Clinical chemistry is a field in which the reliability of measurement results has a major impact on decisions that directly affect human beings. The conditions under which the measurements are performed and the way their results are applied bring about very stringent requirements in regard to the methods used. Measurements are expected to give reliable results after a single determination performed directly on complex matrices like serum or urine, and data should preferably be available within minutes to a few hours. The results need to be reliable (i.e., accurate) enough to enable comparisons with reference intervals and cutpoint values, and the measurement target should be a clinically significant parameter. These requirements can currently be met for hundreds of analytes. The next level of requirement is that measurement results be comparable between laboratories and methods, over time, with common reference ranges for different methods. This has been achieved only for a much smaller number of analytes.

Difficulty in Achieving Comparability of Measurement Results

For a number of clinically relevant analytes, comparability is achieved by establishing metrological traceability to a stable reference [Système International d’Unités (SI)] or quantity values embedded in a material standard for well-defined molecules. For the majority of clinical measurands, however, it is difficult and clinically not meaningful to describe the properties of the analyte of interest as a single chemical entity. In fact, one would need a “fuzzy” definition describing an ensemble of molecules, e.g., “The ensemble of molecular entities with sequence X, possessing on position 42 a Q instead of an E in 14% of the molecules, with an oxidized cysteine in position 98 in about 65% of the molecules, with a 3-dimensional structure such that the root mean square deviation between the atom positions and the atom positions of the crystal structure is smaller than 2.5 Å, with 20% of the molecules in the dimeric form…” This is not only the case in clinical chemistry, but also in many other areas like food and environmental analysis or for measurements of engineered materials.

Turning the Problem Upside Down—Focus First on the Routine Methods

What counts is the measurement of what is clinically relevant, even if it is difficult to define the measurand in molecular terms. Therefore, clinically relevant routine methods should be the first focus of harmonization or standardization efforts, and not the definition of the top of an artificial traceability chain without a proper link to the routine methods. Schimmel et al. (1) have described an approach for the standardization of complex biomolecules that starts with the evaluation of the routine methods and the assessment of their correlations. Methods can be harmonized only if the results for individual patient samples obtained with different methods correlate with each other. Thus, the methods must measure the same analyte, or analytes, present in a constant molar ratio in the calibration standards and the clinical samples.

Thienpont et al. (2) have proposed that, in case of correlated results, the methods could be harmonized by applying correction factors with respect to the all-laboratory trimmed mean, rather than to standardize them. On the basis of this proposal, Miller et al. (3) have described a systematic approach for the harmonization of measurement results. This approach includes the prioritization of measurands, the evaluation of the clinical requirements for harmonization, and the assessment of the harmonization potential using a panel of clinical samples, which are also used for recalibration. This proposal was taken up by the International Consortium for Harmonization of Clinical Laboratory Results. Within the framework of the Consortium, a toolbox of technical procedures for the harmonization of clinical measurements has been developed (4).

In this issue of Clinical Chemistry, Weykamp et al. (5) describe the use of that toolbox for the evaluation of the potential for harmonization of carbohydrate-deficient transferrin.
Proteins in the early 1990s resulted in the development of a rigorously validated reference measurement system for 15 plasma proteins. It included a certified reference material (ERM-DA470), reference procedures for value assignment that were based on optimized routine (immunoassay) methods, and procedures for transferring values from reference materials to the in-house calibrators of the manufacturers. The identity of the certified parameters was operationally defined, and values were in some cases traceable to the SI via well-characterized pure protein preparations. By 1995, after the release of ERM-DA470, the CVs for immunoglobulin measurements had dropped to 5%–10% in United Kingdom National External Quality Assessment Service results, depending on the protein. It has been possible to maintain this state of equivalence of results through the use of the follow-up material ERM-DA470k/IFCC. As such, the plasma proteins form an example of the largely successful standardization of the measurement of complex biomolecules by using a well-controlled reference system comprising a reference procedure (defining the analyte) and a reference material as anchor point for the measurement scale.

The experience with plasma protein measurements has shown that it is difficult and labor-intensive to maintain comparability over a long period of time without standardization. Standardization can be achieved using a reference system based on operationally defined measurands, as has been shown for CDT by Weykamp et al. There are clear requirements for the components of these reference systems; reference materials should be commutable and reference methods must give results that correlate with results from relevant routine methods. These conditions seem to be met for the proposed reference system for CDT.

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