

**CONCLUSIONS OF THE
WORKSHOP ON TRACEABILITY IN LABORATORY MEDICINE
9-11 JUNE, 2002, BIPM, SÈVRES, FRANCE**

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<p style="text-align: center;">CONCLUSIONS OF THE WORKSHOP ON TRACEABILITY IN LABORATORY MEDICINE 9-11 JUNE, 2002, BIPM, SÈVRES, FRANCE</p>
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It was formally agreed to establish the Joint Committee on Traceability in Laboratory Medicine (JCTLM) on 11 June 2002, the final day of the “Workshop on Traceability in Laboratory Medicine”.

JCTLM Mission Statement

The aim of the Joint Committee is to support world-wide comparability, reliability and equivalence of measurement results in Laboratory Medicine, for the purpose of improving health care, by:

- *promoting the concept of traceability of measurement results to the *Système International d’Unités (SI)* or, where necessary, to other internationally agreed references;*
- *promoting close links between Reference Laboratories in Laboratory Medicine and National Metrology Institutes;*
- *co-ordinating and giving guidance in the establishment of Reference Measurement Systems with respect to medical needs*
- *identifying and prioritizing the measurands requiring international traceability and comparability and thereby encouraging appropriate organizations to accept responsibility for the development of suitable reference methods and measurement procedures and certified reference materials;*
- *encouraging the in-vitro diagnostic (IVD) industry to apply the agreed reference measurement systems;*
- *providing support for Reference Laboratories preparing for accreditation;*
- *publicising widely relevant information to interested parties;*
- *providing scientific and organizational expertise to the parties involved.*

JCTLM Structure and Formality:

After discussion, it was agreed that the principal promoters and stakeholders of the JCTLM shall be the worldwide international organisations that will provide the essential formal international references, namely:

- the International Bureau of Weights and Measures (BIPM);
- the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC);
- the International Laboratory Accreditation Cooperation (ILAC); and
- the World Health Organization (WHO) (to be confirmed)

Other key stakeholders will be:

- CRM producers – notably NIST and IRMM
- IVD industry (AdvaMed, EDMA, JACR)
- EQA/PT Organisations, Regulatory Bodies
- WASPaLM, ISTH
- EC-DG Enterprise
- ISO

Creation and Operation

1. It was agreed that the JCTLM would be created through an exchange of letters within the next few months between the four principal promoters and stakeholders, the BIPM, the IFCC,

the ILAC and the WHO, in which the goals and scope of activities of the Committee are defined.

2. The work of the JCTLM shall be based on existing international or inter-governmental agreements and the JCTLM will operate by consensus.
3. The principal activities of the JCTLM shall be carried out by its Working Groups.
4. The membership of the JCTLM will comprise the principal stakeholders, all the identified other stakeholders and the organizations represented at the Workshop.
5. The Executive will comprise representatives of the four principal organizations with a rotating chairmanship; for the first two years (2002-2004), the Chairman will be from the IFCC, and the Secretariat from the BIPM. (The JCTLM website will be hosted by the Secretariat, currently the BIPM.)
6. Costs of involvement in JCTLM activities will be met where they arise, as the responsibility of each participating body; there will, for the time being, be no JCTLM budget.

Participants agreed to the establishment of two JCTLM Working Groups.

Working Group 1: Reference Materials and Reference Procedures

The Terms of Reference of Working Group 1 are to identify reference materials and reference procedures and endorse those appropriate to meet the requirements of the EC Directive regarding in-vitro diagnostic medical devices (IVD MD).¹

Membership [Organisation (Identified Contact)]:

- NIST (W May), IRMM (M Grasserbauer) : Co-Chairs
- IVD Industry: EDMA (W Hoelzel), AdvaMed (C Jain), JACR (N Sugai)
- IFCC (M Panteghini), ILAC (A Squirrell)
- NIBSC (A Bristow)
- WHO (to be determined)
- BIPM (CCQM) (R Kaarls) {Note: It was agreed that NMIs generally would be involved through the CCQM.}
- EQA/PT – CAP (Representative to be determined: President)/EQALM (J-C Libeer)

Working Group 2: Reference Measurement Laboratories

The Terms of Reference of Working Group 2 are to

- a) collect information on existing and candidate reference measurement laboratories (RMLs),
- b) encourage and facilitate the formation of networks of RMLs for different groups of measurable quantities (concerning electrolytes, substrates/metabolites, enzymes, HbA1c, low molecular hormones, ...),
- c) establish a procedure for the approval of RMLs on the basis of their metrological level according to ISO 15195 and their performance as demonstrated in inter-laboratory comparisons linked to an NMI.

Membership [Organisation (Identified Contact)]:

- IFCC (Institut für Klinische Biochemie - L Siekmann, University of Gent - L Thienpont) : Co-Chairs

¹ Although the requirements of the EC IVD MD Directive are the initial driver for this activity, there is no intention of restricting the interest of the group to any one geographical region or trade issue.

- CIPM (R Kaarls)
- NMIs and related institutes (NMI – E de Leer, LGC – J Marriott, NIST – W Koch), CDC (G Myers), IRMM (H Schimmel)
- ILAC (A Squirrell)
- IVD Industry: EDMA (W Hoelzel), AdvaMed (D Sogin), JACR (N Sugai)

Three sub-Working Groups are to be established to coordinate specialist networks:

- WG2A: Enzymes (Reference/expert laboratories conducting enzyme measurements according to new reference methods) (IFCC Chair: Prof Lothar Siekmann at present – to be confirmed at October meeting in Kyoto)
- WG2B: HbA1c (IFCC Chair: C Weykamp/K Miedema ? - to be confirmed)
- WG2C: Cholesterol (CDC Chair - Mary Kimberley)

[WG2D was proposed in the area of “Nucleic acid amplification testing (NAT) /Genetic testing” but it was agreed that this would not be set up yet.]

The Working Group Co-Chairs may invite other members.

It was noted that WGs 1 and 2 should be linked together in the longer term and that WG2 will rely on outcomes from WG1. It was suggested that the appropriate time interval in which the combined JCTLM Working Groups will meet is every second year. One important aspect of these activities is to avoid duplication.

It was proposed that another JCTLM Symposium/Workshop be convened in one year to review progress. The exact timing and venue are yet to be arranged. This is not to be a broadbased Workshop, but a Committee meeting linking the various participant bodies. With regard to publicity, it was agreed that this would be pending the completion of the list of endorsed reference materials and reference procedures by WG1. Information about the JCTLM is available on the websites of the BIPM (www.bipm.org) and the IFCC (www.ifcc.org). A short press release has now also been posted on the BIPM website (at: http://www.bipm.org/enus/2_Committees/JCTLM.shtml).

APPENDIX 1 - GENERAL DISCUSSION RE: ESTABLISHMENT OF JCTLM

Among the points that came out of the general discussion on the final day of the Workshop in relation to the establishment of the JCTLM were the following:

- Dr R Hinzmann (Beckman Coulter) stated that an important goal of the JCTLM should be to provide the community with specifications of uncertainty – what is a medically acceptable coefficient of variance (CV), bias, uncertainty. It is not sufficient to talk about uncertainty of measurement without quantifying this according to medical need and incorporating it into medical decision making processes. Dr A Kallner (IFCC) noted that a document is being produced in WG3 of ISO Technical Committee (TC) 212 regarding specifications of uncertainty for analytical purposes.
- Dr W May (NIST) suggested that the authority for the JCTLM should be identified, with a statement as to who appointed the Committee, and what authority it has, to ensure the usefulness of the Committee and the decisions it makes. Dr Koch (NIST) noted that, in recognition of the limited authority and resources of the JCTLM, its scope should be restricted to what is feasible. Dr Koch noted that, while the CIPM and WHO have some authority to recognize reference materials and reference systems and at least make recommendations, ILAC and the IFCC have influence over what their members do but no formal authority. It was agreed that the authority of the JCTLM is used in the sense of its “competence” or “influence” in the relevant areas of activity, with the JCTLM recognised as an authoritative body. It does not have any independent legal status but is a high level interest group which would provide bodies, such as the European Commission (EC), with harmonised opinion and input. In relation to the EC, Ms Karen Howes (EC) undertook to inform the EC Expert Group on Medical Devices of the outcomes of the Workshop, and to recommend the JCTLM to member states as suitable to undertake these activities.
- Dr D Powers (Powers Consulting Services) recommended that the emphasis of the JCTLM Mission Statement should be on health care rather than metrological traceability.
- Responding to discussion about the feasibility of traceability to SI units in this area, Prof Grasserbauer (IRMM) informed the meeting that the overall intention is to establish a sound measurement system under the authority of the BIPM, as the guardian of the SI, so it would be desirable eventually to achieve traceability to the SI for medical measurements. Dr Koch agreed that, in the long term, these measurements should become traceable to the SI to ensure that a system is in place that is invariant in time and space, even though this is not possible for all measurands in the short term. Dr May added that the goal is comparability of measurements and traceability to the SI is a means of achieving that comparability.
- Further discussion regarding the involvement of the medical profession was concluded with the agreement that the JCTLM’s role is to establish an analytically and metrologically sound reference system, and that dialogue is to be opened with the appropriate organisations within the medical profession at the stage of implementation of specific projects. The JCTLM will operate as a focused, small, central coordinating group with actions that extend to involve special interest groups on a needs-basis.
- Dr May highlighted the importance of having stakeholders that are truly international, representing as far as possible all interested countries.

- Dr B Güttler (PTB) noted that NMIs need to ensure that they have an effective relationship with their national medical institutes.
- Dr S-R Park (KRISS) requested that the JCTLM also help provoke governments to support NMIs' work in these research areas, to establish traceability in laboratory medicine. Dr Quinn responded that the outcomes of the Workshop, the creation of the JCTLM, its aims, participants and the need for support from member governments will be included in the report to the CGPM that is to be sent out by the BIPM in December 2002.

It was agreed that the immediate actions needed to be undertaken by the JCTLM are to meet the needs of manufacturers in addressing the EC IVD MD Directive.

Dr R Lequin (Diagnostics Consultancy) provided an overview of the possible activities of the two proposed Working Groups of the JCTLM, discussing the “essential and basic” features of each. He had also prepared draft compilations of Type A quantities and Type B substances on behalf of the IRMM (which will be submitted as a working document to WG1).

Dr H Parkes (LGC) suggested that the JCTLM's scope, in support of addressing the EC IVD MD Directive, is to prioritise what can be done, according to difficulty, in identifying appropriate reference materials and methods. Dr Koch noted that the CAP and other similar bodies have a lot of information which could provide an efficient starting point. Dr L Penberthy (RCPA) added that existing databases around the world should be accessed, together with input being sought directly from the manufacturers to help identify priorities and problems. Prof W Hoelzel (EDMA) agreed that the requirement of the EC Directive is traceability back to “available reference materials” and “available reference measurement procedures”, such that what is needed now is a simple listing of what is available and what is appropriate, i.e, what is *endorsed*. Dr C Jain (AdvaMed) inquired whether the BIPM database provided a listing of appropriate reference materials. Dr May confirmed that the measurement capabilities provided in the BIPM database have been internationally reviewed and are internationally accepted.

Dr D Sogin (AdvaMed) reiterated that the request from industry is assistance in understanding Type A quantities and Type B substances to help determine what reference materials are appropriate, as well as assistance in identifying appropriate reference methods. Dr Lequin noted that it is up to industry to participate in the JCTLM Working Groups. Dr D Powers (Powers Consulting Services) commented that the JCTLM should make recommendations regarding available materials and methods, with associated criteria to clarify the basis on which the materials and methods are listed.

Discussion specific to establishing Working Group 1: Reference Materials and Reference Procedures

ACTION: By 1 November 2002, WG1 is to compile a list of reference materials and methods that are currently available with criteria for appropriateness.

Prof Grasserbauer requested that the deadline for the provisional list be **January 1 2003**. The manufacturers in the audience responded that November is already too late.

Dr Eckfeldt noted that a similar exercise had been undertaken ten years ago (see website of the American Association for Clinical Chemistry [AACC]: www.aacc.org/standards/default.stm), the results of which could be used as a start. He also recommended that WG1 should include information about costs and turnaround times.

Ms Howes expressed the hope that the JCTLM will use the EC as a conduit for information. She agreed to act as the EC contact person, and added that she would recommend that member states request their notified bodies to support the work of the Committee. She informed the meeting that the EC Medical Devices expert group (which includes regulatory authorities and designating authorities for notified bodies, industry and standards bodies of member states) plans to meet in early July at which time she will provide a report of this activity.

Dr Penberthy informed the meeting that the RCPA, Australia, would be willing to participate if needed.

ACTION: It was agreed that the Co-chairs of the Working Group would inform members of meeting dates, etc. Dr Kaarls will organise direct contact with NMIs. The first meeting of WG1 will be held by the end of August 2002. (This has now been scheduled for August 28-29 2002 at NIST.) WG1 Co-chairs are to provide a short note to the JCTLM on progress to date by 1 October 2002.

Nominations from the CCQM will be provided within a week or two. The criterion for these is to ensure an appropriate spread of expertise. Prof Grasserbauer added that the prime task of the WG is to put together a list of acceptable materials and methods and establish criteria. These criteria for endorsing materials and methods will be made available for comment on the JCTLM Website. He appealed to the CCQM to nominate people with expertise with reference materials.

Discussion specific to establishing Working Group 2: Reference Measurement Laboratories

It was agreed that identified “expert laboratories” participating in WG2 sub-groups should be linked to NMIs, be accredited, and serve the IVD industry. Working Group 2 will be the governing body to set up criteria to meet the measurement needs of industry. The major task is to collect written standards/guidelines on how to demonstrate traceability and comparability for the diagnostic industry. In the area of accreditation, for example, WG2 is to advise on which documents/procedures/standards are valid for which contexts, and to provide criteria and examples to demonstrate traceability and comparability of the test. WG2 could also help identify funding sources (e.g., European Framework programs) and should help provide estimates of relevant costs and turnaround times. The sub-Working Groups will come up with lists of reputable laboratories and then come together for joint work.

ACTION: WG2 to meet at the latest by the end of September 2002.

Prof Siekmann informed meeting participants that he is seeking nominations of appropriate laboratory networks.

APPENDIX 2 - DISCUSSION ARISING FROM WORKSHOP PRESENTATIONS

These comments are provided as additional notes to the presentations posted on the JCTLM website and available shortly on CD.

DAY ONE - SUNDAY, 9 JUNE 2002

The Workshop was opened by Dr Robert Kaarls (CIPM/CCQM).

Dr T Quinn, BIPM, Dr M Müller, IFCC – Welcome and Introductory Remarks

Introductory remarks were made by Dr T Quinn (BIPM) and Dr M Müller (IFCC).

Dr T Quinn, BIPM - Metre Convention, BIPM, CIPM-MRA, CCQM

Dr Quinn provided an overview of the work of the BIPM and the Convention du Mètre, the CIPM MRA and the CCQM.

Dr M Müller, IFCC – The need for traceability in laboratory medicine

Dr Müller then discussed the role of the IFCC and the need for traceability in laboratory medicine.

Dr R Dybkaer, IFCC - Metrological traceability for in-vitro diagnostic medical devices: definitions and ISO/CEN standards

The presentation of Dr R Dybkaer (IFCC) focused on the driver for this activity, the requirement in the EC Directive for metrological traceability of in-vitro diagnostic medical devices (IVD MDs). He informed the meeting that the relevant ISO/CEN standards are being drafted jointly by CEN 140 and ISO Technical Committee TC212 .

During the discussion following Dr Dybkaer's presentation, Prof G Klee (Mayo Clinic) raised the point that, given the heterogeneity of substances, it is not clear how traceability might be attained. Dr Dybkaer agreed that speciation in analytes is a perennial problem in biology. Primary reference procedures are needed that cover everything to be measured and the analyte must be defined. Dr E de Leer (NMI) added that metrological traceability in chemistry is complicated because the primary calibrator is a pure compound, but a secondary calibrator is a pure compound in a matrix, and in some situations there is no pure compound available, in which case it is not clear how to trace back to SI units. A primary reference method may need to be identified to accommodate matrix effects. Dr W Koch (NIST) responded that the key is commutability of the primary reference sample. Dr H Schimmel (IRMM) noted that one has to understand the biological system to define the measurand, which is the sum of the components. Dr H Parkes (LGC) added that it is also very difficult to define the analyte in the case of genetic material. Some level of traceability should be attained, even if this is not through to the SI units.

Dr T Quinn, BIPM, Dr M Müller, IFCC – Developments so far

Dr Quinn then provided the meeting with a synopsis of progress to date in establishing a Joint Committee of Traceability in Laboratory Medicine. Dr C Jain (AdvaMed) proposed that, since the ultimate stakeholders for this activity are the physicians, this group should be included. Dr Dybkaer and Prof L Siekmann (IFCC) responded that the involvement of WHO and IFCC is seen as a means of addressing this to some extent. Dr Quinn noted that WHO could not attend the Workshop but does intend to participate in the activity. Dr Müller added that it is the intention that particular organizations of clinicians will be invited to participate/provide comment regarding specific projects involving their areas of expertise where procedures have been or are being developed, in order to get their agreement and support.

DAY TWO - MONDAY, 10 JUNE 2002

The second day of the Workshop involved a series of presentations to highlight various aspects of traceability in laboratory medicine, including definitions applying in this specialist area, the relevant players and their needs, in order to help identify the aims and potential scope of the proposed Joint Committee on Traceability in Laboratory Medicine.

Session 1 Chairs: Prof W Hoelzel (EDMA), Dr W Koch (NIST)

1: Dr A Bristow, NIBSC - Units and traceability in biological reference materials

During his presentation, Dr Bristow raised the following issues:

- Multiple methods, including some form of bioassay, are used to determine the value of biological standards. Therefore, there are problems in defining a biological standard in terms of one reference method as proposed in the standard prEN ISO17511.
- The measurement of proteins is dependent on the measurement method, and is not unique.
- WHO does not consider it necessary to include the uncertainty associated with reassessing subsequent releases of international standards.

Discussion:

Dr Bristow noted that one cannot define the measurand in the case of growth hormones, and indeed biologicals generally. Prof Siekmann added that the difficulties in defining the measurement procedure are not restricted to biologicals but are true in many metrological situations.

Dr Lequin suggested that WHO should update its definition of a “biological substance”, taking into account measurements based on the principle of activity (e.g., bioassays, enzyme measurements) as opposed to reactivity (immunoprocures).

2: Dr D Meyer, NCCLS - Role of global/international standards in Laboratory Medicine

Dr Meyer noted that national/regional standards need to become global. She informed the meeting that Mexico’s health care system had developed along the lines of the European model.

Discussion:

Dr R Lequin referred to the fact that the NCCLS is supported/accepted by the FDA, and inquired whether the NCCLS tries to obtain support or acceptance from regulatory bodies outside the US. Dr Meyer responded that NCCLS documents are intended to be voluntary but that it was true to say that the FDA does “accept” some. Consideration is being given to putting these documents through the ISO process, to transform them from national into international documents.

3: Dr J Eckfeldt, CAP - Proficiency testing schemes and traceability : the College of American Pathologists (CAP) Perspective

Dr Eckfeldt noted that over 95% of the membership of the CAP (College of American Pathologists) comprises US-based pathologists. He informed the meeting that a CAP survey was conducted in 1994 to estimate calibration and matrix biases. Such a survey needs to be re-done but is costly.

Today, around 20 countries participate in the CAP PT/EQAS (Proficiency Testing/External Quality Assurance Schemes) surveys. The CAP LAP (Laboratory Accreditation Program) has

“deeming authority” from the US federal government’s CMS (Centers for Medicare & Medicaid Services) as a provider of laboratory accreditation. (Note: *Deeming Authority* is the authority granted by CMS to accrediting organizations to determine, on CMS's behalf, whether a laboratory evaluated by the accrediting organization is in compliance with corresponding Medicare regulations.)

Discussion:

Prof Siekmann commented that, from the perspective of a PT/EQAS organizer, manufacturers cannot be asked to follow principles of traceability in preparing kits, etc, when these principles are not followed in external quality assessments, but the problem is how to do this.

Mr A Squirrell (ILAC) noted that the CAP survey seemed to achieve reasonable estimates of bias, but he inquired how these estimates are then used, and whether they are fed back to those writing the measurement procedures. Dr Eckfeldt responded that the survey biases are generally presented, but what is not generally known is the true calibration bias. The results shown in the presentation were from a survey undertaken in 1994, so it is necessary to re-do this work to make it current. Commutability studies should be undertaken on an on-going basis or at least every time samples are changed.

4: Dr E de Leer, NMI - Comparability and traceability: point of view from a metrological institute

In his presentation, Dr de Leer pointed out that traceability, as defined in the VIM (International Vocabulary of Basic and General Terms in Metrology), is *not* related to the measurement process. He noted the inconsistency with the standard ISO/IEC 17025, which talks about measurements made by a laboratory being traceable, therefore referring to the measurement process. He also noted that validation reference materials are very often matrixes.

Discussion:

Prof M Grasserbauer inquired why validation reference materials, which carry a value that is traceable, do not provide traceability themselves. Dr de Leer responded that to assure the quality of the work, a reference material is used with an assigned value to validate the procedure. However, the measurement result is traceable to the calibration materials used, not to the reference material used to validate the procedure.

5: Prof G Klee, Mayo Clinic - Requirements of physicians for standardized/comparable measurements: impact on the medical decision

Points made by Prof Klee included the following:

- physicians requirements are not uniform;
- it is not just a matter of considering the practitioner but also the health care system;
- harmonisation and constancy/comparability over time (with the establishment of health care policy) and space (given changes in the locations of clinics/patients) are important concepts;
- traceability, uncertainty and commutability must all be considered; and
- the move to electronic systems is reinforcing the need for harmonization and traceability.

Prof Klee used the examples of cholesterol and PSA testing to demonstrate that bias effects and consequent uncertainties lead to more/less patients being identified with cholesterol/prostate problems than represents reality, with the associated additional health care costs, etc.

Discussion:

Dr Parkes agreed that standards should be representative of the end-type sample, but there are ethical issues in the case of human samples. Prof Klee commented that information about individual patients can be blocked to ensure that there is no visible link back from the test result to the patient.

6: Ms K Howes, EC-DG Enterprise - Regulations in the EU

Ms Howes informed the meeting that most actions regarding regulations for in-vitro diagnostic medical devices are devolved to EC Member states. The EC Medical Devices experts group consists of representatives from the Departments of Health in each member state, experts from member states, notified/conformity assessment bodies, standards bodies and industry. Directives focus on the control and management of risks. The EC IVD MD Directive deals with both pre- and post-market activities – e.g. the effect of the product once on the market.

Discussion:

Dr de Leer inquired how the word traceability entered the Directive and who controls the metrological content of Directives generally. Ms Howes stated that she could not respond directly to this but that it was felt that this is an area that needs controlling. Dr Dybkaer added that very often during the process of phrasing what is in a Directive there are consultations between Commission staff and experts.

Dr Parkes raised the issue of whether qualitative measurements need to be traceable.

7: Dr S Gutman, FDA - FDA's Role in the Regulation of In-Vitro Diagnostics: The search for gold

Dr Gutman explained that, according to the FDA, a product is considered “old” if it was on the market in or before 1976 or it can be traced to a product on the market in or before 1976. Products that do not fit this criterion are considered “new”. Note that it is not a requirement that “new” products are *better* than “old” products. In this context, Dr Gutman clarified the FDA’s terminology “Premarket Notification” (PMN or 510(k)) and “Premarket Approval” (PMA) of medical devices.²

Discussion:

Mr Squirrell noted that the terms accuracy, precision and bias are being used in different contexts to mean different things and that Workshop participants needs to determine whether they will use the ISO definitions. He asked Dr Gutman if, as a regulator, he thought this is possible. Dr Gutman responded that one of the problems is that the manufacturing and user community in the US is not well informed, so that whatever is done needs to be made understandable. He added that the NCCLS has expressed interest in being the drivers of this.

8: Dr T Kawai, Health Care Technology Foundation (HECTEF) - IVD Regulations in Japan: Innovation towards Global Harmonization

Dr Kawai informed the meeting that the health sector in Japan represents 8% of GDP. In the area of in-vitro diagnostic devices, 36% of devices are imported.

² Final wording of this summary being confirmed.

HECTEF is a non-governmental private company producing and providing reference materials. The JACR (Japan Association of Clinical Reagents) consists of 129 companies with technical committees to draft standards in manufacturing IVD-MDs.

Session 2 Chairs: J C Forest (IFCC), H Schimmel (IRMM)

9: Prof Wieland Hoelzel, EDMA - Point of view of European industry

During his presentation, Prof Hoelzel, following up on an earlier query, stated that the reason for the reference to metrology in the EC Directive was in support of free trade in Europe. He added that, currently, reference materials are listed without uncertainties.

Discussion:

Prof Grasserbauer noted that in key comparisons, different laboratories have different approaches to estimating Type B error and that the GUM (ISO Guide to the Determination of Uncertainty in Measurement) as it stands may not be sufficiently clear to determine uncertainty in the chemical area. Prof Hoelzel responded that it is not just laboratories, but manufacturers as well who use different approaches.

Dr de Leer added to Prof Hoelzel's remark that a 35% uncertainty will not be acceptable to clinicians, saying that this is also true for drug testing in sports, where the concept of uncertainty is not accepted, so the true picture is not provided. The concept of measurement uncertainty must be introduced and understood by the medical community which, in turn, should educate people about how it should be applied. The people who make the decisions should be aware of the whole measurement determination, including the uncertainty.

Dr Dybkaer responded to the two points raised. Firstly, regarding the GUM, he informed the meeting that supplementary documentation is being written on how it should be interpreted, some of which is already available. Secondly, he stated that criteria in the form of cut-off values should **not** have uncertainties attached to them – the results of the *procedures* should have the uncertainties attached to them.

10: Dr D Sogin, AdvaMed - Point of view of American industry

(Presented on behalf of Dr Neil Greenberg)

Dr Sogin stated that manufacturers want standards harmonised globally. They are very familiar with the concept of traceability in terms of the need for calibration. Dr Sogin expressed doubt about the value of uncertainty determinations in terms of their use by clinicians without manufacturers providing additional assistance.

Discussion:

Prof Grasserbauer asked Dr Sogin to define an independent reference laboratory. Dr Sogin responded that it is one in which the relevant ISO documentation is in place, i.e, with independent accreditation.

Dr May noted that NMIs are struggling to support industry and that industry is being asked to meet different requirements. He speculated on how far in the future it would be before regulatory bodies come together to produce harmonized requirements, inquiring if this would be useful to IVD manufacturers. Dr Sogin agreed that it would.

Dr Jain informed the meeting that what manufacturers need is a list of reference materials and methods that are currently available, in order to comply with the December 7 2003 deadline of the EC Directive. Prof Grasserbauer responded that a preliminary survey of available reference materials has been undertaken and that this needs to be validated. (Note that this issue is now being taken up by Working Group 1 of the JCTLM.)

11: Mr Alan Squirrell, ILAC - Accreditation of clinical laboratories: an ILAC overview

Mr Squirrell highlighted the fact that ILAC considers it essential that assessment processes are linked to metrology. The core accreditation document is ISO/IEC 17025, which emphasises the traceability of measurement results and the determination of measurement uncertainties.

There are currently 41 accreditation bodies from 32 countries (with about 10,000 accredited laboratories) participating in the ILAC MRA. These have all undergone evaluation and peer review, to achieve recognition of the equivalence of the accreditation bodies and hence their accredited laboratories. Mr Squirrel noted that there is evidence that the ILAC MRA is a reasonably economical and effective way of demonstrating equivalence. By 1st January 2003 all accredited labs must comply with ISO/IEC 17025. ILAC's position is that putting these structures in place provides a means of ensuring accurate measurement results.

11-1: Dr Regina Robertson, National Association of Testing Authorities, Australia (NATA) - The Australian Experience

Dr Robertson noted that the accreditation process is one of peer review where laboratory peers are involved to establish best practice and to formalise the process. The two relevant standards in this area are ISO 17025 and ISO 15189 for clinical laboratories.

11-2: Dr Sean Peters, South African National Accreditation System (SANAS) - The South African Experience

Dr Peters described the problems of establishing laboratory accreditation in developing economies in the Southern African context. He noted that there are currently 400 laboratories in South Africa providing services, 108 of which are accredited.

Discussion:

Dr R Worswick (LGC) inquired why there seem to be three accreditation standards. Mr Squirrell clarified that ISO 9000 is not an accreditation standard but a certification standard. The ILAC MRA uses ISO 17025 as the core document, but the medical community had asked for something specific to address their requirements, which led to ISO 15189. ISO 15189 picks up some specific issues for clinical laboratories, such as point-of-care testing. Discussion is now underway about whether ISO 17025 can be used as comparable with ISO 15189.

12: Dr H Schimmel, IRMM - The concept of commutability

During his presentation, Dr Schimmel commented that stability and homogeneity-related uncertainty should be included in the determination of uncertainty. Before imposing metrological principles on the community, discussions must be undertaken to ensure the appropriateness of these in biological contexts.

Discussion:

Dr de Leer asked whether, when there is a problem with commutability, this should be considered a problem with the standard or the method. Dr Schimmel responded that the non-commutability may be caused by the preparation of the standard, such that interfering components may be present, and should not be attributed to the method.

13: Dr W Koch, NIST - Certified reference materials for laboratory medicine

Dr Koch informed the meeting that NIST is prepared to provide 40% of the type A analytes required globally, if the EU, Australia and Japan provide the remaining 60%.

Discussion:

Dr D Powers reiterated that what is needed by manufacturers is the identification of reference materials, methods, and laboratories that are available today. He stated that the identification of new materials, etc, should be more of a priority after December 2003.

Dr Jain inquired whether any estimates have been made of the costs of implementing the Directive. Dr Koch responded that it is known that repeat tests in the US cost a considerable amount of money, so that tremendous savings are possible by accepting other people's results. NIST is currently involved in a project with Mayo clinic to put a quantitative value on the financial savings that could be made with the use of accurate standards.

14: Prof J-C Forest, IFCC - Realizing traceability in laboratory medicine: a coordinated approach

Prof Forest's presentation summarised recent traceability-related activities of the IFCC, specifically the work of the IFCC Working Group for standardization of HCG (Human Chorionic Gonadotropin) and the IFCC Working Group for standardization of HbA1c (glycohaemoglobin). He used these two examples to illustrate the success of a collaborative approach to implement reference systems based on clinical needs, encompassing reference methods, production of reference materials and establishment of networks of reference laboratories.

15: Prof L Siekmann, IFCC - Establishing measurement traceability in clinical enzymology

Prof Siekmann discussed the implementation of a reference system for enzymes in terms of:

- identifying appropriate primary reference measurement procedures;
- establishing reference procedures within a network of reference laboratories according to stringent metrological principles; and
- the selection and certification of commutable reference materials by a network of reference laboratories.

He demonstrated how an enzyme reference laboratory could serve to demonstrate the commutability of control materials and the compatibility of manufacturers' routine test procedures with the IFCC primary reference measurement procedures, by parallel measurements of patient samples.

16: Dr J C Libeer, EQALM - Metrological aspects in external Quality Assurance Programs

During his presentation, Dr Libeer commented on the importance of educating clinicians on what uncertainty means and how it should be incorporated.

Discussion:

During the discussion Dr Libeer noted that confidence in results is based on a) the accreditation process, and b) the results of proficiency tests (PTs). However, care must be taken that laboratories use the same approach for proficiency tests to their approach for routine tests. The PT process should be seen as educational, to help improve the laboratory's approach.

GLOSSARY:

AACC: American Association for Clinical Chemistry
AdvaMed: Advanced Medical Technology Association
BIPM: Bureau International des Poids et Mesures
CAP: College of American Pathologists
CCQM: Consultative Committee for Amount of Substance: metrology in chemistry
CDC: Centers for Disease Control and Prevention, USA
CEN: Comité Européen de Normalisation
CIPM: Comité International des Poids et Mesures
CMS: Centers for Medicare & Medicaid Services, USA
CRM: Certified Reference Material
EC: European Commission – EC Enterprise Directorate-General: DG Enterprise
EDMA: European Diagnostic Manufacturers Association
EQA: External Quality Assessment
EQALM: European Committee for External Quality Assessment Programmes in Laboratory Medicine
EQAS: External Quality Assurance Schemes
FDA: Food and Drug Administration, USA
GDP: Gross Domestic Product
GUM: ISO Guide to the Expression of Uncertainty in Measurement
HbA1c: Glycohaemoglobin
HCG: Human Chorionic Gonadotropin
HECTEF: Health Care Technology Foundation, Japan
IEC: International Electrotechnical Commission
IFCC: International Federation of Clinical Chemistry and Laboratory Medicine
ILAC: International Laboratory Accreditation Cooperation
IRMM: Institute for Reference Materials and Measurements
ISO: International Organization for Standardization
ISTH: International Society on Thrombosis and Haemostasis
IVD: In-Vitro Diagnostic – IVD MD: In-Vitro Diagnostic Medical Device
JACR: Japan Association of Clinical Reagents
JCTLM: Joint Committee on Traceability in Laboratory Medicine
KRIS: Korea Research Institute of Standards and Science
LAP: Laboratory Accreditation Program
MRA: Mutual Recognition Arrangement
NAT: Nucleic acid amplification testing
NATA: National Association of Testing Authorities, Australia
NIBSC: National Institute for Biological Standards and Control, UK
NIST: National Institute of Standards and Technology, USA
NMI: National Metrology Institute
NMI: Nederlands Meetinstituut
PSA: Prostate Specific Antigen
PT: Proficiency Testing
PTB: Physikalisch-Technische Bundesanstalt, Germany
RCPA: Royal College of Pathologists of Australasia
RML: Reference Measurement Laboratory
SANAS: South African National Accreditation System
SI: Système International d'Unités
VIM: International Vocabulary of Basic and General Terms in Metrology
WASPALM: World Association of Societies of Pathology and Laboratory Medicine
WG: Working Group
WHO: World Health Organization