Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

Working Standard
IVIG + anti-D (13/148) and Negative Control IVIG (12/300)
NIBSC code: 12/300 & 13/148; Panel 20/112
Instructions for use
(Version 1.0, Dated 22/04/2020)

This material is not for in vitro diagnostic use.

1. INTENDED USE

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

PANEL 20/112 CONSISTS OF 2 AMPOULES EACH OF 13/148 AND 12/300.

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 OR_2R_2 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, positive and negative working standards, 04/132 and 04/140, respectively, were prepared.

The results from an international collaborative study organised by NIBSC, EDQM and CBER confirmed that 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 original study evaluating 02/228 and 02/226 showed that the alternative red blood cell phenotypes OR_1R_1 and OR_1R_2 may be used instead of OR_2R_2 red blood cells, requested by the general method 2.6.26 [2,5]. Stocks of 04/132 and 04/140 were 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]. The level of anti-D in 04/132 defines the maximum permissible titre of anti-D in IVIG products [2,3,5].

More recently, an additional international collaborative study carried-out in 2013 confirmed that new preparations of positive and negative controls coded 13/148 and 12/300 are indistinguishable from the corresponding IRRs, 02/228 and 02/226, respectively using the specified direct haemagglutination method using papain-treated erythrocytes. Furthermore, this study confirmed that 13/148 and 12/300 are indistinguishable from the former corresponding working standards 04/132 and 04/140, respectively. Therefore, the level of anti-D in 13/148 defines the maximum permissible titre of anti-D in IVIG products.

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

Preparation 13/148 has a nominal anti-D titre of 8.

4. CONTENTS

Country of origin of biological material: United Kingdom.
Both 13/148 and 12/300 contain the lyophilized residue of approximately 1 ml normal IVIG (5% IgG, w/v), kindly donated by the Bio Products Laboratory, Elstree, UK. 13/148 was 'spiked' with anti-D (reconstituted 2nd International Standard for anti-D immunoglobulin, 01/572 at 1/6000).

5. STORAGE

Store unopened ampoules at -20oC 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. 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.

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% (w/v) SODIUM AZIDE

Allow several minutes, with occasional vortexing, for reconstitution. Transfer the reconstituted contents to a capped tube and store at 4°C if necessary. 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 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.

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

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

1. Human normal immunoglobulin for intravenous administration. Monograph 0918 Ph. Eur. 5th Ed, Suppl 5.3:3516-8.
2. Test for anti-D antibodies in intravenous immunoglobulin. General chapter 2.6.26. Ph. Eur. 5th Ed, Suppl 5.3:3348

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WHO International Laboratory for Biological Standards,
UK Official Medicines Control Laboratory

3. Thorpe SJ, Fox B, Heath A, Dolman C, Virata ML, Yu MW, Thorpe R. International collaborative study to evaluate a candidate reference preparation to define an appropriate specified limit of anti-D in IVIG products. Vox Sanguinis 2005;88:278-287.
4. Thorpe SJ, Fox BJ, Dolman CD, Lawrence J, Thorpe R. Batches of intravenous immunoglobulin associated with adverse reactions in recipients contain atypically high anti-Rh D activity. Vox Sanguinis 2003;85:80-84.
5. Thorpe SJ, Fox B, Heath A, Behr-Gross M-E, Virata ML, Yu MW. International collaborative study to assess candidate reference preparations to control the level of anti-D in IVIG for use in Europe and the United States. Biologicals 2006;34:209-212.

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

Physical and Chemical properties			
Physical appearance: Lyophilisate		Corrosive:	No
Stable:	Yes	Oxidising:	No
Hygroscopic:	No	Irritant:	No
Flammable:	No	Handling:	See caution, Section 2
Other (specify):	Contains material of human 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 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: 0.1g
Toxicity Statement: Toxicity not assessed
Veterinary certificate or other statement if applicable**.** **Attached:** No

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