

**Distribution: General  
English only**

**Report**

**WHO Consultation on International Biological  
Standards for *in vitro* Diagnostic Procedures**

**Geneva, Switzerland  
14-15 September 2000**



**WORLD HEALTH ORGANIZATION  
Blood Safety and Clinical Technology  
October 2000**

## CONTENTS

	<b>page</b>
<b>1. BACKGROUND AND OPENING REMARKS</b>	<b>1</b>
<b>2. SUMMARY OF PRESENTATIONS</b>	<b>1</b>
<b>2.1 WHO International Biological Reference Materials</b>	<b>1</b>
<b>2.2 Development of International Biological Standards for <i>in vitro</i> Diagnostic Procedures: scientific issues, priorities and needs</b>	<b>2</b>
<b>2.2.1 Standardization of analytes in specific scientific disciplines</b>	<b>2</b>
<b>2.2.2 Regulatory aspects of <i>in vitro</i> Diagnostic Procedures</b>	<b>4</b>
<b>2.2.3 List of on-going and priority projects</b>	<b>5</b>
<b>3. ROUND-TABLE DISCUSSION</b>	<b>5</b>
<b>3.1 Classification and nomenclature of diagnostic analytes</b>	<b>5</b>
<b>3.2 The Reference System</b>	<b>6</b>
<b>3.3 The Reference System and Category B analytes</b>	<b>6</b>
<b>3.4 Calibration and assignment of numerical value to an ICRM</b>	<b>7</b>
<b>4. CONCLUSIONS AND RECOMMENDATIONS</b>	<b>8</b>
<b>5. REFERENCES</b>	<b>9</b>
 <b>Annex I. Listing of on-going projects and priority setting of projects</b>	
<b>Annex II. Agenda</b>	
<b>Annex III. List of participants</b>	
.....	

## 1. BACKGROUND AND OPENING REMARKS

Since the 1920's, biological standardization activities have been promoted under programs organized first by the League of Nations and later by the World Health Organization. Initially, the main objective was to ensure that the functional biological activity of therapeutic products could be standardized, the purpose of which being to ensure quality and efficacy of these materials world-wide. However, over the last thirty years, biological standardization has been applied increasingly also to clinical laboratory investigations and diagnostic procedures.

There have been discussions over many years, within the WHO Expert Committee on Biological Standardization (1) and the International Scientific Organizations (2), concerning the best way to calibrate International Reference Materials for diagnostic measurements as well as to express their biological activities: whether in International Units or other Units. Moreover, an Independent Review of WHO's remit and activities in the Biologicals field (3), carried out in 1998, recommended that the development of International Biological Standards for *in vitro* diagnostics be continued, placing a high priority on microbial agents which could be transmitted to humans.

A Consultation of relevant international professional groups with expertise in the *in vitro* diagnostic field was convened at the WHO in Geneva on 14-15 September 2000. The Consultation was opened by Dr Yasuhiro Suzuki, Executive Director of the Health Technology and Pharmaceuticals Cluster, WHO. Dr Suzuki stated that the objectives of the Consultation were to discuss the scientific issues involved in this work and to seek advice on priorities in the development of appropriate biological reference materials for diagnostic measurements with relevance to global public health.

The conclusions and recommendations resulting from these discussions will help determine the next steps to be taken in this important endeavour and will be reported to the Expert Committee on Biological Standardization (ECBS). This Committee will report and make recommendations to WHO.

Dr J. Löwer acted as chairperson and Dr R. Lequin and Dr A. Bristow were nominated rapporteurs. The agenda and list of participants are attached in Annex II and III.

## 2 SUMMARY OF PRESENTATIONS

### 2.1 WHO International Biological Reference Materials

(A. Padilla, A. Bristow, R. Lequin)

In the context of Biological Standardization, WHO has defined a biological substance as "a substance which cannot be completely characterized by physico-chemical means alone, and which therefore requires the use of some form of a bioassay". The underlying principle of such assays is that they depend on the comparison of the response of the test substance with that of a reference material, and since the 1920's the International Standards, currently supplied by WHO, have, in many cases served as the international biological reference materials for such procedures.

A number of test procedures based on biological activities are now used in *in vitro* diagnostic procedures. In addition to *in vitro* assays for biological function, these also include immunoassays for both ligand and antibodies, gene amplification assays and infectivity

assays. In most cases the basic principle of comparison of a test response with that of a reference material has been maintained, and such assays are usually calibrated against the WHO International Standard.

The WHO catalogue (<http://www.who.int/technology/biological.htm>) currently lists over 300 International Standards (4) in the areas of haematology and blood safety, endocrinology, virology, bacteriology and immunobiology. The activity of such reference materials is usually described by a numerical value in International Units, a concept which offers the advantage of being applicable to poorly defined or heterogeneous analytes such as sera or partially purified preparations. However other unitages have also been applied for preparations used for *in vitro* diagnostic purposes. Within the Group on Blood Products and related Substances, a 70 % of the current International Standards are applied to *in vitro* diagnostic procedures.

In recent years, as biological analytes have become better characterized at the molecular level, there has been a move towards assigning content in mg or in mol. This approach offers advantages of more accurate traceability back to SI units. In both cases however, the principle that WHO International Standards are method-independent has been maintained, and whilst the application of a reference preparation may be restricted to a particular class of assay, such as an International Standard for immunoassays, neither the calibration nor the application are restricted to defined assay procedures within that class.

The standardization of immunoprocedures for heterogeneous analytes such as glycoproteins remains problematical. Such analytes exhibit heterogeneity at the level of glycosylation which may affect their immunoreactivity. Where the test analyte and the reference material exhibit different glycosylation patterns, the principle of measuring like versus like is clearly violated. Further progress in this area, i) to better characterize at a molecular level the components of such analytes, and ii) to improve the selectivity of immunoassay procedures such that diagnostically critical components of a heterogeneous mixture are identified is essential.

## **2.2 Development of International Biological Standards for *in vitro* Diagnostic Procedures: scientific issues, priorities and needs**

### **2.2.1 Standardization of analytes in specific scientific disciplines**

Haematology (M. Lewis, ICSH; F. Preston, ISTH)

Provision of useful WHO International Standards has been achieved in a number of areas of haematological science, most notably in clotting factor standardization, used in the diagnosis and management of haemorrhagic and thrombotic disorders. An aspect of these proteins which is critical to an understanding of their measurement is their multi-functionality, and it remained the opinion of the speakers that a single standardized assay procedure for an analyte such as anti-thrombin, would be neither appropriate or possible, and at worst diagnostically misleading. Useful standardization in this area can only be achieved by understanding and taking into account all of the diagnostically important activities of the analyte being measured.

In addition to the existing International Standards, there remain areas of haematology where methods have not been adequately standardized. These include: cell counting and sizing (erythrocytes, lymphocytes, reticulocytes and platelets), haemoglobinopathy markers, red cell enzymes, diagnostic monoclonal antibodies, intrinsic factor and intrinsic factor antibodies, blood-grouping reagents, and reference materials for virological safety testing.

Control of anti-coagulant activity (near-patient testing) remains a priority for future standardization activity.

#### Virology and nucleic acid amplification techniques (N. Lelie; P. Minor)

In the field of virology, testing for diagnostic analytes is based on three different principles: biological function (infectivity, neutralization), nucleic acid amplification testing, or immunoassays (for either antigen or antibody). Within the scope of diagnostic testing in the field of virology, there is a clear and continued need for international standardization, including the provision of reference materials for: antibodies directed against viral components (HIV p24, HIV gp41/120, HCV C22, HCV C33, HBsAg); antibodies specific for HCV and HIV subtypes; anti-HIV/HCV antiserum panels, HCV RNA, HCV DNA, HIV RNA.

#### Allergens (R. Valenta, IUIS)

Conventional allergen preparations are heterogeneous mixtures of proteins, in which the allergenic components are incompletely characterized. Assaying allergens therefore depends on a biological response, such as IgE production, measured against reference preparations which are equally incompletely understood. The widespread availability of recombinant DNA technology has enabled individual allergenic proteins to be produced and their biological activity characterized. It is predicted that during the next decade, the principle allergenic components of all of the major allergens will be identified, and will be available as recombinant proteins for both therapeutic and diagnostic application. A requirement for significant WHO activity in this field is foreseen, with possibly as many as 60 individual allergen reference materials being required.

#### Clinical Chemistry (M. Müller, J-C. Forest)

The IFCC is currently engaged in a number of standardization projects. These include: plasma proteins, calibrators in clinical enzymology, apolipoproteins, markers of cardiac damage (myoglobin, troponin), human chorionic gonadotropin lipoprotein-A, haemoglobin-A<sub>1c</sub>, prostate specific antigen, serum cortisol, homocysteine, patient sample identification. Establishment of international reference materials for these analytes will be within the concept of a Reference System and will be carried out in collaboration with appropriate scientific and professional bodies, following a specific value transfer protocol.

#### Diabetes mellitus (H. Reinauer, WASP)

Standardization of biological analytes is important in a number of areas of diabetes: in insulin measurement, where the relationship between units and mg needs to be better defined, in the measurement of haemoglobin A<sub>1c</sub>, where a reference material is needed, in the diagnosis of microalbuminuria, where a suitable reference material for the measurement of albumin in urine is needed, and in the measurement of islet cell antibodies (antibodies to GAD65, IA<sub>2</sub>), where standardization of the various identified components of the autoimmune-response is at an early stage.

#### Reference systems and the measurement of analytes (A. Kallner, IUPAC)

Measurement of an analyte is now held to be achieved within the concept of a reference system, a three part concept which comprises reference material, reference method and reference laboratory. CEN and ISO written standards have been elaborated which seek to describe the components of the Reference System.

The reference system takes into account two essential components: traceability and uncertainty. The concept of traceability seeks to maintain, through the application of reference methods in reference laboratories, traceability of the numerical value from the product calibrator to the highest available level of reference material, and with time to previous reference materials. The uncertainty concept seeks to minimize, and, importantly, to quantify and declare, the uncertainty accumulated in descending through the calibration ladder, and in calibrating new reference materials in terms of existing ones. Comparisons with other materials will always increase the uncertainty of the reported value and therefore reproducible measurement procedures should be preferred in establishing the value (concentration, amount) of a new reference preparation.

### 2.2.2 Regulatory aspects of *in vitro* Diagnostic Procedures

(L. Wilson, P. Maxim, M. Nübling, K. Komuro)

Within the European Union, the Directive 98/79/EC on *in vitro* diagnostic medical devices (5), seeks to harmonize conformity assessment procedures to be applied when placing *in vitro* diagnostic devices on the market. For certain of these products (Annex II, List A/B), principally in the areas of blood virology and blood group serology, assessment will be performed with the assistance of a Notified Body.

The central requirements of the Directive in respect of Annex II, List A/B products, are the application of so-called Common Technical Specifications (CTS), assessment of the manufacturer's QC testing, and, in the case of List A products, independent batch verification by the Notified Body.

The scope of products covered in List A/B of the Directive implies additional initiatives at the level of internationally available biological reference materials. These include: an international reference material for HBsAg, reference panel of sera raised by infection with different HCV genotypes, anti-HTLV, and anti-HIV subtype reference panel, internationally available sero-conversion panels, and internationally available reference materials for blood grouping reagents such as anti-D, anti-A and anti-B monoclonal antibodies.

In the USA, *in vitro* diagnostic devices falling under the auspices of FDA may follow two pathways, depending on the product use and perceived level of risk, and are regulated by two Centers: the Center for Biologics Evaluation and Research (CBER) and the Center for Diagnostics and Radiological Health (CDRH). To date, biological standardization within the US has been principally centred on the development of CBER reference panels. Current activities in collaboration with WHO include: blood typing reagents, anti-HCV and anti-HIV subtype reference panels, International Standards for HIV-1, HBV and HCV nucleic acid testing.

Products falling under the auspices of CDRH are typically regulated through two major pathways: by Premarket Approval or by the 510(k) process. The regulatory pathways include a standards-based element whereby standards and reference preparations play an important role which is expected to increase in the future. Reference preparations falling under this umbrella include tumor markers and other serum or urine markers, molecular diagnostics for techniques such as NAT, serum proteins and peptides, including immunoglobulins, hormones, autoimmune markers, allergens, anti-microbiological antisera, haematological markers, and markers for inherited and somatic genetic testing.

In Japan, regulation of *in vitro* diagnostic devices is ensured by compliance with national reference materials for antigens (microbiological antigens) and antibodies (anti-microbiological antisera) and sero-conversion reference panels. The Japanese regulatory

authorities remain committed to active involvement in additional initiatives leading to the development of WHO international biological reference preparations for *in vitro* diagnostic procedures.

### 2.2.3 Listing of on-going and priority projects

The participants at this Consultation represented international professional societies and regulatory bodies as well as IVD Industry. Representatives from International Scientific Societies and Regulatory Bodies presented a list of on-going projects or of priorities of new projects for establishment of biological reference materials. They are enumerated in Annex I.

## 3 ROUND TABLE DISCUSSION

In Laboratory Medicine over 600 parameters are measured or determined using various *in vitro* assay systems, for the purpose of diagnosis and monitoring of disease. In recent years, a number of groups (e. g. the International Organization for Standardization -ISO-) have worked on the development of written standards procedures for the establishment of reference materials and reference assay systems for *in vitro* diagnostic assays. Such standards have largely been developed for application in the field of chemically well-defined analytes. The round table discussion focused on the applicability of these written standard procedures to assay systems and international reference materials for those analytes not completely characterizable by physico-chemical means, elsewhere defined as biologicals (biologics).

The following proposals made in presentations (see above) were discussed:

### 3.1 Classification and nomenclature of diagnostic analytes

It had been proposed that analytes measured in diagnostic procedures may be divided in two broad categories:

Category A: those where results of measurement are *traceable* to SI units, i.e. mole/L. They are chemically well-defined compounds, and for many, reference measurement systems (RMSs; reference measurement procedures and primary reference materials) are in place. Examples are: glucose, cholesterol, urea, steroid hormones, thyroid hormones. To this category belong some 100 compounds.

Category B: those where results of measurement are NOT *traceable* to SI units but are expressed in terms of arbitrary units e.g. WHO International Units. Tests for such analytes may be based on one of three principles: biological function (e.g. clotting assays; enzyme catalytic activity assays, infectivity assays), immunoprocudures (e.g. ELISA) and nucleic acid amplification techniques. "Biological substances" fall into this category. Group B comprises ~ 500 substances/ analytes.

The group recognised that many analytes in Category B exhibit heterogeneity. Examples include post-translational modifications such as glycosylation, binding to serum transport proteins, and various forms of degradation or metabolism. Such variants may react differently in different assays systems employed, and may therefore represent a potential source of assay variability. As the heterogeneity in presently available reference materials, including WHO reference materials, may not truly reflect the heterogeneity of the analyte, reference materials have to be recognized as being surrogates for the analytes present in human biological fluids.

It had been proposed that, for analytes exhibiting such heterogeneity, it is necessary to define precisely the specificity of any assay being used with respect to the various forms of the analyte likely to be present. It was also proposed that the possible refinement of assay specificity to measure individual variants of an analyte should be related to the clinical diagnosis being made.

### **3.2 The reference system**

According to ISO standards, the standardization of diagnostic assays should be achieved within the context of a "Reference System", comprising:

- Reference material
- Reference measurement procedure, internationally agreed
- Reference measurement laboratories, with proven expertise and capability of measurement

The role of the reference system is to ensure that a numerical value assigned to the reference material is:

- Traceable through the defined reference method
- Associated with a specified uncertainty
- Commutable with clinical values

### **3.3 The reference system and Category B analytes**

Category B analytes are poorly defined materials in comparison to Category A analytes, and, at present, reference measurement procedures – independent of routine measurement procedures – are NOT in place. It was proposed that standardization of diagnostic assay procedures for Category B analytes should be achieved within the context of a reference system as set out above.

#### **3.3.1 Establishment of a reference system**

It had been proposed that the establishment of a reference system should be achieved through a process of consensus. This should include:

- Definition of the properties of the reference material (including its method of manufacture) through an international consensus process. This is then called an international conventional reference material (ICRM).

- International agreement on a suitable reference measurement procedure (ICRMP) in order to assign values to the ICRM. Ideally, such measurement procedure should be independent of the routine assay procedure. The material and the procedure together constitute an international conventional reference system (ICRMS) (6).

- Establishment, by internationally agreed accreditation procedures, of reference laboratories (7,8).

#### **3.3.2 Choice of appropriate units**

Where it is possible to determine accurately and precisely the primary and secondary structure of the material, results of measurement may then be expressed in terms of mole per litre i.e. (moving the analyte from Category B to Category A). Where physico-chemical

definition cannot be achieved, expression in terms of International Units (IU) should be retained. The definition of the IU is fully arbitrary. Where the analyte may be measured by means of two different principles, e.g. bioassay and immunoprocures, the unit derived from these procedures should be regarded as completely separate from one another.

### 3.3.3 Consequences of this proposal:

- a reference material which is not traceable to SI units may not be described as a primary international biological reference material. The term international conventional reference material (ICRM) would be used
- assignment of a numerical value to an ICRM would be achieved using an international conventional reference measurement procedure (ICRMP) within a reference system, referred to as an international conventional reference measurement system (ICRMS)
- Reference measurement laboratories would be embedded in a network that can prove their competence in performance and execution of the RMSs in general and ICRMSs in particular. One aspect of the competence will be the low uncertainty in the measurement results. Other aspects include their Quality System and their consistently excellent performance in proficiency/external quality assessment rounds

## 3.4 **Calibration and assignment of numerical value to an ICRM**

As consequence of fully adopting the reference system concept for Category B analytes, calibration of WHO International Standards would follow the strategy outlined below:

### 3.4.1 First establishment

Where the ICRM is the first of its kind, the numerical figure to be assigned is fully arbitrary, i.e. it can be assigned a figure of 1, 10, 100 etc IUs. The arbitrarily assigned unitage should be linked to ICRMS established at the same time. The survey of activity of the candidate ICRM in the various measurement procedures already on the market may have no role in assigning a numerical value to the ICRM.

### 3.4.2 Replacement standards

Where the ICRM is intended to become the replacement of the first established ICRM, an international conventional reference measurement procedure should be in place. Three to six reference measurement laboratories, around the world, then should carefully perform the comparison between the first and the second ICRM using only the ICRMP. The potency estimate of the second ICRM should include the uncertainty of that estimate.

It was pointed out that the conventional collaborative study design for WHO International Standards, whereby the (geometric) mean potency is assessed using a large number of diverse routine measurement procedures already on the market in order to assign the numerical value of the unitage (multi-method assignment), is not consistent with the ICRMS concept.

When an ICRM has been established, the IVD manufacturer would use that material for assignment of values to his working calibrator (also called in-house calibrator) and eventually to his product calibrator.

### 3.4.3 Stability and commutability

The stability of the ICRM would be documented using the ICRMP by the reference measurement laboratories. The relationship between the numerical value assigned to the ICRM and clinical values obtained (commutability) would be investigated and documented using the ICRMS.

### 3.4.4 Biological Substance

The term “biological substance” would be reserved for prophylactic and therapeutic products and would be understood to refer to a defined biological effect, measured or determined in an *in-vivo* or *in-vitro* bioassay. WHO International Biological Standards should be made available for standardization of these biological substances.

For *in-vitro* diagnostic purposes the substance would be called an “analyte”. The measurement or determination of these “analytes” in biological fluids may involve biological function tests, immunoprocedures, and nucleic acid amplification techniques.

### 3.4.5 Labelling

*In the case of WHO International Standards for biological prophylactic and therapeutic products, the label should read: “(number e.g. 1<sup>st</sup>, 2<sup>nd</sup> etc) International Standard for biological substance X; Y IU per ampoule*

It was noted that the instructions for use for these International Biological Standards would need to indicate that for the purpose of calibration of *in-vitro* diagnostic procedures the ICRM should be used.

*In the case of WHO International Standards for the purpose of in-vitro diagnosis of disease the label should read: “(number e.g. 1<sup>st</sup>, 2<sup>nd</sup> etc) WHO International Conventional Reference Material for analyte X, for in-vitro diagnostic procedures; Y IU per ampoule*

The quantity of analyte and matrix present in an ICRM might, if appropriate, be related to the expected concentrations of analyte in patient samples, particularly those concentrations around medical decision limits.

## 4. CONCLUSIONS AND RECOMMENDATIONS

Good progress had been made in identifying and discussing scientific issues related to a global approach to the development of International Biological Standards for *in vitro* Diagnostic Procedures. However, a number of proposals considered by the Group did not meet with the unanimous agreement of all participants, especially regarding the universal applicability of the reference system concept to the establishment of International Biological Standards. The concept of “biological substance” as defined by WHO and the single reference method for analytes which are often multi-functional was also questioned.

During the meeting, the participants, and in particular those from the IVD industry, repeatedly mentioned that consensus should be reached at a *global* level in order to avoid duplication of measurements and calibration. Regional or national requirements for calibration of product calibrators by the manufacturer should be avoided.

Several issues remain to be resolved within the context of the different areas of expertise and clearly further discussion will be needed to develop the new concepts further. The ECBS was requested to consider the Report and to recommend ways to resolve the outstanding issues in establishing International Biological Standards for use in *in vitro* Diagnostic Procedures. Considerations should be given to broadening the consultative procedure through publication, including the WHO Biologicals Web page.

## 5. REFERENCES

- (1) Application of IUPAC/IFCC Recommendations on Quantities and Units to WHO Biological Reference Materials for Diagnostic Use. Document submitted to the 44<sup>th</sup> ECBS Meeting: Document BS/93.1722 (distr.:limited)
  - (2) IFCC Meeting on Reference Materials and Reference Measurement Systems in Laboratory Medicine. Co-sponsored by WHO. Geneva, 5-7 October 1994.
  - (3) Review of Remit and Activities of WHO in the Biologicals field and the Biologicals Unit. Report of review Team, October 1998.
  - (4) WHO Catalogue for International Biological Reference Preparations. Published via Internet: <http://www.who.int/technology/biological.htm>
  - (5) Directive 98/79/EC of the European Parliament and of the Council on *in vitro* Diagnostic Medical Devices, of 27 October 1998. Official Journal of the European Communities, 7.12.98 (L331/1-31)
  - (6) cf prEN ISO 17511: Metrological traceability of values assigned to calibrators and control materials.
  - (7) ISO 15195 entitled Requirements for Reference Measurement Laboratories in the Medical Laboratory.
  - (8) ISO 17025 entitled Requirements of testing and calibration laboratories
-

## **ANNEX I: WHO International Biological Standards On-going and Priority Setting of Projects**

### **ICSH: List of Proposed International Reference Materials**

Blood Cells in defined concentration and cell size as counting and sizing standards  
Platelet counting standard  
Reticulocytes  
Various monoclonal antibodies for identification of lineage of abnormal leucocytes  
Glucose-6-phosphate dehydrogenase and other red cell enzymes  
Haemoglobinopathy markers  
Intrinsic factor and intrinsic factor antibodies  
Transcobalamins  
Thrombopoietin  
Transferrin monoclonal antibodies

### **ISBT: Areas of priority**

Blood typing sera  
Viral safety tests

### **ISTH: International Reference Materials to define biological activity Units**

WHO should continue efforts to develop international biological reference standards to apply in standardization for hemostasis and thrombosis *in vitro* assays. In general, the value assigned to the reference material should be in relation to biological activity as opposed to mass. Traceability should be ensured through well described methods and materials.

### **IFCC: Areas of work**

Uniform definition of Biological Reference Materials in relation to medical needs  
Reference Materials in preparation:

HCG Isoforms  
Lp(a)  
Myoglobin, Troponins  
HbA1c  
PSA  
Homocystein, ATIII  
Osteocalcin  
TSH  
T4/T3  
FV Leiden DNA  
Alkaline Phosphatase  
CRP  
STransf. Receptor

### **CBER: List of proposals on International Biological Standards**

CBER will continue to be involved in all the WHO projects related to the development of viral safety markers applied in the virological safety testing of blood and blood products, both serology and Nucleic Acid Amplification Technology. CBER is placing a high priority to the development of reference materials on microbial agents which could be transmitted to humans.

HCV: anti-c100-3, anti-c22, anti-c33, anti-NS5

HBsAg: adw, ayw

Anti-HBs: anti-adw, anti-ayw

Anti-HBc: anti-HBc, anti-HBe

HIV-1: p-24, anti-p24, anti-gp41, anti-gp120, anti-gp160

HIV-2: anti-p27, anti-gp36, anti-gp120, anti-gp160 (and p27 if possible)

HIV subtype Group M: anti-gp41, anti-gp120 (and anti-gp160 if possible)

HIV subtype Group O: anti-gp41, anti-gp120 (and anti-gp160 if possible)

HTLV: anti-p19 (gag), anti-p24(gag), anti-gp46(env) (and anti-gp21(env) if possible)

All NAT, coagulation and blood banking reference preparations under development should continue as planned. CBER defers to CDRH for all other markers.

### **CDRH: List of proposals on International Reference Materials**

CDRH strongly endorse WHO efforts in promoting the development of International Standards, Reference Preparations and Reference Methods for Biological Standards. This effort on the part of WHO will greatly compliment our programs that are emphasizing a standards based review process whenever possible. In general CDRH concurs with the statements and suggestions made by ISTH and other Hematology groups about a pressing need for standards in the areas of general hematology, hemostasis, thrombosis and for factor assays. Included in this would be d-dimers and Leiden Factor V.

In the area of tumor markers development of reference materials are encouraged for any of the markers currently being used clinically such as CA15-3 and CA125. International standards are also needed for FISH assays and immunohistochemical assays for molecular markers such as HER2/neu and many of the other molecular oncology markers.

In vitro allergy testing is another area that would benefit from the development of international standards. Materials for latex and some of the venoms would be particularly interesting.

International reference materials for Lp(a), bone markers, telopeptides and anti cardiolipins could also be considered.

### **Notified Bodies: International Reference Materials needed**

HBsAg Reference Panel

HCV Ag (core)

Anti-HCV genotype reference panel

Anti-HIV subtype reference panel

HCV-RNA, HBV-DNA, HIV-RNA (geno-, subtypes)

**National Institute of Health, Japan**

Japan will continue to be involved in all the WHO projects related to the development of viral safety markers applied to the virological safety testing of blood and blood products.

---

## ANNEX II

### WHO CONSULTATION ON INTERNATIONAL BIOLOGICAL STANDARDS FOR *IN VITRO* DIAGNOSTIC PROCEDURES

WHO Headquarters, Geneva  
14-15 September 2000

#### AGENDA

#### Opening Remarks

#### WHO International Biological Reference Materials

Background and WHO Catalogue	Dr A. Padilla
International standards: International units, moles or mg	Dr A. Bristow
Problems with immunoprocures in Laboratory Medicine	Dr R. Lequin
International Standards for viral serology and NAT assays	Dr N Lelie

#### Development of International Biological Standards for *in vitro* diagnostic procedures: scientific issues, priorities and needs

##### 1. Views of International Scientific Societies:

###### Session 1:

Standards and standardization for general haematology:	Dr S.M. Lewis, ICSH ISBT, Dr P. Phillips
Issues in the standardization of hemostasis and thrombosis <i>in vitro</i> assays:	Dr F.E. Preston, ISTH
Lunch break	

###### Session 2:

General Aspects and IFCC Strategy for International Standardization:	Müller/ J.C. Forest, IFCC
Reference systems as applied to biological reference materials:	Dr A.Kallner, IUPAC
Biological Standardization in Diabetes Mellitus:	Dr H. Reinauer, WASP
Recombinant allergens for standardization and allergy diagnosis:	Dr R. Valenta, IUIS

## 2. Views of Regulatory Agencies

Use of Reference Preparations in review of *In Vitro* Diagnostic Products:  
Drs L. Wilson, P. Maxim

Biological Standards for diagnostic evaluations by manufacturers and for verification of manufactured products by Notified Bodies: Drs M. Nübling, F. Dati

Need and Use of WHO Standards for *in vitro* diagnostic tests: Views of the Japanese Biological Authorities. Dr K. Komuro

### Round Table

- Requirements for the development of International Biological Standards to apply in the Standardization of in-vitro Diagnosis.
- Needs and priorities: Proposals to submit to the Expert Committee on Biological Standardization.

### Conclusions and Recommendations

**ANNEX III**

**WHO CONSULTATION ON  
INTERNATIONAL BIOLOGICAL STANDARDS  
FOR *IN VITRO* DIAGNOSTIC PROCEDURES**

**WHO Headquarters, Geneva**

**14 -15 September 2000**

**List of Participants**

**Expert Panel on Biological Standardization**

- Dr Rudolf Lequin  
P.O. Box 4963  
Eindhoven 5604 CD  
The Netherlands

**International Association on Biological  
Standardization (IABS)**

- Dr Phil Minor  
National Institute for Biological Standards  
and Control (NIBSC)  
Blanche Lane  
South Mimms, Potters Bar  
Hertfordshire EN6 3QG  
UK

**International Council for Standardization in  
Haematology (ICSH)**

- Dr S. M. Lewis  
ICSH Liaison to WHO  
Department of Haematology  
Imperial College School of Medicine  
The Hammersmith Hospital  
GB-London, W12 0NN
- Dr Ivor Cavill  
Department of Hematology  
University of Wales College of Medicine  
Cardiff CF4 4XN  
UK

**International Federation of Clinical Chemistry  
and Laboratory Medicine (IFCC)**

- Dr Mathias M. Müller  
Department of Laboratory Diagnostics  
KFJ-Hospital  
Kundratstrasse 3  
A-1100 Vienna  
Austria

- Dr Jean-Claude Forest  
Hôpital Saint-François-d'Assise  
Rue de l'Espinay  
Québec, G1L 3L5  
Canada

**International Society on Thrombosis and  
Haemostasis (ISTH)**

- Dr G.C. White  
University of North Carolina Medical  
School  
Chapel Hill NC 27599-7035  
USA
- Dr F.E. Preston  
University Department of Haematology  
Royal Hallamshire Hospital  
Glossop Road  
Sheffield S10 2JF  
UK

**International Union of Immunological  
Societies (IUIS)**

- Dr Rudolf Valenta  
Molecular Immunopathology Group  
Institute of General and Experimental  
Pathology  
Allgemeines Krankenhaus der Universität  
Wien  
Währinger Gürtel 18-20  
A-1090 Vienna  
Austria

**International Union of Pure and Applied  
Chemistry (IUPAC)**

- Dr Anders Kallner  
President  
Department of Clinical Chemistry  
Karolinska Hospital  
S-.171 76 Stockholm  
Sweden

### **World Association of Societies of Pathology and Laboratory Medicine (WASP)**

- Prof. H. Reinauer  
Institute of Standardization and Documentation for Lab Medicine (INSTAND)  
Postfach 4402  
D-4000 Düsseldorf 1  
Germany

### **WHO Collaborating Centres for Biological Standards and Biological Standardization**

- Dr A. Bristow  
National Institute for Biological Standards and Control (NIBSC)  
Blanche Lane  
South Mimms, Potters Bar  
Hertfordshire EN6 3QG  
UK
- Dr Nico Lelie  
Central Laboratory of the Netherlands Red Cross Blood Transfusion Service  
Plesmanlaan 125  
1066 CX Amsterdam  
The Netherlands
- Dr Leonard Wilson  
Chief, Regulatory Project Management Branch  
Division of Blood Applications  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
Bethesda, MD 20892  
USA
- Ms Helen Worst  
Division of Blood Applications  
Center for Biologics Evaluation and Research (CBER)  
Food and Drug Administration (FDA)  
1401-Rockville Pike, HFM-385  
Rockville, Maryland 20852-1448  
USA

### **Regulatory Agencies**

- Dr Katsutoshi Komuro  
Director  
Department of Blood Products  
National Institute of Infectious Diseases  
Murayama Annex  
4-7-1 Gakuen  
Musashimurayama-shi  
Tokyo 208  
Japan
- Dr Peter Maxim  
CDRH/FDA  
HFZ-440  
2098 Gaither Road  
Rockville, MD 20850  
USA
- Dr Woody Dubois  
CDRH/FDA  
HFZ-440  
2098 Gaither Road  
Rockville, MD 20850  
USA
- Dr J. Löwer  
Paul Ehrlich Institute  
51-59 Paul Ehrlich Strasse  
63225 Langen  
Germany

### **European IVD Task Force/Notified Bodies**

- Dr Micha Nübling  
c/o Paul Ehrlich Institute  
51-59 Paul Ehrlich Strasse  
P.O. Box 1740  
63225 Langen  
Germany
- Dr Francesco Dati  
Chief Scientific Officer "In vitro Diagnostics"  
TÜV Rheinland Product Safety GmbH  
Am Grauen Stein  
D-51105 Cologne  
Germany

## Diagnostic Manufacturer Associations

### European Diagnostic Manufacturers (EDMA)

- Dr Wieland Hoelzel  
Roche Diagnostics  
Bahnhofstrasse 9 15  
82327 Tutzing  
Germany
  
- Dr Rob Slobbe  
Organon Teknika  
Boseind 15 PO Box 84  
5281 RM Boxtel  
The Netherlands

### Health Industry Manufacturers Association (HIMA)

- Neil Greenberg, Ph.D.  
Ortho-Clinical Diagnostics  
100 Indigo Creek Drive  
Rochester, NY 14626-5101  
USA
  
- Dr Alex Newhart  
Roche Diagnostics GmbH  
Sandhofer Strasse 116  
D-68305 Mannheim  
Germany

## SECRETARIAT

Dr J.C. Emmanuel, Director BCT  
Dr E. Griffiths, Coordinator VAB/QSB  
Dr C. Heuck, BCT/DIL  
Dr D. Lavanchy, Coordinator CSR/EDC  
Dr Luc Noel, Coordinator BCT/BTS  
Dr S.K. Osmanov, HVI  
Dr Ana Padilla, BCT/QSD (**Secretary**)  
Dr M.D. Perkins, CRD/PRD  
Dr G. Vercauteren, BCT/BTS  
Dr D. Wood, VAB/QSB