Calibrators: commutability, traceability and uncertainty

René Dybkaer
Afdeling for Standardisering i Laboratoriemedicin
Hovedstadens Sygehusfællesskab
H:S Frederiksberg Hospital
Frederiksberg

The main goal of the clinical laboratory is to provide health care personnel and recipients with laboratory results which are relevant and reliable. The reliability concerns both production and transmission to the end user (1). The production phase comprises request, preparation of individual, sampling and transport, preparation of sample, examination including calculation of result with uncertainty, and interpretative information.

Concerning the examination phase, its reliability depends on metrological quality assurance through a coherent reference examination system (2) with the main interrelating elements of

- metrological institutes,
- reference examination laboratories,
- scientific organizations,
- dedicated industries,
- metrological units,
- reference data,
- reference examination procedures,
- reference materials,
- internal quality control, and
- external quality assessment.

Such a system ensures

- vertical reliability, i.e. metrological traceability towards a stated reference entity,
- horizontal reliability, i.e. comparability between laboratories over space, and
- durable reliability, i.e. comparability over time.

The first item of the reference examination system, reference materials, encompasses calibration materials and control materials, both with assigned values, and control materials without such values. Here, the subject for discussion is the concept calibration material, also termed calibrator. The relevant definitions may be worded as follows.

reference material

material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an

apparatus, the assessment of an examination procedure, or for assigning values to materials

[Adapted from VIM:1993-6.13 (3)]

calibration material

calibrator
reference material whose value is used for the independent variable in a calibration function

[prEN ISO/DIS 17511:2000 (4)]

So the function of a calibrator is to provide a measurement with an anchoring value of a quantity of the kind in question.

The availability of adequate calibrators is obviously a necessity for proper laboratory work and as the production is often very expensive, structured planning becomes essential. The phases are

- demonstration of need, metrological level, and priority;
- funding;
- project leader;
- identification of a producer;
- feasibility study;
- production;
- physical, chemical, and functional description;
- certification (optional);
- storage, distribution, check, and renewal.

The process requires collaboration between users, scientific professional organizations, laboratories, industry, and facilitating institutions such as the European body Measurements, Testing, and Infrastructure (MTI, formerly BCR), the JRC body Institute of Reference Materials and Measurement (IRMM), and the World Health Organization (WHO).

Especially concerning the description of a calibrator, its general and specific properties have been listed in great detail elsewhere (2, 5). Some main groups of properties are:

- warnings and safety precautions;
- origin, production, state and form;
- composition, including matrix, purity;
- intended function, metrological level, scope;
- homogeneity, stability, storage;
- instructions for use;
- property with assigned value and uncertainty;
- certificate (optional);
- availability.

The authority of the assigned value depends on its metrological traceability:

traceability

<metrology> property of the result of a measurement or the value of a measurement standard whereby it can be related to stated references, usually national or international measurement standards, through an unbroken chain of comparisons all having stated uncertainties

[≈ VIM:1993, 6.10 (3)]

Here, the measurement standards are reference materials, preferably embodying properties expressed in SI units and especially mole where relevant.

The metrological traceability has achieved prominence with the essential requirement of the European Directive on in vitro diagnostic medical devices stating that "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." (6).

Obtaining traceability of measured results necessitates a calibration hierarchy of alternating measurement procedures and calibrators, leading from the definition of the SI unit, via primary reference measurement procedure assigning value to a primary calibrator which calibrates a secondary reference measurement procedure, and so on through secondary calibrator, manufacturer's reference procedure, working calibrator, and standing procedure to the manufacturer's product calibrator which calibrates the routine procedure of the end-user.

The definition of metrological traceability demands an unbroken chain of comparisons. This means fulfilling three requirements.

Firstly, all measurement procedures must measure the same type of measurand.

Secondly, all measurement procedures must have the same analytical specificity, that is they measure solely the measurand by its chemical nature or after correction. A check is made by applying a reference procedure and the routine procedure on the same samples.

Thirdly, each calibrator must be commutable where:

commutability

degree to which a material yields the same numerical relationships between results of measurements by a given set of measurement procedures, purporting to measure the same quantity, as those between the expectations of the relationships for the same procedures applied to those types of material for which the procedures are intended

[prEN ISO/DIS 17511:2000-3.8 (4)]

In other words, the ratio between the results of two procedures must be the same for the calibrator as for routine samples.

In addition, the definition of traceability demands that each link in the traceability chain has a stated.

uncertainty of measurement

parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand

[VIM:1993, 3.9 (3)]

According to the *Guide to the expression of uncertainty in measurement* (GUM) (7), the combined standard uncertainty at each level of the calibration hierarchy should be computed on the basis of an uncertainty budget. The possible sources of uncertainty of a chemical measurement are often numerous, but -as the combined standard uncertainty is obtained by adding uncertainty variances- only a few will be significant in practice.

The combined standard uncertainty increases as one moves down a calibration hierarchy because that at a given level is incorporated in that of the next. It may therefore pay to eliminate pairs of consecutive measurement procedure and calibrator or vice versa.

For a given type of quantity, an SI unit, a primary measurement procedure, and a primary calibrator may not be available. Then, one should strive to agree on an international conventional calibration material and reference measurement procedure, often giving values in arbitrary non-SI units such as WHO international units. However, the requirements of traceability, analytical specificity, commutability, and uncertainty still apply (8).

The investigation of these properties in each measurement situation requires expert metrological skills, both in the national metrology institutes, collaborating under the International Bureau of Weights and Measures (BIPM), and in the reference measurement laboratories, industry laboratories, and clinical laboratories. They should all be linked vertically, horizontally, and durably, and this infrastructure is being elaborated presently at all levels.

In order to aid the understanding and implementation of traceability, the International Organization for Standardization (ISO) and the European Committee for Standardization (CEN) are producing five standards on:

- Presentation of reference measurement procedures (EN 12286 = ISO/DIS 15193);
- Description of reference materials (EN 12287 = ISO/DIS 15194);
- Metrological traceability of values assigned to calibrators and control materials (prEN ISO 17511);
- Metrological traceability of values for catalytic concentration of enzymes

assigned to calibrators and control material (prEN ISO 18153);

Requirements for reference measurement laboratories in laboratory medicine (prEN ISO 15195).

In conclusion,it should be realized that the study and use of the concepts of commutability, traceability, and uncertainty are imperative for:

- national metrology institutes and reference measurement laboratories within the metrological infrastructure providing the highest levels of the calibration hierarchies (4);
- industry in fulfilling the essential requirements of the European *in vitro* diagnostic directive and providing useful calibrators (6);
- routine clinical laboratories seeking accreditation where demonstrated traceability and uncertainty statement are required (9, 10).

In the end, these concepts provide summaries of our ability to deliver adequate service to the community.

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