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Metrological Reliability of Medical Devices

E Costa Monteiro¹ and LF Leon²
¹,²Postgraduate Program in Metrology, Pontifical Catholic University of Rio de Janeiro, Brazil

E-mail: beth@puc-rio.br

Abstract. The prominent development of health technologies of the 20th century triggered demands for metrological reliability of physiological measurements comprising physical, chemical and biological quantities, essential to ensure accurate and comparable results of clinical measurements. In the present work, aspects concerning metrological reliability in premarket and postmarket assessments of medical devices are discussed, pointing out challenges to be overcome. In addition, considering the social relevance of the bio-measurements results, Biometrological Principles to be pursued by research and innovation aimed at biomedical applications are proposed, along with the analysis of their contributions to guarantee the innovative health technologies compliance with the main ethical pillars of Bioethics.

1. Introduction

The first discussions concerning traceability in measurements for biosciences occurred during the 20th General Conference on Weights and Measures (CGPM), held in 1995. The theme has been directly addressed in the 21st CGPM (1999), when, recognizing the need of accurate measurements traceable to the International System of Units (SI) in the fields of human health, environmental protection, among others, it was recommended the establishment of an adequate international measurement infrastructure to ensure traceability in biotechnology (11th resolution). Afterwards, in 2000, a Working Group on Bioanalysis (BAWG) was established at the 6th meeting of the Consultative Committee for Amount of Substance: Metrology in Chemistry (CCQM) to address metrological issues in biotechnology and molecular biology. However, to ensure accuracy and comparability of clinical measurement informations, validity not only of biological, but also of physical and chemical measurements are required.

The accelerated evolution of medical devices in the 20th century increased their complexity and capability of measuring physiological parameters essential to diagnosis, prevention, treatment, supporting life and clinical monitoring. On the other hand, the Harvard Medical Practice Study (HMPS), published in 1991, indicated that medical device-related adverse incidents were a common component of hospital care (3.7% of the hospitalizations), with 13.6% of them resulting in death [1].

In the 22nd CGPM (2003), discussions to promote international collaboration led the Consultative Committees to establish strong links, among others, with the World Health Organization (WHO). As a

¹ To whom any correspondence should be addressed.
result, in 2004, WHO Consultation on Global Measurement Standards and their use in the in vitro biological diagnostic field was held to discuss metrological traceability and measurement uncertainty. In 2007, the World Health Assembly adopted its first resolution for health technologies with WHO objectives of improving access and quality, but no approach to metrological reliability was considered.

An important step toward traceability was given in 2009, with the Workshop on “Physiological Quantities and SI Units”, at the BIPM, including discussions concerning WHO International Standards and SI, the new ISO/IEC series 80003 standards “Quantities and units used in physiology” under development, besides the role of Consultative Committees in their domain of activities. However, no emphasis has been placed on traceability for medical devices in the subsequent BIPM meeting for biomedical measurements in 2011 [2], as well as, during the first and second WHO Global Forum on Medical Devices, held in 2011 and 2013, respectively.

The neologism Biometrology was mentioned in the 24th CGPM meeting in 2011, while announcing a BAWG symposium on “Biometrology in support of Clinical Diagnostics”. Considering Biometrology as metrology applied to biosciences, aiming at contributing to the comparability and reproducibility of its wide range of bio-measurements associated, Biometrological Principles should be pursued by research and innovation developments for biomedical application [3].

In the next sessions, metrological reliability in premarket and postmarket assessments of medical devices are discussed and the Principles of Biometrology are presented, along with their contributions to compliance with the main ethical principles of Bioethics.

2. Metrological Reliability of Medical Devices

The earliest initiatives recognizing the need of metrological traceability of health technologies occurred in the area of radiation dosimetry, since the nineteen-sixties [4]. In 1976, the International Atomic Energy Agency (IAEA) together with the WHO established a network of Secondary Standard Dosimetry Laboratories, known as the IAEA/WHO SSDL Network. However, worldwide regulatory systems for medical devices are less developed than those for medicines or vaccines.

In this section, some aspects concerning the metrological reliability, premarket and postmarket evaluation of medical devices are discussed.

2.1. Premarket Evaluation.

Regulatory requirements vary from country to country, but in most of them there is a national authority responsible for implementing medical device regulations. The pre-market approval applied by many of these National Regulatory Agencies requires medical devices to satisfy safety and performance, quality system and labelling requisites, according to a risk-based classification, for manufacturers to launch in the consumer market. Technical standards, published by the International Electrotechnical Commission (IEC) and the International Organization for Standardization (ISO), provide wide-ranging requirements for medical device that are used by regulators for conformity assessment. The 60601 series of standards published by IEC since 1977, contains requirements for medical electrical equipment conformity assessment, with comprehensive general and specific contributions, including requirements for environmentally conscious design (IEC 60601-1-9:2013). Likewise, the International Organization for Standardization (ISO), with a broad range of technical committees targeted at bio-measurement and healthcare issues, contributes for health technology reliability in several aspects that include, for instance, requirements for effective management of the risks associated with the use of medical devices (ISO 14971:2007). However, traceability and uncertainty are not yet emphasized.

The International Organisation of Legal Metrology (OIML) publishes recommendations that may be adopted as national metrological regulations. The OIML metrological characteristics requirements for measuring instruments include the specification of methods and equipment used for conformity assessment and take into account the traceability to SI. In addition, OIML recommendations cover both pre-market and post-market operational life, by means of initial and subsequent verifications,
respectively. Among 130 OIML Recommendations already published, only 17 publications consist of a direct contribution to the healthcare sector.

The Quality by Design (QbD) concept, already used in pharmaceutical industry since 2004 [5], consists of a systematic approach that aims to ensure quality by employing statistical, analytical and risk-management methodology in the design, development and manufacturing [6], being a possible tool to be applied to medical device development as well as design the manufacturing processes to meet predetermined quality, safety, and efficacy requisites [7]. The QbD approach implementation aims at improving speed to market and operating efficiency, as well as reducing product variation and costs at all stages of the process [8]. Although being a premarket approach, the QbD proactive quality system is built to reduce post market potential problems [8]. Metrological traceability requirements, however, do not appear in the QbD concept literature and, therefore, should also be incorporated into the predefined objectives considered in the quality approach.

2.2. Post-market evaluation

Aiming at ensuring reliability of devices in use, many regulatory systems adopt post-market surveillance and vigilance, with adverse event reporting. By disseminating the reported informations, it is possible to reduce the likelihood or prevent repetition of adverse events, or alleviate consequences of such repetition [9].

However, with the very few exceptions of medical devices for which there are technical regulations based on OIML international recommendations, the approaches used by each country during post-market phase do not include preventive periodic evaluations to avoid adverse incidents caused by health technologies in use.

An increasing number of reported adverse incidents added to results found in the literature showing non-compliances in safety and performance evaluations of medical devices in use [3, 10, 11, 12, 13, 14, 15, 16], point out to the insufficiency of surveillance and adverse incident schemes to ensure metrological reliability and guarantee safety of the medical equipment in use, underlining the substantial need for post-market periodic evaluation [3, 10, 16].

Voluntary accreditation of health care facility, including periodic calibrations requirements, is an alternative for reliability of biomedical equipment in use, but the benefit is socially restricted. In 2007, IEC Standard 62353 has been published including test procedures, test methods and test intervals which can be used during post-market phase. Another aspect to be considered in order to ensure access to appropriate medical devices, is the proper management and use of medical equipment by means of the inclusion of clinical engineers with expertise in the field of metrology among the members of hospital staff.

Additional challenges to be overcome are the insufficiency of accredited laboratories enable to perform conformity testing of medical devices, the possible inadequacy between maximum permissible measurement error and the precision required in certain diagnostic and therapeutic procedures, the lack of requisites of measurement uncertainty and metrological traceability among the technical standards requirements and the existing gaps in the availability of national or international measurement standards to establish metrological traceability [3, 11, 16, 17].

3. Principles of Biometrology and contributions to Bioethics

Considering the social relevance in healthcare of the application of the science of measurement to biosciences, able to contribute to an ethical orientation of science and technology and to improve global safety and health, the following “Biometrological Principles” should be pursued by research, development and innovations in life-sciences:

- high accuracy, high precision, traceability to SI units and measurement uncertainty;
- low-cost for production/operation;
- low operational complexity;
- social, environmental and economic sustainability;
• non-invasiveness; and
• innocuousness.

The application of these Biometrological Principles contributes to satisfy the requirements of Bioethics, a recent academic inter-disciplinary field consisting of a systematic investigation of human conduct in the area of life sciences and healthcare, encompassing the study of the ethical and moral implications of new biological discoveries and biomedical advances [18].

The context that led to the emergence of bioethics, in the early 1970s, consisted of the advances provided by the scientific and technological development. Although such advances represent hopes of improving the quality of life, there were clear evidence of contradictions that indicated the need for a responsible analysis aiming at ensuring stability and future well-being of the human species and of life itself on the planet.

A commonly used bioethical analysis model is the "principlism", developed in the late 1970s [19]. In this system, ethical frameworks and procedures consider the Four Principles Approach: beneficence, non-maleficence, respect for autonomy and justice. These principles are key points in the life sciences practice. The observation of these principles contributes to the preservation of human dignity, protects the patient from undesirable results and also the professional implications on ethical or legal sphere in view of complications [19].

In this session, the contribution of the here proposed Principles of Biometry to assure the healthcare technology compliance with the Principles of Bioethics is evaluated by means of the concept association analysis between both principles approaches, structured from the definition and description of the fulfilment of each ethical principle.

The principle of beneficence is characterized by the need to maximise the benefit to the patients. The contribution for an effective and safe medical procedure provided by the biometrological principle of high accuracy, high precision, traceability to SI units and measurement uncertainty, allows for achieving the primary goal of highly accurate diagnosis and therapy. The high accuracy pillar, reducing the uncertainties in the procedures, makes the desired effect preponderate over the foreseeable risks. In addition, the biometrological pillar of low-cost for production and operation guaranties the possibility of same goal expanded to the population at large.

The principle of non-maleficence, universally enshrined by the Hippocratic aphorism: "Primum non nocere", which enforces that the benefit is not accompanied by harm, refers to potential risks. Biometrological Principles concerning accuracy, precision, traceability, measurement uncertainty, sustainability, low operational complexity, non-invasiveness and innocuousness of biomedical procedures and technologies contribute for high performance and safety, reducing the occurrence of adverse events such as misdiagnoses, sequelae of treatments, accidents and iatrogenic injuries, evils still common in biomedical practice [20].

The principle of respect for autonomy implies the allocation of power to the patient to make decisions about medical issues, being the basis for the practice of “informed consent” in the physician/patient transaction regarding health care. Before implementing the medical care plan, it is now commonly accepted that the patient must be given an opportunity to make an informed choice. Although still not considered, this information should include explicit mention of the level of uncertainties associated, an essential database for correct decisions and provision of free and informed consent.

The availability of information concerning reliability of healthcare procedures and techniques, with stated accuracy, precision, metrological traceability to the SI, measurement uncertainty and corresponding adequacy for the given purpose, is a contribution provided by the biometrological principle to promote the autonomous decision of the patient. Awareness of risk-benefit associated with the diagnostic and therapeutic orientation, with disclosed information about quality comparability among bio-measurement results achieved by different establishments, contributes to the decision authority of patients.
Finally, the bioethical principle of Justice establishes the pursuit of equity as a fundamental condition. Adopted in 1946, the Constitution of the World Health Organization marks the first formal demarcation of a right to health in international law. In turn, the WHO Constitution defines the right to health as "the enjoyment of the highest attainable standard of health", including, among other principles of this right, the equitable dissemination of medical knowledge and its benefits. Likewise, Article 25 of the Universal Declaration of Human Rights (1948), the first international declaration of fundamental human rights, everyone has the right to medical care. Many people worldwide suffer because they don’t have access to high quality, affordable health technology with the problem being more acute in low- and middle-income countries. In 2013, WHO published the Compendium of Innovative Health Technologies for Low-Resource Settings, strengthening the necessity to meet the ethical principle of justice.

The complete group of recommended pillars of Biometrology gives contributions to the universal and equitable access of benefits of life sciences advances, and, consequently, to fulfill the principle of justice.

The biometrological pillars of low-cost and low complexity for production and operation will lead to the development of innovations whose benefits can be widely accessed. On the other hand, metrological performance aspects such as accuracy, precision, metrological traceability to the SI and measurement uncertainty disclosure, also contribute to the principle of Justice, through the reduction of expenses with false positives, represented by costs of misguided treatments or the treatments of the damage to health caused by misguided treatments; with false negatives, including costs of treatments of the complications of not early enough diagnosed diseases; and with the repetition of tests.

By means of the respect to the social, environmental and economic sustainability principle, the benefit provided to those who demand health technology innovation, is not accompanied by damage to others, caused by an unfair distribution of risks, for instance, as a result of non-compliance with the sustainability concepts along the manufacturing process.

In conclusion, concerning health technologies, the Principles of Biometrology provide a technical basis for the practical implementation the ethical foundations of bioethics.

4. Conclusion
In the present work, metrological reliability in premarket and postmarket assessments of medical devices were discussed, and, considering the social relevance of the bio-measurements results, Biometrological Principles to be pursued by research and innovation aimed at biomedical applications were proposed, along with their contributions to meet the main ethical pillars of bioethics.

Although the existence of a regulatory control for medical devices comprising pre-market approval and post-market surveillance based on adverse incident reporting; essential requirements to ensure the reliability, as metrological traceability and periodic evaluation of medical devices in use are not requested. In turn, regulations based on OIML recommendations include metrological requirements and preventive evaluations by means of subsequent verifications of devices in use. However, there are only a few recommendations published for health applications. A possible future implementation of QbD approach to medical device research, development, manufacturing and distribution can give contributions to reliability, but metrological traceability requirements have yet to be incorporated in the quality system. Voluntary health care accreditations have been an alternative to promote metrological reliability of medical devices in use, but with restricted access. An appropriate support of accredited laboratories network sufficient to meet the national demands; the lack of traceability and measurement uncertainty requirements comprised in technical standards and regulations; besides unavailability of national or international measurement standards are challenges to be overcome.

The proposed Principles of Biometrology provide a technical basis for practical implementation of ethical requirements, enabling to achieve complete compliance of healthcare technologies with the ethical foundations of bioethics. Their application aims at providing highly accurate diagnosis and therapy; reducing the occurrence of adverse events and expenses with false positives/negatives and
repetition of tests; and contributing to the decision authority of patients and the universal access of benefits of life sciences advances; fully respecting the three aspects of sustainability.

Accuracy, precision, traceability to SI, measurement uncertainty, low-cost, low complexity, full sustainability, non-invasiveness and innocuousness should characterize the innovative health technologies of the new millennium.

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