Introduction

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BIPM in Paris in 2021

This is a “living document”, version 2021-10-17. Suggestions for improvements are gratefully received.

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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 tools 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 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 therefore increased (1-4). Bias in measuring systems in Laboratory Medicine has multiple causes. The choice of reference materials and of reference measurement systems, i.e. traceability of results, may be one of the most important single causes, as we will detail and discuss here (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 large clinical studies at unsurmountable efforts and costs. Global measures of for example length, mass, volume have been standardized for more than a decennium by tracing for example measures of mass to a 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 common reference which is the cornerstone in standardization and in traceability is a definition of a *SI-unit*, a *certified reference material* or a *reference measuring system*. In Laboratory Medicine this is generally feasible for small molecules that exist in the organism in a unique molecular form. However, several of the macromolecules of interest in Laboratory Medicine are present in a multitude of different molecular forms due to enzymatic cleavage or other types of post-translational modifications. Such heterogenous 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 forms depending on the homeostatic state of the organism including effects of hormones and of possible disease. Calibrators for such molecules are usually prepared from extracts of human tissues and therefore represent mixtures of molecules which 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 catering for consensus, and are therefore called *international conventional calibrators* (WHO).

Lacking SI-traceable calibrator or reference measuring systems or an appropriate international conventional calibrator an international harmonization protocol and commutable *international harmonization reference materials* can be used. These materials include assigned values which are averages of the results from several measuring systems used internationally.

Measurands in Laboratory Medicine are usually present amongst high concentrations of other molecules in natural patient samples which potentially influence the measurement results, and 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 which regulators, manufacturers and users of measuring systems are just beginning to climb in earnest.

Knowledge and experience of special relevance to Laboratory Medicine has 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 special interest for metrological traceability in Laboratory Medicine represent an important part of the

present document. Their essense is included for educational purposes - to provide necessary background information, facilitate their understanding and implementation and highlight the main principles laid down in the standards, to make them better known, and to discuss their present and remaining challenges, pros, and cons as appropriate. Only the original standards contain the entire information needed to adhere to them. The original standards must therefore be consulted before making any claim of adherence to them.

Physics is the mother discipline of metrology in Analytical Chemistry and in 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 important bulwark of stability as 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 especially important 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 in fact 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 quality of examinations and measurement results in Laboratory Medicine. The introduction of quality systems , standards and the watchful eyes of accreditation agencies in the laboratories 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.

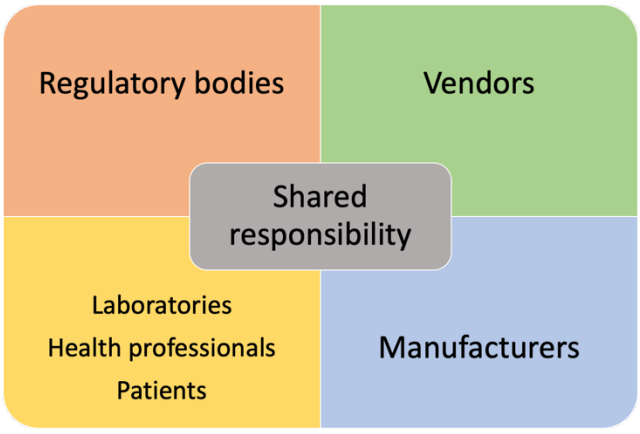

Figure 1: Fitness for the intended use of in-vitro measureing systems is dependent on well-functioning co-operation between *regulatory bodies* including the FDA, The National Medical Products Administration (NMPA) in China, the EU and accreditation authorities, *manufacturers*, *vendors,* and the *users* of the measuring systems.

Quality in the individual medical laboratories, the activities of health professionals and of individual patients is fundamentally equal to fitness for the intended use of the results of examinations and of 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 feedbacks 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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