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Opinion Paper

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Metrological traceability and harmonization of medical tests: a quantum leap forward is needed to keep pace with globalization and stringent IVD-regulations in the 21st century!

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Abstract: In our efforts to advance the profession and practice of clinical laboratory medicine, strong coordination and collaboration are needed more than ever before. At the dawn of the 21st century, medical laboratories are facing many unmet clinical needs, a technological revolution promising a plethora of better biomarkers, financial constraints, a growing scarcity of well-trained laboratory technicians and a sharply increasing number of International Organization for Standardization guidelines and new regulations to which medical laboratories should comply in order to guarantee safety and effectiveness of medical test results. Although this is a global trend, medical laboratories across continents and countries are in distinct phases and experience various situations. A universal underlying requirement for safe and global use of medical test results is the standardization and harmonization of test results. Since two decades and after a number of endeavors on standardization/harmonization of medical tests, it is time to reflect on the effectiveness of the approaches used. To keep laboratory medicine sustainable, viable and affordable, clarification of the promises of metrological traceability of test results for improving sick and health care, realization of formal commitment among all stakeholders of the metrological traceability chain and preparation of a joint and global plan for action are essential prerequisites. Policy makers and regulators should not only overwhelm the diagnostic sector with oversight and regulations but should also create the conditions by establishing a global professional forum for anchoring the metrological traceability concept in the medical test domain. Even so, professional societies should have a strong voice in their (inter-) national governments to negotiate long-lasting public policy commitment and funds for global standardization of medical tests.

Keywords: globalization; IVDR 2017/746; metrological traceability; test harmonization; test standardization.

Introduction

Medical laboratories in developed countries routinely produce millions of medical test results per year. Medical test results are highly relevant as the majority of downstream medical decisions are based on laboratory test results in pathology reports. Laboratory results are only meaningful if the results are interpreted through comparison to either population-specific reference intervals, clinical decision limits or previous results from the same patient (the so-called delta check) [1].

In making a comparison, it is vital that test results and reference intervals or decision limits are “comparable”. To that end, analytical bias, imprecision and selectivity of medical tests should be within predefined analytical performance specifications, in line with the EFLM Milan consensus hierarchy, which contributes to introduction of tests that are *fit for clinical purpose* [2]. If not, underdiagnosis and overdiagnosis occur in case of, e.g. disease-defining analytes such as Hb for anemia, glucose for gestational diabetes, HbA_{1c} for diabetes mellitus and TSH/FT4 for subclinical hypothyroidia. Comparable test results are essential in order to be able to apply Evidence-Based Laboratory Medicine principles, (inter)national clinical guidelines and common reference intervals or decision limits [3].

The process used to make different test results comparable is through implementation of the metrological traceability concept. According to its formal definition, metrological traceability is *the property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each*

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contributing to the measurement uncertainty [4, 5]. Comparable and traceable test results allow exchange of patient laboratory data on the local, national and global level. Non-comparable test results in Electronic Health Reports mislead doctors in their diagnosis and treatment in case that patients are, e.g. referred from primary to secondary or tertiary care settings, and bring along unacceptable management risk and additional costs in case of repeat testing.

Since 1947, attempts have been made to improve interlaboratory comparability of test results. History and updates have been described by renowned authors in recent editorials or other peer-reviewed literature [6–9]. Notwithstanding major scientific advances, appearance of international guidelines (global harmonization task force, ISO-guidelines, …) and landmark legislation (e.g. EU IVDD 98/79/EC and recently the EU IVDR 2017/746), the establishment of the Joint Committee on Traceability in Laboratory Medicine (JCTLM) in 2002, which publishes databases yielding approved Reference Materials, Reference Measurement Procedures and Reference Measurement Systems, and the IVD manufacturer uptake of the metrological traceability concept, progress of medical test standardization/ harmonization in the past decennia is experienced as too loose and too noncommittal [8]. For too long, the pressing need for global test harmonization has been underrated and insufficiently integral addressed. The time is there that all stakeholders involved with development, manufacture and use of *in vitro* diagnostic medical tests should join forces and take their responsibility, for the sake of sustainable and affordable laboratory medicine in the 21st century.

The role of regulators

Regulators aim to regulate the trade in active implantable Medical Devices, Medical Devices (MD) and *In Vitro* Diagnostic (IVD) Medical Devices on specific markets, and by doing so, to guarantee the safety, suitability and performance as well as safeguard the health and ensure the necessary protection of patients, users and other persons (WHO-definition, 2001). This is a generic phenomenon worldwide, carried out by, e.g. the Therapeutic Goods Administration (TGA) Commonwealth Government agency in Australia, the US Food and Drug Administration (FDA) in the USA, the China Food and Drug Administration in China (CFDA) and the European Commission's regulatory framework in the European Union (EU). International legislation is periodically revised, and a global trend towards increased stringency is observed. As a representative example of stricter regulations, with impact on metrological traceability of test results, the rationale and significance of the latest EU legislation will be highlighted.

Due to a recent hip replacement scandal (2010) and a breast implant scandal (2012) causing harm to patients, regulators in the EU were forced to revise and strengthen the existing (active implantable) Medical Device Directives into formal Regulation (named EU MDR 2017/745). In parallel, the *In Vitro* Diagnostic (IVD) Medical Devices Directive 98/79/EC has concomitantly been transformed from a directive into an enforced regulation (named EU IVDR 2017/746). Both regulations are officially published in the EU official journal and can be found at http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2017:117:TOC. These regulations have entered into force on May 26, 2017, marking the start of a stormy transition period for companies bringing medical devices and IVDs on the European market. The product owners of IVDs are currently facing one of the greatest challenges ever, where all IVDs have to be categorized into respective risk classifications and where 80%–90% of the medical devices and IVDs have to undergo conformity assessment by notified bodies. This is a big contrast compared to the past situation under the EU Directives, where almost 80% of IVDs sold in Europe are controlled by the self-declaration mechanism. These regulations bring over legislation that is directly applicable in EU-member states, not giving room for local interpretation. Hence, medical laboratories face the shift and implementation from a "good will" approach into formal legal regulations, which have to be fully applied by May 26, 2020 (MDR), and by May 20, 2022 (IVDR). The burden for IVD manufacturers is huge with this transition from a preapproval stage selection of medical devices and IVDs into a full life-cycle approach with regular updates either upon request (for class A and class B IVDs) or annually (for class C and class D IVDs).

The new EU regulations also impact medical laboratories that perform *in-house* tests. Although health institutions running *in-house* tests are exempted from the regulations, several additional requirements have to be fulfilled. According to preamble 29 in the IVDR 2017/746, health institutions should have the possibility of manufacturing, modifying and using *in-house* tests and thereby addressing, on a non-industrial scale, the specific needs of target patient groups, which cannot be met at the appropriate level of performance by an equivalent device available on the market. In that context, it is foreseen that certain rules of the regulation, as regards *in-house* tests manufactured and used only within health institutions, including hospitals as well as institutions, such as laboratories and public health institutes that

support the health care system and/or address patient needs, but which do not treat or care for patients directly, do not apply, because the aims of this regulation would still be met in a proportionate manner. Additional requirements that EU health institutions running *in-house* tests should fulfill are as follows:

1. Manufacture and use within only one institution ("legal entity");
2. Implementation of an appropriate quality management system;
3. Compliance with EN ISO 15189 or further national requirements (e.g. accreditation);
4. Documentation that the health facility has given due consideration as to whether the target patient group's specific needs cannot be met or cannot be met at the appropriate level of performance by an equivalent device available on the market;
5. Provide, upon request of the competent authority, information regarding the use of the in-house devices including a justification for manufacture, modification, use;
6. Make publicly available a declaration of conformity with product details;
7. Present complete and detailed validation documentation for IVDs of class D that enables the competent authority to assess whether the requirements are met;
8. Facilitate product monitoring during the entire life cycle of the device or IVD.

Metrological traceability in laboratory medicine – for both CE-IVDs and *in-house* tests – is internationally governed by ISO 17511:2003 and is a requirement of the original IVD Directive 98/79/EC in the EU. Both the ISO 17511:2003 guideline [*In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control materials*] and the EU Directive expect traceability of values assigned to calibrators and controls but do not literally prescribe the traceability of the end result for the patient. As the ISO 17511:2003 has been in place for 15 years, it is currently under revision in ISO TC 212 WG 2. It can be anticipated that the new ISO 17511 version will solve this problem and will take into account metrological traceability of human samples, which is a big step forward to global harmonization and standardization of test results. Disappointingly, the new IVDR 2017/746 in the EU does not prescribe that metrological traceability extends to the final patient's result, which is a missed opportunity leading to a mismatch with the new, upcoming ISO 17511. It remains to be seen how stakeholders will deal with this topic and what will be the consequences.

The role of professional and scientific societies and academia

Principles on metrological traceability and measurement uncertainty are relatively new in laboratory medicine and gradually started gaining attention since the publication of the EU IVDD 98/79/EC Directive in 1998, which was fully applied in 2003. The metrological traceability concept diffused into the production processes of the IVD-industry, with the help of JCTLM, ISO guidelines such as 17511:2003 and the supportive activities of multiple reference laboratories.

Discussions with professional and scientific societies reveal that basic concepts in metrology and the science of measurement, including traceability and commutability, are generally not an integral part of academic or college curricula. It is obvious that professional societies of, e.g. laboratory medicine, should revise their curricula both in the non-academic and academic setting and add modules that guarantee basic knowledge and backgrounds on the relevance of metrological traceability, measurement uncertainty and commutability of secondary, matrix-based reference materials [10–12] as essential prerequisites for medical test equivalence in a global world.

Landmark textbooks for laboratorians such as the *Tietz Textbook of Clinical Chemistry* should also give sufficient attention to the concepts of metrological traceability, measurement uncertainty and commutability. The *Tietz Textbook of Clinical Chemistry* describes these concepts in more detail since the 6th edition (2017), whereas the explanations were rather limited in the previous versions.

Since 2016, the JCTLM working group on Traceability, Education and Promotion (WG-TEP) produces and promotes educational materials to demonstrate the value of traceability in laboratory medicine as a means to reduce between method variability in the interests of improved clinical outcomes and patient safety (https://www.jctlm.org/about-us/).

The role of IFCC Executive Board and IFCC Scientific Division

Laboratory medicine has to operate in an ever changing context with an increasing number of stakeholders involved with either implementation (ISO 15189:2012) or oversight (new regulations such as the EU IVDR 2017/746) of the metrological traceability concept. In the test development phase, newly discovered biomarkers are

developed to medical tests in case they fulfill unmet clinical needs and contribute to better patient outcome (i.e. the new test should have proven clinical effectiveness). Before medical tests can be put on the market, they should be CE-IVD marked and meet the stringent regulatory requirements of the IVDR. Manufacturing tests that give the right answers by means of traceable test results derived from useful medical tests and keeping pace with new regulatory demands is a challenging task.

The IFCC Scientific Division (SD) has a very important role in international test standardization c.q. harmonization. Although the IFCC SD successfully manages standardization c.q. harmonization projects in six Committees and 17 Working Groups (http://www.ifcc.org/ifcc-scientific-division/; accessed March 18, 2018) [13], the progress made with standardization/harmonization of tests by implementing the metrological traceability concept for single prioritized tests is slow and in volume not more than a drop in the ocean. That is only about 10%–15% of the routinely requested medical tests are well standardized.

The 21st century brings along population aging with increasing healthcare needs and struggles with financial constraints. Consequently, one can wonder whether the traditional approach of standardizing/harmonizing medical tests is sufficiently future proof and adequate. Also, the number of stakeholders involved in the oversight on the safety and effectiveness of medical tests further increases under the new MDR/IVDR as also designated notified bodies, competent authorities and expert laboratories will have a role in the conformity assessment of medical devices and medical tests, before registration and market entry.

IFCC SD should likely reconsider its approach to advance the science of Clinical Chemistry and Laboratory Medicine and the application of the metrological traceability concept to the practice of Clinical Laboratory Science, due to the new ISO 17511, the new MDR 2017/745 and IVDR 2017/746, the generation Y with millennials who have huge expectations, the globalization of the MD and IVD markets and the urgent need for comparable test results in laboratory medicine because of globalization. Accelerated implementation of metrological traceability of test results and improved adoption and adherence of laboratory professionals to metrology concepts likely demands adequate training and revised curricula, educational tools, innovative approaches and collaborations with more clout, e.g. using flexible and e-proof network solutions and standardized approaches encompassing all relevant stakeholders of the traceability chain. To make healthcare in general and laboratory medicine specifically more sustainable, strong coalitions and overarching professional, non-voluntary structures have to be established between laboratory medicine, clinical and scientific societies, IVD manufacturers, reference material providers, metrology institutes and IFCC EB/SD.

The role of individual laboratory professionals

Laboratory professionals are expected to demonstrate clinical leadership by proactively taking their role in the adequate implementation of the metrological traceability concept. To that end, medical laboratory professionals should have deep awareness about the absolute necessity of comparable test results and take coresponsibility for standardizing and harmonizing test results. They should have a clear ambition to contribute to equivalence of test results, according to the calibration hierarchies described in ISO 17511:2003 and its upcoming successor ISO 17511:20XX (under discussion in ISO TC 212 WG2). Laboratory professionals should also take their responsibility as end users of CE-IVDs and *in-house* tests by selecting medical tests that have well-defined, clinically understood measurands; adequate selectivity; correct units; and limited measurement uncertainty as deduced from their performance in EQA schemes. To that end, laboratory professionals should principally select manufacturers who put into service CE-IVDs in line with the latest views on test standardization/harmonization and commutability, and who are transparent regarding their test traceability chains. Laboratory professionals should collectively have the ambition to add value by contributing to equivalent and traceable test results in a global world. Ambitions can only be realized if there are shared promises among all stakeholders of the traceability chain, and if there is constant commitment and proper action. That is all three components of the equation below should be in place.

$$\text{Ambition}_{\text{Test Result Traceability and Equivalence}} = \text{Promises} * \text{Commitment} * \text{Action}$$

Yet, lack of commitment towards the striving for traceability of patients' test results in order to get the right answer for patient management can be deduced from typical decisions taken so far by medical laboratory directors. First, the fact that the majority of medical laboratories still measure plasma creatinine (and pseudochromogens) with non-selective Jaffé methods instead of more selective (enzymatic) methods, notwithstanding the consequences for chronic kidney disease classification, demonstrates the ignorance towards detrimental effects

of unselective tests on patient outcome. Second, notwithstanding the fact that reference measurement systems are in place for, e.g. serum enzymes and/or plasma proteins since the nineties of the past century, there are still manufacturers who bring CE-IVDs on the European market who are not standardized according to the latest insights. Third, laboratory professionals deny basic analytical chemistry principles due to an attitude of conservatism and/or pragmatism; i.e. so far, faulty mass units are used instead of mass-independent SI units for protein analytes that are genetically polymorph and/or very heterogeneous. Fourth, laboratory professionals select tests without knowing the measurands or the biologically active molecular forms. Fifth, laboratory professionals agree with the coexistence of partly tuned reference measurement systems for the same analytes developed by different National Metrology Institutes and Reference Laboratories across the globe (e.g. for cholesterol, HbA_{1c}, C-peptide, etc.). Does our current uncritical behavior towards measurand definition, test selection and metrological traceability principles in contemporary medical laboratories mean that we are more bothered with budgetary constraints and providing efficient laboratory services rather than with getting the right answers by means of traceable test results derived from clinically effective tests that impact patient outcome with an acceptable benefit to harm ratio? Financial constraints are fact of life and should not take us away from the primary goal to improve patient outcome. In order to strengthen and not to further undermine the academic basis of laboratory medicine, the value of laboratory services for patient care, e.g. by standardizing or harmonizing medical tests, should come on the first place.

We conclude that standardization of medical tests in laboratory medicine is running behind as compared to standardization in other branches [8]. The lack of overarching professional structures that tightly engage all stakeholders responsible for implementing the traceability concept and the voluntary participation of members hardly compare to the level of harmonization needs. To ultimately realize the ambition of comparable and traceable medical test results worldwide, shared promises, tight commitment and joint action by all stakeholders are essential. A quantum leap forward towards test standardization/harmonization requires a global approach with matching professional structures.

> 'Knowing is not enough; we must apply.
> Willing is not enough; we must do.'
> Source: JW von Goethe

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