

**Report of the 7th meeting of the JCTLM Executive Committee
11 December 2008, BIPM, Sèvres, France**

List of participants:

Prof J-C. Forest (JCTLM Chairman, IFCC)
Dr R I Wielgosz (JCTLM Secretariat, BIPM)
Dr G. Jones (ILAC)
Prof M.Müller (IFCC)
Dr M. Panteghini (IFCC)
Prof L. Siekmann (JCTLM WG 2 Chair)
Mr A. Squirrell (ILAC)
Prof L. Thienpont (JCTLM WG 2 Chair)
Prof A. Wallard (BIPM)
Dr. S. Maniguet (BIPM)
Dr H. Schimmel (JCTLM WG1 Chair)
Dr R. Kaarls (BIPM)
Dr W.E. May (JCTLM WG1 Chair)

Report of meeting:

1. Approval of the agenda [JCTLM-EXEC/08-01]

Dr May requested that an additional agenda point on future activities of the JCTLM be dealt with under any other business.

2. Report of 6th JCTLM Executive Committee Meeting

There were no comments related to the report of the 6th Executive Committee meeting.

2.1 Review of action points arising from the 6th meeting [JCTLM-EXEC/08-02]

Dr Wielgosz summarized the action items that were still outstanding:

(A/05-09) The JCTLM Secretariat to develop new nomination forms that would be consistent with the revised ISO 15194 standard and to issue these in 2009.

The issuing of the new nomination forms has been delayed as the new version of ISO 15194 is yet to be published.

(A/05-17) Deputy Review Team leaders need to be named for a number of review teams.

Apart from the existing Deputy Review Team Leader for the Vitamins group, this action was not completed.

Action (A/06-17): Prof Wallard to write to the Commission requesting that their note be modified to refer to the full list of mandated standards, and also request that the note be published following the publication of the new ISO 15194 standard.

This action will be taken up by the JCTLM Secretariat. The presentation from a representative of DG Enterprise at tomorrow's workshop will give an opportunity to clarify the current situation.

3. JCTLM Framework and Declaration of Cooperation

3.1 JCTLM membership [JCTLM-EXEC/08-30]

Dr Wielgosz informed the Committee that one application had been received for JCTLM Membership, from the Buenos Aires External Quality Assessment Scheme – Prog BA.

Prof Panteghini commented that he had concerns that the organization represented a local EQAS scheme, and not a national or international one. Acceptance of the organization as a JCTLM Member would mean this would open the door for other similar organizations. He stated that membership should be limited to national or international organizations, and the membership of local organizations would be covered via their membership of national or international bodies.

Prof Siekmann replied that organizations with similar status were already members of the JCTLM. Therefore, on this point, he had no objection to granting membership status.

Dr Jones asked what were the privileges and obligations of member organizations? For example, was there a requirement for the organization to implement the philosophy of the JCTLM, which could mean using JCTLM listed reference methods for an EQAS provider?

Dr Wielgosz referred to the relevant text and noted that although it had always been the expectation that member organizations would follow the philosophy of the JCTLM this was not clearly stated.

Prof Forest concluded that the Secretariat would write to the organization confirming the Executive's approval of membership. He requested that the letter state that Members were expected to adopt the philosophy of the JCTLM with respect to traceability of measurement results. A similar letter would also be sent to all other JCTLM Members. Furthermore, he asked the Secretariat to draft an additional paragraph on the obligations of JCTLM Members. This would be sent for comment to the Executive, and once approved it would be added to the JCTLM Declaration of Cooperation document.

Prof Panteghini accepted the decision of the Executive, but requested that his objection to local organizations being granted membership of the JCTLM be noted.

Action (A/07-01): JCTLM Secretariat to write to Prog BA.

Action (A/07-02): JCTLM Secretariat to write to all JCTLM Member Organizations regarding privileges and obligations of Members.

Action (A/07-03): JCTLM Secretariat to draft additional text on Membership obligations for approval by the Executive.

3.2 Representation on the Executive

Dr Wielgosz reminded the Committee that at last year's meeting it had been agreed that the positions of Chair and Secretary of the JCTLM would be reviewed as described in the Executive Committee Procedure documents.

Prof Forest confirmed that his term as JCTLM President would come to an end at the next Executive meeting at the end of 2009. He stated that the procedure to elect a new President of the Committee would be followed, which would require the Secretariat to inform the JCTLM sponsoring organizations for the need to nominate candidates for the post of JCTLM President.

Dr May stated that it should be a prerequisite for the candidates to be familiar with the activities of the JCTLM.

Action (A/07-04): JCTLM Secretariat to contact IFCC, BIPM and ILAC on 1 June 2009 for nominations for JCTLM President.

3.3 JCTLM Working Groups

3.3.1 Review of JCTLM Review Teams and RT Members [JCTLM-EXEC/08-07, 20, 21]

Dr Wielgosz presented documents JCTLM/08-07, 20, 21 which summarized review team membership by working group and analyte type, and new applications for membership of review teams. The JCTLM Executive approved the following membership applications: Dr H. Andres for Metabolites and Substrates; Dr S. Wunderli for Electrolytes; Drs G. d'Onofrio and J.J. Hoffmann for blood cell counting.

Dr May added that in the future the JCTLM should adopt targeted requests for experts to act on Review Teams.

Actions:

Action(A/07-05): JCTLM secretariat to contact new review team members and inform them of their approved applications;

3.4 Funding of the JCTLM Secretariat

Dr Wielgosz reported that the work of the secretariat for 2007 had been supported by financial contributions from the IFCC and the BIPM. The operating costs of the JCTLM Secretariat were expected to be in line with the five year budget as presented previously (JCTLM-EXEC/06-16).

There was a general discussion on funding of JCTLM activities. The issue of financial support of the JCTLM through membership fees was raised, and may need to be considered again in the future.

3.5 JCTLM Secretariat Procedures

Dr Wielgosz presented document JCTLM-EXEC/08-28, which contained the procedures which had been developed for the Secretariat, and took into account all comments received following last year's meeting. Dr Forest confirmed that the procedures should now be published.

Actions:

Action(A/07-06): JCTLM Secretariat to publish JCTLM Secretariat Procedures.

3.6 JCTLM Executive Procedures

Dr Wielgosz presented document JCTLM-EXEC/08-27, which contained the procedures which had been developed for the Executive Committee, and complemented the quality manuals for the JCTLM working groups. The Executive has also received comments on the procedures from Dr Jones (document JCTLM-EXEC/08-08).

The document submitted by Dr Jones raised a number of issues which were discussed by the Executive:

- the Executive agreed that the procedures needed to include a statement which recognised the Executive Committee as an organ within the JCTLM that had the right to undertake tasks that were not covered in the procedures;
- the Executive agreed that the process of reaching agreement within the Executive was by consensus. If consensus could not be reached among the individual members of the

- the Executive agreed that it was the duty of members serving on the Committee to familiarize themselves with the JCTLM procedures;
- the Executive agreed that it was important to ensure continuity in the Committee, and recommended that individuals should be expected to be active for at least three years on the Committee. The Executive agreed that the Secretariat would send a letter to the sponsoring organizations every three years requesting the participation of representatives for a three year period.

Actions:

Action (A/07-07): JCTLM Secretariat to modify and publish procedures based on the Executive Committee decisions.

3.7 JCTLM Database

Dr S. Maniguet provided an overview of the JCTLM database. The database was receiving over 1000 visits a month.

3.8 Use of the JCTLM logo [JCTLM-EXEC/08-18]

Dr Wielgosz brought the Committee's attention to the announcement of a recent meeting on Standardization in Clinical Enzymology, for which the Executive Committee had agreed the use of the JCTLM logo.

Dr Jones asked whether the JCTLM logo or 'brand' could or should be used as a trusted sign of traceability, and therefore whether it is a brand that should be proposed to end-users in laboratories. For example, could an IVD manufacturer indicate that results of a method were traceable to a CRM listed on the JCTLM database. This would be a shorthand whereby the personnel of a laboratory could assess the accuracy basis for a product without having to look up the material, method or reference laboratory themselves. Thus "JCTLM" could be a trusted brand for laboratories and therefore provide greater reason for manufacturers to use listed materials for traceability.

Dr Wielgosz replied that a major issue would be that there were many steps in the process between choosing a Reference Materials or method and delivering the result from a test kit. The JCTLM had no control over this process, nor on the final result.

Dr May replied that the NIST had experience in developing a service mark, which was for the NTRM programme. He pointed out that developing a programme to use a service mark would require a considerable amount of input, not least in developing specifications for products and then ensuring that these specifications were met.

The President summarized the discussion, by saying that for simple cases such as promoting events such as conferences, the procedure for obtaining approval to use the JCTLM logo would require contacting the JCTLM Secretariat with a written request for permission. In order to consider the more complicated case related to the quality and specifications of products, a position paper and proposal for a process would need to be developed.

4. JCTLM WG1 – Reference Materials and Reference Measurement Procedures

4.1 Report from the JCTLM WGs meeting, July 2008, Gaithersburg US [JCTLM-EXEC/08-04]

Dr May summarised the JCTLM WG1 and 2 joint meeting which was held at the NIST on 25 July 2008. The first part of the meeting was a closed session during which new nominations and outstanding issues for nominations of reference materials, methods and measurement services were discussed. The afternoon session was open to all participants and addressed the following issues: the ISO-REMCO initiative for reference materials for nominal properties; criteria for the publication of reference materials with nominal properties in the JCTLM Database; definitions and activities of Laboratory Networks; Central and Satellite Laboratory Accreditation; IFCC EQAS results; updates of the JCTLM quality manuals; ISO 15194 and 15194 revisions.

4.2 Review Criteria for Nucleic acid Reference Materials – Nominal Properties [JCTLM-EXEC/08-29]

The Nucleic Acid Review Team has drafted document JCTLM-EXEC/08-29 which lays out criteria for evaluating the quality or traceability of Reference Materials for Nominal Properties of Nucleic acids, notably sequence.

Dr May asked whether the purity of the reference material was a property which needed to be demonstrated.

Dr Wielgosz stated that he had difficulty in understanding the phrase ‘traceable’ to a base nucleotide, and stated that the sequence determination was based on a procedure, and it seemed that the veracity of this procedure needed also to be documented and demonstrated.

Dr Panteghini stated that the IFCC had an expert group working in the area, and he would ask them to comment on the criteria document.

Actions:

Action (A/07-08): Prof Panteghini to circulate JCTLM-EXEC/08-29 to IFCC expert group and request comments by 30 January 2009.

4.3 Approval of Cycle V RM and RMP nominations [JCTLM-EXEC/08-22,23]

Dr Maniguet summarised the current status of Cycle V nominations. Five reference material nominations had been recommended for approval (2 for metabolites and substrates; 1 for non-electrolyte metals; 2 for non-peptide hormones). Sixteen reference materials (Electrolytes) were still under review and one nomination (Proteins) had been deferred to the next cycle. Seven nominations for reference measurement procedures were still under review (two for electrolytes and five for blood cell counting).

The JCTLM Executive approved the five recommended reference materials for publication in the database.

4.4 Delisting of RMs and RMPs

Two reference materials were delisted from the JCTLM database this year, as the materials had been sold out, bringing the total number of reference materials no longer listed in the database to thirty six.

4.5 Progress / plans for Cycle VI call for RMs and RMPs

Dr Wielgosz confirmed that the new call for nominations for Reference Materials, Methods and Measurement Services would be launched in January 2009.

4.6 Revisions of ISO 15194 and 15193

Dr Wielgosz stated that ISO process for review, voting and publication of the new revisions of ISO 15194 and 15193 was not complete, but he hoped that this would be finished in 2009. This meant that nominations for materials and methods would be based on current standards for 2009, and the revised nomination forms based on the new standards would not be used until 2010.

4.7 JCTLM WG1 quality manual

Dr Wielgosz reported that no requests for changes to the WG1 quality manual had been received.

4.8 JCTLM Industry Workshop, Nucleic Acids and Immunoassays, July 2008. Washington US [JCTLM-EXEC/08-09]

Dr May provided a report on the workshop that had been organized on the day following the JCTLM WG meetings in July. The workshop which had been designed to identify the needs of the IVD industry for RMs and RMPs for Nucleic Acid Testing and Immunodiagnosics had been a considerable success, with forty five attendees including senior technical leaders from industry. He noted that a session on Metrological Traceability had been organized for the 2009 AACC meeting, and he and Dr Wielgosz would be giving presentations.

5. JCTLM WG 2 – Reference Measurement Laboratories

5.1 Report from the JCTLM WG2 meeting, July, 2008 [JCTLM-EXEC/08-04]

Prof Siekmann reported that WG2 issues had been discussed during the joint meeting in July. He noted that a number of issues related to nominations in previous cycles had been resolved:

- a) In general reference measurement services designed for serum, plasma or urine are in appropriate for pure materials. However, for Enzymes, ‘pure materials’ are understood as recombinant materials;
- b) ‘Calibration solution’ was to be understood as ‘surrogate serum’ for a number of nominations received.

5.2 Problems encountered with accreditation of Reference Measurement Service Providers [JCTLM-EXEC/08-03,06]

Dr Panteghini explained the problems he had encountered in finding an accreditation body (AB) to carry out an accreditation of his laboratory’s reference measurement services based on ISO 17025 and 15195. The AB in his own country did not provide this service. He had approached the AB of another country that did carry out such accreditations, but they had been unwilling to provide this service outside of their country.

Mr Squirrell asked in which countries the various laboratories were located, and whether the laboratories had indeed all contacted their respective accreditation bodies?

Dr Wielgosz replied that the laboratories currently listed in the JCTLM database were located in the following countries: United Kingdom; Canada; Japan; The Netherlands; Germany; Italy; Denmark; Belgium; Spain; and Sweden. There were sixteen laboratories in total, which were required to have made an application for accreditation by 1 January 2009, if they wished to remain listed in the JCTLM database. However, it appeared that only five of these laboratories would meet this deadline.

The members of the Executive Committee expressed their concern over the relatively small number of laboratories that would meet the accreditation status requirements to remain in the JCTLM database. Before deciding how to proceed, the Executive asked the Secretariat to contact laboratories to determine whether the failure to submit an application for accreditation was a decision of the laboratory or a result of their national accreditation body being unable to provide this service. The laboratory services would remain listed in the database until the Executive reached a decision on this issue.

Actions:

Action (A/07-09): JCTLM Secretariat to send out questionnaire to Laboratories. (Responses collected and circulated to Executive Committee Members on 12/02/09)

Action (A/07-10): ILAC to send out questionnaire to Accreditation Bodies to confirm whether or not they are able to offer an accreditation service to ISO 15195 (Responses collected and posted on the JCTLM website on 12/04/09)

5.3 Approval of Cycle III Laboratory RMS nominations [JCTLM-EXEC/08-24,25]

Dr Maniguet summarised the current status of Cycle III nominations. Twenty nine measurements services from four laboratories had been submitted for review. Seventeen reference measurement services were recommended for approval (6 for enzymes; 6 for metabolites and substrates; 5 for non-peptide hormones. The remaining nominations (3 for drugs; 3 for Electrolytes; 5 for metabolites and substrates; and 1 for proteins) were not recommended for approval.

The JCTLM Executive approved the seventeen recommended reference measurement services for publication in the database.

5.3.1 Extension of the accreditation deadline

The Executive Committee decided that the decision on the accreditation deadline would be taken after analysis of the questionnaires sent to laboratories and accreditation bodies.

5.3.2 Re-review of database entries – post accreditation deadline (2010)

The agenda point was not discussed.

5.4 Progress/plans for Cycle IV call for Reference Measurement Services

Dr Wielgosz confirmed that the new call for nominations for Reference Measurement Services would be launched in January 2009 in parallel to the call for Reference Materials and Methods.

5.5 JCTLM WG2 procedure/quality manual

Dr Wielgosz informed the Committee that changes of the accreditation deadlines to 1 January 2009 (application) and 1 January 2010 (accreditation) requested at the last meeting had been implemented.

5.6 Update on IFCC EQAS results

Prof Siekmann informed the Committee that the number of participants in the IFCC EQAS scheme was increasing each year, with a substantial increase in the last year, particularly with the participation of laboratories from South East Asia. The scheme currently operated by

charging participants the same transport costs independent of their location. However, it now seemed unlikely that the scheme could maintain this system and that transport charges would need to reflect the true cost of shipping samples. This would be discussed at the next meeting of the IFCC CTLM.

5.7 Revision of ISO 15195

Mr Squirrel stated that he had been unable to obtain further information on the status of the revision of ISO 15195, but that the standard would be coming up for general review in six months' time.

5.8 Reference Laboratory Networks and the JCTLM [JCTLM-EXEC/08-11]

Dr Wielgosz presented document JCTLM-EXEC/08-11, which was a letter from Dr C. Weykamp, requesting that established Networks of Reference Laboratories be added to the searchable list of reference measurement services in the JCTLM database as well as a general item to be dealt with by JCTLM WG2.

The JCTLM Executive noted that Laboratory Networks were a valuable resource; however there remained problems in endorsing laboratory activities that did not meet the requirements for publication as reference measurement services in the JCTLM database. Information on a number of laboratory networks was already accessible from the website by following links on activities of Member Organizations. The Executive also requested the IFCC to consider the the role and tasks set for networks, and recognised that the JCTLM and Laboratory Networks were working towards the same goal of improving the reliability of measurement results.

Action (A/07-11): JCTLM Secretariat to send response to Dr Weykamp.

5.9 Hypothetical assessment of a Laboratory Network [JCTLM-EXEC/08-10]

Dr Wielgosz commented that the assessment performed by R. Robertson (NATA) and M. Kimberly (CDC) had been presented during the JCTLM WG meetings in July. He noted that M. Kimberly had concluded that the cost of accrediting a network, as opposed to individual laboratories, did not lead to a significant cost reduction.

6. Documents submitted by JCTLM Members and Stakeholders for consideration by the Executive Committee

No documents were submitted for consideration by the Executive Committee.

7. Liaison with the EC

7.1 Correspondence from DG Enterprise

The JCTLM Secretariat had been in contact with DG Enterprise, and M. Bourguignon of DG Enterprise would be attending the JCTLM Members and Stakeholder's meeting.

7.2 Liaison with the Global Harmonization Task Force (GHTF) [JCTLM-EXEC/08-05,06]

Letters had been exchanged with Mrs N. Shadeed, the Chairperson of IVD Subgroup Study Group 1 of the GHTF. The IVD subgroup is currently working on summary technical documentation which will discuss the type of information that manufacturer should submit with regards to traceability. The proposed text was not however ready for distribution.

Actions:

Action (A/07-12): JCTLM Secretariat to contact GHTF to enquire on progress with the documentation on traceability.

8. Liaison with the WHO

8.1 Issues arising from the WHO-ECBS meeting

Prof Forest commented that he had attended the last WHO –ECBS meeting in Geneva. He was happy to report that the WHO had recognised the need to move towards metrological traceability. The WHO was looking to establish new collaborative centres, and to prioritise their activities.

9. Liaison with ISO TC 212

Meetings of ISO TC 212/ WG2 and WG1 were held on the previous day in Geneva. WG2 dealt briefly with the revisions of ISO 15194 and 15193, with the majority of the meeting dedicated to the draft technical specifications on measurement uncertainty.

10. Publicity for the JCTLM

Dr G. Jones reported that he had been invited to Taiwan to give presentations on the activities of the JCTLM, which had been well received.

11. Future meetings of the JCTLM

11.1 Meetings for 2009 and 2010

It was proposed that JCTLM WG meeting be held in parallel to the AACC meeting. The following dates were fixed:

18 July 2009, JCTLM WG1 and 2 Business meeting, Hyatt Regency Chicago, US.

19 July 2009, NIST/JCTLM/CCQM Workshop: Measurement and Standards Needs for Next Generation Healthcare Delivery, Hyatt Regency Chicago

The 8th meeting of the JCTLM Executive Committee would be held at the BIPM on 3 and 4 December 2009, with an additional day set aside for planning future activities.

11.2 JCTLM Symposium and Stakeholder's meeting [JCTLM-EXEC/08-19, 13,14,15,16,17]

The JCTLM Members and Stakeholder's meeting would be held tomorrow at the BIPM. The morning session would summarise current activities in traceability in laboratory medicine in Europe, North America and Asia. The afternoon session would deal with future challenges and activities, and forty nine participants were expected to attend.

12. Any other business

Prof Forest stated that the issue of future activities of the JCTLM would be dealt with during the next annual meeting, and an extra day would be set aside for this.

Dr Kaarls gave a brief summary of the CCQM-USP meeting that had been held during the previous week at the BIPM. Issues of Metrological Traceability with the Pharma and Bio-Pharma industries had been dealt with.

Prof Forest thanked the participants for their contributions and closed the meeting.

R.I. Wielgosz (BIPM)
10 April 2009

Revised 28 April 2009

Annex 1: Summary List of Actions

Actions from the 7th Executive Meeting:

- Action (A/07-01):** JCTLM Secretariat to write to Prog BA.
- Action (A/07-02):** JCTLM Secretariat to write to all JCTLM Member Organizations regarding privileges and obligations of Members.
- Action (A/07-03):** JCTLM Secretariat to draft additional text on Membership obligations for approval by the Executive.
- Action (A/07-04):** JCTLM Secretariat to contact IFCC, BIPM and ILAC on 1 June 2009 for nominations for JCTLM President.
- Action(A/07-05):** JCTLM secretariat to contact new review team members and inform them of their approved applications;
- Action(A/07-06):** JCTLM Secretariat to publish JCTLM Secretariat Procedures.
- Action (A/07-07):** JCTLM Secretariat to modify and publish procedures based on the Executive Committee decisions.
- Action (A/07-08):** Prof Panteghini to circulate JCTLM-EXEC/08-29 to IFCC expert group and request comments by 30 January 2009.
- Action (A/07-09):** JCTLM Secretariat to send out questionnaire to Laboratories. (Responses collected and circulate to Executive Committee Members on 12/02/08)
- Action (A/07-10):** ILAC to send out questionnaire to Accreditation Bodies to confirm whether or not they are able to offer an accreditation service to ISO 15195 (Responses collected and posted on the JCTLM website on 12/04/08)
- Action (A/07-11):** JCTLM Secretariat to send response to Dr Weykamp.
- Action (A/07-12):** JCTLM Secretariat to contact GHTF to enquire on progress with the documentation on traceability.

JCTLM WGI. NUCLEIC ACID REVIEW TEAM:**CRITERIA TO ASSESS THE QUALITY OF NOMINATED NUCLEIC ACID REFERENCE MATERIALS WITH STATED NOMINAL PROPERTIES****1. BACKGROUND:**

The JCTLM quality manual requires expert review of nominated certified reference materials, to assure they meet the quality requirements of the JCTLM for inclusion in its database of available higher order reference materials and methods/procedures, In accordance with JCTLM Quality Manual WG1-P-01, nominated materials are reviewed to assure compliance with quality criteria cited in ISO 15194:2003 and ISO Guide 34.

However, it has been recognised by ISO TC 212 WG2 and JCTLM that ISO 15194 applies fully to CRMs with assigned values of differential or rational quantities, and only very brief guidance on how to deal with nominal properties and ordinal quantities is given. The concept of metrological traceability, is applicable to ordinal quantities but not to nominal properties (See Appendix I). Therefore, although there are some common quality criteria for all reference materials to be considered in accordance with ISO 15194 and ISO Guide 34 (e.g. stability, homogeneity and commutability) there is limited guidance on the criteria that need to be fulfilled to consider a reference material for nominal properties as of higher order or high quality.

JCTLM review teams are currently expected to review reference materials for nominal properties, and have been charged with considering and documenting criteria which should be applied to assess the quality of such reference materials.

2. JCTLM NUCLEIC ACID REVIEW TEAM APPROACH:

The JCTLM Nucleic Acid Review Team leader invited international expert opinion on criteria which could/should be applied to assess the "quality" and "higher order traceability" of JCTLM database nominated reference materials - in this case nucleic acids, for which there are only have stated "nominal qualities" - most usually nucleic acid sequence.

The JCTLM nucleic acid review team (Appendix II) was consulted and contributions solicited by email "discussion" and related document sharing. The majority (7/8) of expert members actively participated in the process, contributing criteria and opinion. Additional expert opinion was also obtained from other internationally recognised experts in molecular biology and nucleic acid reference material development (Appendix II).

The existing knowledge base of relevant guidance documents for nucleic acid assays and reference materials and international standardisation initiatives in qualitative genetic analysis, was also reviewed with respect to stated criteria for nucleic acid method validation, test and material quality criteria and sequence identity confidence. (Appendix III).

The consultation process was very broad as the team believes co-ordination is required to ensure harmonisation, although to date very little specific reference has been made to quality criteria for sequence verification.

Draft nucleic acid sequence quality criteria were also discussed in a presentation given to JCTLM members and other relevant stakeholders at the 2008 JCTLM WG meeting, prior to preparation, review team review and submission of this consensus document.

3. NOMINAL PROPERTY QUALITY CRITERIA FOR NUCLEIC ACID RM REVIEW

These criteria for quality review of stated nominal properties, specifically - sequence, of a JCTLM nominated nucleic acid based CRM are to be used to complement the JCTLM CRM Review Checklist - ISO 15194, WG1-P-03-F-01.

For nucleic acid CRM identity the following criteria will be additionally applied in reviewing the nominal quality “sequence”:

1. Quality-scored bi-directional sequencing as the logical 'gold standard' method of choice for traceability shall be applied (Note 1)
2. Ideally verification should be by:
 - alternative sequence assays
 - inter-laboratory studies (to validate use of reference material)(Note 2,3,4)
3. The uncertainty can then be expressed as the probability of a miss called base or bases in the sequence of nucleic acids in the target, for example using a PHRED score / confidence statement (ordinal quantity!) (Note 2,3)
4. The CRM is then considered to be “Traceable” to base nucleotide reference. (Note 5)

Note 1. Sequencing may not be considered appropriate for all RMs (eg tri-nucleotide repeat disorders). Decisions must be made on a case by case basis in accord with expert opinion and the JCTLM nominated nucleic acid CRM.

In accordance with ISO Guide 34 and ISO 15194 revisions, reference materials created by PCR, cell culture and plasmid –generated must be sequenced per batch, Otherwise strong evidence would have to be provided that the production

process is sufficiently reproducible and that fluctuations would not have an impact on the homogeneity, stability and characteristics of the material

Note 2.

Guidance document on the use of reference materials in genetic testing - EUROAGENTEST

4.6 Identity checks

In the case of the identification of a nucleic acid sequence, DNA sequencing can be considered as one of the more robust methods. For validation purposes, attention should be paid that the sequence of interest has been obtained using forward and backward sequencing primers spanning the same target region. The uncertainty can then be expressed as the probability of misreadings in the sequence of nucleic acids in the target, for example using a PHRED score

Note 3.

External RNA Control Consortium (ERCC) guidance on Certification of Sequence ~100,000 bases of DNA

- sequence with multiple methods
- sequence both strands
- sequence with redundant coverage
- estimate error rates from data
- classify regions of sequence eg "*Most Confident*," "*Very Confident*," "*Confident*," and "*Ambiguous*."

Note 4

Additional verification by sequencing with alternative methods may not be possible or practical – dependent on size of RM sequence, and confidence of sequence quality.

Note 5.

Statements of DNA sequence traceability

- Sequence results will be traceable to the identities of the individual nucleotides. (Not an SI unit, but traceability to an internationally accepted reference unit)

5. Summary

Expert and documented opinion on criteria for determination of the nominal property nucleic acid sequence "quality" has been reviewed and collated. The above criteria for sequence verification represent the majority opinion of the review team, and are closely aligned with other developing standardization initiatives in the area. Sequencing may not be considered appropriate for all RMs (eg tri-nucleotide repeat disorders), therefore nucleic acid based RMs with nominal properties need to be reviewed on a case by case basis taking expert advice from the review team.

6. Further Recommendations:

Although the above nucleic acid sequence quality criteria have been formulated on the basis of the current “best practice” guidance available and expert opinion, it is recognised by the review team and other expert stakeholders that nucleic acid based analytical technology, and associated reference material development is evolving rapidly. For example, conventional Sanger sequencing is being increasingly displaced by next generation (ultra high throughput) sequencing, and non-coding RNA with non-linear or 2nd dimension sequence for which there are different considerations for quality criteria. The JCTLM nucleic acid nominal property review process and quality guidance should be flexible and adaptive and reviewed annually, in order to take account of emerging nucleic acid CRM nominations.

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Current members of, and consultants to, the nucleic acid review team contribute to the other standardisation initiatives discussed, so are well placed with relevant expertise to:

- Continue to review knowledge and update criteria to reflect evolving best practice and technological changes in RM production / QA
- Continue to contribute to related international initiatives including ISO REMCO WG developing standards for CRMs for qualitative analysis

Appendix I

DEFINITIONS:

a. ISO REMCO definition of a CRM

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability

Note 1: The concept of value includes qualitative attributes such as identity or sequence. Uncertainties for such attributes may be expressed as probabilities.

Note 2: Metrologically valid procedures for the production and certification of reference materials are given in, among others, ISO Guides 34 and 35

b. INTERNATIONAL VOCABULARY OF METROLOGY VIM (JCGM 2008)

1.30

Nominal property

Property of a phenomenon, body, or substance, where the property has no magnitude

- eg. sex of a human being
- eg. colour of paint
- eg. sequence of amino acids in a polypeptide

SEQUENCE OF BASES IN A NUCLEIC ACID = NOMINAL PROPERTY
(YES/NO - QUALITATIVE IDENTITY TEST)

Appendix II EXPERT CONTRIBUTION

JCTLM Nucleic Acid Review Team:

1. Helen Parkes – Senior Consultant Biomeasurement, LGC, UK
2. Morag Ferguson - NIBSC (WHO / IU RMs) ✓
3. Joan Gordon - President, Maine Molecular QCI ✓
4. Tomoshige Hori - Director, Standardisation and Strategy, Japanese Bioindustry Association ✓
5. Lisa Kalman - GeT-RM, Laboratory Practice Evaluation and Genomics Branch, CDC, Atlanta ✓
6. Roberta Madej - Director, Global Standardisation, Roche Molecular Systems & Chair CLSI molecular methods area committee ✓
7. Heinz Schimmel - IRMM, Life Science RMs ✓

Other experts consulted:

8. Marc Salit - NIST, ERCC RM certification, MGED
9. David Gancberg – IRMM, Eurogentest documentation on genetic testing RM
10. Carole Foy – LGC, EMERALD, USP nucleic acid chapter expert
11. David Smith – Associate Director Scientific Awareness, Luminex Corporation

Appendix III

Existing Knowledge Base reviewed:

Supporting documents:

1. CLSI MM17-A- Verification and Validation of Multiplex Nucleic Acid Assays; Proposed Guideline
2. CLGGS (draft) - Characterisation of DNA Microarray Controls
3. ERCC - External RNA Controls Consortium (2005) Proposed methods for testing and selecting ERCC external RNA controls. BMC Genomics 6:150
4. Eurogentest - _Guidance document on the use of reference materials in genetic testing (approval) Project : NoE EuroGentest, Unit 1, WP1.6 D. Gancberg, P. Corbisier, H. Schimmel, H. Emons
5. IRMM - Certified Reference Materials for Genetic Testing Eurogentest presentations 2007, 2008 D. Gancberg
6. OECD - OECD guidelines for quality assurance in molecular genetic testing 2007
7. JBA - Trends in international standardization of molecular genetic testing for clinical application
8. CLSI C53 (P): Characterisation and Qualification of Commutable Reference Materials for laboratory medicine
9. ISO REMCO N863 - ad hoc group (AHG 01) gap analysis report on CRMs for qualitative analysis (testing of nominal properties)

International Standardization Initiatives

International committees considering additional quality guidelines on qualitative analysis

10. Various standardisation bodies (ISO REMCO, ISO TC 212, etc)
11. Professional organisations (CLSI, AOAC, IUPAC, Eurachem, etc)
12. Networks (ERCC, EUROGENTEST, MGED, JCTLM, Genomics Standards Consortium etc)