WHO Reference Panel
First International Reference Panel for antibodies to SARS-CoV-2 variants of concern
NIBSC code: 22/270
Instructions for use
Version 1.0, Dated 20/04/2023

1. INTENDED USE
The First WHO International Reference Panel of antibodies to SARS-CoV-2 variants of concern (VOC) consists of the equivalent of 0.25 mL of freeze-dried pool of plasma or serum from individuals recovered from Coronavirus Disease 2019 (COVID-19). The panel was evaluated in two WHO International Collaborative studies (1, 2). Individual panel members are NIBSC code 21/296 (pre-VOC), 21/300 (Alpha), 21/312 (Delta), 22/126 (Gamma) and 22/128 (Omicron BA.1). It is intended that the panel is used in the assessment and development of assays used in the detection and quantitation of anti-SARS-CoV-2 antibodies. The preparation has been solvent-detergent treated to minimise the risk of presence of enveloped viruses (3).

2. CAUTION
The preparation contains material of human origin, and either the final product or the source material from which it is derived have been tested and found negative for HBsAg, anti-HIV and HCV RNA. Sample 21/312 was found positive for anti-HIV antibodies and HBsAg. The product has been solvent-detergent treated and deemed not infectious for shipping.

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
No unitage has been assigned to the panel members. The potencies, reported as geometric means of the values relative to the second WHO International Standard for anti-SARS-CoV-2 immunoglobulin, 21/340 or for Omicron, to the First WHO International Standard to antibodies to SARS-CoV-2 variants of concern, 21/338, were obtained during the collaborative study (1) for 21/296, 21/300 and 21/312 or (2) for 22/126 and 22/128. These values are provided to the end users as guidance only. Actual values may vary between assays.

<table>
<thead>
<tr>
<th>Neutralising Ab</th>
<th>Early 2020</th>
<th>Alpha</th>
<th>Beta</th>
<th>Gamma</th>
<th>Delta</th>
<th>Omicron</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/296</td>
<td>21/300</td>
<td>21/312</td>
<td>22/126</td>
<td>22/128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutralising Ab</td>
<td>373</td>
<td>599</td>
<td>1075</td>
<td>1110</td>
<td>261</td>
<td>498</td>
</tr>
<tr>
<td>Early 2020</td>
<td>1814</td>
<td>3872</td>
<td>2953</td>
<td>3333</td>
<td>1020</td>
<td>1386</td>
</tr>
<tr>
<td>Alpha</td>
<td>399</td>
<td>708</td>
<td>1190</td>
<td>887</td>
<td>504</td>
<td>831</td>
</tr>
<tr>
<td>Beta</td>
<td>746</td>
<td>891</td>
<td>1601</td>
<td>1315</td>
<td>368</td>
<td>1599</td>
</tr>
<tr>
<td>Gamma</td>
<td>203</td>
<td>380</td>
<td>1498</td>
<td>1155</td>
<td>442</td>
<td>3840</td>
</tr>
<tr>
<td>Delta</td>
<td>1904</td>
<td>756</td>
<td>105</td>
<td>157</td>
<td>122</td>
<td></td>
</tr>
</tbody>
</table>

anti-S1 IgG     | 397        | 2666  | 507  | nt     | nt     | 122     |
anti-N IgG      | 132        | 756   | 105  | 157    | 122    |

Ab: antibody; IU: International Unit; BAU: binding antibody unit; RBD: receptor binding domain; S1: subunit 1 of the spike protein; N: nucleoprotein; IgG: immunoglobulin G; nt: not tested

4. CONTENTS
Country of origin of biological material: Brazil, Kenya, South Africa, United Kingdom and United States of America.

Each ampoule contains the equivalent of 0.25 mL of human plasma or serum.

5. STORAGE
The ampoules should be stored at t -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.

Each ampoule 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

10. ACKNOWLEDGEMENTS
We would like to wholeheartedly thank the anonymous donors of the plasma and serum samples for their consent which has allowed this study to be undertaken. We thank our partner organizations for the recruitment of the donors and provision of the material: Heili Harvala and Hatice Baklan from NHS Blood and Transplant (United
Kingdom), Amos Ndhere and Luca Tina from ACE Research (Kenya), Sumi Paranjape and Colleen Lammers from Bloodworks NorthWest (WA, USA), Silvano Wendel and Roberta Fachini from Hospital Sírio Libanês (Brazil), and Justin Devine and Nondumiso Shongwe from Synexa Life Sciences (South Africa). We would also like to thank MHRA Standards Production team for the formulation of the standards; Graham Prescott and Katrina Ternouth for the blood virology testing and Corinne McDonough for the distribution of study samples.

The project has been funded by the Coalition for Epidemic Preparedness Innovations.

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**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance:</td>
<td>freeze-dried</td>
</tr>
<tr>
<td>Stable:</td>
<td>Yes</td>
</tr>
<tr>
<td>Hygroscopic:</td>
<td>No</td>
</tr>
<tr>
<td>Flammable:</td>
<td>No</td>
</tr>
<tr>
<td>Human origin (specify):</td>
<td></td>
</tr>
</tbody>
</table>

**Toxicological properties**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</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*:</th>
<th>United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity Statement:</td>
<td>Non-toxic</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/TRS32Annex2_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.