1. INTENDED USE

These materials are reference preparations for haemagglutination tests performed to control the level of anti-D in normal intravenous immunoglobulin products.

PANEL 05/242 CONSISTS OF 2 AMPOULES EACH OF 04/132 AND 04/140.

The European Directorate for the Quality of Medicines (EDQM) and the Center for Biologics Evaluation and Research (CBER) of the United States Food and Drug Administration (FDA) have undertaken necessary steps to implement a limit and a test for anti-D in human normal immunoglobulin for intravenous administration (IVIG) products [1-3]. A reference preparation of IVIG containing anti-D at 0.0475 IU/ml and having a nominal titre of 8 using direct haemagglutination of papain-treated OR2R2 red blood cells was deemed suitable to define the anti-D limit [2-4]. This preparation (NIBSC code 02/228) and a negative control IVIG preparation (NIBSC code 02/226) were established by the World Health Organization (WHO) as International Reference Reagents (IRRs) to standardise haemagglutination testing for anti-D in normal IVIG products. Stocks of 02/228 and 02/226 were shared with CBER/FDA for distribution as Immune Globulin Intravenous (Human) containing anti-D (anti-Rho), Lot 1A, and a negative control, Lot 1N-a, respectively. As stocks of IRRs are limited, new candidate positive and negative controls, 04/132 and 04/140, respectively, were prepared.

The results from an international collaborative study organised by NIBSC, EDQM and CBER have shown that the new positive and negative controls, 04/132 and 04/140, are indistinguishable from the corresponding IRRs, 02/228 and 02/226, respectively, using the specified direct haemagglutination method using papain-treated erythrocytes [5]. The study results also showed that the alternative red blood cell phenotypes OR1R2 and OR2R1 may be used instead of OR2R2 red blood cells, requested by the general method 2.6.26 [2,5].

Stocks of the new controls 04/132 and 04/140 have been shared with EDQM and CBER for use as Ph Eur (re-coded as 23613 and 23614, respectively) and US FDA (re-coded as CBER Lots 1B and 1N-b, respectively) reference preparations to control the level of anti-D in IVIG according to the corresponding specifications [1-3]. It is proposed that the level of anti-D in 04/132 defines the maximum permissible titre of anti-D in IVIG products [2,3,5].

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

N/A

4. CONTENTS

Country of origin of biological material: United Kingdom.
Both 04/132 and 04/140 contain the lyophilized residue of approximately 1 ml normal IVIG (5% IgG, w/v). (kindly donated by the Bio Products Laboratory, Elstree, UK); 04/132 was “spiked” with anti-D (reconstituted candidate 2nd International Standard for anti-D immunoglobin, 01/572 at 1/6000).

5. STORAGE

Store unopened ampoules at -20°C or below.
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.

Care should be taken on opening to prevent loss of contents.

7. USE OF MATERIAL

No attempt should be made to weigh out any portion of the freeze-dried material prior to reconstitution.

RECONSTITUTE THE CONTENTS OF THE AMPOULE WITH 1.0 ML DISTILLED OR DEIONIZED WATER CONTAINING 0.02% SODIUM AZIDE

Allow several minutes, with occasional vortexing, for reconstitution. Transfer the reconstituted contents to a capped tube and store at 4°C. Users should determine the stability of the reconstituted material according to their own storage facilities.

The reconstituted contents are 5% (w/v) IgG.

The reconstituted material is to be used in direct haemagglutination tests using papain-treated erythrocytes for anti-D activity in IVIG products [1-3,5].

8. STABILITY

Reference materials are held at NIBSC and CBER/FDA within assured, temperature-controlled storage facilities. Reference Materials should be stored on receipt as indicated on the label.

For information specific to this biological standard, contact NIBSC or CBER.

Users who have data supporting any deterioration in the characteristics of this reference preparation are encouraged to contact NIBSC or CBER.

NIBSC and CBER/FDA follow the policy of WHO with respect to their reference materials. It is the policy of 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.
9. REFERENCES

10. ACKNOWLEDGEMENTS
IVIG was donated by the Bio Products Laboratory, Elstree, UK.

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>
<th>Toxicological properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance: Lyophilisate</td>
<td>Effects of inhalation: Not established, avoid inhalation</td>
</tr>
<tr>
<td>Stable: Yes</td>
<td>Effects of ingestion: Not established, avoid ingestion</td>
</tr>
<tr>
<td>Hygroscopic: No</td>
<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 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.

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: 0.1g
- Toxicity Statement: Toxicity not assessed
- Veterinary certificate or other statement if applicable. Attached: No