


Process for comparing certified values of the same measurand in multiple reference materials (CRMs)			 Accurate results for patient care
Date: 27 January 2017 Version : 3.0	Authorized : JCTLM Executive	JCTLM DB P-04A	

Process for comparing certified values of the same measurand in multiple reference materials (CRMs)

1. Purpose

This document describes JCTLM process which can be followed by the producers of Certified Reference Materials (CRMs) for demonstrating the extent-of-equivalence of CRMs that are nominally fit for the identical purpose(s). The process is intended to ensure that information to indicate the extent-of-equivalence is available for these materials. When more than one material is listed by the JCTLM, potential CRM users need such information to make an informed selection of the material(s) best suited to their needs.

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3. Scope

This procedure applies to all nominations of CRMs that are submitted for evaluation by JCTLM DB WG for inclusion in the JCTLM database where there are JCTLM listed materials that are nominally fit for the same purpose; i.e., the materials have nominally identical matrices and they carry certified values for one or more of the same measurands. Replacement lots of certified reference materials (CRMs) are deemed to be new materials and are thus subject to the extent-of-equivalence testing procedures described for new materials.

4. Acronyms and definitions

All acronyms and definitions employed in the procedures of the JCTLM DB WG Quality Manual are given in the procedure document JCTLM EXE-G01, Glossary of terms and definitions.

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5. Responsibilities and Authorizations

- 5.1. The JCTLM Executive has the following responsibilities under this procedure.
 - 5.1.1. DB WG's recommendations for listing in the JCTLM Database extent-of-equivalence reports of CRMs evaluated for the same measurand.
- 5.2. The JCTLM Secretariat has the following responsibilities under this procedure.
 - 5.2.1. To appropriately post approved material extent-of-equivalence reports on the JCTLM Database website.
- 5.3. The DBWG vice-Chairs have the following responsibilities under this procedure.
 - 5.3.1. To review RT's recommendations
 - 5.3.2. To communicate DB WG's recommendations to the JCTLM Secretariat for Executive approval.
- 5.4. The RT leaders have the following responsibilities under this procedure.
 - 5.4.1. To ensure that representative comparison data for material extent-of-equivalence demonstration are available for evaluation by the review team if necessary.
- 5.5. The RTs have the following responsibilities under this procedure.
 - 5.5.1. To review the extent-of-equivalence data as part of the evaluation of nomination of CRM.
- 5.6. The CRM nominator has the following responsibilities under this procedure.
 - 5.6.1. To initiate extent-of-equivalence evaluation when two or more CRMs are identified as being fit for the same purpose
 - 5.6.2. To define an appropriate measurement performance criteria for the particular measurand(s) in the given matrix.
 - 5.6.1. To define an appropriate measurement protocol.
 - 5.6.2. To perform the necessary measurements.
 - 5.6.3. To prepare a report of analysis that suitably documents the performed measurements and the measurement systems used
 - 5.6.4. In collaboration with whom may be actively involved in the evaluation, to draft a Final Report for the extent-of-equivalence determination of the evaluated CRMs. The attachments to this document provide examples of draft reports of extent-of-equivalence demonstrations for potassium and cholesterol in human serum.
 - 5.6.5. When appropriate, to publish the results of extent-of-equivalence studies in peer-reviewed and trade journals.

6. Procedure


- 6.1. The process for demonstrating the extent-of-equivalence of materials will be initiated by CRMs nominators whenever two or more materials that are nominally fit for the same purpose are identified in the JCTLM database. The extent-of-equivalence demonstration process should be completed when the producer of a CRM submits a nomination for evaluation by DB WG RT.

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6.2. Identify Measurement Performance Requirements. Extent-of-equivalence evaluation requires adequate relative, not absolute, measurements of measurand levels in the different materials. The major considerations for selecting an appropriate measurement system for these relative measurements are sensitivity, selectivity, linearity, and repeatability. It is the responsibility of the CRMs nominator to establish fit-for-purpose criteria for these performance metrics for each set of multiple materials, given the stated purpose of the materials and the certified values and uncertainties of the measurands.

The following apply separately to each measurand evaluated:

- 6.2.1. Sensitivity: the measurement system must provide an adequately sensitive signal at the lowest level certified in any of the materials.
 - 6.2.2. Selectivity: the measurement system must provide an adequately selective signal given the materials' general matrix and any explicitly stated material components.
 - 6.2.3. Linearity: the measurement system must provide an adequately linear signal to allow direct proportional comparison between the signals of the lowest and highest levels certified in any of the materials.
 - 6.2.4. Repeatability: the measurement system must provide adequate repeatability precision over the time course of all measurements required for the comparison. This repeatability is relative to the certified uncertainties of the materials being compared.
- 6.3. If adequate extent-of equivalence data are unavailable, CRM producers are encouraged to acquire the needed among-CRM extent-of-equivalence data as a component of their certification process.
- 6.3.1. For established CRMs, other interested parties may have performed and published the needed information. The CRM nominator will investigate the availability of extent-of-equivalence information and, if it exists, evaluate the data against the criteria established above.
 - 6.3.2. If the existing data are adequate, proceed to Section 6.5; if no information is available or the available information is not adequate, proceed with Section 6.4.
- 6.4. If adequate extent-of-equivalence data are not available, the responsible CRM nominator should initiate a program to acquire adequate data.
- 6.4.1. A laboratory capable of adequately performing the measurements must be identified. The CRM producers involved are the likely candidates, but any laboratory that has demonstrated measurement competence for the given measurand(s) in the given sample matrix should be considered.
 - 6.4.1.1. Operation according to the requirements of ISO 17025 and ISO 15195 is expected of laboratories that operate outside the CIPM MRA.
 - 6.4.2. An appropriate measurement protocol must be developed that has good potential for satisfying the performance criteria of Section 6.2. The protocol should provide for at least two independent replicate determinations of the measurand(s) for each unit of each material analyzed. The protocol should not require consumption of more than two units of each of the relevant CRMs. Example protocols are provided in the attachments to this procedure.

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- 6.4.3. The identified measurement laboratory performs the measurements and prepares a report of analysis that documents: the analytical measurement process employed, the measurement linearity over the measurand levels of interest, measurement repeatability over the measurand levels of interest and the measurement results for each material.
- 6.4.4. The measurement laboratory will send the report of analysis to the CRM nominator who solicited the study. In the event of unanticipated measurement difficulties or results that do not meet the performance criteria of Section 6.2, the CRM nominator and the measurement laboratory should together attempt to resolve the difficulties or deficiencies. If the data remain insufficient for valid comparison, the measurement performance criteria should be re-evaluated and/or a new measurement effort must be initiated.
- 6.5. When adequate extent-of-equivalence data are available, the CRM nominator will determine the extent-of-equivalence of the materials.


- 6.5.1. Given sufficiently unbiased measurements such as those summarized in Table 1 and Figures 1a and 1b of the potassium example in Attachment 1, extent-of-equivalence can be evaluated from the extent of overlap between the 95% confidence intervals of the measured value, $X_i \pm U_{95}(X_i)$, and the certified value, $C_i \pm U_{95}(C_i)$, of each material. The least squares regression of the measured X_i as a linear function of the certified values, $X_i = a + bC_i$, enables evaluation of bias: within their asymptotic uncertainties, the intercept is zero and the slope is one.

While Figure 1a displays both the measured and certified value intervals, it is difficult to visually compare them due to the range of measurand levels in the CRMs. Figure 1b provides a much more interpretable display by expressing the intervals relative to the certified values: $X_i/C_i \pm U_{95}(X_i)/C_i$ and $1 \pm U_{95}(C_i)/C_i$. For all materials, there is a nearly complete overlap between the measured and certified intervals: these CRMs are fully and about equally comparable for potassium.

- 6.5.2. Relative extent-of-equivalence can be evaluated using biased measurement systems. The measured and certified values summarized in Table 2 and Figures 2a and 2b of the cholesterol example in Attachment 2 are linearly related; however, while the intercept is zero to within model error, the slope is not unity, i.e., the measurement system is proportionally biased. The measurement and certified value intervals must be suitably adjusted before they can be compared.

Figure 2b displays the relative measurement interval, $X_i/C_i \pm U_{95}(X_i)/C_i$ and the slope-scaled certified intervals, $b \pm U_{95}(C_i)/C_i$. While the intervals for all materials do overlap, the overlap for two of the materials is marginal. Thus, while these CRMs are comparable for cholesterol, a few of the materials are less comparable than are the majority. The variability in the size and overlap of the measurement and certified value intervals in Figure 2b suggest that the certified uncertainties (including the material homogeneity component) of several materials should be re-evaluated.

- 6.5.3. In general, extent-of-equivalence can be demonstrated whenever an adequately descriptive functional relationship between measured and certified values can be

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established. For complex relationships, one or more research chemometrics experts should be involved in the study.

- 6.6. A draft report of the extent-of-equivalence of the evaluated CRMs will be prepared by the CRM nominator. When resources allow, preparation of the report for publication in an appropriate peer-reviewed forum will help assure potential users of the study's probity as well as publicizing the JCTLM's efforts. In any case, a version of the report suitable for web-publication will be prepared. All parties actively involved in the study should co-author the report.
- 6.7. Once the report is approved by all co-authors, the CRM nominator will submit the Final Report to the DB WG for review as part of the nomination process. Experts of the review teams will assess the Final Report for the extent-of-equivalence demonstration for evaluated CRMs for its publication in the JCTLM database when appropriate. In the event of an adverse decision by the JCTLM Executive, the DBWG vice-Chair(s) will coordinate timely communication of the Executive's concerns and suggestions to the CRM nominator.
- 6.8. If the results of an approved extent-of-equivalence study indicate discordance among the evaluated CRMs relative to fit-for-purpose criteria, the DBWG Chair will refer all CRMs within the comparison set to their producers for further investigation to resolve the discrepant results. A comment noting that the extent-of-equivalence of the materials is under further review will be added to all of the listing of all of the CRMs in the study until resolution is achieved or one or more of the CRMs is withdrawn by its producer.

7. Related documents

- JCTLM DB WG-P-00 Quality Policy and Definitions
- JCTLM DBWG-P-01A Outline of JCTLM Procedures for Evaluating Materials and Methods to be Listed as Being of Higher Metrological Order
- JCTLM DBWG-P-03A Process for Review and Approval of Nominated Certified Reference Materials and Reference Measurement Methods

8. Attachments

- Attachment 1 Example, Comparison of Certified and Measured Values of Potassium in Human Serum CRMs
- Attachment 2 Example, Comparison of Certified and Measured Values of Cholesterol in Human Serum CRMs

9. Revision History

Version number	Date of Issue/Review	Summary of change
1.0	09/15/2004	Initial issue of WG1 Quality System Procedures
2.0	10/15/2005	Separation of comparison of reference measurement procedures using the same principle of measurement to WG1-P-04B Corrections to grammar and terms where identified. Resolution of inconsistencies.
2.1	24/01/06	Correction of minor textual errors

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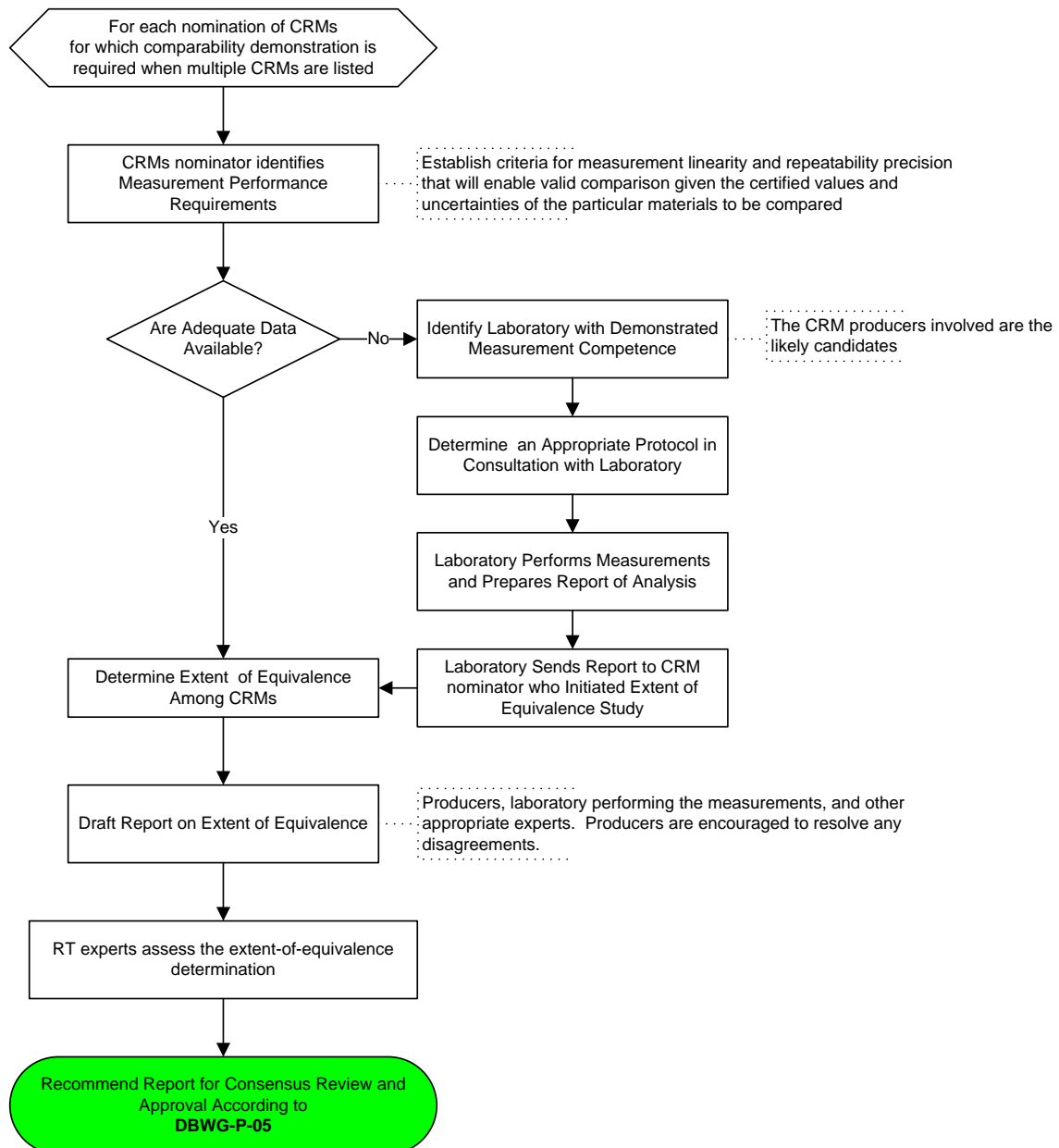
27/01/2017

Document revised for implementing modifications requested by EC's at its 17th meeting

10. Flowchart

January 2017

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Attachment 1 Potassium Example

Table 1: Protocol, Measurements, and Summary Statistics for the Comparison of Certified and Measured Values of Potassium in Human Serum CRMs
All values are in nmol/L.

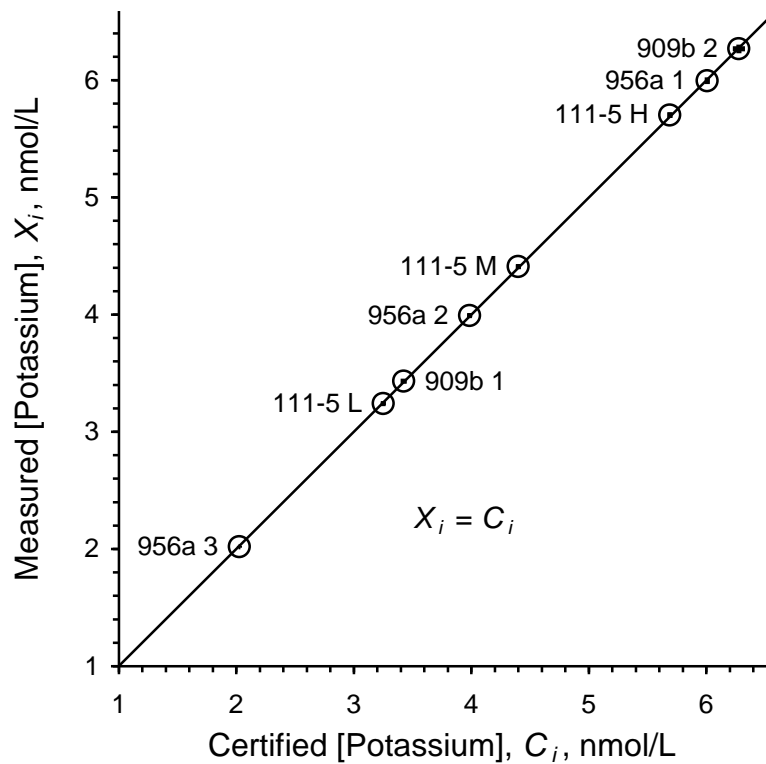
CRM ^a	Certified ^b		Measured ^c				Summary Statistics				
	Value	U ₉₅	Campaign 1		Campaign 2		Mean	SD	R ^d	u _c ^e	U ₉₅ ^f
			Value	U ₉₅	Value	U ₉₅					
JCCRM 111-5, L	3.250	0.020	3.241	0.027	3.241	0.025	3.241	0.000	0.013	0.013	0.026
JCCRM 111-5, M	4.400	0.020	4.419	0.027	4.400	0.034	4.410	0.013	0.015	0.020	0.041
JCCRM 111-5, H	5.690	0.020	5.698	0.047	5.706	0.044	5.702	0.006	0.023	0.023	0.047
SRM 909b, Lv 1	3.424	0.025	3.437	0.028	3.425	0.027	3.431	0.008	0.014	0.016	0.032
SRM 909b, Lv 2	6.278	0.052	6.286	0.052	6.248	0.048	6.267	0.027	0.025	0.037	0.073
SRM 956a, Lv 1	6.008	0.020	5.983	0.049	6.008	0.046	5.996	0.018	0.024	0.030	0.059
SRM 956a, Lv 2	3.985	0.020	3.993	0.033	3.993	0.031	3.993	0.000	0.016	0.016	0.032
SRM 956a, Lv 3	2.025	0.008	2.022	0.017	2.016	0.016	2.019	0.004	0.008	0.009	0.019

- a CRMs suitable for the calibration or verification of potassium in human serum proposed for listing by the JCTLM as of May, 2003. Materials with prefix 'JCCRM' are available from the HECTEF Standard Reference Center Foundation, Japan; those with prefix 'SRM' are available from the National Institute of Standards and Technology (NIST), USA.
- b Certified values and 95% confidence level uncertainties as listed on the CRM Certificates.
- c Measured values and fully evaluated 95% confidence level uncertainties. The determinations were performed at NIST using isotope dilution mass spectroscopy. The potassium level of each level of every CRM was fully evaluated in two separately analyzed vials of the material. The two sets of vials were analyzed in separate measurement campaigns.
- d Expected repeatability standard deviation of a single determination in this matrix in this laboratory using the given method, estimated as one-half of the pooled Campaign 1 and 2 U₉₅ values:

$$R = 0.5 \sqrt{\frac{U_{95,1}^2 + U_{95,2}^2}{2}}$$

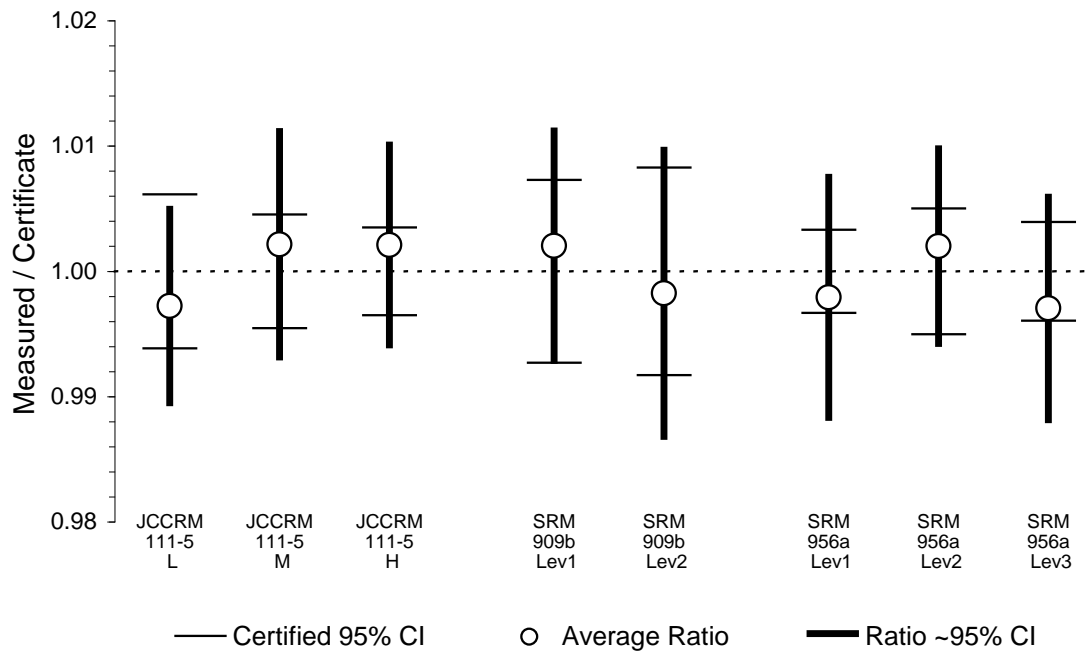
- e Combined uncertainty, $u_c = \sqrt{SD^2 + R^2}$.
- f Approximate 95% confidence expanded uncertainty, $2u_c$.

Figure 1a: Scattergram Display of the Extent-of-equivalence of Potassium in Human Serum CRMs



The horizontal axis reports the certified values, C_i ; the vertical reports the average measured values, X_i . Each level of each CRM is displayed as approximate 95% uncertainty intervals along both axes. The intersection of these intervals is bounded by an open circle to aid visual inspection. The line denotes the identify function: $X_i = C_i$. This model was chosen after finding that the intercept of the linear model was not significantly different from zero and the slope was not significantly different from unity:
 $X_i = (0.003 \pm 0.013) + (0.9993 \pm 0.0028) \times C_i$.

Figure 1b: Ratio Display of the Extent-of-equivalence of Potassium in Human Serum CRMs



The horizontal axis reports the CRMs evaluated. The vertical axis reports the ratio between the average measured and certified values of each CRM, X_i/C_i . The open circles denote these average ratios; the dark vertical lines represent the approximate 95% uncertainty interval on these averages. The light horizontal lines represent the certified 95% confidence intervals. The dotted line represents the expected ratio for the suite of all materials given the observed identity between the measured and certified values.

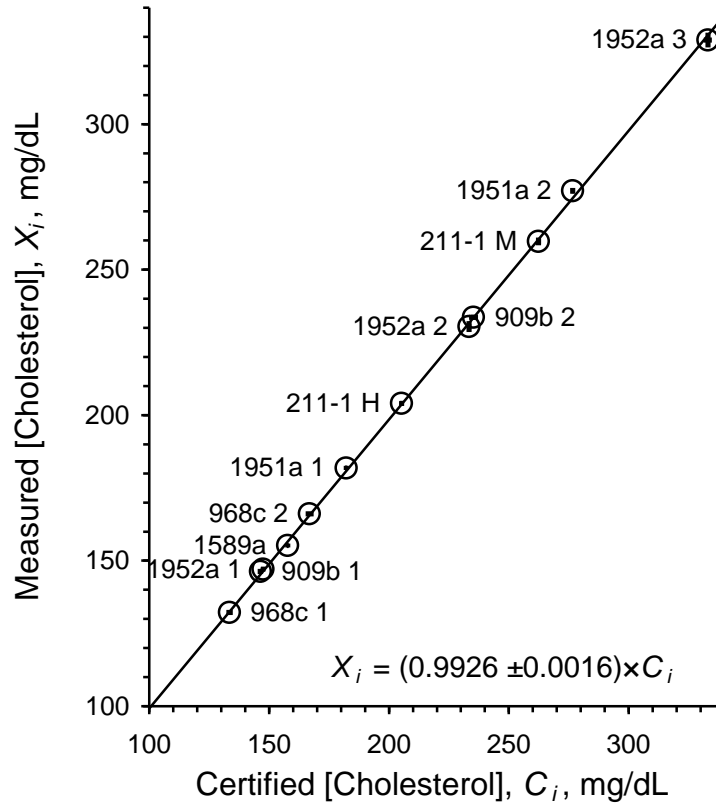
Attachment 2 Cholesterol Example

Table 2: Protocol, Measurements, and Summary Statistics for the Comparison of Certified and Measured Values of Cholesterol in Human Serum CRMs
All values are in mg/dL.

CRM ^a	Certified ^b		Measured ^c		Summary Statistics				
	Value	U ₉₅	Set 1	Set 2	Mean	SD	R ^d	u _c ^e	U ₉₅ ^f
JCCRM 211-1, H	205.20	0.80	203.80	204.20	204.00	0.29	0.72	0.78	1.55
JCCRM 211-1, M	262.40	1.00	259.02	260.35	259.68	0.94	0.92	1.32	2.63
SRM 909b, Lv 1	146.40	1.11	146.21	146.40	146.31	0.13	0.52	0.54	1.08
SRM 909b, Lv 2	235.30	1.85	233.45	233.80	233.63	0.24	0.83	0.87	1.73
SRM 968c, Lv 1	133.50	1.30	132.08	132.40	132.24	0.22	0.47	0.52	1.04
SRM 968c, Lv 2	166.90	1.70	166.11	166.20	166.15	0.06	0.59	0.60	1.19
SRM 1589a	157.76	0.37	154.97	155.50	155.24	0.37	0.55	0.67	1.34
SRM 1951a, Lv 1	182.15	0.45	181.63	182.10	181.86	0.34	0.64	0.73	1.45
SRM 1951a, Lv 2	276.67	0.55	277.14	276.95	277.05	0.14	0.98	0.99	1.98
SRM 1952a, Lv 1	147.50	0.96	147.04	147.20	147.12	0.11	0.52	0.53	1.07
SRM 1952a, Lv 2	233.40	0.96	231.68	229.25	230.47	1.72	0.82	1.90	3.81
SRM 1952a, Lv 3	333.00	1.65	327.28	330.45	328.87	2.24	1.19	2.53	5.07

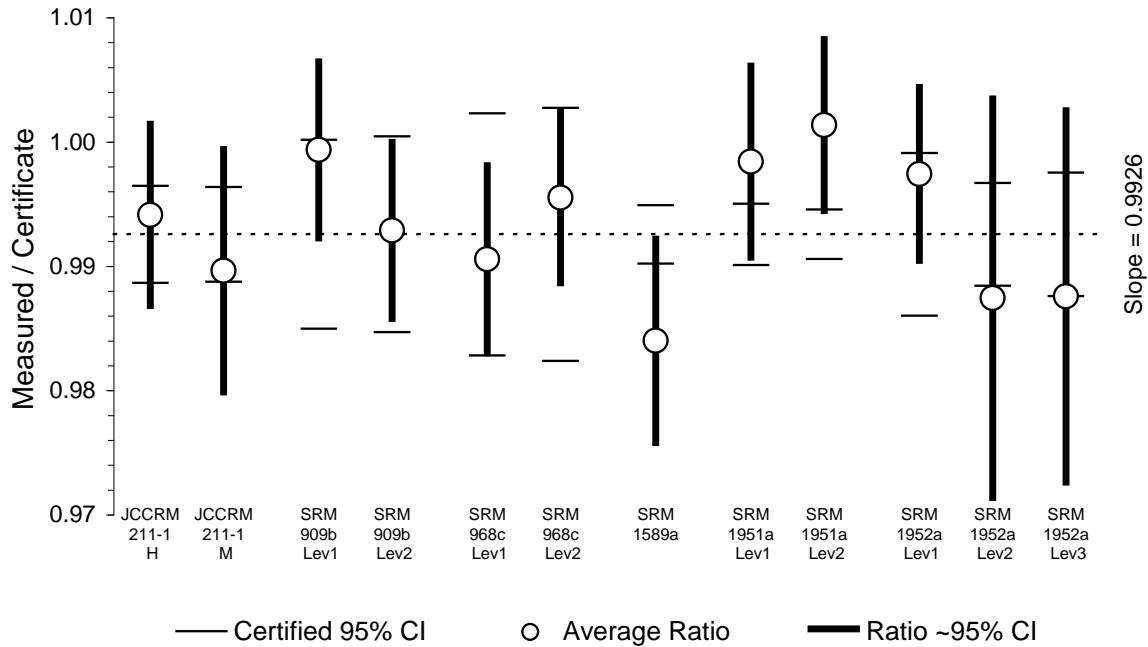
- a CRMs suitable for the calibration or verification of cholesterol in human serum proposed for listing by the JCTLM as of May, 2003. Materials with prefix ‘JCCRM’ are available from the HECTEF Standard Reference Center Foundation, Japan; those with prefix ‘SRM’ are available from the National Institute of Standards and Technology (NIST), USA.
- b Certified values and 95% confidence level uncertainties as listed on the CRM Certificates.
- c Measurements performed at NIST using isotope dilution/gas chromatography/mass spectroscopy. The cholesterol level of each level of every CRM was determined in two separately analyzed aliquots. Each set of aliquots was analyzed during a single 24-hour period.
- d Expected repeatability standard deviation of a single determination in this matrix in this laboratory using the given method, 0.35% of the measured value.
- e Combined uncertainty, $u_c = \sqrt{SD^2 + R^2}$.
- f Approximate 95% confidence expanded uncertainty, $2u_c$.

Figure 2a: Scattergram Display of the Extent-of-equivalence of Cholesterol in Human Serum CRMs



The horizontal axis reports the certified values, C_i ; the vertical reports the average measured values, X_i . Each level of each CRM is displayed as approximate 95% uncertainty intervals along both axes. The intersection of these intervals is bounded by an open circle to aid visual inspection. The line denotes the best linear model for the relationship between the measured values and the certified values: $X_i = (0.9926 \pm 0.0016) \times C_i$. This proportional model was chosen after finding that the intercept of the linear model was not significantly different from zero: $X_i = (0.92 \pm 1.27) + (0.9885 \pm 0.0059) \times C_i$.

Figure 2b: Ratio Display of the Extent-of-equivalence of Cholesterol in Human Serum CRMs



The horizontal axis reports the CRMs evaluated. The vertical axis reports the ratio between the average measured and certified values of each CRM, X_i/C_i . The open circles denote these average ratios; the dark vertical lines represent the approximate 95% uncertainty interval on these averages. The light horizontal lines represent the certified 95% confidence intervals, scaled by the proportional model for the relationship between the measured values and the certified values: $X_i = (0.9926 \pm 0.0016) \times C_i$. The dotted line represents the expected ratio for the suite of all materials given the observed proportionality between the measured and certified values.