

Activities of PTB to establish traceability of measurement results in Laboratory Medicine (Report to the JCTLM Executive Committee)

The Physikalisch-Technische Bundesanstalt (PTB) the National Metrology Institute of Germany with scientific and technical service tasks. It is a scientific and technical higher federal authority falling under the competence of the Federal Ministry for Economic Affairs and Energy. PTB measures with the highest accuracy and reliability – metrology as the core competence - and stands for progress and reliability in metrology for the benefit of society, trade and industry, as well as science including medicine.

Modern medicine is based on the quantitative measurement of both physiological quantities and cellular and molecular processes. Quantitative measurement procedures play a key role in the detection of changes in the individual measurement values of patients in correspondence to therapy as each patient responds differently. PTB supports this tendency to an evidence-based and personalized medicine, especially in the fields of laboratory medicine, imaging and environmental technology.

About 70 % of all medical diagnostic decisions are based on results of measurements in clinical laboratories which are mainly based on the quantitative analysis of body fluids. Thereby, the concentration of biomolecules, among others, is determined which can be used as diagnostic markers, e.g. for the diagnosis of cardiovascular diseases or virological or bacterial infections. This requires the **secure identification of relevant molecules and their exact quantification**. Procedures used in clinical practice must have been validated by means of primary measurement procedures. Currently, these are generally based on mass spectrometry which can be used for smaller molecules with molar masses up to 1000 g/mol. However, many important diagnostic markers are macromolecules with molar masses up to several million g/mol. Routine procedures to analyze these markers often do not provide concordant results. The urgently required traceability of those measurands requires completely new strategies for primary procedures. Here, solutions will be developed on the basis of biotechnological and optical-analytical measurement procedures. As these molecules present complex challenges a multi-modal approach is taken at PTB to analyse the biomarkers using both elemental and organic mass spectrometry as well as optical means to ensure the identity and reliable quantification. For this means, PTB is also in close cooperation with various other National Metrology and Designated Institutes worldwide.

Establishing Traceability of Laboratory Results to the International Reference Framework

In order to link up working level results in clinical laboratories with the international reference framework, or, expressed in other words, to disseminate the units of measurement, traceability infrastructures are required also at the national level. This is necessary because the large number of field laboratories (this may be more than a thousand in a single application field such as clinical chemistry) cannot interact directly with the NMIs. In the following the national traceability infrastructure for chemical measurements in Germany is described.

The results of chemical testing laboratories are made traceable to the international reference framework via national measurement standards. Such measurement standards can be reference materials as well as reference methods of high metrological quality. Primary methods are used, if available, for realising the national standards.

The infrastructure consists of three levels:

At the top of the structure a network of national laboratories provides the national chemical measurement standards and ensures that these are linked up with the international reference framework for chemical measurements. An intermediate level consisting of accredited chemical calibration laboratories, in the field of laboratory medicine also referred to as

reference measurement laboratories, is connected to the national standards level via transfer standards and comparison measurements. The accreditation as a calibration laboratory is granted by the Germany's National Accreditation body (DAkkS) according to ISO/IEC 17025, in laboratory medicine also according to ISO 15195. This intermediate level has an important 'multiplier' function. It is firmly linked to the national standards and provides traceable calibration means to the clinical laboratories which are required to give evidence to the German Medical Council (Bundesärztekammer (BÄK)) that their measurement results are traceable to recognised references.

In clinical chemistry, the primary references are disseminated to the medical laboratories at the working level mainly via interlaboratory tests on well characterised samples which are traceable to the primary references. Measurements are conducted within the framework of the so-called external quality assurance as required by the guidelines of the BÄK. Each calibration laboratory is connected to the national standards level via comparison measurements using laboratory samples taken from the calibration laboratory. The advantage of this way of transferring standards over the transfer of reference materials from the shelf is that these standards perfectly match the matrices occurring in the calibration laboratory. The samples are analysed by the national standards laboratory and the calibration laboratory to be accredited or re-evaluated in regular intervals. Agreement within predefined limits is required as a proof of the competence of the calibration laboratory. Samples with a known value undisclosed to the participants are then used by the calibration laboratory as measurement standard for the quality control of a large number of medical laboratories; again, agreement within predefined limits is required. In case of non-compliant results a medical laboratory has to discontinue its service until evidence for improved results is provided. The procedure is repeated at quarterly intervals. This way, many thousand interlaboratory test measurements are performed every year by several thousand medical laboratories.

Because of the large number of analytes with clinical relevance traceability can only be provided for a selected group of measurands. Priority lists were established by the BÄK for this reason. On this basis traceability can be established for a large majority of all measurements in clinical chemistry. The list is continually updated and PTB strives to provide reference measurement procedures for those priority analytes.