Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

WHO International Standard
1st International Standard for antibodies to SARS-CoV-2 variants of concern
NIBSC code: 21/338
Instructions for use
(Version 2.0, Dated 09/12/2022)

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1. INTENDED USE

The 1st WHO International Standard for antibodies to SARS-CoV-2 variants of concern (VOC) is the freeze-dried equivalent of 0.25 mL of pooled plasma obtained from 265 individuals infected with one of the early 2020 SARS-CoV-2 isolates or a VOC (including Alpha, Beta and Delta). All individuals were vaccinated with one or more of these vaccines: Pfizer/BioNTech Comirnaty, Moderna Spikevax, Oxford/AstraZeneca Covishield/Vaxzevria, Sinopharm BBIBP/CorV, Johnson & Johnson/Janssen Jcovden. The preparation has been evaluated in a WHO International Collaborative study (1). The preparation has been solvent-detergent treated to minimise the risk of the presence of enveloped viruses (2).

The intended use is for the calibration and harmonization of serological assay detecting neutralising antibodies to SARS-CoV-2 variants of concern circulating during or after 2022, such as Omicron sub-lineages. The preparation does not contain any convalescent plasma from Omicron-infected individuals; however, in the collaborative study, 21/338 has shown neutralising activity against Omicron BA.1 and BA.2 (1). Feedback received from users has also confirmed neutralising activity against BA.4 and BA.5.

The standard should be used for comparison of results between neutralisation assays using the same variant, not between variants.

2. CAUTION

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. This preparation is not for administration to humans or animals

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 assigned unitage of the 1st WHO International Standard for antibodies to SARS-CoV-2 variants of concern is 4250 IU/ampoule for neutralising antibody activity against Omicron sub-lineages and other VOC which should emerge after June 2022. After reconstitution in 0.25 mL of distilled water, the final concentration of the preparation is 17000 IU/mL.

Prior to establishment as an International Standard, 21/338 was available as a Working Standard with neutralising antibody potencies relative to the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin, 20/136, as reported below. These values are based on the geometric mean of the results from the assays used in the collaborative study together with the 95% confidence interval (95% CI) and are intended for guidance only.

Isolate	Potency (IU/mL)	95% CI
Early 2020	4705	3568-6417
Alpha	5584	2945-10590
Beta	7079	3939-12722
Gamma	5138	3009-8773
Delta	4476	3363-5963

4. CONTENTS

Country of origin of biological material: United Kingdom and Cameroon.
Each ampoule contains the equivalent of 0.25 mL of human plasma.

5. STORAGE

21/338 should be stored at -20°C or below upon receipt.
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
This material should be reconstituted in 0.25 mL distilled water. Following addition of water, the ampoules should be left at ambient temperature for approximately 30 minutes until dissolved and then mixed thoroughly, avoiding the generation of excessive foam.

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.

9. REFERENCES

(1) Bentley EM et al. Establishment of the 2nd WHO International Standard for anti-SARS-CoV-2 immunoglobulin and Reference Panel for antibodied to SARS-CoV-2 variants of concern. 2022, WHO Expert Committee on Biological Standardization. WHO/BS/2022.2427
(2) Dichtelmüller et al. Robustness of solvent/detergent treatment of plasma derivatives: a data collection from Plasma Protein Therapeutics Association member companies. Transfusion. 2009;49:1931–43

10. ACKNOWLEDGEMENTS

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UK Official Medicines Control Laboratory

World Health Organization

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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: freeze-dried		Corrosive:	No
Stable:	Yes	Oxidising:	No
Hygroscopic:	No	Irritant:	No
Flammable:	No	Handling: See caution, Section 2	
Other (specify):	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: 0.25 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 http://www.who.int/bloodproducts/publications/TRS932Annex2_Inter_biolefstandardsrev2004.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.