Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Reference Reagent
Anti-A and Anti-B in IVIG: LIMIT REFERENCE PREPARATION
NIBSC code: 23/232
Instructions for use
(Version 2.0, Dated 10/11/2025)

This material is not for in vitro diagnostic use

1. INTENDED USE

This material serves as a reference preparation for the standardisation of haemagglutination tests and for establishing specifications to control the levels of anti-A and anti-B antibodies in normal intravenous immunoglobulin (IVIG) products.

Preparation 23/232 defines the recommended maximum limits, where applicable, for IVIG products that exhibit higher anti-A and anti-B titres than those found in the positive control preparation, "Anti-A and Anti-B in IVIG: Positive Control", NIBSC code 23/218. "Anti-A and Anti-B in IVIG: Negative Control", NIBSC code 23/230 is intended for use as the negative control in the same assay.

These preparations were validated in an international collaborative study (coded CS739 – BSP126) jointly organised by NIBSC, EDQM, and ANSM. The study demonstrated that preparation 23/232 exhibits anti-A and anti-B titres in the two-fold range of 32–64, as determined by direct haemagglutination using papain-treated A_1 and B red cells. [1,2,3,4]

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 23/232 exhibited anti-A and anti-B titres typically in the 2-fold range 32–64 using direct haemagglutination of A_1 and B red cells. [1,2]

4. CONTENTS

Country of origin of biological material: Netherlands.
This preparation is a 5% solution of purified human immunoglobulins, developed and manufactured by a European company for the EDQM/BSP. The IVIG preparation was spiked with purified human anti-A and anti-B antibodies to achieve titres of 1:64, as determined by the direct agglutination assay. These titres were independently confirmed by five laboratories, including official control laboratories and manufacturers, prior to the production of the lyophilized product. The mean weight of the dispensed solution was 0.5155 g, with a filling imprecision (coefficient of variation, CV) of 0.33%. The residual moisture of the final lyophilised product was 0.73% (N = 12).

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. 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
Reconstitute the contents of the ampoule with 0.5 mL of distilled or deionized water containing 0.02% sodium azide. Allow several minutes for complete reconstitution, with occasional vortexing. Once reconstituted, transfer the contents to a capped tube and store at 4 °C. Users should determine the stability of the reconstituted material based on their own storage conditions.

The reconstituted solution contains 5% (w/v) IgG.

Usage and Reference:
Preparation 23/232 specifies the recommended maximum limits, where applicable, for IVIG products with higher anti-A and anti-B titres than those in the 'Anti-A and Anti-B in IVIG: Positive Control' 23/218 when assessed using the direct "spin" haemagglutination method with papain-treated red cells.
In the collaborative study, the percentage of tests yielding a particular titre against A_1, B, or O cells, using the direct method across all participating laboratories, was recorded for preparation 23/232. [1]

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 WHO not to assign an expiry date to their international reference materials. They remain valid with the assigned activity and status until withdrawn or amended.

Accelerated degradation studies on 23/232 have been carried-out after storage of ampoules at -70°C, -20°C, 4°C, 20°C, 37°C, 45°C and 56°C for 12 months. Although the haemagglutination titres are not suitable for analysis using the usual Arrhenius model of accelerated degradation, there is no haemagglutination or HPLC data to suggest that 23/232 will not be adequately stable at -20°C and at ambient temperature for distribution.

9. REFERENCES

[1] The latest ECBS report is available from the WHO (www.who.int/). Document number:WHO/BS/2025.2488.
EDQM-European Directorate for the Quality of Medicines & HealthCare; ANSM-Agence nationale de sécurité du médicament
[2] Chapter 2.6.20: Anti-A and Anti-B Haemagglutinins, Method B. European Pharmacopoeia (PhEur) (ninth ed.) (2016), pp. 203-204
[3] World Health Organization (WHO). Manual of Basic Techniques for a Health Laboratory, 2nd ed. Geneva: WHO; 2003. Section 9.4: Serological Tests.

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

World Health Organization

[4] SJ Thorpe, BJ Fox, CD Dolman and R Thorpe. Anti-A and anti-B activity in batches of different intravenous immunoglobulin products determined using a direct haemagglutination method. Biologicals 2005; 33: 111-116.

10. ACKNOWLEDGEMENTS

We thank the manufacturer who kindly provided the IVIG batch used in the production of 23/232 and EDQM for procurring these materials. We also thanks the lyophilisation team at MHRA for the development work.

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:	Yes	Irritant:	Unknown
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 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: 0.043 g
Toxicity Statement: Non-toxic
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. The reference materials are established according to the WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards https://www.who.int/publications/m/item/annex2-trs932(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.