



Standardisation in Laboratory Medicine:

Current Activities of the IFCC

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Reference Measurement Systems

- **Reference measurement procedures**
- **Reference materials**
- **Networks of reference laboratories**
- **Reference intervals and decision limits**

**Most activities of standardisation in
close collaboration with international
(national) organisations, manufacturers
and academics**

Clinical and Laboratory Standards Institute (CLSI)

- **+/- 20 ongoing projects or just completed;**
- **7 guidelines released with IFCC (C-45, C-48, I/LA 26, EP17, MM16, POCT2/3);**

INSTITUTE FOR REFERENCE MATERIAL AND MEASUREMENT (IRMM)

- **Recertification of serum protein CRM470;**
- **AST= stability check; ALT: Asahi mat.;
Myoglobin: sensitivity ok, repeatability
evaluated; Prothrombin ref mat: frozen and
lyophilised materials, BNP....**

NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY (NIST)

- **Reference material for troponin I (NIST SRM 2921) collaboration with C-SMCD;**
- **Reference material for homocysteine & folate (SRM 1955) at three levels;**
- **List of 10 more SRMs to be released (within 2 years), of interest for IFCC.**

IFCC standardisation activities carried by committees (theme oriented) and working groups (task oriented)

NOMENCLATURE, PROPERTIES AND UNITS (C-NPU)

- **Current projects include Clinical Molecular Biology and Toxicology ;**
- **Future of Database: discussions with CLSI;**
- **Participation to JCGM(VIM GUMM).**

MOLECULAR DIAGNOSTICS (C-MD)

- **Position paper: Guidelines for the use of Molecular Diagnostics in Laboratory Medicine;**
- **Number of projects through a Network of locus specific Molecular Diagnostic Centres**

NETWORK OF IFCC MOLECULAR DIAGNOSTIC CENTRES

- 1. Methodology and Quality Control (M. Pazzagli)**
- 2. Pharmacogenetics (RHN van Schaik)**
- 3. Molecular diagnostics in triplet repeat diseases (F. Rousseau)**
- 4. Hemochromatosis and Thrombophilia (C. Mamotte)**
- 5. Molecular diagnosis of cancer (to be activated later if considered appropriate)**
- 6. Infective diseases?? (to be activated later if considered appropriate)**

PLASMA PROTEINS (C-PP)

- **Recertification of serum protein standard CRM470 in collaboration with IRMM;**
- **Discussions with the Human Proteome Network, monitoring of the field and eventual use of CRM 470 as a standard for proteome measurements;**
- **Establishment of a simplified procedure for transferring values from RMs to commercial protein assays.**

STANDARDISATION OF MARKERS OF CARDIAC DAMAGE (C-SMCD)

- A project on standardisation of BNP assays has commenced, recombinant/synthetic BNP candidate materials selected **(to be discussed with IRMM)**; Ref Mat. for troponin I now available (NIST/SRM 2921); Myoglobin stability investigated (IRMM);

C-SMCD: Members

- **Fred Apple PhD, Chair, USA**
- **Robert Christenson PhD, USA**
- **Allan Jaffe MD, USA**
- **Johannes Mair MD, Austria**
- **Jordi Ordonez-Llanos MD, PhD, Spain**
- **Franca Pagani PhD, Italy**
- **Jillian Tate, Australia**

C-SMCD: Activities Past and Present

Development of quality specifications for immunoassays

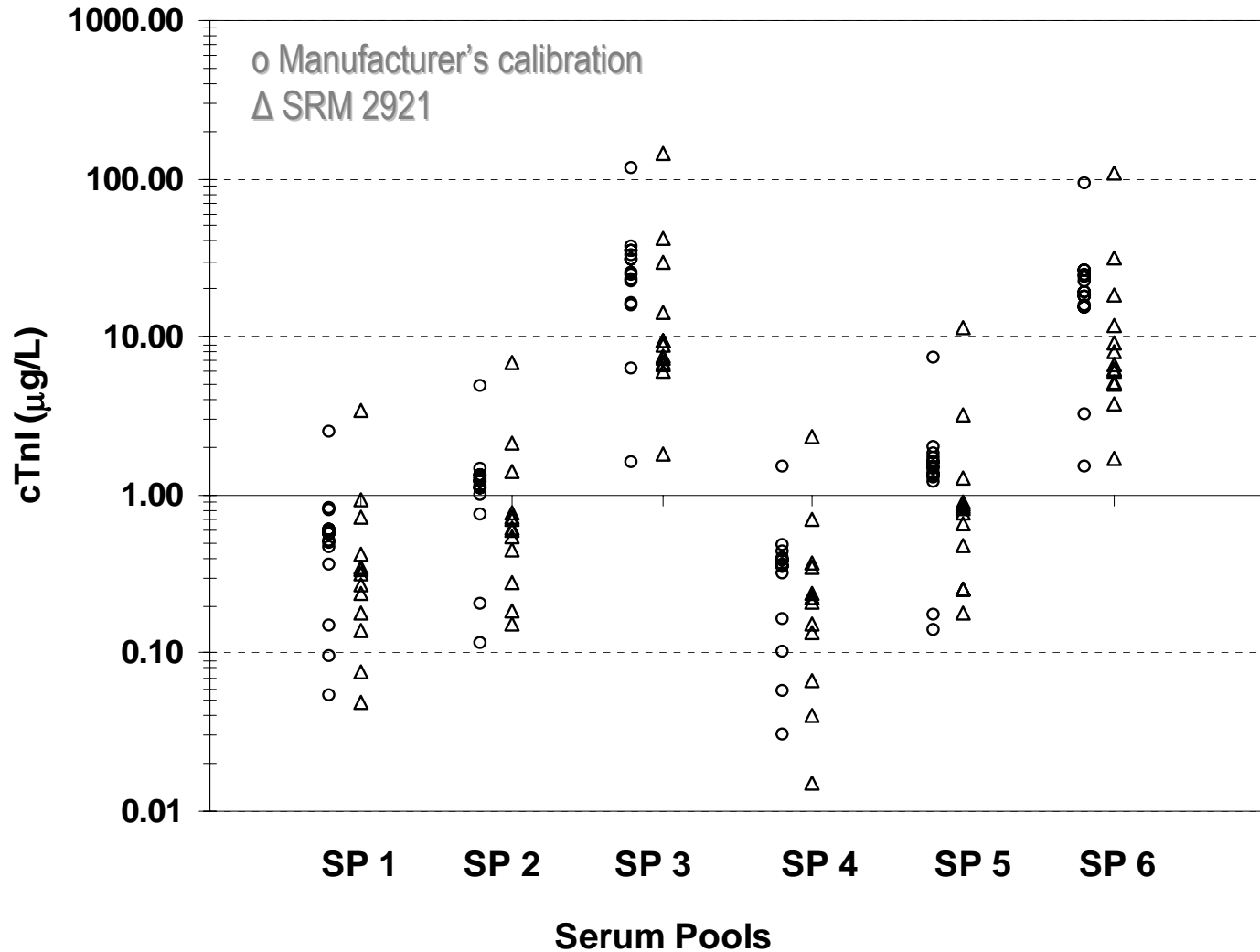
- **Panteghini M, Gerhardt W, Apple FS, Dati F, Ravkilde J, Wu AH. Quality specifications for cardiac troponin assays. Clin Chem Lab Med 2001; 39:175-9.**
- **Apple FS, Panteghini M, Ravkilde J, Mair J, Wu AHB, Tate J, Pagani F, Christenson RH, Jaffe AS. Quality specifications for B-type natriuretic peptide assays. Clin Chem 2005, 51: 486-93.**
- **Apple FS, Wu AHB, Mair J, Ravkilde J, Panteghini M, Tate J, Pagani F, Christenson RH, Mockel M, Danne O, Jaffe AS. Future biomarkers for detection of ischemia and risk stratification in acute coronary syndrome. Clin Chem 2005; 810-24.**
- **Revision of cardiac troponin document in 2006**

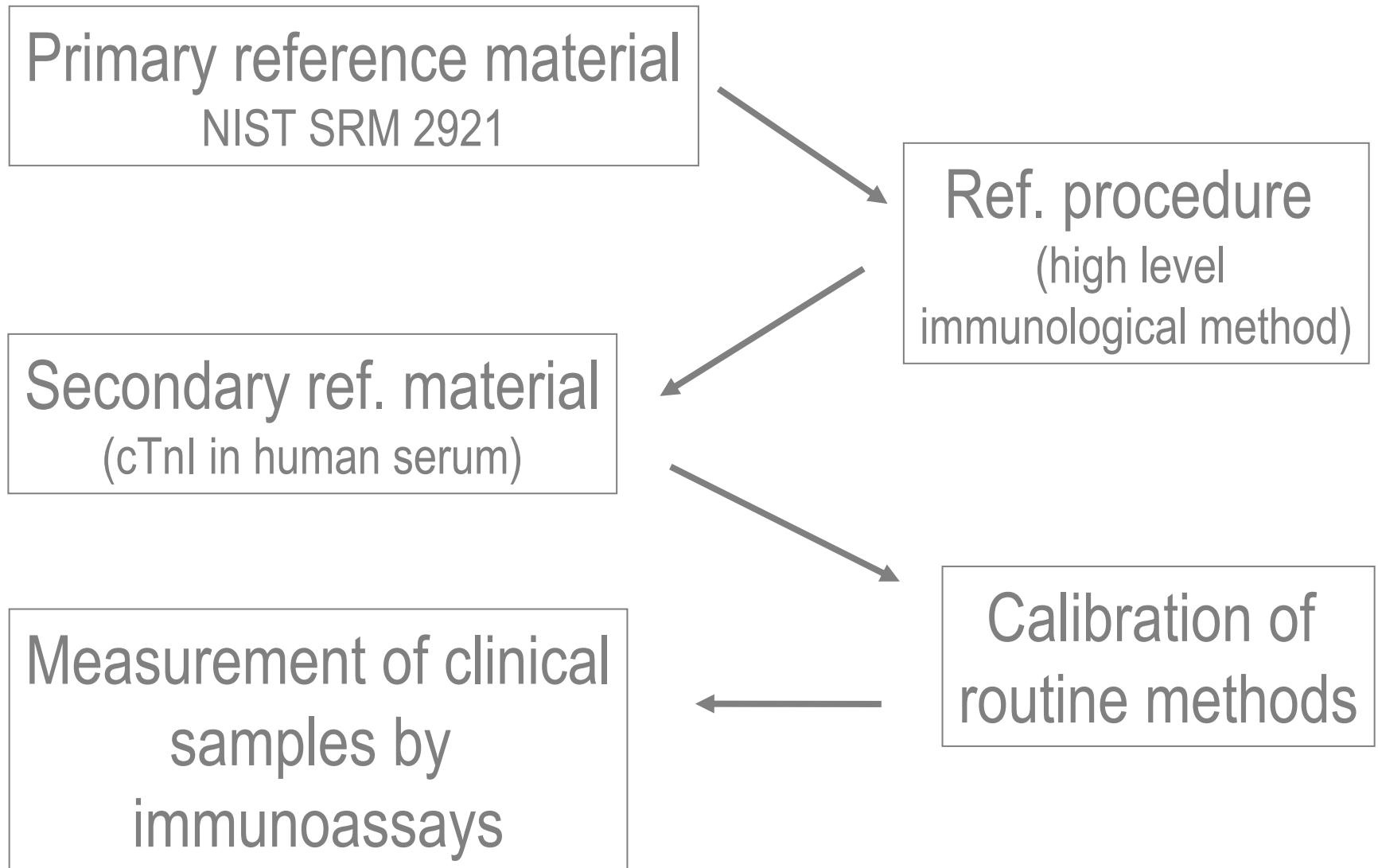
C-SMCD: Activities Past and Present

Standardisation efforts for cardiac biomarkers

- **Myoglobin: in collaboration with IRMM**
 - **Panteghini M, Linsinger T, Wu AHB, Dati F, Apple F, Christenson RH, Mair J, Schimmel H. Standardization of immunoassays for measurement of myoglobin in serum. Phase I: evaluation of candidate reference materials. Clin Chim Acta 2004; 341; 65-72 (on-going)**
- **Cardiac Troponin I: in collaboration with AACC and NIST**
 - **Christenson RH, Duh SH, Apple FS, Bodor G, Bunk D, Dalluge J, Panteghini M, Potter J, Welch M, Wu AHB, Kahn S. Standardisation of cardiac troponin I assays: round robin performance of ten candidate reference materials. Clin Chem 2001; 47: 431-7 (on-going)**
- **BNP (B-type natriuretic peptide): in collaboration with NIST, IRMM**
 - **Current primary initiative of committee**

Use of SRM 2921 as common calibrator does not improve cTnI standardization





BNP Standardisation: Develop Primary & Secondary Reference Materials

- **Collection of BNP, proBNP and NT-proBNP materials from 2 sources**
- **NIST (National Institute of Standards and Technology, USA) characterization of purity of materials**
- **Protocol development for cross-reactivity studies for all materials on all commercial immunoassays for BNP and NT-proBNP**
- **Selection of material(s) to be evaluated for reference material**
- **Evaluation of candidate materials in collaboration with manufacturers**

C-SMCD: Activities Past and Present

Guideline Efforts

- **Collaborative effort with National Academy of Clinical Biochemistry (NACB) in developing analytical guidelines for biochemical markers in acute coronary syndromes and heart failure**
- **Collaborative effort with European Society of Cardiology and American College of Cardiology (ESC/ACC) Global Task Force for the Definition of Myocardial Infarction, addressing quality specifications necessary for analytical issues pertaining to cardiac troponin assays**

C-SMCD: Development of Web-Based Repository of Biomarkers

- **Initiation of process to establish a web-based link on the IFCC website that would document both analytical and clinical characteristics of cardiac troponin and natriuretic peptide assays**
 - **Information collection from published literature**
 - **Information collection for manufacturers**
 - **Direct link with manufacturers website to package inserts**
- **Track old, evolving revisions, and new assays, with twice a year updates**
- **Invaluable source of accurate information for clinicians and laboratorians worldwide**

C-SMCD: Activities Past and Present

Educational Efforts

- **Continuation of committee's involvement at national and international congresses/meetings**
- **2005**
 - **IFCC Orlando USA**
- **2006**
 - **XVII Latin American Congress in Clinical Biochemistry Asuncion, Paraguay, April**
 - **American Association for Clinical Chemistry, Chicago USA, July**
 - **Spanish Society of Clinical Chemistry, Bilbao, Spain, October**

REFERENCE SYSTEMS OF ENZYMES (C-RSE)

- Operation of the network (**support for the ring trials**);
- Requirement for suitable reference intervals;
- Certification of AST RM (IRMM), stability check, material under evaluation; ALP rmp has been completed ; manuscript of amylase rmp ballot; standardisation of Lipase assay method studied;

POINT OF CARE TESTING (C-POCT)

- **The document "IFCC Recommendation: Guidelines for sampling, measuring and reporting ionized magnesium in undiluted serum, plasma or blood" accepted;**
- **Participation project IFCC/CLSI, two POCT Guidelines;**

TRACEABILITY IN LABORATORY MEDICINE (C-TLM)

- **Preparation of a Procedure Manual suitable for operating and assessing the performance of laboratories participating in ring trials for IFCC; (available on web site www.dgkl-rfb.de:81)**

REFERENCE INTERVALS AND DECISION LIMITS (C-RIDL)

- **Terms of reference defined;**
- **First meeting of the Committee on Reference Intervals and Decision Limits, Orlando 07/ 2005;**
- **Work to begin with common reference intervals:**
- **Analytes for which appropriate reference intervals are available.**

REFERENCE METHODS FOR APOLIPOPROTEINS (WG-MA)

- Reference material SP3-07 included in the JCTLM WG-1 list type 1;
- Production and characterisation of SP3-08 may represent technical issues with regards to ISO 15194 (uncertainty of measurement + commutability).

STANDARDISATION OF HUMAN CHORIONIC GONADOTROPIN (WG-SHCG)

- **NIBSC was permitted to use another fraction of the reference materials to prepare a second batch of standards (150mg);**
- **Manuscript (Establishment value assignment and charac....six forms HCG) in Clin Chem,**
- **+ another on nomenclature;**
- **External QA conducted to assess impact of new RMs on assay performance;**
- **Establishment of RMPs for intact + free beta-chain, free beta-chain, and intact HCG.**

STANDARDISATION OF HbA1c/GLYCOHEMOGLOBIN (WG-HbA1c)

- Presentations have been made reporting the work of the WG (Campaign on Diabetes);
- Meeting held with various international organizations concerning utilization of standardized method for HbA1c.
- 14 laboratories are in the network participating twice a year to ring trials (**coordination with C-TLM**);
- Implementation Gr will meet in 02/2006, need to complete IFCC recommendation (name and unit).

STANDARDISATION OF THYROID FUNCTION TESTS (WG-STFT)

- **Linda Thienpont new chair since Jan. 1st 2005.**

Members of WG-STFT

- **Prof. Dr. J. Thijssen (Utrecht, NL)**
- **Prof. Dr. C. Ronin (Marseille, FR)**
- **Mr. R. Miller (Dade Behring, Newark, DE, USA)**
- **Dr. M. Rottmann (Roche, Penzberg, DE)**
- **Dr. N. Christofides (Ortho-Clinical Diagnostics, Cardiff, UK)**
- **Dr. J. Faix (Stanford University Medical Center, CA, USA)**
- **Dr. G. Miller (Virginia Commonwealth University, Richmond, USA)**
- **Dr. B. Toussaint (JCR-IRMM, Geel, BE)**
- **Dr. G. Beastall (British Thyroid Association)**
- **European Thyroid Association**
- **Other Thyroid Associations (American, Japanese, Asian & Oceania) requested to nominate a delegate**

IFCC WG-STFT

In follow-up of
EU project G6RD-CT-2001-00587



Study the feasibility of developing
a Reference Measurement System (RMS) for the
establishment of metrological traceability of
measurements of:

- Serum Thyrotropin (TSH) (Chair: C. Ronin)
- Serum total Thyroxine (T4) and Triiodo-thyronine (T3) (Chair: L. Thienpont)
- Serum free Thyroxine (f-T4) (Chair: L. Thienpont)

**→ Project successful:
Feasibility documented**

Achievements of the EU project

See publications

- Donadio S ... Ronin C *et al.* A feasibility study to develop new calibrants for TSH immunoprocudures based on the remodeling of rec. TSH to mimic glycoforms in patients with thyroid disorders. (submitted to Clin Chem).
- Thienpont LM *et al.* Metrologic traceability of total thyroxine measurements in human serum: efforts to establish a network of reference measurement laboratories. Clin Chem 2005; 51:161-8.
- Thienpont LM *et al.* Feasibility study of the use of frozen human sera in split-sample comparison of immunoassays with candidate reference measurement procedures for total thyroxine and total triiodothyronine measurement. Clin Chem 2005 (in press).
- Clinical Laboratory and Standards Institute (CLSI). Measurement of Free Thyroid Hormones; Approved Guideline (chairholder: Thienpont LM). CLSI document C45-A [ISBN 1-56238-548-8].CLSI, Wayne, PA, USA (2004).

Achievements of the EU project

Available to the IFCC WG-STFT

- **TSH**

- Three candidates for a new reference material for TSH, produced by glyco-engineering of recTSH. Characteristics: the candidates mimic TSH glycoforms and display epitope expression comparable to the TSH circulating in hypothyroid patients, which is not so obvious for current TSH calibrators (WHO IRPs pitTSH & recTSH)

- *To do: Investigate the frequency of disease-related TSH glycoforms*

- *If relevant, change standardisation of TSH measurements*

Achievements of the EU project

Available to the IFCC WG-STFT

- **TT4 & TT3**

- T4 & T3 primary calibrators (IRMM)
- SI-traceable reference measurement procedures (ID-LC/MS) performed in a Network
- Missing: Serum matrix-based reference materials (evidence of non-commutability)
 - *To do: Study how commutability of matrix-based reference materials is influenced by processing of the serum*
 - *Develop commutable (serum) reference materials*
 - *Do worldwide standardisation*

Achievements of EU project

Available for the IFCC WG-STFT

- **f-T4**
 - Equilibrium dialysis (ED) and ultrafiltration do not give an identical T4-content in the dialysate and ultrafiltrate → Trueness-based standardization not possible
 - Recommended 'higher order' procedure: ED combined with ID-LC/tandem MS measurement of T4 in the dialysate
 - Missing: Serum matrix-based reference materials (evidence of non-commutability)
 - *To do: Further optimize ED-ID-LC/tandem MS*
 - *Develop commutable serum matrix-based reference materials*
 - *Do worldwide standardisation*

Objectives of the IFCC WG-STFT

2006: Standardization of serum TT4, TT3 & f-T4 measurements

Partners?

- International *in-vitro* diagnostics industry
- *Call for interest to be launched end of 2005*

How?

- Develop 2 panels of ~ 30 single-donation sera
- Develop best conditions for processing of sera and give proof of commutability
- Certify the panels with the TT4/TT3/f-T4 measurement procedures of higher order
- Do measurements in parallel with field assays
- Compare methods
- Give support to industry for establishing and/or validation of metrologic traceability
- *Data to be discussed satellite to an international congress (e.g., 2006 AACCC in Chicago)*

Objectives of the IFCC WG-STFT

2007: Change in standardization of serum TSH immunoassays?

Partners?

- International *in-vitro* diagnostics industry

How?

- Investigate frequency of thyroid disease related TSH glycoforms (mainly in overt primary or hypothalamic hypothyroidism)
- If sufficiently relevant, substitute current TSH international Reference Preparations (2nd IRP pitTSH (80/558) or 1st IRP recTSH (94/674)) with new glyco-engineered recTSH reference material that best satisfies epitope similarity with disease-related TSH glycoforms

STANDARDISATION OF HEMOGLOBIN A2 (WG-HbA2)

- **The project is progressing as scheduled;**
- **Primary RMs for HbA0 and HbA2 (98,7-99,3 % pure);**
- **Primary calibrators at 6 levels (0-7% HbA2);**
- **Development of RMP (trypsin vs. Lys-C endoprotease digestion);**
- **Secondary RM at 3 levels being prepared, will be sent to IRMM for testing.**

STANDARDISATION OF CARBOHYDRATE-DEFICIENT TRANSFERRIN (WG-CDT)

- **The project is progressing as scheduled;**
- **WG met in Orlando, July 2005, with 4 of the 5 interested assay kit manufacturers.**

STANDARDISATION OF CYSTATIN C (WG-SCC)

- **WG met in Orlando, May 2005; a plan was adopted to develop a RM and a RMP;**
- **Candidate recombinant material is available (Dako).**

STANDARDISATION OF GLOMERULAR FILTRATION RATE ASSESSMENT (WG-GFRA)

- **WG met in Orlando, July 2005; 4 goals;**
- **Support international circulation of documents on Rationale for reporting estimated GFR;**
- **Preparation of an IFCC recommendation for the use of proper (ie enzymatic) assays for creatinine;**
- **Establishment of an IFCC reference laboratory network for creatinine (with C-TLM);**
- **Development of Guidelines to coordinate global introduction of standardised creatinine together with the new GFR estimating equation...education.**

STANDARDISATION OF MICROALBUMIN ASSAY IN URINE (WG-SMA)

- **WG met in Glasgow in May & Orlando, July 2005;**
- **Current task: to develop a strategy for the project.**

PROJECT PROPOSALS

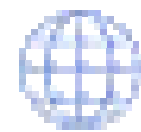
- **Kevin Spencer; establishment of a Working Group on Standardisation of Pregnancy associated Plasma Protein A(WG-PAPP-A**
- **Project limited to PAPP-A for prenatal screening.**

PROJECT PROPOSALS

- **Cathy Sturgeon; establishment of a Working Group on Growth Hormone (WG-GH), with the main objectives of:**
 - **assessment of the commutability of WHO 98/574**
 - **determination of the clinical decision levels for specific assays**
 - **identification of a reference procedure for GH**



Thank you



IFCC

*International Federation
of Clinical Chemistry
and Laboratory Medicine*

PROJECT PROPOSALS (pending)

- **G Schmidt: “Preanalytics of Biobanking”:** there is a requirement for documentation to provide standard operating procedures for the collection of specimens suitable for biobanking and quality control systems to monitor the performance of analyses.....



The WG is closed.