EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 20 October 2017

Report on a Collaborative Study for Proposed 1st WHO International Standard for Lupus (anti-dsDNA) antibodies (15/174)

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NOTE:
This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Comments MUST be received by 18 September 2017 and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Technologies, Standards and Norms (TSN). Comments may also be submitted electronically to the Responsible Officer: Dr M. Nübling at email: nueblingc@who.int.

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Summary

Systemic Lupus Erythematosus (SLE) is a severe auto-immune connective tissue disease, in which antibodies are generated to a range of autoantigens. Among these autoantigens, antibodies to double stranded DNA (anti-dsDNA), are highly specific for SLE, occurring in 70% of cases of SLE (against a non-SLE background of <5%). The levels of anti-ds DNA antibodies can also reflect the disease activity. As a result, measurement of anti-dsDNA is widely used as a diagnostic test for SLE, and there are a range of kits and diagnostic tests available.

In 1985, a freeze-dried preparation of plasma obtained from a patient with definite SLE was established as the first WHO International Standard for anti-dsDNA antibodies, and has been used to assign units to diagnostic tests. This material is now exhausted, and calls have been made for its replacement with a suitable preparation.

In the present study, oligo-specific SLE plasma was prepared as a lyophilised candidate standard for anti-dsDNA antibodies. The candidate standard was examined in an international collaborative study (36 laboratories in 17 countries), and compared with

- Local standards some of which were previously calibrated and traced to the first WHO IS for anti-dsDNA antibodies
- Three individual plasma donations from patients with SLE, to support evaluation of commutability of the candidate IS.

(The previous WHO IS was not available)

In all laboratories and test methods the candidate standard exhibited the reactivity of an anti-dsDNA antibody preparation. In approximately half of the laboratories the material behaved in an apparently similar way to local standards, and by inference to the previous IS. However in a similar number of laboratories there was observable non-parallelism, and no quantitative traceability to the unitage of the previous IS could be established. Moreover, across the entire study, it was not possible to establish commutability, as a consistent ranking order for the three patient samples was not obtained.

Given the apparent lack of qualitative comparability of this candidate material with the previous IS, it is considered that it would be unwise to establish this material as a replacement IS, with a defined unitage in IU. Accordingly it is proposed that the preparation 15/174 is established as the 1st WHO International Standard for Lupus (oligo-specific) anti-dsDNA antibodies with a nominal potency of 100 International Units per ampoule.
**Introduction**

Oligo-specific SLE plasma was donated to NIBSC and prepared as a lyophilised candidate standard for anti-dsDNA antibodies. This report describes the international collaborative study carried out on candidate IS preparation 15/174.

**Materials**

Plasma (2.4l) from a single donor, formally diagnosed as having oligospecific SLE, was donated by Professor Meroni, University of Milan. The preparation was de-fibrinated and 0.5ml filled into 5ml ampoules and lyophilised at NIBSC, using procedures approved for the production of international biological standards. Summary characteristics of the finished product are shown in Table 1.

**Table 1:**

<table>
<thead>
<tr>
<th>Code</th>
<th>15/174</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean fill weight</td>
<td>0.515g</td>
</tr>
<tr>
<td>Fill weight cv</td>
<td>1.0%</td>
</tr>
<tr>
<td>Mean residual moisture level</td>
<td>0.682%</td>
</tr>
<tr>
<td>Moisture level cv</td>
<td>12.88%</td>
</tr>
<tr>
<td>Head space oxygen</td>
<td>0.11%</td>
</tr>
<tr>
<td>Mean dry weight</td>
<td>0.026g</td>
</tr>
<tr>
<td>Dry weight cv</td>
<td>0.75%</td>
</tr>
<tr>
<td>Number of recovered ampoules</td>
<td>4382</td>
</tr>
</tbody>
</table>

In addition to the candidate material, two SLE patient samples containing anti-dsDNA antibodies in the range 100-200 IU/ml were donated by Drs Dahle and Lindbeck of Linkoping hospital, and a third sample, containing anti-dsDNA antibodies in the range 1000-2000 IU/ml was donated by Dr Gullstrand of Lund University. These materials were prepared in lyophilised ampoules using the same procedures outlined above, and are referred to in this report as S1, S2 and S3.

**Collaborative study**

Laboratories routinely performing quantitative estimations of anti-dsDNA antibodies were invited to participate, and requested to contribute:

- Full dilution comparisons and content estimates of 15/174 with local standards
- Where possible estimates of the 15/174 in IU, derived from previous calibrations against the 1st WHO IS
- Three independent assays (here defined as a dilution series prepared from a fresh ampoule rather than a stored aliquot) performed over three separate occasions, with within-occasion duplication of each dilution series
- Estimates of the patient sera against local standards and against the candidate standard 15/174.

Participants returned data from 36 laboratories in 17 countries.
Methods

Methods used in the study fall into three classes:

- Immunofluorescence using *Crithidia luciliae*. *C. Lucilae* is a flagellated trypanosome which has a kinetoplast composed of complex double stranded DNA, which can act as a specific substrate for anti-dsDNA antibodies.
- EIA
- Farr assay, in which ammonium sulphate is used to precipitate complexes of antibody and radioactively labelled dsDNA).

The *C. lucilae* immunofluorescence tests (CLIFT) report in end-point titres. All other assays report in IU/ml, derived from historical value assignments of in-house standards to the 1st WHO IS. Specific laboratory methods included in the study are listed in Table 2.

Table 2: Laboratory methods

<table>
<thead>
<tr>
<th>Laboratory code</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,4,5,6,8,9,11,13,14,16,18,20.3, 20.4,21,22,26,28,30,33,35,36</td>
<td>Crithidia Lucilae immunofluorescence (CLIFT)</td>
</tr>
<tr>
<td></td>
<td><strong>EIA</strong>’s</td>
</tr>
<tr>
<td>1,8, 27.1, 35,32</td>
<td>Bioplex 2200</td>
</tr>
<tr>
<td>2,4,6,7,10,11,22,23,25,28,30,</td>
<td>Phadia EliA</td>
</tr>
<tr>
<td>3,</td>
<td>Eurodiagnostica ELISA</td>
</tr>
<tr>
<td>9.2</td>
<td>Trinity Biotech Captia ELISA</td>
</tr>
<tr>
<td>9.3</td>
<td>Immco ELISA</td>
</tr>
<tr>
<td>12,17, 33</td>
<td>Orgentec ELISA</td>
</tr>
<tr>
<td>13</td>
<td>Immunoconcepts EIA</td>
</tr>
<tr>
<td>14</td>
<td>Phadia VarelisA</td>
</tr>
<tr>
<td>26</td>
<td>Orgentec ALEGRIA</td>
</tr>
<tr>
<td>18.1</td>
<td>Theradiag ELISA</td>
</tr>
<tr>
<td>18.2</td>
<td>Theradiag FDIS MX005 dsDNA</td>
</tr>
<tr>
<td>18.3</td>
<td>Theradiag FDIS MX1117 Connective Profile</td>
</tr>
<tr>
<td>19</td>
<td>Innova Quanta flash</td>
</tr>
<tr>
<td>20.1</td>
<td>EUROIMMUN anti-dsDNA ELISA</td>
</tr>
<tr>
<td>20.2</td>
<td>EUROIMMUN anti-dsDNA NcX ELISA</td>
</tr>
<tr>
<td>21</td>
<td>Theradiag FDIS</td>
</tr>
<tr>
<td>27.2</td>
<td>Bio-Rad Kallestad (Evolis system)</td>
</tr>
<tr>
<td>27.3</td>
<td>Bio-Rad EIA (PhD system)</td>
</tr>
<tr>
<td>29.1</td>
<td>Innova-quanta lite ELISA 708510</td>
</tr>
<tr>
<td>29.2</td>
<td>Innova-quanta lite HA ELISA 704615</td>
</tr>
<tr>
<td>29.3</td>
<td>Innova-quanta lite dsDNA ELISA 704650</td>
</tr>
<tr>
<td>29.4</td>
<td>Innova Quanta flash (CIA) 701178</td>
</tr>
<tr>
<td>24</td>
<td>Zeus Athena (Luminex technology)</td>
</tr>
<tr>
<td>34.1</td>
<td>Bio-RAD ELISA</td>
</tr>
<tr>
<td>16</td>
<td>In-house fluoroimmuno assay (binding ratio)</td>
</tr>
<tr>
<td>31</td>
<td>Alpha Diagnostica ELISA</td>
</tr>
<tr>
<td><strong>Farr Immunoassays</strong></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>IBL International dsDNA Farr RIA</td>
</tr>
<tr>
<td>9.1, 34.2, 36</td>
<td>Trinity Farr RIA</td>
</tr>
</tbody>
</table>
Statistical analysis

Potency estimates for candidate IS 15/174 and Samples 1-3 calculated at NIBSC
Estimates in IU/ml at each sample dilution as reported by participants were used directly in the analysis to calculate the potency of the candidate IS (15/174) and Samples 1-3. A geometric mean (GM) of results corrected for dilution was calculated for each sample in each assay run, excluding any dilutions not on a linear section where necessary. Dilutional linearity (parallelism with “kit standard”) was concluded if a linear relationship with a fitted slope between 0.80 and 1.25 was observed for log estimated concentration against log dilution. Where this was not observed, no calculated estimate relative to kit standard has been reported. Where fewer than half of the assays performed by a laboratory gave valid results for a sample, no laboratory mean result is reported for that sample.

Reported potency estimates for candidate IS 15/174 and Samples 1-3
As not all laboratories provided estimates at individual dilutions, final potency estimates reported for each sample in each assay, or overall, are also presented for comparison. A geometric mean was used to combine results from individual assays. It should be noted that these estimates are not based on a consistent approach as the dilutions used for this purpose varied by laboratory and assay method.

Potency estimates for Samples 1-3 relative to candidate IS 15/174
Relative potency estimates for Samples 1-3 to candidate IS 15/174 were calculated using a parallel-line model with log estimated concentration as assay response. Where the ratio of fitted slopes for the samples under consideration was not in the range 0.80 to 1.25, non-parallelism was concluded and no relative potency has been reported.

Combination of results
Results from all valid assay runs were combined to generate unweighted geometric means for each laboratory and these laboratory means were used to calculate overall unweighted geometric mean potency estimates. Variability between laboratories has been expressed using geometric coefficients of variation (GCV = \(10^{-1}\times100\%\) where s is the standard deviation of the log\(_{10}\) transformed estimates). For the purposes of this report, “outliers” were defined as results more than (1.5 x IQR) higher than the upper quartile or (1.5 x IQR) lower than the lower quartile, where IQR denotes the interquartile range.

Stability
To predict stability on extended storage, ampoules of 15/174 were stored at elevated temperatures for 1.3 years before measuring the residual activity in a commercial anti-dsDNA assay. The relative potencies of the accelerated thermal degradation samples were used to fit an Arrhenius equation relating degradation rate to absolute temperature assuming first-order decay [REF: Kirkwood], and hence predict the degradation rates when stored at a range of temperatures.
Results

Data returned for analysis
Data were contributed by 36 laboratories, performing 29 different methods (CLIFT, 26 EIA’s, 2 Farr assays). In total, 69 individual CLIFT, 238 EIA and 24 Farr assays were performed, although not all samples were tested in each assay.

Assay validity (EIA and Farr assays)
Individual assay estimates and instances of non-parallelism (with “kit standards” or 15/174) are shown in Appendix Table A1 (calculated at NIBSC from reported results) and Table A2 (calculated relative to 15/174 by parallel line analysis). A summary of the extent of non-parallelism is shown in Table 3.

Table 3: Summary of observed non-parallelism

<table>
<thead>
<tr>
<th>Sample</th>
<th>Percentage of labs with non-parallelism (total number of labs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15/174</td>
<td>33% (39) Relative to local standards</td>
</tr>
<tr>
<td>S1</td>
<td>38% (26) Relative to local standards</td>
</tr>
<tr>
<td>S2</td>
<td>17% (23) Relative to local standards</td>
</tr>
<tr>
<td>S3</td>
<td>22% (23) Relative to local standards</td>
</tr>
</tbody>
</table>

Potency of 15/174 and Samples 1-3 (EIA and Farr assays)
Laboratory geometric mean potency estimates are summarized in Table 5 (calculated at NIBSC), Table 6 (as reported by participating laboratories), Table 7 (calculated relative to 15/174 by parallel line analysis) and Figures 1-11.

Crithidia assay results
End-point titre results returned for Crithidia assays are summarized in Table 8 and shown for each assay in Appendix Table A4 and graphically in Figures 12-15.

Stability of 15/174
Estimates of the potency of ampoules stored at elevated temperatures for a period of 1.3 years are summarized in Table 4. Analysis showed a predicted loss of potency per year of 0.09% when stored at -20°C, which fell to <0.001% predicted for storage at -70°C.

Table 4: Stability prediction of 15/174

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>Potency</th>
<th>Time (years)</th>
<th>95% LCL</th>
<th>95% UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>0.99</td>
<td>1.3</td>
<td>0.96</td>
<td>1.02</td>
</tr>
<tr>
<td>4</td>
<td>0.97</td>
<td>1.3</td>
<td>0.95</td>
<td>1.00</td>
</tr>
<tr>
<td>20</td>
<td>0.89</td>
<td>1.3</td>
<td>0.87</td>
<td>0.91</td>
</tr>
<tr>
<td>37</td>
<td>0.56</td>
<td>1.3</td>
<td>0.55</td>
<td>0.58</td>
</tr>
<tr>
<td>45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Would not reconstitute</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predicted degradation rates

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>K</th>
<th>S.E. (K)</th>
<th>% Loss per Year</th>
<th>95% UCL % Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>-70</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Discussion, conclusions and proposed recommendations

Projects aimed at replacing an exhausted WHO International Biological Standard generally follow a typical outline:

- Securing a starting material with similar properties to the original standard.
- Preparing a candidate standard.
- Carrying out a collaborative study to establish a quantitative relationship with the previous standard using a range of methods reflecting the proposed use of the standard.
- Assigning a value derived from the collaborative study data.
- Seeking agreement and endorsement of participants and formal adoption by WHO.

For a number of reasons, this process is of limited applicability to the current project:

i) The first IS for anti-dsDNA is exhausted and has been unavailable for many years.
ii) Some methods included in the study can provide a historical linkage to the unitage assigned to the 1st IS through earlier calibration exercises, although many cannot, and none can be confirmed due to the unavailability of the 1st IS.
iii) The replacement paradigm may not be readily applicable in the case of standardizing antibodies of autoimmune pathologies using patient’s sera where the candidate replacement is unlikely to be identical to the original.

Point iii) above is likely to be particularly significant in the case of lupus anti-dsDNA antibodies:

- Patients with SLE contain many different autoantibodies against a range of antigens, including dsDNA.
- There will be a different range of autoantibodies in different patient sera.
- It is known that different methods may detect different populations of anti-dsDNA so there are discrepancies in ‘potencies’ depending on the type of test when applied to individual patients.

With these caveats in mind, a number of summary observations may be made about the data reported in the study, as a whole:

- Generally, the methods reported fall into two broad classes, quantitative immunoassay methods (EIA’s and Farr assays) which report in units of a local standard, in some cases historically traceable to the first WHO IS, and Crithidia Luciliae binding assays based on immunofluorescence (CLIFT) which report in absolute titres.
- In all assays reported in the study, the candidate standard, 15/174, exhibited anti-dsDNA binding activity.
- Despite the universally recognised anti-dsDNA antibody activity, the study revealed widespread instances of non-parallelism between the candidate material, 15/174, and local standards (33% of labs), and to a lesser extent between the candidate material and each of the clinical samples, S1 (14%), S2 (14%) and S3 (18%).

- Non-parallelism was also widely seen between the local standards and the clinical samples, S1 (38% of labs), S2 (17%) and S3 (22%). Non-parallelism between the test materials and the standard was not therefore a feature specific to the candidate standard, but is in fact widely existing in the portfolio of already established assay methods, and considering all assay methods is actually improved when using the candidate standard.

- Where statistically valid estimates could be obtained, estimates for 15/174 in terms of local kit standards or for clinical samples in terms of kit standards or relative to the candidate standard tended to be highly variable. Estimates of the candidate standard, 15/174 against kit standards, for example, ranged from 56 IU/ml to a high of 847 IU/ml, although the majority of estimates fell in the 100 to 200 IU/ml range (Table 5 and Figure 1). Similar variability of estimates was seen for the clinical samples against either the candidate or kit standards (Tables 5, 6 and 7). End point titre estimates from the CLIFT assays were similarly highly variable, for example ranging from 50 to 1000 for 15/174 (Table 8).

- Notwithstanding this variability, again considering those assays where statistically valid estimates could be obtained, calculation of estimates in terms of a common candidate standard invariably produced a reduction in between-assay variability. The effect was most noticeable in the CLIFT assays (Table 8) where comparing the estimates in terms of absolute titres with those obtained relative to 15/174, the GCV’s were reduced from 153% to 47% (samples S1), 143% to 46% (S2) and 259% to 88% (S3). For quantitative immunoassays, comparing estimates reported in terms of local kit standards (Table 6) against those calculated in terms of 15/174 (Table 7) showed reductions in GCV for clinical samples S1 (123% to 86%) and S2 (184% to 42%) , but not for S3 (93% to 117%), based on results after exclusion of outliers.

- Formal demonstration of commutability would require a consistent relationship between the estimates obtained for the clinical samples in terms of the candidate standard and those obtained against local standards. Notwithstanding the absolute variability of estimates, the means of all quantitative immunoassays for samples S1, S2 and S3 were 1.32, 1.35 and 8.20 relative to 15/174 (Table 7), and 200, 199 and 1406 IU/ml in terms of local standards (Table 6). Within the limitations of a small sample set and highly variable estimates, it is concluded that the condition of commutability is approximately satisfied.

- The candidate standard showed no evidence of loss of activity on accelerated thermal degradation after 16 months, with a predicted rate of loss of 0.09% per year at -20°C.
In summary:

- The field of autoantibodies, where individual patients cannot be assumed to be qualitatively or quantitatively similar, nor to produce consistent assay estimates between assay methods, imposes severe limitations on what can be achieved in terms of standardization.
- With no statistically meaningful overall assay estimate, nor an overall demonstration of assay parallelism, the current candidate standard cannot be shown to be equivalent to its predecessor, and establishment of the current candidate as the next IS must inevitably involve a discontinuity.
- Notwithstanding this discontinuity, the study shows that the field would benefit from the availability of a common standard, and that the current situation, with manifest differences in performance between different assays ostensibly measuring the same thing, would be improved.

Draft Proposals:

1. The preparation 15/174 should be established as the first WHO IS for Lupus (oligo-specific) anti-dsDNA antibodies. The proposed name intentionally emphasises the non-continuity with the first IS for anti-dsDNA antibodies.

2. The candidate standard should have an assigned value of 100 IU/ampoule (the assigned value is arbitrary rather than a formal calibration).

3. Information for users should emphasize the caution needed in transferring the unitage to existing assay methods.

4. WHO should be asked to recognize the need to develop a formal scientific paradigm for achieving continuity of standardization in the area of auto-antibodies.

Instructions for Use

The draft Instructions for Use to accompany 15/174 are provided in Appendix 6.

Acknowledgements

The study organisers thank Professor Meroni for donating the plasma used for the candidate IS, and Drs Dahle, Lindbeck and Gullstrand for donating clinical samples. We thank the staff of the Centre for Biological Reference Materials, NIBSC, for ampouling the candidate IS and samples. We are extremely grateful to the study participants for contributing data.
References


Participants feedback

The draft report was distributed between all participants for comment and all but one participant (Lab 20) agreed with the draft proposals. Laboratory 18 provided additional results using a different dilution buffer. Their comments and results are as follows:

Laboratory 18

After investigations, the titers differences between ours and other participants results is explained by the high sensitivity of the FIDIS dsDNA and Connective kits. Their dilution buffer enhances the binding of all anti-dsDNA antibodies, even those with low affinity. The proposed standard (15/174) and the associated samples (S1, S2, S3) tested with another FIDIS dilution buffer (used in other kits) have expected titers, as you can see in the table below:

<table>
<thead>
<tr>
<th></th>
<th>March 2016</th>
<th>November 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>FIDIS Connective kit</strong></td>
<td><strong>FIDIS Connective kit</strong></td>
</tr>
<tr>
<td></td>
<td>Batch 124580</td>
<td>Batch 127688</td>
</tr>
<tr>
<td>Standard 15/14</td>
<td>898</td>
<td>939</td>
</tr>
<tr>
<td>1/2</td>
<td>444</td>
<td>459</td>
</tr>
<tr>
<td>1/4</td>
<td>218</td>
<td>263</td>
</tr>
<tr>
<td>1/8</td>
<td>97</td>
<td>119</td>
</tr>
<tr>
<td>Sample 1</td>
<td>325</td>
<td>329</td>
</tr>
<tr>
<td>1/2</td>
<td>225</td>
<td>240</td>
</tr>
<tr>
<td>1/4</td>
<td>142</td>
<td>137</td>
</tr>
<tr>
<td>1/8</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>Sample 2</td>
<td>1349</td>
<td>1348</td>
</tr>
<tr>
<td>1/2</td>
<td>712</td>
<td>645</td>
</tr>
<tr>
<td>1/4</td>
<td>378</td>
<td>299</td>
</tr>
<tr>
<td>1/8</td>
<td>186</td>
<td>165</td>
</tr>
<tr>
<td>Sample 3</td>
<td>3298</td>
<td>3730</td>
</tr>
<tr>
<td>1/2</td>
<td>2506</td>
<td>2227</td>
</tr>
<tr>
<td>1/4</td>
<td>1546</td>
<td>1128</td>
</tr>
<tr>
<td>1/8</td>
<td>700</td>
<td>575</td>
</tr>
</tbody>
</table>
In conclusion, standard 15/174 and the three tested samples probably contain some anti-dsDNA antibodies with low affinity which are detected by our FIDIS kits with their high sensitivity buffers.

**Laboratory 20**

1. We have doubts that the preparation 15/174 would be a suitable international standard. As you have outlined in your summary (bulletpoint 2), there are difficulties in parallelism. In fact, the variation and non-parallelism to local standards for 15/174 seems to be high (non-parallelism in 33% of labs), whereby the included clinical samples S2 and S3 showed non-parallelism to local standards to a much lesser extent (only 17-22% of labs). We wonder if there couldn’t be better preparations and would like to suggest to not propose 15/174 as the new “international standard for Lupus (oligo-specific) anti-dsDNA antibodies”. We agree, that a new IS could not be identical to the earlier IS, but it would be worth striving for a preparation performing as good as possible and comparable to the earlier IS. This might not be the case for the preparation 15/174.

2. We want to point to the fact that our assays shall be used and are validated for serum or plasma samples but not for plasmapheresis material. Independent from the variability or comparability to Wo/80, we want to express our serious concerns on the usage of plasmapheresis material as a standard.

**NIBSC response to Laboratory 20**

From the results of an ECFSG study, Professor Johan Rönnelid recommended to NIBSC the plasma used for 15/174 to replace Wo/80, also prepared from the plasma of one patient collected by plasmapheresis (stocks of which are exhausted). There is a pressing need for a replacement standard now and your reservations are pointed out in the report. No knowledge of another such preparation exists and the limitations of this preparation will be detailed in the Instructions for Use.
Participants of the collaborative study (in alphabetical order of country):

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carolien Bonroy</td>
<td>Ghent University Hospital, Ghent, Belgium</td>
</tr>
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Throughout this report these laboratories are cited by a code number which does not reflect the order of listing above.

Table 5: Geometric mean potency estimates (IU/ml) calculated at NIBSC

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Summary excluding outliers

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* denotes an outlier, NP = non-parallel

### Table 6: Geometric mean potencies (IU/ml) based on laboratory-reported estimates

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**Summary**
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### Table 7: Geometric mean potency estimates relative to 15/174 based on parallel line analysis

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Figure 1: Geometric mean potency estimates (IU/ml) for 15/174 based on NIBSC calculations

Figure 2: Geometric mean potency estimates (IU/ml) for S1 based on NIBSC calculations
Figure 3: Geometric mean potency estimates (IU/ml) for S2 based on NIBSC calculations

Figure 4: Geometric mean potency estimates (IU/ml) for S3 based on NIBSC calculations
Figure 5: Geometric mean potencies (IU/ml) for 15/174 based on laboratory-reported estimates

Figure 6: Geometric mean potencies (IU/ml) for S1 based on laboratory-reported estimates
Figure 7: Geometric mean potencies (IU/ml) for S2 based on laboratory-reported estimates

Figure 8: Geometric mean potencies (IU/ml) for S3 based on laboratory-reported estimates
Figure 9: Geometric mean relative potencies of S1 to 15/174 calculated by parallel line analysis

![Parallel line analysis graph for S1 to 15/174](image)

Figure 10: Geometric mean relative potencies of S2 to 15/174 calculated by parallel line analysis

![Parallel line analysis graph for S2 to 15/174](image)
Figure 11: Geometric mean relative potencies of S3 to 15/174 calculated by parallel line analysis
Figure 12: Geometric mean end-point titres of 15/174 from Crithidia assays

Figure 13: Geometric mean end-point titres of S1 from Crithidia assays
Figure 14: Geometric mean end-point titres of S2 from Crithidia assays

Figure 15: Geometric mean end-point titres of S3 from Crithidia assays
Appendix Table A1: Assay potency estimates (IU/ml) calculated at NIBSC

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NL = Non-linear
NP = Non-parallel
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### Appendix Table A4: Assay end-point titres in Crithidia assays

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Appendix 5  Collaborative study protocol

COLLABORATIVE STUDY PROTOCOL TO ASSIGN A POTENCY TO THE PROPOSED 2nd INTERNATIONAL STANDARD FOR SERUM ANTI-dsDNA (15/174)

Scientific advisors and co-ordinators
Dr Carl Dolman and Dr Susan J Thorpe (study co-ordinators)  
National Institute for Biological Standards and Control (NIBSC)

Professor Johan Rönnelid  
University of Uppsala  
Chairman of the “European Consensus Finding Study Group on Autoantibodies”  
(ECFSG)

Professor Pier Luigi Meroni  
University of Milan

Statistician
Mr Peter Rigsby (NIBSC)

1Collaborative study co-ordinators: carl.dolman@nibsc.org; susan.thorpe@nibsc.org; susanthorpe@outlook.com

Tel: +44 (0)1707 641267 or +44 (0)1707 641251; Fax: +44 (0)1707 641057
1. **AIM**

To assign a nominal potency to the candidate 2\textsuperscript{nd} International Standard for serum anti-dsDNA (15/174).

2. **MATERIALS PROVIDED**

3 ampoules of the candidate 2\textsuperscript{nd} International Standard for serum anti-dsDNA (15/174)  
*Approximate potency 130-250 IU/ml*

3 ampoules of Sample 1  
*Potency approx. 1-2x that of 15/174*

3 ampoules of Sample 2  
*Potency approx. 1-2x that of 15/174*

3 ampoules of Sample 3  
*Potency approx. 10-15x that of 15/174*

*The potencies above are approximations and intended only as a guide for making dilution series*

*Store all ampoules at \(-20^\circ C\) until reconstitution and use. Do not reconstitute until the day of use.*

Reconstitute the contents of each ampoule with 0.5 ml distilled/deionized H\textsubscript{2}O according to the ‘Instructions for Use’ sheets supplied with the materials. Vortex gently and inspect contents to ensure complete dissolution. Transfer reconstituted contents to a capped tube. May be stored at 4\textdegree C after use for repeat assays, if necessary.  
Additional ampoules can be provided on request in the case of breakages or errors.

3. **ASSAY DESIGN**

**DAY 1:**

Reconstitute one ampoule of each of 15/174, Sample 1, Sample 2 and Sample 3.

*For ELISAs:*

Assay 2 independent dilution series (e.g., neat, 1 in 2, 1 in 4, 1 in 8 etc) in your usual assay diluent of each of the reconstituted preparations alongside your usual standard dilutions, also in
replicate, in the same assay run. Each replicate dilution series should be prepared separately from the neat, reconstituted ampoule contents, including any pre-dilution required by your assay; do not assay duplicates of a single dilution series. Please indicate clearly on the results sheets whether the dilutions tested relate to a pre-dilution or the neat, reconstituted ampoule contents.

Perform a second assay to include all preparations as above, with 2 fresh independent dilution series prepared separately from the ampoule contents of each preparation, including any pre-dilution required by your assay, adjusting the dilutions if necessary to ensure responses fall within the measureable range of your assay.

Therefore, a total of 4 independent dilution series from each reconstituted preparation should have been tested in 2 assays (2 dilution series per assay).

**For Crithidia assays:**
Titre each of the reconstituted ampoule contents according to your usual method, and record the intensity of staining of the kinetoplast at each dilution. Record the highest titre which gives a clear positive result. Also record whether significant nuclear staining is present.

**For Farr assays:**
Please adapt the ELISA protocol as necessary.

**DAY 2:**

Reconstitute a second ampoule of each of 15/174, Sample 1, Sample 2 and Sample 3.

Perform 2 separate ELISAs/Farr assays and a Crithidia assay as for Day 1.

**DAY 3:**

Reconstitute a third ampoule of each of 15/174, Sample 1, Sample 2 and Sample 3.

Perform 2 separate ELISAs/Farr assays and a Crithidia assay as for Day 1.

**4. RECORDING RESULTS**

Please enter the raw ELISA data, i.e., dilution factor and response (e.g., absorbance for manual tests or concentration for automated tests), on the Excel results sheets (preferred; sent electronically) or Word results sheets provided. Please adapt the sheets as necessary to record Farr assay data.
Please enter the Crithidia assay results and titres on the Word results sheets provided.

Please enter your own estimates of the anti-dsDNA concentrations (in IU/ml) of 15/174, Sample 1, Sample 2 and Sample 3 relative to your own standard on the Excel (preferred) or Word summary sheet provided, along with any comments.

Return electronic copies of the results to susan.thorpe@nibsc.org, susanthorpe@outlook.com, and carl.dolman@nibsc.org.

PLEASE RETURN YOUR RESULTS BY 25th MARCH 2016
Appendix 6 Draft Instructions for Use

WHO International Standard
Lupus (oligo-specific) anti-dsDNA antibodies
NIBSC code 15/174
Instructions for use
(Version 2.00, Dated 16/01/2017)

1. INTENDED USE
Preparation 15/174 was subjected to an international collaborative study in 2016, consisting of 36 laboratories in 17 countries. The study did not show a statistically meaningful overall assay estimate, nor an overall demonstration of assay parallelism, so 15/174 cannot be shown to be equivalent to its predecessor, and establishment of the next IS must inevitably involve a discontinuity. Established as the first WHO IS for Lupus (oligo-specific) anti-dsDNA antibodies, the name internationally emphasises the non-continuity with the first IS for anti-dsDNA antibodies (Wo82). Notwithstanding this discontinuity, the study showed that the field would benefit from the availability of a common standard, and that the current situation, with manifest differences in performance between different assays ostensibly measuring the same thing, would be improved. This preparation is intended to be used to align test methods quantifying levels of anti-dsDNA antibodies to a common standard.

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. VINTAGE
15/174 cannot be shown to be equivalent to its predecessor (Wo82) and has been assigned an arbitrary value of 100 IU/ampoule. In this situation, noting imitations across assay platforms, end-users will need to define their own limits. Exercise caution when transferring this vintage to existing assay methods.

4. CONTENTS
Country of origin of biological material: United Kingdom.
Each ampoule contains the lyophilised residue of 0.5 ml defibrinated plasma i.e., serum, containing anti-dsDNA.

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.
Tap the ampoule gently to collect the material at the bottom (labeled) 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 any portion of the freeze-dried material prior to reconstitution.
Ensure the lyophilised contents are at the bottom of the ampoule. Reconstitute the ampoule contents with 0.5 ml distilled or deionised water, using a calibrated pipette. Vortex VERY gently and inspect contents to ensure complete dissolution. Transfer contents to a clean tube.

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.

Accelerated degradation studies on 15/174 indicate that the lyophilised material will be adequately stable at -20°C. Once reconstituted, diluted or aliquoted, users should determine the stability of the material according to their own method of preparation, storage and use.

NIBSC follows the policy of WHO with respect to its reference materials.

9. REFERENCES
N/A

10. ACKNOWLEDGEMENTS
We thank Professor Meroni, University of Milan, for donating the plasma.

11. FURTHER INFORMATION
Further information can be obtained as follows;
This material: enquiries@nibsc.org
WHO Biological Standard:
http://www.who.int/biologicals/en/
JCTLM Higher order reference material:
http://www.bimp.org/en/committees/jctlm/
Derivation of International Units:
http://www.nibsc.org/products/biological_reference_materials/frequently_asked_questions/how_are_international_units.aspx
Ordering standards from NIBSC:
http://www.nibsc.org/products/ordering_information/frequently_asked_questions.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

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National Institute for Biological Standards and Control
Potters Bar, Hertfordshire, EN6 3QG, T: +44 (0) 1707 64 1000, nibsc.org
WHO International Laboratory for Biological Standards,
UK Official Medicines Control Laboratory

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Medicines & Healthcare products
Regulatory Agency

<table>
<thead>
<tr>
<th>Storable:</th>
<th>Yes</th>
<th>Oxidising:</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroscopic:</td>
<td>No</td>
<td>Irritant:</td>
<td>Unknown</td>
</tr>
<tr>
<td>Flammable:</td>
<td>No</td>
<td>Handling:</td>
<td>See caution, Section 2</td>
</tr>
<tr>
<td>Other (specify):</td>
<td>Consists of lyophilised human serum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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

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### 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**: 0.05g
- **Toxicity Statement**: Toxicity not assessed
- **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_internationalstandardsrev2004.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.