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Report

WHO Consultation on Global Measurement Standards and their use in the *in vitro* Biological Diagnostic Field

**Geneva, Switzerland
7-8 June 2004**



WORLD HEALTH ORGANIZATION
Essential Health Technologies
Health Technology and Pharmaceutical Cluster

Introduction

Dr Steffen Groth, Director Essential Health Technologies (EHT) opened the meeting. He reminded the Consultation that in 2003, a WHO Working Group on Hepatitis and HIV Diagnostic Reference Materials completed the preparation and final assessment of a replacement material to the 1st International Standard (IS) for Hepatitis B surface antigen (HBsAg). The data obtained in this assessment were extensively reviewed in several meetings with experts, and on the basis of their recommendations, the new reference material was established by the Expert Committee on Biological Standardisation (ECBS) as the 2nd WHO International Standard for HBsAg.

During meetings held to review the data, the Working Group discussed assigning a range to the value given to the 2nd compared to the 1st HBsAg International Standard, based on experimental data obtained in the WHO Collaborative Study. Because this raised an issue of a principle that also applies to all of WHO's biological standards, it was decided to hold a separate meeting to discuss to what extent certain general principles of "*metrology*", such as assignment of an uncertainty value to a replacement standard, are applicable to the WHO biological reference materials.

The WHO Consultation on Global Measurement Standards and their use in the *in vitro* Biological Diagnostic Field was held to discuss how the concepts of metrological traceability and measurement uncertainty could be applied to biological reference materials with assigned values for biological activity. Data from the WHO collaborative study on the 2nd HBsAg IS as well as from WHO collaborative studies on selected blood coagulation and hormone protein standards were considered as models for the discussions.

This meeting was also deemed appropriate in light of new European regulations concerning *in vitro* diagnostic devices. These regulations involve new requirements to show consistency of laboratory results based on metrological parameters. It is essential for competent regulatory authorities and manufacturers to have standards in the "higher order" category under the above regulations, and the WHO International Standards would meet this need.

Professor Pim van Aken acted as Chairman of the Consultation, and Dr Richard Decker and Professor Jos Thijssen were nominated as Rapporteurs.

Sessions I and II:

Infectious diseases markers: The 2nd WHO International Standard (IS) and the Reference Panel for HBsAg

The intended use of the WHO HBsAg International Standard and the HBsAg Reference Panel is to provide an indication of the analytical sensitivity of assay kits for HBsAg. Assigned values in these preparations can be used to compare analytical sensitivity of test kits, from state-of-the-art ELISAs to rapid tests. However, both the International Standard and the Reference Panel should be used as only part of a more comprehensive evaluation of fitness for purpose. This may involve testing a range of specimens, i.e., positive samples from different stages of disease including also subtype consideration, seroconversion panels, ‘difficult’ specimens, potentially interfering samples and normal blood donor specimens. Such additional collections of specimens are important to show a more complete picture of the clinical sensitivity and specificity of test kits.

The need for a global reference material for HBsAg expressed in International Units (IU) became apparent when 5 different reference materials were compared during the WHO Collaborative Study (WHO/BS/03.1987) of the 2nd WHO IS for HBsAg in 2003 (1). The results between the reference materials expressed in nanograms (ng) differed by more than 11-fold. The WHO Collaborative Study used the multiple test method of analysis. Ten different commercial tests were used by 6 participating centres, and each method was used by at least two laboratories.

Figure 1 shows the distribution of detection limits of 30 ELISAs and rapid tests used around the world when tested with dilutions of the 2nd HBsAg IS. The data indicated that the range of differences among ELISA tests is small and not significant in terms of public health impact (e.g. blood safety) and that some rapid tests can reach the same level of analytical sensitivity as for ELISA tests. On the other hand, a few rapid tests had significantly lower sensitivity than the majority and may not be suitable for use in blood screening. The value of the International Standard as a tool for regulatory authorities to differentiate the analytical sensitivity of the tests moving in their territories or Regions is well illustrated in this Figure.

Uncertainty factors from the WHO Collaborative Study of HBsAg include test kit format and bias, lab-to-lab variables, and fill volume, reconstitution, stability, and inhomogeneity between ampoules. The data revealed that uncertainty values due to differences between the methods used in the study far surpassed in magnitude the variability of the other factors. Testing errors were minimised because each test kit was used in triplicate in at least two laboratories.

The heterogeneity of the HBsAg and the lack of a reference immunoassay method made it not possible to express units in absolute (SI) terms. The raw material for the candidate 2nd International Standard was analyzed by biochemical, physical and immunological procedures, and was compared to a native HBsAg reference plasma preparation of a similar genotype that had itself been extensively characterized in this manner (2). Some physical and biochemical differences between the two antigens were observed which may be due to a heating process that

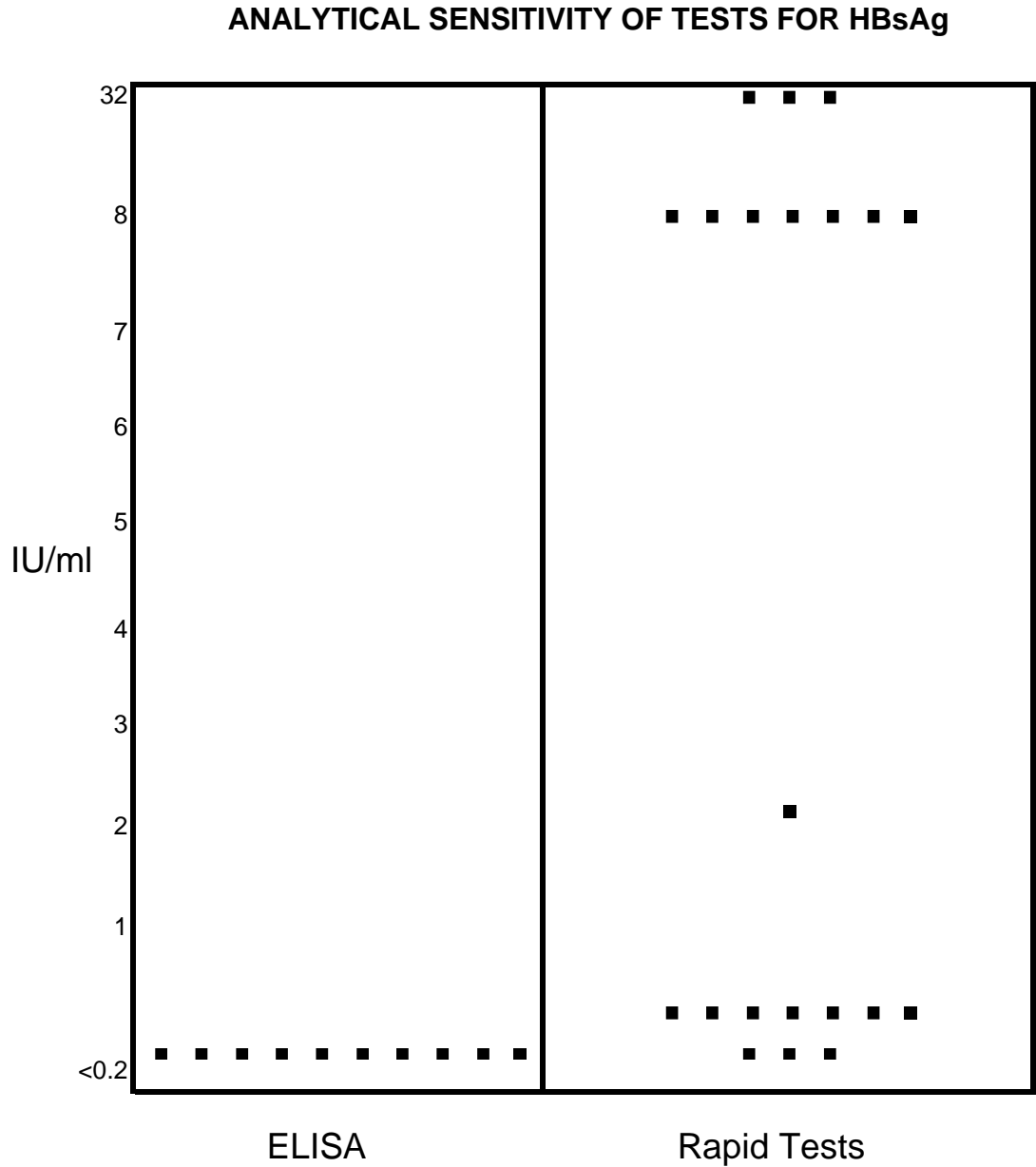


Fig. 1. Information on the analytical sensitivity of methods used to detect HBsAg, obtained from the WHO Collaborative study for establishment of the 2nd International Standard for HBsAg (BS/03.1987)

was necessary to inactivate infectivity of the preparation (3). The inactivated IS was found to contain very little preS protein, and the major S protein produced a more diffuse band than native HBsAg by gel electrophoresis. Despite these differences, the “a antigenic region” that is the main target of immunoassay test kits was found to be well preserved, and the material was judged to be suitable for use as a global measurement standard (data to be published).

The 2nd IS was compared with the previous IS and 4 other reference materials, one of which was the biochemically characterized reference plasma mentioned above (2). Aliquots of this material have been stored at -80C for 30 years, and it had been used in the WHO Collaborative Study to establish the suitability of the 1st WHO HBsAg IS in 1980 (4,5). The new collaborative study in 2003 demonstrated that, even though different assay methods were used, the quantitative relationship between the biochemically characterized reference material and the 1st IS has not changed in over 20 years.

The WHO IS and Reference Panel for HBsAg corresponds to the genotype A2 of Hepatitis B virus. Current test kits for HBsAg can detect the antigen of several genotypes of HBV. However, other genotypes are found more predominantly in some parts of the world and the relative quantitative sensitivity of commonly used kits for those genotypes of HBV is not known. Objective data from the scientific literature on this point appear to be lacking. It was agreed that detection of HBsAg from all genotypes should be investigated. Quantitative differences in test sensitivity towards genotypes could influence the appropriate use of the IS.

The use of the WHO IS for HBsAg requires that it be diluted serially into a matrix. Kits are validated for use with human serum or plasma, and some tests will show differences in sensitivity when different diluents are used as the matrix. Manufacturers recommend use of serum or defibrinated plasma when making dilutions of specimens for any reason. Diluting the WHO HBsAg IS should follow these guidelines. Such sera or plasma must be negative for anti-HBs antibodies because these will interfere with the measurements and thus with test results. The serum/plasma diluent should also be free of HIV and HCV viral markers for safety reasons. Concern was expressed that such diluents are not readily available worldwide.

Conclusions:

Uses of WHO IS for HBsAg: The WHO IS for HBsAg is intended to aid Regulatory Authorities worldwide in assessing the analytical sensitivity of HBsAg kits. The Consultation was informed that the WHO HBsAg IS will be used by the European Commission to replace the previous standards currently used for the analytical requirement in the Common Technical Specifications (CTS) of the IVD Directive. However, the IS should not replace a more comprehensive evaluation of fitness for purpose. This may involve testing a range of specimens, i.e., positive samples from seroconversion series or different stages of disease, potentially interfering samples and normal blood donor specimens to obtain more data on diagnostic sensitivity and specificity.

Traceability: The WHO Collaborative Study to establish the 2nd International Standard included an independent HBsAg reference plasma preparation that had been biochemically characterised in 1975 (2) and used in the Collaborative Study establishing the 1st IS. Both the

independent reference plasma and the 1st IS had been carefully stored for 30 and 23 years respectively. This comparison between the 1st IS and the biochemically documented reference plasma showed that the relationship between immunoreactivities of the 1st IS and the reference plasma was maintained. Therefore, the immunoreactivity of the 1st IS was considered to be unchanged.

Continuity: Based on data from the WHO collaborative study in which 10 kits were used to calibrate the new (2nd) IS vs. the 1st IS, the unitage assigned to the new IS is as close to that of the 1st IS as technically possible.

Uncertainty: Factors contributing to the uncertainty of the measurements in the WHO collaborative study were dominated by the inherent biases of the different test kits. Bias arises from differences in the specificity of the antibodies used to manufacture the test kits. The complete data regarding the various factors contributing to the variability found in the study are available in the reports of the WHO collaborative study (1, 6).

Commutability: The commutability of the 2nd WHO HBsAg IS was discussed during a previous WHO Consultation held to review data from the collaborative study supporting its establishment. Among several reference materials compared, one was the native plasma preparation that had been frozen but otherwise untreated. The consensus among experts was that variability during this and other comparisons was within a sufficiently narrow range for the 2nd IS to be deemed commutable (6).

Genotypes: Concern was raised that some or all commercial kits for HBsAg may be less sensitive for genotypes of HBV other than genotype A2. These types are found more frequently in developing countries. It was agreed that the contribution of other genotypes on the sensitivity of test kits for HBsAg should be investigated further. It is recommended that Regulatory Authorities devise panels for kit evaluation that include HBsAg reactive specimens with subtypes and genotypes from their local regions.

Session III:

III a. International Standards for the calibration of blood coagulation factors in secondary reference plasmas

The WHO International Standards (IS) for the measurement of blood coagulation factors (and inhibitors) in plasma are used by manufacturers and reference laboratories to calibrate their secondary standards. This assures a correct diagnosis of clotting factor deficiencies and monitoring of treatment with certain plasma products such as in patients with haemophilia. In the assignment of values to the WHO IS, the level of uncertainty (coefficient of variation) appears to be relatively low (4-8%) and is based on the average of multiple methods included in the WHO collaborative study (7). In addition, the unitage assignment of clotting factors and inhibitors also takes into account an external reference point, namely the concentration in 1 ml of "average fresh human normal plasma". In the preparation of "average fresh human normal

plasma" it is necessary to adhere to defined conditions for blood collection and to take care that the composition of the plasma pool (e.g. distribution of age, sex, blood groups, use of drugs etc.) is representative of the normal population. Appropriate requirements related to the preparation of plasma pools for developing global plasma reference materials will be discussed with the correspondent standardization subcommittee of the International Society for Thrombosis and Haemostasis.

The lifespan of the current WHO IS's for measurement of blood coagulation factors such as factor VIII is relatively short (i.e. about 5 to 8 years) due to the frequent use of these materials by reference laboratories and manufacturers. Consequently, for the replacement of these IS, it is necessary to consider how to minimise uncertainty with regard to the continuity of the unitage defined.

Replacement by a similar plasma pool is one way to reduce the uncertainty in the continuity of the Unit. In addition, a cross check versus a fresh normal plasma pool as well as versus the previous reference preparation minimises drift in unitage. Ideally, a cross check with the 1st IS would help although logistical difficulties such as storage of large quantities of materials may make this impossible. The use of the above measures was considered to have achieved continuity of the unit in practice. However it was clear that, for the development of new international reference preparations, inclusion of the continuity requirement in the design of the study is essential.

The quality of the collaborative study, the reproducibility of assay methods and the similarity of the IU can be found in the Report of the WHO Collaborative Study (7). Every effort should be made to improve and assure the dissemination of the WHO Reports containing data supporting the establishment of International Standards.

Conclusions:

Uses of WHO International Standards for Blood Coagulation Factors: International Standards, plasma pool reference preparations with assigned activities of coagulation factors (and inhibitors) in International Units, are used by manufacturers and reference laboratories for the calibration of their secondary standards.

Traceability: International Units of blood coagulation factors and inhibitors have originally been defined as the amount of functional activity in 1ml of "average fresh normal plasma". As such the International Unit is traceable to fresh normal human plasma.

Continuity: In order to maintain the continuity of the unit during replacement of the IS, the new candidate preparation is compared against the current standard. In addition, comparison of the replacement standard against pools of fresh normal plasma provides an additional mechanism of minimizing drift of the unit. It was agreed that efforts should be made to assure a standardized methodology in the preparation of fresh normal plasma pools.

Uncertainty: Use of similar preparations (“like vs. like”) for replacement standards means in practice that typical variations are low (2-5%), and accumulated uncertainty values from the current IS to the new one have not been used. With measures described above, additional evidence on the consistency of the unit can be obtained, and this allows for a more realistic estimate of uncertainty and possible drift of the unit.

III b. International Standards for the calibration of secondary standards for Thromboplastins

Thromboplastin reagents are used to monitor oral anticoagulant therapy with vitamin K-antagonists for patients with thromboembolic disorders. The calibration of secondary standards for the standardization of thromboplastin reagents by manufacturers and reference laboratories requires the assignment of an International Sensitivity Index (ISI) for each International Standard (IS). Currently, three ISs for thromboplastin are available: a recombinant human thromboplastin and two native ISs of rabbit and bovine origin. The ISI for each new IS is established from a multicentre study in which all current ISs (i.e., human, rabbit and bovine) are included using the manual (tilt tube) technique for clotting time determination (8,9).

The uncertainty in the ISI for each IS is the result of within-laboratory variation of the calibration and between-laboratory variation caused by differences among technicians and pre-analytical conditions. Furthermore the long-term stability of ISs needs to be taken into account. Long-term stability monitoring could be approached by a few designated reference laboratories testing the ISs at regular intervals using batches of deep-frozen or freeze-dried plasmas. The relative stability of thromboplastins can be determined also by repeated ISI calibration using different ISs and fresh plasma samples.

Although thromboplastins are lipid-protein preparations susceptible to deterioration, the ISs for the three different species are expected to be stable at low temperature. If their ISI inter-relationship is stable, it is very likely that their absolute ISI values are stable as well. On the other hand, if the inter-relationship has changed, at least one of the ISs or the pre-analytical conditions have changed. Recent studies have shown that the relative ISI values for the human and rabbit ISs have changed to a limited extent over the last 5-6 years (10). This change would lead to a slight bias for human compared to rabbit thromboplastin but this would be below the accepted 10% level of clinical relevance.

The ISI is defined in terms of the first IS of thromboplastin (preparation 67/40, which is no longer available). Each time when an IS is replaced by the next, the uncertainty in the ISI of the new IS is slightly greater than that of the predecessor. Increase in ISI uncertainty can be limited by including a large number (e.g., 20) of laboratories in the collaborative study. In this respect, it is worthwhile to include the bovine IS in each multicentre study for replacement of the rabbit and human IS, because the bovine IS is the only IS which had been compared directly to the first IS (preparation 67/40). The bovine IS thus serves as an "internal" standard, as long as it will be available. A statistical model to assess the (cumulative) uncertainty of the ISI should be developed.

Conclusions

Uses of International Standards (IS) for Thromboplastins: The Thromboplastin ISs are used to calibrate secondary standards of the correspondent species prepared by manufacturers and reference laboratories in order to assure comparability of the thromboplastin reagents worldwide.

Traceability: Currently the ISs for thromboplastins are of rabbit and bovine origin as well as derived from recombinant human material. A unitage, the International Sensitivity Index (ISI), for the IS's is derived from a WHO Collaborative study.

Continuity: Continuity of units in the replacement of IS's is based on comparative calibration with the previous IS. Comparing new standards with previous and/or current IS provides additional evidence on the stability of the unit.

Uncertainty: Uncertainties of the ISI of the new IS for thromboplastin result from variables during the multicentre studies to assign the ISI value. The uncertainties of the value transfer process from previous IS to a new preparation can be limited by including a large number (e.g., 20) of laboratories in the collaborative study.

Session IV:

Hormones and other protein reference materials

Some basic issues related to standardisation of biological substances were addressed. In a comparison of the establishment of reference systems for substances that can be characterised adequately by chemical or physical means with that for a biological substance, evidence was presented that one "reference method" can not be used for most of the biological products considered under the WHO standardization programme. On the other hand, to derive an uncertainty value using a multi-method collaborative study is problematic since the major contributor to the spread of estimates is assay bias rather than random effects of the measurement. Thus, the overall uncertainty in a multi-method collaborative does not reflect the probability of measurements by any particular method deviating from the mean.

Data were presented on the behaviour of measurements using currently available methods for the determination of Thyroid Stimulating Hormone. Knowledge is lacking on the composition of thyrotropin in patient plasmas. Although all the TSH diagnostic tests have been calibrated against the appropriate WHO IS (11), differences between the sets of reagents in clinical use can be demonstrated by using data obtained in 2003 from External Quality Assessment Schemes, as used in the Netherlands and Germany. It was shown that changes in the glycosylation-pattern of the compound under consideration do play a role in the divergent results obtained.

For human Chorionic Gonadotrophin (hCG) six different hCG-related proteins have been isolated and characterized. The amount of substance present in an ampoule of each of these 6

fractions is based on amino acid analysis and the content has been declared in absolute terms, in mols per ampoule. During preparation care was taken to maintain the biochemical/immunological properties of the preparations (12). This offers an example where traceability to SI units and use of uncertainty values can be achieved. As the measurand can be defined on the basis of a specified reference method, the case of hCG would not fall within the current WHO definition for biological products.

The principles described in ISO Guides 30 to 35 were presented with regard to quantitative measurements of SI traceable measurands. Due to possible heterogeneity or instability of a reference material ISO Guide 35 requires a positive demonstration of the homogeneity and stability of the material rather than showing the absence of heterogeneity or instability. Positive proof of homogeneity and stability requires highly repeatable methods.

The problems related to non-commutable reference materials were illustrated. Examples were given using two methods which correlated with each other in measuring the same measurand in patient samples. A reference material falling amongst the patient samples is considered commutable, and calibration of the methods with such a material would improve comparability of measurement results. However if a reference material would fall outside the group of patient samples, the preparation would be non-commutable and would have adverse effects on the comparability of measurement results.

The standardisation efforts related to quantitative measurements of Haemoglobin A1c and plasma proteins, both measurands consisting of groups of compounds, were given as examples for the successful standardisation of SI traceable measurands. The potential impact of reference materials on the standardisation of a particular analyte is largely dependent on understanding of the underlying biology. It also depends on the type of methodology applied and the commutability and proper use of the reference materials. The aforementioned aspects and state of the art knowledge need to be considered case by case for the definition of the appropriate approach to standardise quantitative measurements of proteins and other biochemical measurands.

Conclusions

Uses of WHO IS for protein hormones: Tests that measure protein hormones and similar analytes are used to diagnose acute and chronic diseases. They are also used to monitor changes in or therapy for the patient's condition. Values of serum concentrations of many clinically significant proteins are given in absolute amounts, and accuracy of analytical measurements is essential.

Traceability: Two different examples of traceability were given. For TSH, a standard in IU replaces a previous standard in IU, and the traceability path is to the current IS. On the contrary, hCG illustrates a case of a SI traceable measurand through a defined reference measurement procedure (amino acid analysis). In this case the traceability path is through the measurement procedure to the SI unit.

Continuity: The case of TSH illustrates the WHO approach to maintain continuity by assigning value of unitage through a multimethod protocol. Caution was raised because there is no certain proof that a multi-method comparison will be accurate, especially when the variation is large.

Uncertainty: TSH illustrates an example where, when making a replacement IS for most protein analytes, the unit of the previous IS ceases to exist and is re-established by the new IS. As such it has no uncertainty arising from calibration assigned to it. hCG illustrates the example where the use of SI units with a defined method would appear to require the assignment of an uncertainty value.

Commutability: The concept of commutability attempts to address the way different assay systems are affected by different reference materials. This is an intrinsic property of a reference material and should be addressed in the design of collaborative studies for diagnostic materials using an accepted metrological definition of commutability.

General Discussion

The European Directive 98/79/EC on *in vitro* diagnostic medical devices (13) has some essential requirements for a diagnostic test to be placed on the market. Among them, “The traceability of values assigned to calibrators and control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.” Representatives from Competent Regulatory Authorities of the European Union and the European Commission considered it essential for WHO International Standards to be within the category of "higher order" under the European legislation.

The criteria given in the ISO International Standard 17511, section 5.5 (14) provide guidance for establishing international reference materials for biological products. The concepts of *traceability*, *uncertainty* and *commutability* are critical parameters under this guidance.

During the discussions at the Consultation, different features regarding uncertainty took on more or less importance depending on the biological substance being discussed. The various components of uncertainty should be considered depending on the biological substance or the methods used to measure it and depending on whether the unit is maintained from the current reference standard to the new one. For example, uncertainty values are successfully used with standards of small molecule analytes that have clearly definable chemical characteristics and can be assessed with a single reference methodology. The situation becomes more complicated when the *measurand* is heterogeneous and large. HBsAg is both a large particle and is heterogeneous. Precision of measurements has the constraints of the inherent biological variability both from the measurand and from the test procedures.

In the WHO collaborative studies for establishing a new biological standard, a relation between the previous and the new standard is obtained within the uncertainties related to the measurements applied for comparison. The reports of these studies include a consideration of different sources of variability obtained. The major factors contributing to the spread of

estimates is more often due to test bias than to other factors contributing to uncertainty of the measurement. However, the overall uncertainty may not reflect the probability of any one method deviating from the mean. The necessary traceability path will not be the same for all standards, and it is necessary to define this in any WHO reference material to avoid inappropriate uncertainty values, or conversely, an underestimate of uncertainty.

As shown in this report, the approach taken for biological products is considered distinct from chemically-defined entities. Ideally one would link all control materials to a chemically defined substance calibrated on the basis of a reference method, but for biological products this is in general not possible. In the case of biologicals (“a measurand of biological origin which cannot be characterized adequately by chemical and/or physical means alone”) the first biological material developed as, for instance a WHO standard, is assigned an arbitrary unitage (IU). Such a unitage is traceable to a defined part of the content of an ampoule, not to a chemical substance measured by one reference test method. Arbitrary assignment in SI units is not acceptable. As such the IU also has no uncertainty assigned to it. In subsequent replacement preparations of this Standard, the replacement IS redefines the measurand and the value assigned to it redefines the unit. The use of a multiple-method collaborative study for value assignment of the IS reflects the aim of making the value of the replacement unit as close as possible to that of the previous unit for the greatest number of assay systems. The specificity or bias of test systems does however make it inevitable that some methods will experience a discontinuity. The importance of not changing standards too often and of giving thought to its eventual replacement at the time of establishing a standard was emphasized.

Uniform and consistent nomenclature should be given continued attention. Definition of the *measurand* remains difficult in many cases. A measurand does not necessarily refer to a defined compound. It also can refer to groups of components, antigen epitopes, catalytic activity, immunoreactivity or infectivity; and there may be need for some differentiation of the general category of "biologicals".

The design of a collaborative study to establish a new standard requires taking into account the best available scientific knowledge. The intended use of the preparation should have a high priority in the design. The value of working groups of experts representing the specific scientific fields as well as experts familiar with the materials and processes related to the standardisation of the particular measurand was underlined.

Protocols for the Collaborative Study should include careful considerations regarding commutability in the study design. For quantitative assays with diagnostic applications, studies should include the use of clinical specimens where appropriate. It is recommended that a guidance document be developed that will help study groups to evaluate commutability.

The process for establishing new reference materials has to take into account that the material will need to be replaced in the future. Therefore a significant number of ampoules should be reserved for future comparisons, and these must be stored at very low temperatures. The crucial role of longevity in diagnostic reference materials should be more clearly recognised.

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Annex 1

**WHO CONSULTATION ON
GLOBAL MEASUREMENT STANDARDS AND THEIR USE
IN THE *IN VITRO* BIOLOGICAL DIAGNOSTIC FIELD
WHO Headquarters, Geneva
7 - 8 June 2004**

AGENDA

SESSION 1

- Statistical aspects of unitage assignment in WHO International Standards. The use of uncertainty values in the calibration of secondary standards. Dr A. Heath/Dr P. Minor

SESSION 2

- Uncertainty values in infectious diseases markers: International Standard for HBsAg
- Biochemical characterization: Prof W. Gerlich
 - An industrial view: Dr J. Diment
 - Regulatory perspective: Dr S. Nick

SESSION 3

- Levels of uncertainty in international reference materials for blood coagulation factors and their consequence in the calibration of secondary standards. Dr T. Barrowcliffe
- Levels of uncertainty in international reference materials for Thromboplastins and their consequence in the calibration of secondary standards. Dr A. van den Besselaar.

SESSION 4

- Traceability, uncertainty and units for biological reference materials: WHO standards for Thyroid Stimulating Hormone and Human Chorionic Gonadotrophin. Dr A. Bristow
- TSE determinations in clinical practice: Prof J. Thijssen
- Concepts to estimate the uncertainties of values assigned to protein reference materials.
Mr H. Schimmel

CLOSED MEETING:

Proposals for submission to the Expert Committee on Biological Standardization

Annex 2

**WHO CONSULTATION ON GLOBAL MEASUREMENT STANDARDS AND THEIR USE
IN THE *IN VITRO* BIOLOGICAL DIAGNOSTIC FIELD**

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