Introduction

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Introduction

Laboratory Medicine has its roots and reasons for being in clinical medicine and epidemiology and its goal in facilitating the health of individuals and populations. The science of measurement = metrology is a technical cornerstone of the science and practice of Laboratory Medicine. Metrology provides the theoretical and practical tools for *traceability* of the results of measurements and examinations, which provides the means to ensure that results of measuring a quantity in samples are and remain the same regardless of which measuring system is used, where, when, by whom.

Developments in chemistry, automation, electronics, and information technology continue to improve=decrease the uncertainty of measuring systems, especially their imprecision. The relative importance of *bias* in relation to imprecision in the traceability, measurement uncertainty, and ultimately in the diagnostic uncertainty in Laboratory Medicine has increased (1-4). Bias in measuring systems in Laboratory Medicine has multiple causes. The choice of reference materials and reference measurement systems, i.e., traceability of results, maybe one of the most critical single causes, as we will detail and discuss (5-13).

What matters most in Laboratory Medicine is the practical *equivalence* of measurement results, "equivalence" being "agreement of measured values among different measuring systems intended to measure the same measurand, where the differences in measured values on the same human samples do not affect clinical interpretation" (14). Otherwise, measuring system-specific reference intervals and decision limits need to be established by extensive clinical studies commonly at unsurmountable efforts and costs.

Global measures of length, mass, and volume have been standardized for more than a decennium by tracing measures of mass to universally agreed common references such

as the meter and the kilogram. The same basic principle of metrological traceability to a common reference is a cornerstone of the efforts of Laboratory Medicine to obtain and maintain equivalent measurement results independent of measuring systems, location, time, or other variables.

Optimally, the standard reference that is the cornerstone in standardization and traceability is a definition of an *SI-unit*, a *certified reference material,* or a *reference measuring system*. In Laboratory Medicine, this is generally feasible for small molecules in the organism in a unique molecular form. However, several of the macromolecules of interest in Laboratory Medicine are present in many different molecular forms due to enzymatic cleavage or other post-translational modifications. Such heterogeneous macromolecules cannot be manufactured in a unique and stable mixture of molecular forms present in a stable form in the organism traceable to SI and are usually found in the organism in varying molecular conditions depending on the organism's homeostatic state, including effects of hormones and possible disease. Calibrators for such molecules are usually prepared from extracts of human tissues and therefore represent mixtures of molecules that may or may not reflect a spectrum characteristic of health or disease. Usually, such calibrators are manufactured by or under the auspices of well-established international organizations (e.g., the World Health Organization, WHO) used to cater for consensus and are therefore called *international conventional calibrators* (WHO).

An international harmonization protocol and commutable international harmonization reference materials can be used without SI-traceable calibrator or reference measuring systems or an appropriate international conventional calibrator. These materials include assigned values which are averages of the results from several internationally used measuring systems.

Measurands in Laboratory Medicine are usually present amongst high concentrations of other molecules in natural patient samples, potentially influencing the measurement results. The *selectivity* of measurement methods differs for various molecules and molecular forms of interest. Traceability is, therefore, a daunting challenge in the metrology of Laboratory Medicine; in fact, a mountain of challenges that regulators, manufacturers, and users of measuring systems are just beginning to climb in earnest.

Knowledge and experience of relevance to Laboratory Medicine have been *condensed* into numerous ISO standards and *guidelines* from other organizations, which detail both theoretical stringency and practical actions to realize traceability in the interest of patients. The approach of these standards and guidelines of particular interest for metrological traceability in Laboratory Medicine represents an essential part of the present document. Their essence is included for educational purposes - to provide

necessary background information, facilitate their understanding and implementation, highlight the main principles laid down in the standards, make them better known, and discuss their present and remaining challenges, pros, and cons appropriately. Only the original standards contain the complete information needed to adhere to them. Therefore, the actual standards must be consulted before claiming adherence to them.

Physics is the mother discipline of metrology in Analytical Chemistry and all specialties of Laboratory Medicine. The theoretical backbone, concepts, and terms in metrology have been established in and by physics since the beginning of the nineteenth century. This may seem a constraint but represents an essential bulwark of stability as an increasing number of sciences, including the disciplines of Laboratory Medicine and the humanistic sciences (for example, Psychology, Sociology, Pedagogics), bring their diverging traditions, concepts, and terms to the table of metrology.

The role of *manufacturers* of measuring systems, including their reagents and calibrators, is vital in the metrology of Laboratory Medicine since the bulk of all measurement results in the field are produced using their measuring systems (Figure 1). Manufacturers of measuring systems in Laboratory Medicine should be honored for the continued successful development of their products in service of Laboratory Medicine and patients in need of its services.

There is also a risk of forgetting the increasingly important role of *regulators* for the quality of examinations and measurement results in Laboratory Medicine. The introduction of quality systems, standards, and the watchful eyes of accreditation agencies has substantially contributed to better quality and competency in the laboratories, especially since the 1990ies. The increased emphasis by the regulators on results from clinical studies (15) regarding the use of in-vitro diagnostic measuring systems is likely to remain a primary focus in the coming decade.

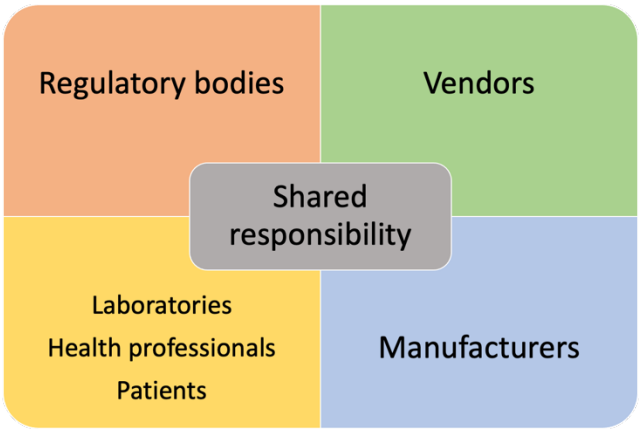

Figure 1: Fitness for the intended use of in-vitro measuring systems is dependent on well-functioning cooperation between *regulatory bodies,* including the FDA, The

National Medical Products Administration (NMPA) in China, the EU, and accreditation authorities, *manufacturers*, *vendors,* and the *users* of the measuring systems.

Quality in the individual medical laboratories, the activities of health professionals, and individual patients is fundamentally equal to fitness for the intended use of the results of examinations and the measurement results. The *vendors* need the proper training conducted by the *manufacturers* to give the right training to the users of the measuring systems and as a prerequisite for the necessary flow of information between the users and the manufacturers in continuous improvements of the measuring systems. Another example is developing and arranging communication channels between the vendor and manufacturer for exchanging data regarding feedback and complaints. The regulatory bodies make the rules and regulations governing which properties measuring systems sold in the country must have or decide on permits for individual measuring systems. All concerned parties must work together.

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