XXI IMEKO World Congress "Measurement in Research and Industry"
August 30 – September 4, 2015, Prague, Czech Republic

TRANSCRANIAL MAGNETIC STIMULATION CONFORMITY ASSESSMENT

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Abstract – A comparison of the current regulatory status of Transcranial Magnetic Stimulation (TMS) devices in several regions of the world is presented. Examples of differences between countries in compliance assessment and certification are analyzed. Harmonization of terminology and reporting, as discussed in the literature, is taken into account, while critical issues are pointed out, aiming at the advancement of the metrological reliability of the technique.

Keywords: Transcranial Magnetic Stimulation, Metrological Reliability, Safety, Standards, Harmonization

1. INTRODUCTION

Transcranial Magnetic Stimulation (TMS) is a technique in which a rapidly changing current is passed through a small coil which is placed on the scalp [1]. The magnetic field generated by the coil allows getting electric energy across the scalp and skull without the side effects of direct percutaneous electrical stimulation.

The TMS pulses can depolarize neurons and, when repeated pulses are applied, they can modulate cortical excitability, depending on the parameters of stimulation. This has behavioral consequences and therapeutic potential [2]. Typical TMS treatments will use frequencies below 25 Hz [1], which are often called Extremely Low Frequencies (ELF) [3].

TMS is currently approved by Health Surveillance Agencies of Israel, Canada, New Zealand, Brazil, Australia, United States, European Union, among others [2, 4, 5].

Besides the complete and proper stimulus description, aspects regarding device reliability, including safety and performance checks should be satisfactorily considered [6, 7]. To be registered by health agencies, TMS devices must demonstrate compliance with several technical standards. However, up to the present, no particular standard for TMS devices was published.

The World Health Organization (WHO) has addressed the issue of magnetic field safety in several publications [8,9]. Notably, it has encouraged the use of exposure limits defined on the guidelines published by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) [10].

However, institutions in several countries and regions create their own guidelines and standards with differences that range from the terminology used to the actual values of safe limits defined. The WHO has created a database of such standards with the EMF project [11].

The existence of various non harmonized standards implies the possibility of differences in conformity assessment on different regions, sometimes even for the same device.

This work aims at identifying information relevant to the ELF range for TMS devices, allowing for the suggestion of some key aspects for a future particular TMS standard, considering the harmonized standard framework suggested by WHO [8] and the harmonized reporting framework and terminology discussed in recent literature [12, 13]. Several examples of non harmonized standards and conformity assessment for TMS devices are analyzed in this paper. Furthermore, based on published technical standards and guidelines, this work targets to identify the most relevant documents to be considered in the case of a future development of a technical standard with specific requirements for TMS equipment.

2. TECHNICAL GUIDANCE AND REGULATORY DOCUMENTS FOR TMS

Technical standards, published by the International Electrotechnical Commission (IEC) and the International Organization for Standardization (ISO), provide wide-ranging requirements for medical devices that are used by regulators for conformity assessment.

The IEC 60601 series, promulgated by the IEC, features several aspects pertaining to the basic safety and essential performance of electrical devices for medical electrical (ME) devices. As such, they aim to specify general requirements and to serve as a basis to particular standards [15].

Notably, collateral standards specify general requirements for basic safety and essential performance applicable to a subgroup of ME equipment or to a specific characteristic of all ME equipment not addressed on the more general IEC 60601-1 document. These can be identified by codes using the format 60601-1-X.

Furthermore, particular standards (codes with format 60601-2-X) may modify, replace or delete requirements contained in the IEC 60601-1 standard, as appropriate for a given particular type of ME equipment.

Up to this point, there is no IEC particular standard concerning TMS devices [12]. However, there are several

compliance evaluations in which either IEC standards, or national/regional deviations based on those, such as the UL/CSA/EN60601-1, were explicitly applied.

In order to analyse the harmonization of conformity assessment for TMS devices, documents and certificates regarding six TMS equipments from several locations (United States of America, Brazil, Russia and Europe) were analysed.

Among the three TMS equipments, TMS_A, TMS_B and TMS_C, approved by the Food and Drugs Administration (FDA), compliance to the IEC 60601-1 was observed in TMS_A and TMS_B. TMS_C was complying instead to the national/regional equivalents UL/CSA/EN60601-1. TMS_A and TMS_B also comply with the collateral standard IEC 60601-1-2 and to a guidance document by the FDA rTMS guidance, with TMS_B further complying to the ETSI EN 301 489-1 V 1.8 standard, which deals with electromagnetic compatibility for radiofrequencies.

The FDA rTMS guidance [13] is a Special Control Guidance for repetitive Transcranial Magnetic Stimulation (rTMS) Systems issued in 2011. This document was developed to support the classification of rTMS devices for the treatment of major depressive disorder into Class II (special controls). The requirements there provided, associated with general controls, are expected to reasonably assure safety and effectiveness of the rTMS systems for the treatment of major depressive disorder in patients who have failed to achieve satisfactory improvement from at least one prior antidepressant medication at or above the minimal effective those and duration in the current episode, and who are currently not on any antidepressant therapy.

Devices TMS_B and TMS_C were evaluated regarding their conformity to this document, while device TMS_A wasn't, probably because it predates the guidance.

In Russia, two certificates for TMS_D state compliance to a series of Russian standards and documents.

The first certificate for TMS_D cited the ГОСТ Р 50444-1992, a standard regarding general specifications for Medical instruments, apparatus and equipments; and the three following having corresponding comparable IEC standards of the 60601 family: ГОСТ Р 50267.0-92, ГОСТ Р 50267.0.2-2005, ГОСТ Р МЭК 60601-1-1-2007.

A second certificate of compliance for TMS_D mentions the documents МСанПиН 001-96, СанПиН 2.2.4.1191-03, ГН 2.1.8/2.2.4.2262-07 and ГН 2.3.3.972-00. Notably the first two are sanitary regulations with limits for the exposure to magnetic fields. They are part of the WHO EMF project database for regulatory documents concerning electromagnetic field safety, for Russia. They deal respectively with Electromagnetic fields in occupational environment and with permissible values for physical factors during use of domestic articles.

The limits defined at СанПиН 2.2.4.1191-03 encompass the range of low frequency fields relevant to TMS devices (0-25 Hz, approximately). The requirements, however, are different to the limits for the same frequencies given by issued ICNIRP guidelines.

Furthermore, this second certificate of compliance for TMS_D makes extra suggestions for the safe use of the equipment, and mentions the safe distance operators should maintain from the TMS coils. Namely, the distance mentioned is 70 cm.

In Brazil, the TMS_D is registered by the national agency of health surveillance and assessed regarding its conformity to several IEC standards: NBR IEC 60601-1, NBR IEC 60601-1-2, IEC 60601-1-4 and IEC 60601-2-10. The latter is a particular standard for neuromuscular stimulation devices. While on one hand there are no particular standards for TMS devices yet, and this can be seen as an approximation attempt, on the other hand the scope of this standard states that it does not apply to devices and systems intended to stimulation of the brain or neurological research.

This further hints at the need for a particular standard for these devices.

The TMS_E and TMS_F, present stated compliance to the Council Directive 93/42/EEC, often cited as the European Medical Device Directive (MDD). This directive applies to medical devices and accessories, and as stated on its Article 2, member states of the European Union shall take all necessary steps to ensure that devices may be placed on the market and/or put into service only if they comply with the requirements laid down on that directive [16].

Furthermore, as stated on Article 5 of MDD, compliance is presumed for devices in conformity with relevant national standards adopted pursuant to the harmonized standards, the references of which have been published in the Official Journal of the European Communities.

Notably, the IEC 60601 series and particular EN equivalent standards appear among the list of harmonized standards considered, on the Official Journal of the European Communities.

For products to obtain the CE marking necessary to be put into the European market, they must comply to the MDD.

Furthermore, in the brochure for TMS_E is stated that it complies with the Canadian Medical Device Regulation, the ISO 13485:2003 standard and the US 21 CFR 820.

3. EXPOSURE LIMITS

The International Comission on Non Ionizing Radiation Protection (ICNIRP) has issued guidelines for protection against non ionizing radiation [10, 17, 18]. The 1998 guideline has requirements for a frequency range spanning from 0 Hz to 3 GHz, with the 2010 and 2014 guidelines revising the recommendations for 1 Hz to 1 kHz and static fields, respectively. In 2003 there was also an additional document with information for measurement procedures regarding testing compliance with the 1998 guideline [19].

Considering that TMS is a technique which involves delivering a dose of non ionizing radiation, several aspects are raised regarding exposure and associated definitions and concepts.

The ICNIRP guidelines can be used as a basis to determine which distances would be within occupational safe limits considering the exposure to the fields emitted by the TMS device, for operators [20, 21].

In [20], by means of measurements performed with a calibrated coil, following the 2003 ICNIRP guidance, a safe distance of 70 cm was indicated. In [21], using a phantom to study the exposure, the identified safe distance was 110 cm. It is worth noting that these two publications did not consider the same brand and model of TMS device for their studies.

4. REPORTING FRAMEWORK

Another aspect relevant to the discussion of TMS safety is that of a harmonization of terminology and the formulation of a consistent reporting framework. The idea of discussing which parameters fully characterize the use of TMS was already present in the publication of safety recommendations stated by an international consensus [2].

The publications that can be used as a basis for the harmonization of relevant terminology and definitions for this matter, if and when a particular standard for TMS devices arise, are discussed in [12].

Notably, in [14] a complete list of all relevant quantities intending to fully and satisfactorily define the dosage provided in a TMS application is provided.

5. DISCUSSION

Over time, the ideal scenario would be that a unified, harmonized particular standard for TMS devices could arise, to be used along with the more general documents. It is worth noting that the FDA rTMS guidance document has several characteristics that could make a good candidate as a basis for this future standard.

The single document to mention the safe distance an operator should maintain from a TMS device is one of the Russian compliance certificates for TMS_D, adopting 70 cm as safe distance. This is most likely based on the study described in [20], which, in turn, is based on only one brand and model of TMS device, and on the 1998 and 2003 ICNIRP guidelines [10,19]. However, both the model and brand of the device certified in this case were different to the one studied in [20], and Russian documents follow the ELF frequencies set by СанПиН 2.2.4.1191-03, with different limits as those set by ICNIRP. This fact prompts the need for more studies to confirm this minimum safe distance according to the specificities of the various devices available.

As efforts to unify exposure and emission limits advance (such as those by the WHO EMF Project or similar initiatives), the relevant limits could also be added to the safety and performance requirements of the TMS devices, either on the same particular standard or in a more general standard concerning exposure and emission as a whole.

An analysis of the “Device Description” section of the FDA rTMS guidance shows that all the parameters relevant to characterizing the stimulus waveform and coil configuration, as mentioned in [14] are considered. This indicates that the proposed method of characterization given by this FDA guidance could be used, a priori, as a basis for future standards.

However, uncertainty of measurements are not mentioned in FDA rTMS guidance. This document seems to address this parameter by suggesting the representation of an interval of possible values for some quantities (namely Pulse width, Frequency, Pulse train duration and Inter-train interval) based on the respective accuracies. It is worth noting that according to the International Vocabulary of Metrology (VIM) [22], note 1 of reference number 2.13, accuracy is not a quantity and is not given a numerical value. The FDA document, thus, is most likely referring to either the device’s resolution, the measurement error, or measurement uncertainty associated with those quantities.

It would possibly be very beneficial to extend this reasoning to all other quantities involved in this problem, especially the magnetic field intensities of the output, and to use a representation of the associated uncertainties as per the Guide to expression of Uncertainty in measurement [23], while also respecting the VIM terminology, to assure harmonization and avoid ambiguities. This would greatly help in future studies concerning the effect of uncertainties on matters of exposure to non ionizing radiations and dosage definition, or comparisons with guidelines such as the ICNIRP ones.

The IEC 60601-2-10 standard used on the Brazilian case for TMS_D conformity assessment, could also be considered for possible contribuitions concerning its structure and possible recommendation of a measuring parameter also useful for evaluation of TMS devices.

6. CONCLUSIONS

The results of the present overview concerning the most relevant technical documents used by regulators for conformity assessment of Transcranial Magnetic Stimulation, evaluated for six different TMS equipments used in four regions of the world, indicated a great variability of adopted requirements. This lack of harmonization in conformity assessment emphasizes the need for an international particular standard for these devices, with appropriate requirements for TMS devices.

Technical documents such as FDA rTMS guidance, IEC 60601-2-10, as well as the Russian standards and aspects already discussed in literature should be considered in a future possible international standard with specific parameters. The inclusion of the relevant exposure limits requirements could also be considered to the safety and performance requirements of the TMS devices. However, among other aspects, further studies to analyse the completeness of measuring requirements considering the differences of the specificities of the equipments, such as coil configuration, must be performed in order to be addressed in a future particular standard for TMS.

ACKNOWLEDGMENTS

We thank the Brazilian funding agency CNPq for financial support.

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