kind donation of
materials for the study. We further like to thank the ISTH/SSC Factor XIII
and Fibrinogen Subcommittee for their support.

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:

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

Page 1 of 2
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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance:</td>
<td>Freeze-dried powder</td>
</tr>
<tr>
<td>Stable:</td>
<td>Yes</td>
</tr>
<tr>
<td>Hygroscopic:</td>
<td>Yes</td>
</tr>
<tr>
<td>Flammable:</td>
<td>No</td>
</tr>
<tr>
<td>Corrosive:</td>
<td>No</td>
</tr>
<tr>
<td>Oxidising:</td>
<td>No</td>
</tr>
<tr>
<td>Irritant:</td>
<td>Unknown</td>
</tr>
<tr>
<td>Handling:</td>
<td>See caution, Section 2</td>
</tr>
<tr>
<td>Other (specify):</td>
<td>Contains material of human origin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicological properties</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of inhalation:</td>
<td>Not established, avoid inhalation</td>
</tr>
<tr>
<td>Effects of ingestion:</td>
<td>Not established, avoid ingestion</td>
</tr>
<tr>
<td>Effects of skin absorption:</td>
<td>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>
</tr>
</thead>
<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>
<tr>
<td>Net weight: 0.08g</td>
</tr>
<tr>
<td>Toxicity Statement: Non-toxic</td>
</tr>
<tr>
<td>Veterinary certificate or other statement if applicable. Attached: No</td>
</tr>
</tbody>
</table>

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_esstandardsrev2004.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.