Standards and Reference Materials for Laboratory Medicine for Better Patient Care

Emil Voelkert,
Chairman CEN/TC 140
in vitro diagnostic medical devices
Laboratory medicine contributes to better patient care

- Screening of populations for early diagnosis
- Confirmation of presence or absence of disease
- Choice of treatment
- Monitoring of therapeutic levels of drugs
- Monitoring of patient care (e.g. diabetes)
  - Self-management of patients
- Safety of blood products
- Compatibility of transplants
- Predisposition for diseases
Spectrum of disciplines

- Clinical Chemistry
- Immunology (hormones, proteins, tumour markers ...)
- Serology
- Hematology – Hemostaseology
- Histology
- Microbiology
- Virology
- Nucleic Acid Techniques (DNA, RNA)
Development of technology - pregnancy testing

1960

1980
Development of Nucleic Acid Technologies
The Directive 98/79/EC on *in vitro* diagnostic medical devices

The Directive regulates the development and marketing of *in-vitro* diagnostics. It addresses mainly manufacturers of *in vitro* diagnostics, but has implications for the users as well.

- It specifies requirements on the *quality* and *safety* of products intended to be placed on the market in the European economic area.
- Amongst other requirements it aims at comparable results for patient data across methods, time and geographical region.
Mandated standards

- To support the directive CEN/TC 140 was charged with the development of appropriate standards
  - Labelling and performance evaluation
  - Quality systems and quality management
  - Biological staining and culture media
  - Reference systems
  - IVDs for self-testing
  - External quality assessment
  - Specimen containers
Traceability - the approach

- Definition of SI-unit
- Primary calibrator
  - Primary reference measurement procedure
- Secondary calibrator
  - Secondary reference measurement procedure
- Working calibrator
  - Manufacturer's selected measurement procedure
- Product calibrator
  - Manufacturer's standing measurement procedure
- Routine sample
  - User's routine measurement procedure

Result

Uncertainty
The importance of reference systems

- US Foot
- Mainz
- Hessia
- Saxonia
- Bavaria
- Brunswick
- Hannover
- Lübeck
- Mecklenburg
- Nuremberg
- Thuringia
- Lombardia
- Silesia
- Russia
Traceability

- For implementation of the concept in its complete form, i.e. traceability to the highest metrological order we need
  - a clear definition of the analyte
  - a description of the reference measurement procedure
  - a suitable reference material

- There are some 1500 different analytes which are determined in clinical laboratories - but only for some 60 of them these requirements are met on an international level

- In many cases there are no reference materials available in a suitable matrix
The importance of WHO biological standards

- They are most widely used as reference material to calibrate IVD-products.
- However, they do not necessarily guarantee identical findings in patient results in all cases, even when different manufacturers claim traceability to the same preparation.
- There are considerable lot-to-lot variations which make them unsuitable for calibration of in vitro diagnostic procedures.
- But they are the only reference materials presently available.
Pragmatic solutions are required

- Physicians need consistency of results
  - In many cases the measured analyte is in fact a mixture of many substances (Isoforms). Immunological procedures will differ, because usually different epitopes are addressed
  - Carefully selected panels of human samples are the most appropriate surrogates
  - In nucleic acid testing the use of synthetic material representing the genetic sequence are under investigation
Industry supports the traceability concept

- It is a legal requirement (IVD-Directive and national transposition) in EU-countries
- It is accepted not only in Europe, but also in other countries
- It is promoted by IFCC and other scientific organisations
- It will provide the basis for direct comparability of patient results over geographical regions and time and thus provide a benefit to patients and physicians
- It will allow manufacturers to base their calibration on internationally harmonized reference systems and will permit global marketing of products
Standards provide a suitable framework – WHO support is needed

- The organization is globally present and has access to suitable samples
- Its scientific and educational expertise could provide invaluable assistance
- By taking into account the requirements and needs of laboratory medicine for appropriate reference materials and panels it would contribute to better healthcare
- This would benefit patients, physicians, licensing authorities and manufacturers
Requirements for reference materials

- Values assigned by appropriate procedures
- Homogeneity
- Stability
- Commutability
  - nature of matrix
  - nature of constituents (e.g. Isoenzymes, Isoforms)
  - processing (stabilisers, additives, lyophilisation, freezing / thawing)

In many cases only surrogate materials are feasible - carefully selected panels of human samples are the most appropriate surrogates
JCTLM - Joint Committee on Traceability in Laboratory Medicine

Organized by BIPM (Bureau International des Poids et Mesures) and IFCC

- Supported by interested constituencies (IRMM, NIST, metrological institutes, scientific organisations, reference laboratories, industry etc.) on a global scale

- Exchange of information and establishing a network

- To set priorities for projects
  - medical relevance
  - possibility of improvement
  - resources

WSC workshop