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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 21 October 2011

A Proposed 1st WHO Reference Reagent
Anti-human neutrophil antigen 1a (anti-HNA-1a)
09/284

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Summary

Twenty four laboratories participated in an international collaborative study to assess the suitability of a freeze-dried plasma preparation as a WHO Reference Reagent for the detection of anti-HNA-1a. The participants evaluated doubling dilutions of the material in their own in-house routine assays and recorded the highest dilution where the antibody could be detected.

The NIBSC code number of the material is 09/284. The material is intended for use as a minimum sensitivity standard which laboratories can use to assess the sensitivity of their own techniques. Conclusions from this study indicated that 1 in 4 would be a suitable minimum dilution at which anti-HNA-1a should be detected. All of the study participants approved this recommendation.

Introduction

Transfusion-related acute lung injury (TRALI) was first described by Popovsky and Moore in 1985 [1] and is now recognised as the most frequent cause of mortality and morbidity following blood transfusion both by the Serious Hazards of Transfusion (SHOT) haemovigilence scheme in the UK [2-4] and the Food and Drug Administration (FDA) in the USA [5].

It occurs as a result of an immunological reaction between the recipient and the transfused donation(s). Usually, antibodies in donor plasma against the recipient's white cells and/or endothelial cells lead to the trapping of leucocytes in the small blood vessels of the lung. The resultant damage to the pulmonary endothelium results in leakage of fluid and inflammatory cells into the lungs. The antibodies are typically directed against Human Leucocyte Antigen (HLA) class I, HLA class II or Human Neutrophil Antigens (HNA) expressed by the recipient. Occasionally TRALI is caused by antibodies in the recipient reacting with neutrophils in the donation. Also, in some cases WBC antibodies cannot be found, and it is now accepted that other factors can also initiate the cascade of events that lead to lung injury.

Increased awareness of TRALI has led to more laboratories setting up tests for neutrophil antibodies. However, unlike other areas of blood cell antibody testing, there are no certified reference reagents available for laboratories to determine the sensitivity of detection of their assays. A request to make a neutrophil antibody reference material was received by NIBSC from the UKBTS Standing Advisory Committee on Immunohaematology ('Red Book' SAC). A specific need for a standard or reference material to assist clinical laboratories that test for neutrophil antibodies in patient samples was identified. The primary use of this reagent would be as a sensitivity control for different techniques and it was envisaged that it would be used by laboratories setting up new in-house methods or commercial techniques, or for validating existing techniques after a change of reagents, operator or equipment. The existence of a

reference material may also encourage other laboratories to develop testing for neutrophil antibodies. The proposal to make a WHO Reference Reagent was approved by the WHO Expert Committee on Biological Standardization in October 2008.
Anti-HNA-1a is a clinically relevant anti-neutrophil antibody involved in TRALI and alloimmune neonatal neutropenia and the donation of a significant volume of plasma containing this antibody allowed the project to go ahead.

Aims of study

The aim of the international collaborative study was to test the suitability of the material as a WHO Reference Reagent (minimum potency). The results of the study allowed us to establish a maximum dilution at which most laboratories can be expected to detect the antibody.

Participants

A pilot study on trial fill material was carried out in 14 laboratories, Appendix 1. These laboratories were selected because they were already participants of the ISBT Granulocyte Immunology Workshop and therefore considered to be expert laboratories.
For the collaborative study of the definitive material a larger international study was organised and participation was widened to include more laboratories carrying out granulocyte antibody testing of clinical samples on a routine basis. Thirty-two laboratories were invited to take part, 27 labs agreed to participate and 24 returned results. Sixteen different countries were represented among participants returning results, Appendix 2.
Each laboratory was assigned a code number which does not reflect the order of listing in the appendices.

Materials

The candidate material 09/284 is recalcified plasma donated by the mother of a baby with neonatal alloimmune neutropenia and supplied by Helen Pearson from the Australian Red Cross Blood Service (ARCBS) in Sydney, Australia. The material has been tested and found negative for HBsAg, anti-HIV 1+2 and HCV RNA by PCR. 1mL aliquots of the plasma were freeze-dried in glass ampoules for long-term stability. Table 1 shows the product summary for the material.

Table 1. Product summary of the candidate material.

NIBSC Code	09/284
Date filled	12.02.10.
Coefficient of variation of the fill (%) (n=78)	0.13
Residual moisture after lyophilisation (%) (n=6)	0.41
Mean dry weight (g) (n=6)	0.0812
Mean residual oxygen% (n=6)	0.40
No of ampoules available	1924
Presentation	Sealed, glass 3mL DIN ampoules
Excipient	none
Address of facility where material was processed	NIBSC, Potters Bar, Herts, UK
Present custodian	NIBSC, Potters Bar, Herts, UK
Storage temperature	-20°C

This standard is intended to be used in the *in vitro* diagnostics field and it relates to BS EN ISO 17511:2003 Section 5.6.

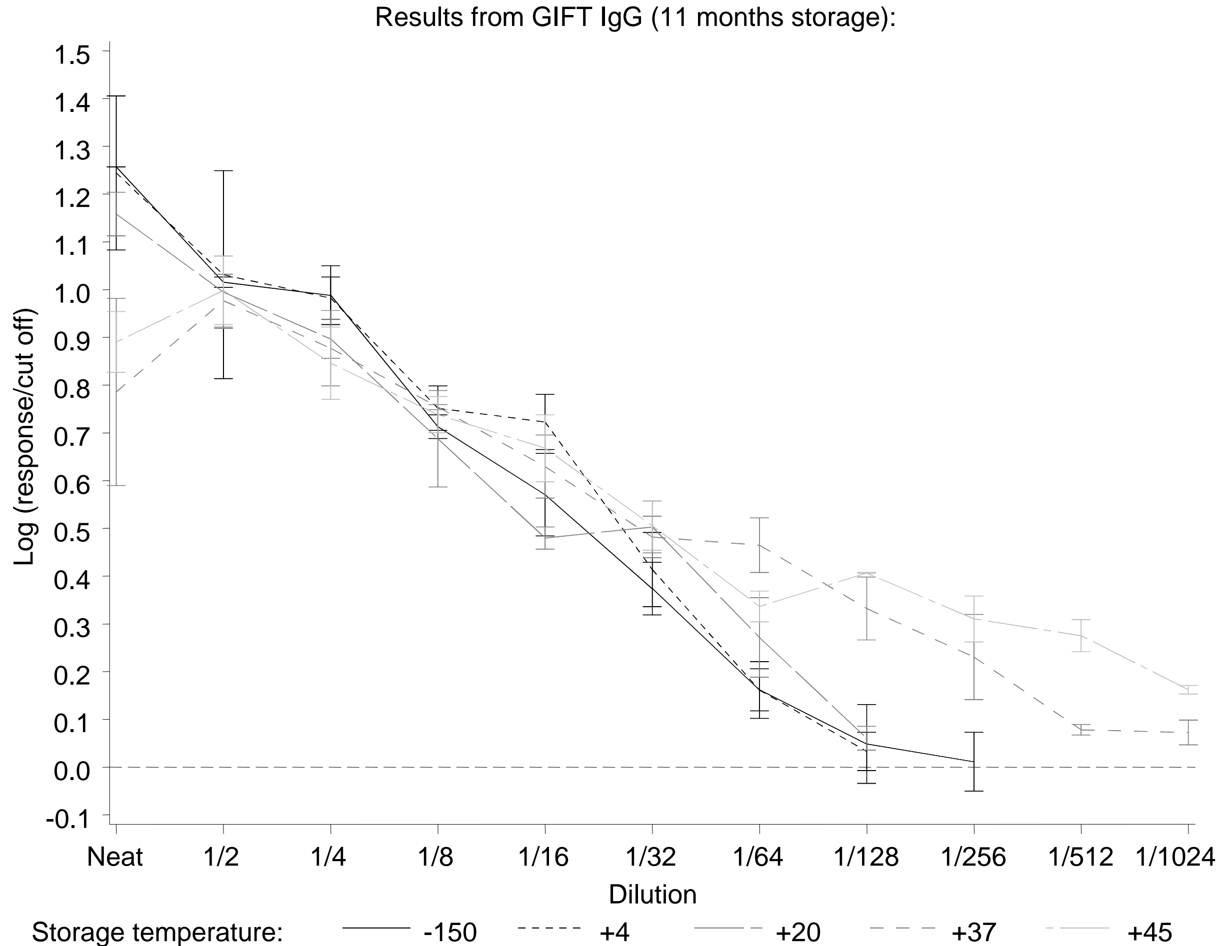
Stability studies

Accelerated degradation studies were carried out on samples stored at elevated temperatures compared with others stored at -150°C (see table 2 below) using the Granulocyte Immunofluorescence test (GIFT).

Table 2. Samples tested in accelerated degradation studies.

Duration of storage	**-150°C**	**-20°C**	**+4°C**	**+20°C**	**+37°C**	**+45°C**
10 weeks	✓				✓	✓
6 months	✓			✓	✓	✓
11 months	✓		✓	✓	✓	✓

To date, no degradation has been detected in any of the samples stored at elevated temperatures, compared to samples stored at -150°C, however, testing will continue at regular intervals. Figure 1 below shows the results of tests carried out after 11 months storage, where no significant difference can be seen between those samples stored at elevated temperatures and those stored at -150°C.



Study design

In the pilot study a small scale freeze-dried preparation was sent to 14 expert laboratories who were asked to check the antibody specificity and titre the anti-HNA-1a. Expert laboratories were chosen at this stage in order to maximise the chance of detecting any other antibodies which might interfere with the detection of the anti-HNA-1a. These laboratories also determined the titre of the anti-HNA-1a so that, if required, the material could be further diluted before the large-scale definitive preparation was carried out.

In the main study a larger number of laboratories took part, see above. Two ampoules of the definitive freeze-dried material (coded 09/284) were sent to each laboratory with instructions for storage and reconstitution. Participants were asked to titre the anti-HNA-1a using any method in routine use in their laboratory. The two ampoules were to be tested on different days against

HNA-1a1a and HNA-1b1b cells. Laboratories were asked to report both their interpretation of each individual test and the raw data. The antibody titre for each laboratory was assigned by taking the highest dilution which the lab reported to be 'positive' and all 'dubious positive' results were ignored.
As a consequence of the results from the first trial, laboratories were advised not to use the MAIGA assay with Mab 3G8 and they were not asked to test for other HNA or HLA antibodies as none had been demonstrated in the pilot study.

Methods

A range of techniques were used for HNA antibody detection and the number of laboratories using each technique is shown below in Table 3. Some laboratories used more than one technique.

Table 3. Methods used by participants.

Method	**Laboratory code**	**Total**
Granulocyte immunofluorescence test [6] read by microscope (GIFT-M)	3, 4, 6, 7, 13, 15, 16, 20, 24	9
Granulocyte immunofluorescence test read by flow cytometer (GIFT-F)	1, 2, 5, 8, 10, 11, 12, 13, 14, 17, 18, 19, 20, 21, 22, 23	16
Granulocyte agglutination test (GAT) [7]	3, 5, 6, 12, 13, 14, 16, 20	8
Granulocyte chemiluminescence test (GCLT) [8]	22	1
Monoclonal antibody-specific immobilization of granulocyte antigens assay [9] using mab DJ130C (MAIGA DJ130C)	1, 3, 5, 6, 14, 15, 20	7
Monoclonal antibody-specific immobilization of granulocyte antigens assay using mab MBC238.7 (MAIGA MBC238.7)	9, 10, 22	3
Monoclonal antibody-specific immobilization of granulocyte antigens assay using mab LNK16 (MAIGA LNK16)	14	1
Monoclonal antibody-specific immobilization of granulocyte antigens assay using mab 3G8 (MAIGA 3G8)	4, 6	2

Results

Pilot study. The material performed well in the pilot studies. A small scale freeze-dried preparation was sent to 14 expert laboratories who were asked to check the antibody specificity and titre the anti-HNA-1a. Critically, no other HNA or HLA antibodies were reported, indicating that the material would make a useful mono-specific reagent. Additionally, the range of titres obtained (Figure 1) showed that there was no need to dilute the antibody.

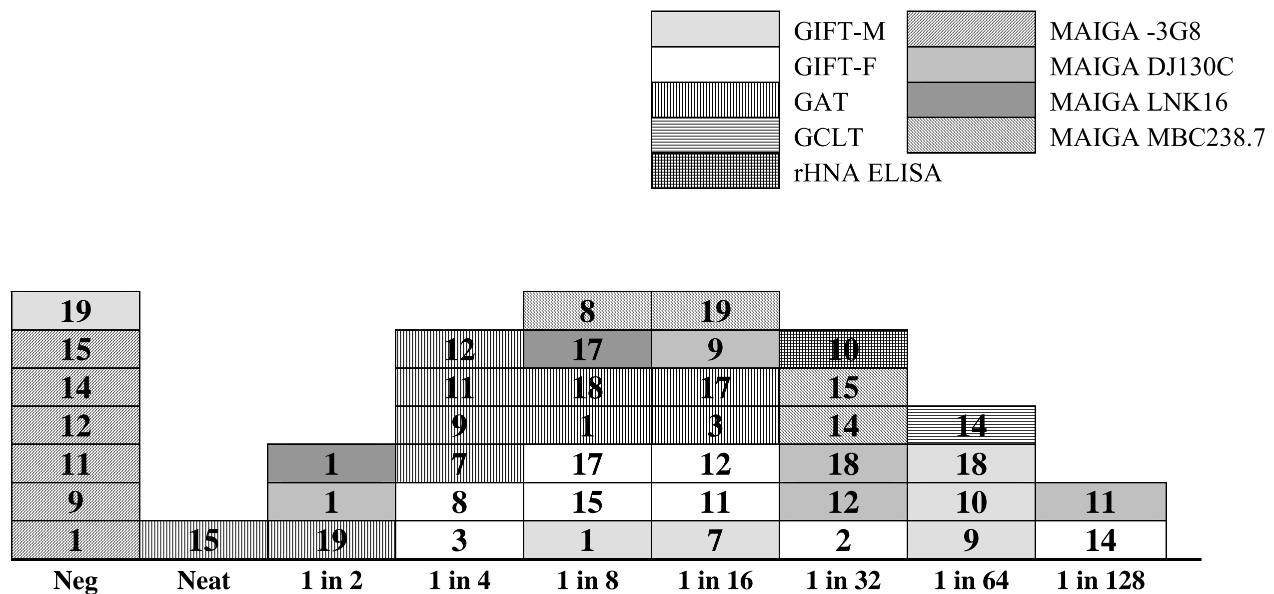


Figure 1. Anti-HNA-1a titrations from pilot study. Box indicates maximum dilution where anti-HNA-1a could be detected using HNA-1a1a cells. Numbers in boxes indicate laboratory code number for this study only. Shading in box indicates technique used, see Table 3. Neg: no anti-HNA-1a detected at any dilution. rHNA ELISA: ELISA using recombinant Human Neutrophil Antigen-1a.

It can be seen that anti-HNA-1a was not detected when monoclonal antibody 3G8 was used as the capture antibody in the MAIGA assay, presumably due to an overlap between the epitopes recognized by the monoclonal antibody and the human HNA-1a antibodies in the reference material, however, other monoclonal antibodies worked well in the MAIGA.

Main study. All the participating laboratories were able to reconstitute the materials, make doubling dilutions and obtain useful results. Each laboratory was assigned a code number which does not reflect the order of listing in the table of participants and it is not related to the laboratory coding in the pilot study. All laboratories tested two ampoules of the materials on

separate occasions, except labs 4 and 5 where only one ampoule was tested in one of their assays. The results of the endpoint titrations for all laboratories, tested on two occasions, are shown in Figure 2 below.

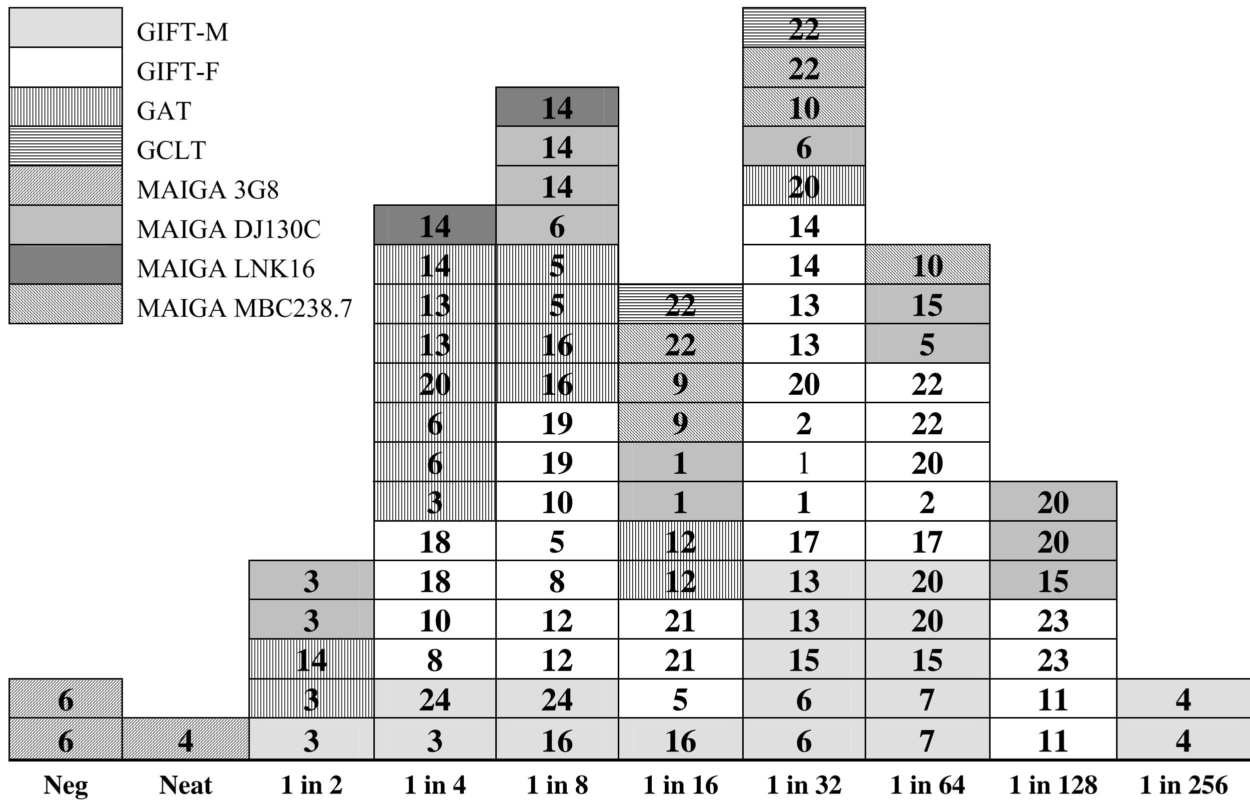


Figure 2. Anti-HNA-1a titrations from international collaborative study. Laboratories were asked to test two ampoules and report results separately. Box indicates maximum dilution where anti-HNA-1a could be detected using HNA-1a1a cells. Numbers in boxes indicate laboratory code number for this study only**.** Shading in box indicates method used, see Table 3. Neg: no anti-HNA-1a detected at any dilution.

Two laboratories (coded 4 and 6) used the monoclonal antibody 3G8 despite being advised against this in the study protocol. Three laboratories reported weak positive reactions with the neat samples and HNA-1b1b cells using GAT (x2 labs) and GIFT-F (1 lab) assays and one laboratory reported a strong positive reaction with HNA-1b1b cells using the GCLT, with only one of the ampoules and only with the neat sample. However, these were isolated positive signals which did not titrate further and these were not thought to be significant.

As shown above, there was a wide variation in the sensitivity of antibody detection by different laboratories, irrespective of the technique used. Excluding methods that were performed by less than 3 laboratories (GCLT, MAIGA with mab LNK16 & MAIGA with mab 3G8), the relative sensitivity of the different antibody assays was compared by analysis of variance of the log transformed geometric mean dilutions for each lab/method. The results showed a significant difference in sensitivity (p=0.043) due to the GIFT-M and GIFT-F methods being significantly more sensitive than the GAT method (p=0.046 and p=0.049 respectively in Tukey's multiple comparison test).

Reproducibility within laboratories was good; out of 46 tests carried out in duplicate, 26 tests gave the same result on both days, 17 were only one doubling dilution apart and there were only 2 tests where the results were more than one doubling dilution apart.

Participant Responses

Participants were offered the chance to comment on the materials supplied and the way the study was organised, however, no comments were received.

Discussion

Testing for neutrophil antibodies is a specialised field but it is slowly enlarging. However, unlike red cell, and platelet and lymphocyte serology, no reference materials exist, and it is difficult for laboratories involved in this work to determine and maintain the sensitivity of their detection techniques.

Following the donation of a bulk plasma sample from an individual with a potent antibody against HNA-1a, two studies were carried out. The first involved experienced reference laboratories and the results showed that the candidate material did indeed contain anti-HNA-1a and no other HNA or HLA antibodies. Twenty-four laboratories participated in a subsequent larger study to assess the suitability of a freeze-dried plasma preparation as a WHO Reference Reagent for the detection of anti-HNA-1a. The study was designed to determine how well the material performed in a large number of laboratories, using a variety of methods, and which dilution was the most appropriate to set as the minimum dilution that routine laboratories could expect to detect the antibody. Laboratories were asked to use their routine techniques, rather than a prescribed protocol, as these would be the tests utilised for routine patient testing. The GIFT, GAT and MAIGA methods were used by several laboratories and the reference material is recommended for use in all three. The GCLT and the rHNA ELISA techniques were each used

by only one laboratory and while the reference material performed satisfactorily in these tests, the number of participants was too small to draw any conclusion.

The pilot study clearly showed that monoclonal antibody clone 3G8 cannot be used in the MAIGA to detect the presence of this particular example of anti-HNA-1a. This is probably the result of overlapping epitopes on the FcγRIII glycoprotein. This phenomenon has been described before with samples circulated amongst the expert laboratories that participate in the ISBT granulocyte immunology workshops both for HNA-1a antibodies [10] and for HNA-2 antibodies on CD177 [11]. Reference is made to the unsuitability of this particular clone in the Instructions for Use which will be supplied with the material, however, several other clones are available which do not cause a problem.

A wide range of titres was reported by the participants, clearly demonstrating the need for improvements in sensitivity in some laboratories. However, overall the study showed that the material is suitable for use as a reference material and we proposed that the minimum sensitivity required should be set at a dilution of 1 in 4. As a minimum, laboratories should be able to obtain an unequivocal positive result at this dilution. This proposal was endorsed by all participants in the study and the International Society for Blood Transfusion (ISBT) Granulocyte Immunobiology Working Party, see Appendix IV.

Conclusions and Proposal

The wide spread of results clearly demonstrates the need for improvements in sensitivity in some laboratories. However, overall the study showed that the materials are suitable for use as a reference material and we propose that the minimum sensitivity required should be set at a dilution of 1 in 4. We would like to propose the material be established as the 1st WHO Reference Reagent for the detection of anti-HNA-1a.

Acknowledgements

We would like thank Helen Pearson at ARCBS, Sydney for donating the raw materials used in this study and the participants of the study for taking part and returning data.

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Appendix I. List of Participants in the Pilot Study.

Participant	Institute	Country
Penny Hassell	Australian Red Cross Blood Service - Queensland	Australia
Ketty Lee	EFS Ile de France	France
Brigitte Flesch, Frank Schauland	University Hospital Schleswig-Holstein, Kiel	Germany
Ulrich Sachs	Justus-Liebig University, Giessen	Germany
Jürgen Bux, Angelika Reil	DRK Blutspendedienst West, Hagen	Germany
Nelson Tsuno	University of Tokyo	Japan
Leendert Porcelijn	Sanquin Diagnostic Services, Amsterdam	Netherlands
K Maslanka	Institute of Haematology & Transfusion Medicine, Warsaw	Poland
Marjeta Macek Kvanka	Blood Transfusion Centre of Slovenia	Slovenia
Eduardo Muñiz Diaz, Nuria Nogues	Hospital Vall d'Hebron, Barcelona	Spain
Agneta Tanne-Wikman	Karolinska University Hospital	Sweden
Geoff Lucas	NHS Blood and Transplant, Filton	UK
Brian Curtis	Blood Center of Wisconsin	USA
Randy Schuller	American Red Cross - North Central Region, St Paul	USA

Appendix II. List of Participants in the Main Collaborative Study.

Participant	**Institute**	**Country**
Carlos Daniel de la Vega Elena	Hospital Italiano Garibaldi, Rosario	Argentina
Penny Hassell	Australian Red Cross Blood Service - Queensland	Australia
Grant Mraz	Australian Red Cross Blood Service - Victoria	Australia
Rita Fontão-Wendel, Silvano Wendel	Hospital Sírio Libanês, São Paulo	Brazil
Guo-Guang Wu	Nanning Institute of Transfusion Medicine	China
Maja Tomicic	Croatian Institute of Transfusion Medicine, Zagreb	Croatia
Kim Varming	Aalborg Hospital	Denmark
Ketty Lee	EFS Ile de France	France
Marie Audrain	CHU de Nantes	France
Brigitte Flesch, Frank Schauland	University Hospital Schleswig-Holstein, Kiel	Germany
Ulrich Sachs	Justus-Liebig University, Giessen	Germany
Jürgen Bux, Angelika Reil	DRK Blutspendedienst West, Hagen	Germany
Xuan Duc Nguyen	Institute of Transfusion Medicine and Immunology, Mannheim	Germany
Hartmut Kroll	Institute for Transfusion Medicine, Dessau	Germany
Nelson Tsuno	University of Tokyo	Japan
Leendert Porcelijn	Sanquin Diagnostic Services, Amsterdam	Netherlands
K Maslanka	Institute of Haematology & Transfusion Medicine, Warsaw	Poland
Marjeta Macek Kvanka	Blood Transfusion Centre of Slovenia	Slovenia
Eduardo Muñiz Diaz, Nuria Nogues	Hospital Vall d'Hebron, Barcelona	Spain
Agneta Tanne-Wikman	Karolinska University Hospital	Sweden
Geoff Lucas	NHS Blood and Transplant, Filton	UK
Irene Gray	N.E. Scotland Blood Transfusion Service, Aberdeen	UK
Brian Curtis	Blood Center of Wisconsin	USA
Randy Schuller	American Red Cross - North Central Region, St Paul	USA

Appendix III. Proposed Instructions For Use

1st WHO Reference Reagent,
Anti-HNA-1a (minimum potency)
NIBSC code *09/284*
Instructions for use
(Version 1.0, Dated 13/06/2011)

1. INTENDED USE
This material was established in 2011 as the 1st WHO Reference Reagent, Anti-human neutrophil antigen 1a (anti-HNA-1a), by the Expert Committee on Biological Standardization (ECBS) of the World Health Organization (WHO).
When reconstituted and diluted as described below, it should be used as a reference reagent for minimum acceptable potency for the detection of antibodies against the human neutrophil antigen 1a. This material should not be put to any other use.

2. CAUTION
This preparation is not for administration to humans.

The preparation contains material of human origin, which has been tested and found negative for HBsAg, anti-HIV 1+2 and HCV RNA by PCR 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 units are assigned to this material.

4. CONTENTS
Country of origin of biological material: Australia.
Each ampoule contains the residue after freeze-drying of 1 ml pooled human plasma. The plasma was collected from one donor and anticoagulated with citrate.

5. STORAGE
Store all unopened ampoules of the freeze-dried preparations at -20°C or below.

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 (labelled) 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.

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 one ampoule with 1.0 ml distilled water using gentle mixing. The ampoules do not contain bacteriostat and the preparation should not be assumed to be sterile.
Dilute the reconstituted material immediately before use by adding 1 volume of reconstituted material to 3 volumes of phosphate buffered saline containing bovine serum albumin. Diluted material should then be tested for the presence of IgG anti-HNA-1a antibodies using HNA-1a1a neutrophils. This dilution (1in 4) is the minimum dilution expected to be detectable in GIFT-M, GIFT-F, GAT and MAIGA assays. However, many laboratories can detect the anti-HNA-1a at higher dilutions, as shown in the collaborative study report which is available upon request.
N.B. the mab clone 3G8 is not suitable for use in the MAIGA to detect this antibody.

8. STABILITY
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 potency and status until withdrawn or amended.
Accelerated degradation experiments indicate that the freeze-dried materials in ampoules are stable after incubation at +45°C for at least 11 months.
Users who have data supporting any deterioration in the characteristics of any reference preparation are encouraged to contact NIBSC.

9. REFERENCES N/A

10. ACKNOWLEDGEMENTS
We would like to thank ARCBS, Sydney for supplying the raw materials

11. FURTHER INFORMATION
Further information can be obtained as follows;
This material: enquiries@nibsc.ac.uk
WHO Biological Standards: Http://www.who.int/biologicals/en/
Derivation of International Units:
Http://www.nibsc.ac.uk/products/faq.asp
Ordering standards from NIBSC:
Http://www.nibsc.ac.uk/products/faq.asp
NIBSC Terms & Conditions: Http://www.nibsc.ac.uk/terms.html

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.ac.uk

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

Physical and Chemical properties			
Physical appearance:	Pale yellow freeze-dried powder	Corrosive:	No
Stable:	Yes	Oxidising:	No
Hygroscopic:	Yes	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 skin contact		
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

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The Institute shall not be liable to the Recipient for any economic loss whether direct or indirect, which arise in connection with this agreement.

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.

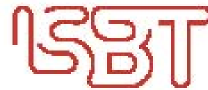
Net weight of each ampoule: 0.0812g

Toxicity Statement: Non-toxic

Veterinary certificate or other statement if applicable**.**

Attached: No

Appendix IV. Endorsement from the International Society for Blood Transfusion (ISBT) Granulocyte Immunobiology Working Party.



Working Party on Granulocyte Immunobiology

Chair: Lin Fung PhD
Critical Care Research Group
The University of Queensland and The Prince Charles Hospital,
Rode Road, Chermside,
Queensland, Australia.

28th June 2011

Proposed WHO Reference Material: Anti-HNA-1a standard (09/284)

The ISBT Working Granulocyte Immunobiology Party collaborated with NIBSC in a study on the anti-HNA-1a standard (09/284). From the results obtained in this study and on behalf of the Working Party, we wish to endorse that the material (09/284) provides a minimum sensitivity standard for the detection of anti-HNA-1a when used at a minimum dilution of 1 in 4, excepting that it is not detectable by MAIGA assay when used with CD16 monoclonal antibody clone (3G8).

Lin Fung
Chair

International Society
of Blood Transfusion

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