

**Distribution: General
English only**

Report

**WHO Working Group on
International Reference Preparations for
Testing Diagnostic Kits used in the
Detection of HBsAg and anti-HCV Antibodies**

**Geneva, Switzerland
6-7 October 2003**



**WORLD HEALTH ORGANIZATION
Essential Health Technologies
November 2003**

WHO Working Group on International Reference Preparations for Testing Diagnostic Kits used in the Detection of HBsAg and anti-HCV Antibodies

WHO Headquarters, Geneva
6 - 7 October 2003

I. Opening Remarks

Dr Steffen Groth, Director Essential Health Technologies (EHT) opened the meeting and updated the Group on organizational changes at WHO. The Department of Essential Health Technologies is the new name for the Department of Blood Safety and Clinical Technology in the Health Technology and Pharmaceuticals cluster. EHT encompasses Blood Products and Related Biologicals, Blood Transfusion Safety, Diagnostic Imaging and Laboratory Services, Medical Devices, and Surgery, i.e., the essential technologies required by all Member States. He reminded the Group that WHO International Biological Reference Materials are intended to help doctors, scientists, manufacturers and regulatory authorities to communicate in a common language when it relates to the biological activity of different products.

The need for global biological reference materials was exemplified by the situation that exists for the standardization of HBsAg diagnostic tests. These tests have been employed for 35 years and there are many reference materials for estimation of their analytical sensitivity. However, as the collaborative studies for discussion at this meeting demonstrate, the units of measurement of 4 widely used reference materials vary up to 12-fold. It is clear that for scientists to communicate in common technical language, agreement on the use of a single global reference material for measuring the analytical sensitivity of test kits is in everyone's interest. The candidate reference panel proposed covers a broad range of concentrations which will be useful in estimating the sensitivity of all assays. It is inactivated and lyophilized and therefore easy to transport as non-infectious.

For anti-HCV diagnostic tests, the second topic of discussion at this meeting, Dr. Groth urged the Group to consider pragmatic and novel approaches, such as the development of monospecific antibody reference materials, that may be relevant when assay kits are designed to detect multiple antibodies.

Dr Richard Decker was proposed as Chair and Dr Morag Ferguson as Rapporteur.

II. Background

Dr Padilla reviewed for the Group how WHO Biological Reference Preparations are developed and established and how the WHO International Working Groups have

contributed to this process through discussions of the scientific issues, selection and characterization of candidate materials, design of collaborative studies, harmonization of procedures and reagents and giving advice on the appropriate use of materials.

The Working Group on International Reference Preparations for testing Hepatitis B, Hepatitis C and HIV Diagnostic kits first met in 1996. Discussions were focused on the type of reference preparations most needed to assist regulatory authorities and manufacturers of Member States as a tool for quality control and process consistency characteristics of these materials, and how should these materials be used.

At meetings held in March 1998 and January 2000 with regard to the appropriate use and calibration of HBsAg reference materials, the Group proposed an inactivated freeze dried reference panel with concentrations ranging from approximately 25 IU to 0.04 IU/ml. The WHO Collaborating Centres for Biological Standards met in February and December 2001 to finalize plans for production and control of such a panel, and a collaborative study for its calibration.

Dr Padilla reviewed the agenda for this meeting: the goals in the discussion of the HBsAg reference panel were to assign a unitage based on data from the study; to consider the data collected on traceability of the HBsAg reference materials; and to define the appropriate uses of the panel. For the second day, the group would discuss proposals for preparations containing monospecific antibodies to HCV, namely anti-core and antibodies to non-structural proteins (NS3, NS4, NS5). The Group was to consider how useful such materials might be in defining analytical test sensitivity, providing a tool for inter-laboratory comparison and helping to provide a basic structure for QC programs.

III. International Standard and Reference Panel for the control of HBsAg diagnostic tests

The Candidate HBsAg material and Collaborative Study:

Dr Ferguson described the preparation of the HBsAg candidate reference panel and the results of the collaborative study to characterize it. Purified and inactivated HBsAg subtype adw2, was obtained from Dr N Lelie, Sanquin Blood Supply, the Netherlands. Its preparation involved precipitating HBsAg with PEG followed by a series of centrifugation steps to remove Dane particles. The material was heat-inactivated according to a documented protocol and was subjected to further purification by centrifuging through a KBr gradient. The purified HBsAg had a concentration of 66000 PEI units/ml and 98000 IU/ml (estimated with Ausria II by parallel line analysis). This material was diluted in negative human serum and was used to generate a series of 5 four-fold dilutions, starting at approximately 25 IU/ml. These bulk dilutions were transported to Dr Ferguson, NIBSC where they were aliquoted and freeze-dried. Negative control diluent was also aliquoted, freeze-dried and included to make a 6-member panel. Six different laboratories participated in the collaborative study. In the study, the most concentrated panel member was calibrated by titration against the 1st

International Standard for HBsAg and 4 currently available reference materials using 10 different test kits. The study was designed so that at least 6 sets of data were available for each test kit. In addition to the International Standard, the 4 reference materials assayed were: a) a primary HBsAg reference material developed by Drs. Gerlich and Thomssen (subsequently to become the first Paul Ehrlich Institute standard); b) the current Paul Ehrlich HBsAg standard; c) the French HBsAg standard, and d) the Abbott HBsAg standard. The studies demonstrated that the unit values assigned to these commonly used HBsAg reference preparations are not equivalent. Data showed that 1 IU is equivalent to 0.58 PEI units (primary) or 0.43 PEI units (current) or 1.93 French 'ng' or 5.59 Abbott 'ng'.

The overall mean potency in IU of the HBsAg candidate reference panel member 1 was 33 IU/vial. Panel members 2-6 were assayed undiluted. Although the design of the study did not include calibration of the panel members, the overall mean potencies in IU of proposed panel members 2-5 were calculated from the dose response curves of the International Standard. All panel members except panel member 6 scored reactive in all assays. The only significant deviation between values calculated and values predicted for the fourfold dilutions of panel member 1 was found with panel member number 2 (6.7 IU/vial calculated vs. 8.25 IU/vial predicted). Dr Ferguson pointed out that the signals for this specimen were above the linear portion of the dose-response curve in all the assay systems, and subsequent examination of raw data revealed that any quantitative number calculated from data on this specimen would be invalid. Panel member 6 is a negative control sample and scored negative in all assays. The panel was also tested in seven other laboratories around the world using a wide range of locally produced and rapid assays. These studies demonstrate that the panel clearly identifies differences in the sensitivities of assay kits.

Dr Lavanchy explained that a large increase in locally produced diagnostic tests and reagents is expected in the next years. WHO should be able to provide some tools to Member States for comparability of these tests globally. He indicated that the proposed reference panel would be of importance to assess this comparability

Traceability:

Dr Gerlich described studies relating to the traceability of HBsAg and its unitage. Reference material prepared by him and Prof. Thomssen in 1974 form a basis for traceability to the current and candidate IS. He first described the known biophysical characteristics of HBsAg particles that are composed of small, middle and large proteins. The different particles – Dane particles, filaments and smaller spheres – are complex and have variable composition. He therefore suggested that it was inappropriate to use 'ng' in assigning unitages to HBsAg. In addition, artifacts are produced during purification, and an accurate protein measurement is then difficult to obtain.

He reminded the group of the relationship of unitages when the International Standard was first assessed in a collaborative study in 1980: 1 old PEI unit = 1 active ng = 2 IU. Since HBsAg involves a conserved set of epitopes on assembled particles, he felt that IU should be considered in reference only to the small spherical particles.

Dr Gerlich provided details on his biochemical characterization of the HBsAg material obtained from Dr. Lelie and used to produce the candidate standard and panel. The purified HBsAg material was assayed by quantitative immunoelectrophoresis (QIE) and characterized by size exclusion chromatography, UV spectrum, PAGE followed by silver staining and Western blot with antibodies to PreS and S proteins. The candidate HBsAg was found to be sufficiently similar to the original PEI material of HBsAg subtype ad.

It consisted of small heterogeneous HBsAg particles with a bimodal distribution in size exclusion chromatography: Circa 60 % of the particles were about 16 nm diameter, and ca 40 % were about 24 nm. Using the same technique, native HBsAg from HBV carrier plasma had a similar distribution pattern, but a size of 20 and 27 nm. The smaller (ca 3nm) diameter may be explained by the fact that the candidate material does not contain preS domains in contrast to the native HBsAg. In silver stained polyacrylamide gels only the P24/GP27 doublet of the small HBsAg protein was detected after SDS electrophoresis, but no middle or large HBsAg protein. Furthermore the two bands were more diffuse than in the native material. Western blots using monoclonal antibodies against preS1 or preS2 epitopes were negative for the candidate material but positive for native HBsAg. These findings suggest that the preS domains were removed during purification of the candidate material by unknown proteases. The lack of preS domains has no disadvantage with respect to its use as reference material, because all known commercially available assays for HBsAg are exclusively or predominantly directed against the small HBsAg protein. Assays targeting preS epitopes of HBV may be potentially useful according to some literature, but the WHO candidate material would not be useful for standardization of such assays.

The material contains 2.8×10^6 genome equivalents of HBV DNA as determined by a published in-house real time PCR. This means that the purification of the material had removed HBV-particles approximately by a factor of 1000; highly viremic HBV-carriers typically contain 10^9 - 10^{10} HBV particles/ml. The residual content of HBV DNA does not mean that the material is infectious because its inactivation has been confirmed in previous extensive chimpanzees studies and was confirmed by its safe use as vaccine.

Amplification and subsequent sequencing of the S gene from the HBV DNA in the material allowed for genotyping and subtyping: It was identified as HBV genotype A and HBsAg subtype adw2.

The amount of antigenically active HBsAg was determined by quantitative immunoelectrophoresis in comparison to a reference plasma which was calibrated in "old" PEI units. A polyvalent antiserum against epitopes conserved in HBsAg subtypes adw2 and ayw2 was used for detection and yielded ca. 60,000 PEI units/ml of the undiluted source material. This is in very good agreement with the titration using the radioimmunoassay Ausria II.

Dr Ferguson presented additional information from the present studies demonstrating that the candidate IS and the PEI standard characterized by Gerlich and Thomssen in 1975 have the same relationship as existed when they were assessed in a collaborative study over 20 years ago. In the current studies, 100 IU was found to be

approximately equal to 58 primary PEI units whereas in the collaborative study in 1980 that 100IU was approximately equivalent to 55 PEI units. These data, along with the studies undertaken by Dr Gerlich, confirm traceability of the IU to the PEI unit and to the original Gerlich studies.

Unitage:

In 1979, 1 IU was understood to be approximately equal to 1Abbott 'ng', but in the current studies 1 IU was approximately equal to 5.6 Abbott 'ng'. The Working Group questioned why the Abbott standard is so different now from what it was in 1980. The reason for drift is not known but it was agreed that Abbott should be asked if there was any explanation. The group also queried the difference between the French 'ng' and the IS/PEI primary standard. The French 'ng' is calibrated against Batch No 8 of Institut Pasteur Production (IPP) vaccine. The group asked for further information on how the IPP vaccine was inactivated.

It was evident from these data that different 'ng's were not equivalent to each other. Dr Field indicated that people have used the term 'ng' for years. Many National Regulatory Authorities in developing countries assign the minimum sensitivity of their assays based on Abbott 'ng', and this has caused confusion; he stated that the 'ng' is in reality an arbitrary unit.

The nanogram ('ng') should be a biochemical constant. However, because of the different ways in which a 'ng' of HBsAg has been defined over the years and the resulting discrepancies noted in the collaborative studies, it was the consensus of the Group that the term 'ng' should no longer be used in regard to HBsAg reference materials. The term implies a biochemical constancy that may not exist. The Group agreed that the candidate HBsAg for the new International Standard would be defined in IU using the current IU as the point of reference.

Subtypes, genotypes, and mutants:

The influence of HBsAg subtypes, genotypes and escape mutants on test kit detectability was discussed. Some felt that assay kits used in developed countries may not detect genotype F well. Others pointed out the need for larger collections of specimens and seroconversion series to accurately define clinical sensitivity. Despite these limitations, the consensus of the Group remained that there is a role for quantified, standardized HBsAg to define a kit's analytical sensitivity. Dr Fields indicated that a panel of 200 samples of all HBV genotypes is being prepared by the International Consortium on Blood Safety (ICBS) and will meet some of these needs.

Other discussion points:

Dr Schimmel indicated that ideally the unitage assigned to the IS should be traceable to SI units. He queried whether commutability studies with different sera and a panel of assays had been undertaken, as some reference materials are not suitable for use with some assays. However, since the candidate International Standard and reference panel had been assayed in over 20 assays and versus 5 different reference materials,

the data concerning commutability should be found in the tables of the collaborative study, e.g., Tables 6 and 7. Indeed, there is no evidence of a significant bias in these data.

Several uncertainty issues were discussed. The fill volumes determined gravimetrically had a low CV and indicate good vial-to-vial reproducibility. However Drs Dybkaer and Diment commented on the high CV when the current IS was used as reference to compare test kit results with the other reference standards. Although the mean found was 33 IU/ml no kit gave this actual value and the kits from different manufacturers ranged from 22.0 to 47.3 IU/ml with a GCV of 30%. This variability was found to be considerably less when the candidate International Standard was used as the reference. Dr Diment expressed the opinion that regulatory authorities should be made aware of this variability should take this into consideration when setting sensitivity requirements. He felt it would be better to state the uncertainty around the 33 IU/ml. Assigning an uncertainty range for the unitage was discussed. Dr Wood told the group that International Standards prepared in accordance with published guidelines of WHO at present do not have an uncertainty assigned. However, updated requirements for the production and assessment of International Standards are under review, and when these are published it is likely that uncertainty values will be considered.

The group agreed that the range of concentrations of the candidate panel was appropriate and would be useful for the quality control of the in vitro diagnostic tests, even if panel member 1 were established as the 2nd IS and distributed separately. It was agreed that the unitage of the panel should be referred to as a series of four-fold dilutions of 33 IU/vial, i.e., the candidate IS.

The use of merthiolate was discussed because some participants thought that its presence as an antimicrobial could be unacceptable to regulatory authorities. However, regulatory authorities present at the meeting informed that there are no regulations at this time in place in the diagnostic area.

A draft memorandum for the candidate panel was presented to the Group. Dr Ferguson agreed to prepare two draft memoranda/instructions for use -one for the candidate IS and one for the candidate reference panel – to be circulated to the Group for review prior to presentation to the Expert Committee.

Conclusions and Recommendations:

The group agreed that:

- The candidate International standard should be assigned a unitage in IU and that it was no longer appropriate to use 'ng' as a unit of measure.
- There has been no drift in the quantitative relationship between the IU and PEI unit, indicating that the IU has not drifted since establishment in 1985.
- Both the candidate International Standard and reference panel are commutable in that the HBsAg raw material has been used with other reference materials in a range of assays methods without a bias.

The group proposed that:

- The candidate IS be established as the second International Standard for HBsAg, subtype adw2, genotype A with an assigned unitage of 33 IU/vial. The issue around the uncertainty should be referred to in the insert supplied with the standard material.
- Panel members 2-6 (now identified as A-E) be established as a WHO reference panel for use in the assessment of the analytical quantitation of assay kits. The reference panel is primarily addressed to assist regulatory authorities in developing countries.

IV. Development of a monospecific anti-HCV antibodies reference panel

Dr Decker described the efforts of the Group to date to generate an anti-HCV reference material. In the past the WHO Working Group on Reference Standards for Hepatitis and HIV Diagnostic Kits had designed, produced and tested a candidate anti-HCV genotype 1b reference. However, when the Group proposed this preparation for use as a WHO Reference Material to the ECBS it was not favorably received by the Committee because of the difficulties in the characterization of a pool sera being insufficient to determine the analytical sensitivity of kits that detect multiple antigens.

The Working Group also proposed the preparation of an inactivated freeze-dried anti-HCV genotype reference panel produced from single donations, to be diluted as little as possible, with high reactivity against individual proteins. The end point dilutions against each relevant protein by RIBA would be determined. Since 2001, the Group agreed to prepare a reference material for each of 4 antibodies deemed appropriate for detection by the commercial kits manufactured: anti-core, anti-NS3, anti-NS4, and anti-NS5.

Dr Padilla had written to several organizations in efforts to source the materials, the so-called monospecific antibody sera. In March 2003, Chiron Corporation offered to help in obtaining the monospecific antibodies of HCV. Scientists at Chiron proposed that these could be obtained by purifying antibodies from polyclonal antisera by affinity chromatography, and they offered their technical expertise.

Dr Harrington of Chiron Corp. summarized the possible approaches considered by Chiron for developing monospecific antibodies in this manner. The specifications for the starting sera were:

- A plasma with all four RIBA band reactivities.
- The plasma with titers of >1:250 for each of the four RIBA bands.
- Anti-HCV of genotype-1 had been used, being most common in US specimens

The initial strategy employed for purification of specific antibodies was to absorb the specific antibodies from the serum using HCV antigen affixed to affinity columns and to elute the absorbed antibodies by various methods (acid, NH₄SCN, etc). Yeast

recombinant proteins were coupled to CNBr activated-Sepharose® 6B (Pharmacia). Peptides were coupled to activated Thiol-Sepharose® 4B through their cysteine residue(s). Anti-c100, anti-c22, anti-c33c and anti-NS5 antibodies were purified in this manner, and all of the purified antibodies titered out in RIBA™ HCV 3.0 SIA at 0.5 – 2.0 mg/ml. However, all of the purified HCV antibodies had low recoveries (10 – 20% of input) and had trace amounts of the other HCV immunoreactivities.

A second strategy for antibody preparation – by sequential antibody depletion – was then considered. The advantages of this would be that a serum clearly reactive to only one RIBA band could be produced and that there would be minimal loss of immunoreactivity in the processing. The disadvantage would be that immunoreactivities not represented in the RIBA or ELISA assays would remain in the serum, e.g. anti-HCV envelope antibodies or NS4 antibodies to regions outside the two c100 RIBA peptides. To summarize the procedures, 1000ml of serum was processed in a series of sequential absorption steps through columns of Sepharose to which the appropriate antigens were bound but omitting an absorption step for one of the antigens. This process was repeated omitting an absorption step for a different antigen so that 4 preparations of 250 ml, each containing predominantly the desired monospecific antibodies, were obtained. As there are large amounts of antigenic proteins on the columns they can be reused to produce large amounts of sera. Initial tests indicated that there were no undesired reactivities present in “monospecific” HCV preparations.

Dr Harrington also described the potential of these affinity methods for generating monospecific HIV antibodies. Chiron has recombinants of the main HIV immunogenic proteins, but a strategy for using such antibodies as reference materials needs to be considered carefully.

The availability of other monospecific anti-HCV materials was discussed, and various offers were made:

- Dr Lelie reported that he has attempted to identify suitable units with RIBA reactivity predominantly against a single protein. RIBA banded donations having a single dominant band and giving a positive NAT value are rare. Dr Lelie has one genotype 3a donation that is anti-NS3 dominant, but thus far, he has been able to identify only small volumes of specimens that are monospecific for anti-c22 or anti-NS3, and these have not been genotyped. Dr Fields offered to genotype them.
- Dr Biswas indicated that CBER has lot-release panels used by FDA and manufacturers. Some could be made available for study on a limited basis.
- Dr Mizuochi reported that the Japanese Red Cross is producing a reference panel, and he agreed to see if it could be made available to WHO.
- Dr Visona sees many low positive anti-core NAT positive from Nicaragua, possibly in the window period and said she would try to get samples.

- The International Consortium for Blood Safety (ICBS) has a large panel of anti-HCV sera. Dr Fields suggested that Dr Padilla ask whether some samples of this panel could be released to WHO, should they be of use to the reference panel proposed.

Dr Lavanchy considered it important to establish the reactivities of these candidate materials across different genotypes. This would be of high relevance for assessing diagnostic tests globally. Several members of the group considered whether they could be used as a tool for batch release or a tool for detection of levels of antigen in the diagnostic tests.

The limitations of a sensitivity panel of monospecific antibodies were discussed. Some of the group questioned the value of such minimum reference materials for evaluating diagnostic kits worldwide. It was agreed that, to define kit detectability fully, regulatory authorities and manufacturers should use collections of positive specimens from local populations and seroconversion panels when available. However, the consensus was that a monospecific reference panel would have unique value in evaluating the quality of assays kits worldwide.

There was extensive discussion on characterization studies involving different expressed proteins and genotypes. RIBA contains conserved proteins that react across genotypes but possibly have varying sensitivities. Sera detected on kits containing antigens from other genotypes can be confirmed by RIBA.

Dr Diment indicated that it was unlikely one could calibrate secondary standards against these preparations and this could create supply issues for this panel as licensing authorities and manufacturers would require stocks of them. However Dr Lelie pointed out that manufacturers already have in-house reference materials for assessing the coating of plates.

Dr Harrington indicated that Chiron prefers to make a transfer of material so that WHO can proceed independently in its course of action.

The group agreed that the next step would be more characterization of the monospecific preparations by WHO collaborating centers. Dr Biswas suggested that a few labs repeat the testing that Chiron has done and show the reagents can be used with kits produced outside US and Europe.

Various offers of anti-HCV test kits were made:

- Dr Mizuochi reported that 30 kits were on the market in Japan, some Japanese-made, some imported.
- Dr Kim indicated that he could supply Korean kits. Although genotypes 1a and 2b are the most common in Korea, the agreement between Korean kits and imported kits is around 95%.

- Dr Kumara requested that Indian kits be included in the studies and offered to supply them as they get kits from Korea, Abbott, Ortho, Mitra for evaluation prior to purchase.
- Dr Nick from PEI offered to test the sera on kits in use in Europe which are produced from different antigens and technologies, e.g., Roche, Murex, new Abbott. PEI also has kits on test for ICBS, including one from Singapore.

Dr Padilla proposed that WHO select representative kits from Japan, China, India and Korea, with preference given to kits made with non-genotype 1_a antigens, if available. These kits would be sent to one or two collaborating centers for evaluation with the Chiron monospecific sera. As some kits require dedicated equipment, it was agreed that such kits not be used in preliminary studies.

Dr Lelie proposed that, since small aliquots of native monospecific sera are available, they could be calibrated against purified materials by parallel line analysis at comparable concentrations in different kits. It was proposed that a dilution series of each sample be tested in each kit on 3 occasions.

Conclusions and Recommendations

The group agreed that:

- There is a role for a panel of quantified, monospecific anti-HCV sera to define the analytical sensitivities of test kits for anti-HCV antibodies. The value of such a panel against different genotypes will be studied.
- A protocol should be drafted to perform a feasibility study involving the candidate materials identified. The protocol should include the samples to be tested, the test kits with which they are to be evaluated, and the responsibility of each collaborating center in the study.
- Drs Decker and Lelie agreed to coordinate the development of the protocol. Dr. Harrington will send the monospecific antibody materials to the Sanquin Diagnostics Division, Alkmaar, NL. Dr. Lelie will make preliminary evaluations of the concentrations and will then assemble and distribute the panel to the designated WHO collaborating centers along with the protocol.

Dr Padilla indicated that the protocol should be circulated to participants and submitted to ECBS so that they are made aware of progress in the studies. She also indicated that data on the feasibility study should be submitted to ECBS 2004.

V. References

Gerlich W, Thomssen R. Standardized detection of hepatitis B surface antigen: determination of its serum concentration in weight units per volume. *Developments in biological standardization* 1975; 30:78-87

World Health Organization. Hepatitis B surface antigen (subtype ad). *Technical Report Series* 1987; 745: 18

Seagroatt V, Ferguson M, Magrath DI, Schild GC, Cameron CH. The British reference preparation of hepatitis B surface antigen. 1982; *Lancet* (ii) 391-392

Lelie PN, Reesink HW, Niessen J, Brotman B and Prince AM. Inactivation of 10^{15} chimpanzee infectious doses of hepatitis B virus during preparation of a heat-inactivated hepatitis B vaccine. *Journal of Medical Virology* 1987; 23, 298-295

ISO 17511: 2003: In vitro diagnostic medical devices – measurement of quantities in biological samples – metrological traceability of values assigned to calibrators and control materials.

ISO 15193: 2002: In vitro medical devices – measurement of quantities in samples of biological origin – presentation of reference measurement procedures

ISO 15194: 2002: In vitro diagnostic medical devices – measurement of quantities in samples of biological origin – description of reference materials

WHO Working Group on International Reference Preparations
for Testing Diagnostic Kits used
in the Detection of HBsAg and anti-HCV Antibodies

**Room C: WHO Headquarters, Geneva
6-7 October 2003**

List of Participants

Dr R. Biswas

Division of Emerging and Transfusion
Transmitted Diseases
Center for Biologics
Evaluation & Research
Food & Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852
USA

Dr Richard H. Decker

Hepatitis and AIDS Research
924 Castlewood Lane
Deerfield, Illinois 60015
USA

Dr John Diment

EDMA Representative
Scientific & Technical Manager
N. Europe, Asia Pacific and Export
Ortho-Clinical Diagnostics
Mandeville House
62 The Broadway
Amersham
Buckinghamshire
HP7 0HJ
UK

Dr Kim Dokeun

Research Scientist/Reviewer
Division of Viral Products/
Center for Biologics Evaluation
Korea Food and Drug Administration
Nokbun-dong 5, Eunpyung-gu
Seoul 122-704
Korea

Dr Rene Dybkaer

International Standards Organization
(ISO) Representative
Head of Department of Standardization
in Laboratory Medicine
H.S. Copenhagen Hospital Corporation
Frederiksberg Hospital
Nordre Fasanvej 57
(Road/Vej 3, Entrance 7, 2nd Floor)
DK-Frederiksberg 2000
DENMARK

Dr Morag Ferguson

Virology Division
National Institute for Biological
Standards and Control
Blanche Lane
South Mimms
Potters Bar
Herts EN3 6QG
United Kingdom

Dr Howard Fields

Hepatitis Branch
Division of Viral Diseases
National Centre for Infectious Diseases
Centres for Disease Control and
Prevention
Atlanta, GA 30333
USA

Professor Dr Wolfram H. Gerlich

Klinikum der Justus Liebig Universitat
Frankfurter Strasse 107
D-Giessen 35392
Germany

Dr Charles Harrington
ADVAMED Representative
Director, Blood Testing Development
Chiron Corporation
4560 Horton Street
Emeryville, CA 94608-2916
USA

Dr Shashi Khare
Consultant (Micro) and
Head of Microbiology Division
National Institute of Communicable
Diseases
Ministry of Health
22 Shamnath Marg.
Delhi 110052
India

Dr P.N. Lelie
VQC Laboratory
Sanquin Diagnostics Division
Jan Steenstraat 1
Alkmaar 1867 CT
The Netherlands

Dr P. Minor
Virology Division
National Institute for Biological
Standards and Control
Blanche Lane
South Mimms, Potters Bar
Herts EN3 6QG
United Kingdom

Dr Toshiaki Mizuochi
Chief, Immunohematology Laboratory
National Institute of Infectious Diseases
1-23-1
Toyama, Shinjuku-ku
Tokyo 162-8640
Japan

Dr Sigrid Nick
Paul Ehrlich Institute
51-59 Paul Ehrlich Strasse
P.O. Box 1740
63225 Langen
Germany

Dr Micha Nuebling
Paul Ehrlich Institute
51-59 Paul Ehrlich Strasse
P.O. Box 1740
63225 Langen
Germany

Dr Francis Poisson
Agence Française de Sécurité Sanitaire
des Produits de Santé (AFSSAPS)
DEDIN
Département de Diagnostique in vitro
Unité Evaluation
143 147 Blvd Anatole France
93285 Saint Denis
France

Mr H. Schimmel
European Commission - JRC - IRMM
Retieseweg
2440 Geel
Belgium

Prof.Dr. Jos H.H. Thijssen
Univ. Med. Ctr. KE03.139.2
PO Box 85090
3508 AB Utrecht
the Netherlands

Dr K.A. Visona
P.O. Box CR 321
025240
Miami 33102 FL
USA

Dr Robert Wielgosz
BIPM
Pavillon de Breteuil
92312 Sèvres Cedex
France

Dr Zhenglun Liang
National Institute for the Control of
Pharmaceutical and Biological Products
Tiantanxili 2#
100050 Beijing
People's Republic of China

WHO Secretariat

Dr S. Groth, Director HTP/EHT

Dr J. A. Cunningham, TDR/PRD

Dr D. Lavanchy, Coordinator, CSR/LYO

Mr P.H.L. Lewalle, HFS/CAS

Dr Ana Padilla, EHT/QSD (Secretary)

Dr D. Wood, A/Coordinator EHT/QSD