Safety and certification of clinical electroporators

Aleksandra Cvetkoska, Damijan Miklavčič, Matej Reberšek

University of Ljubljana, Faculty of Electrical Engineering, Tržaška 25, 1000 Ljubljana, Slovenija
E-mail: aleksandra.cvetkoska@fe.uni-lj.si

Abstract. *"Quality means doing it right when no one is looking." – Henry Ford. Not many of us are aware of what it takes to develop a device. Developing a device can be easy, but doing it by standards and regulations, i.e. assuring safety, quality and efficiency, can be quite challenging. Getting approval for selling the device on the market and having a post-market surveillance takes additional effort. This is especially demanding for manufacturers when developing and manufacturing a medical device where patient's safety comes at first place.*

In this paper we present some of the requirements with an emphasis on safety of clinical electroporators, standards to be considered and medical regulation to be followed in order to get approval for selling a clinical electroporator on the European market.

1 Introduction

The phenomenon termed electroporation stands for the event where cells or tissues are exposed to high-voltage (HV), short-duration pulses which increase the plasma membrane permeability. Thus, transmembrane transport of molecules that are otherwise unable to cross the membrane is enabled [1]. The pulses are generated by a pulse power generator known as an electroporator and delivered to the load via electrodes.

Currently, electroporation is widely used for different applications in biomedicine, biotechnology [2], food technology and environmental science [3]. Electroporation is already a well-established method in medicine, where combined with administration of otherwise low-permanent chemotherapeutic drugs to tumor cells, brings a new way for efficient antitumor therapy called electrochemotherapy (ECT) [4]. Electroporation in medicine [5] is also used as a method for ablation of malignant tissue using nonthermal irreversible electroporation (IRE) [6]. Moreover, it is applied in the field of gene electrotransfer (GET) for delivering DNA molecules to cells as a non-viral gene delivery method. In all of these cases, HV electroporators for pulse generation are used which should not introduce a potential risk for adverse event both for the patient and operator or interfere with other (life-supporting) devices. Therefore, electroporators used in clinical environment are considered to be medical devices and thus, patient and operator safety has to be ensured under both normal and single-fault conditions. Furthermore, clinical electroporators, as medical devices are obligated to meet medical standards and follow requirements determined by local medical regulations [7], e.g. in US they are subject to Food and Drug Administration (FDA) and in Europe, they fall under the new Medical Device Regulation (MDR) 2017/745 which is intended to harmonize the laws related to medical devices in order to get approval for selling the device on the market – get a certification mark (CE). This regulation is meant to ensure medical device's safety and efficacy and it will be fully applied in May 2020. In United Stated, FDA is responsible for regulating companies who manufacture, repackage, relabel and/or import medical devices.

2 Safety as part of the development

To help verify the safety of medical devices, electrical safety standards have been established in the United States (US), European countries and other parts of the world. Standards can differ in criteria, measurements and protocols. The International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC) provide standards worldwide, including standards for medical electrical equipment. The first medical standard for medical electrical equipment, IEC 60601 was published in 1977 which is a family of technical standards whose scope covers the safety, essential performance and electromagnetic compatibility of medical electrical equipment and systems. As of 2011 it consists of a general standard for medical electrical equipment, 10 collateral standards and about 60 particular standards. Collateral standards define the general requirements for certain aspects of safety and performance. Particular standards define requirements for specific products or specific measurements built into products and explain how to simplify implementation of the general standard to a particular device type.

In spite of the 60 particular standards, a particular standard for clinical electroporators currently, does not exist. Therefore, it will be necessary to define additional rules for safe manufacturing and use of clinical electroporators as relatively new medical devices, in addition to those defined by ISO and EN/IEC standards. Safety for all medical devices have to be predominantly considered according to EN 60601-1:2006/A1:2013 in EU or IEC 60601-1:2005/A1:2012 in US. Thus, we point to the most important safety key factors for clinical electroporators considering the general standard for basic safety and essential performance for medical electrical equipment EN 60601-1:2006/A1:2013.

2.1 Voltage and energy limitations

As clinical electroporators are high-voltage (HV) medical devices, according to the standard EN 60601-1:2006/A1:2013, protection against electric

shocks must be provided and thus, voltage and energy should be limited. The voltage to earth or to other accessible parts shall not exceed 42.4 V peak AC (~30 V RMS) or 60 V DC in normal condition or in single fault condition. The DC limit of 60 V applies to DC with not more than 10 % peak-to-peak ripple. If the ripple exceeds that amount, the 42.4 V peak limit applies. The energy dissipated shall not exceed 240 W for longer than 60 s, or the stored energy available shall not exceed 20 J at a potential of 2 V or more.

2.2 Insulation and leakage currents

Clinical electroporators are medical devices type BF (Body Floating), fitted in protection class II medical devices. The applied part is isolated from all other parts of the equipment to such a degree that the leakage current flowing through a patient to ground does not exceed the allowable level, even when the voltage between the applied part and ground equals to 110% of the rated power line voltage. This means that the protection will not rely only on basic insulation (only on device's enclosure), but it will include an additional safety precaution such as double or reinforced insulation (Figure 1). Insulation is not only defined as a solid insulating material applied to a circuit, but also to spacing that establishes creepage distances and air clearance between parts and should protect both from electric shock and ensure that the design is fail-safe. As clinical electroporators are high-voltage systems, reinforced insulation has to be used. Reinforced insulation (Figure 1.b) combines the equivalent of double isolation (Figure 1.a) into one barrier and provides reduced power consumption and increased efficiency while maintaining the leakage currents within the limitation allowed by the standard EN 60601-1:2006/A1:2013 (Table 1 as stated in the standard, section 8.7.3, Table 3).

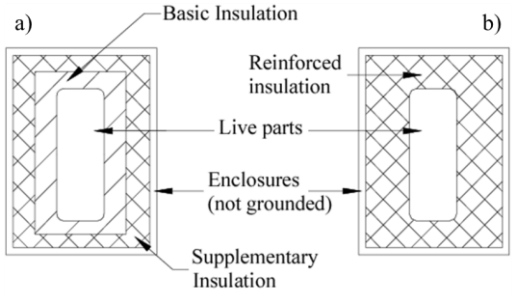

Figure 1. a) basic + supplementary = double insulation; b) reinforced insulation

Leakage current can be resistive or capacitive. The reason for resistive current leakages is that no insulation material is a perfect insulator and all insulators do conduct electricity to some degree. On the other hand, capacitive leakage currents are caused by alternating currents passing through capacitances in transformers and between conductors. Leakage currents normally occur in the power cords and other components of the device and they are conducted away through the earth wire, so they do not affect the patient. The problem occurs when broken earth wires cause the leakage current to be conducted to the patient through the medical device. This is the most common electrical fault in hospitals and precautions have to be taken.

Table 1. Leakage currents limitations under normal conditions (NC) and single fault conditions (SFC) for type BF medical device

Leakage current (µA)	NC	SFC
Earth leakage current (mA)	5	10
Touch current (µA)	100	500
Patient leakage current AC (µA)	100	500
Patient leakage current DC (µA)	10	50
Patient leakage current on applied part (µA)	-	5000
Patient auxiliary current AC (µA)	100	500
Patient auxiliary current DC (µA)	10	50

Clinical electroporators must be designed with such features that prevent generating dangerous leakage currents and propagating leakage currents from other faulty devices. One way to minimize the leakage currents is by using galvanic separation between primary circuit and applied part. This protective separation can be made in the power supply circuit or at the output of the device. In this way, sensitive circuity can be isolated from high-voltage environments using optocoupler-based (for data signals) or transformer-based (for power signals) approaches.

2.3 Creepage distances and air clearances

However, in order to comply with the EN 60601-1:2006/A1:2013 insulation requirements, clinical electroporators must also meet component-creepage, clearance and test-voltage requirements depending on the insulation level of the interface. Creepage distance is defined as the shortest distance along the surface of the insulating material between two conductive parts and the air clearance is the shortest distance through air between two conductive parts (Figure 2).

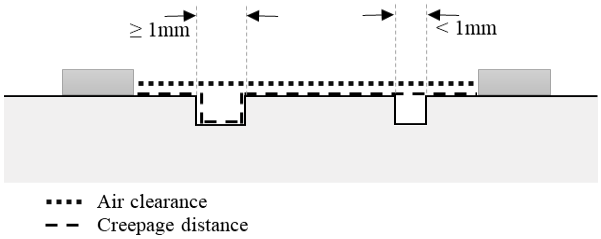

Figure 2. Air clearance and Creepage distance

The minimum separation distance between elements of two parts is determined by the working voltage between parts as well as by the insulation type (basic or

reinforced) required to afford protection against electrical shock. (Table 2 as stated in the standard EN 60601-1:2006/A1:2013 section 8.9.1.15, Table 12).

Table 2. Minimum creepage distances and air clearances providing means of patient protection for reinforced insulation

Working Voltage (V_{DC})	Working Voltage (V_{RMS})	Creepage (mm)	Air Clearance (mm)
85	60	4.6	2.4
177	125	6	3.2
354	250	8	5
566	400	12	7
707	500	16	9
934	660	21	12
1061	750	24	13

2.4 Electromagnetic Compatibility (EMC) and Electromagnetic Interference (EMI)

To meet EMC requirements presented in the collateral standard EN 60601-1-2:2015 – Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic disturbances – Requirements and tests, clinical electroporators must be immune to electrostatic discharge, radio-frequency (RF) interference from nearby transmitters and other sources and power disturbances that can cause device malfunctions. In addition to these requirements, the electroporator's own emissions, through either conduction or radiation, may interfere with communications sources or other equipment and thus, should be minimal. As stated in the standard, the devices must have electrostatic discharge protection as high as 8 kV through air and 6 kV on contact. They must be immune at frequencies of 80 MHz to 2.7 GHz and 3 V/m of RF electromagnetic field for non-life supporting equipment (10 V/m for life-supporting equipment). The device has to be tested according to these tests and prove that it will not have any component failures, changes in programmable parameters, resetting to factory defaults, changes in operating modes or false alarms.

3 Medical Device Regulation 2017/745 and standards to be considered

Medical Device Regulation 2017/745 (MDR) is composed of 17 Annexes and it is intended to harmonize the laws related to medical devices within the European Union [8]. This regulation is meant to ensure medical device's safety and efficacy and it will be fully applied in May 2020. Each manufacturer of medical devices must submit technical documentation providing evidence of conformity with the Regulation in order to obtain certification mark (CE) for EU. During the development and manufacturing phase of the clinical electroporator it is important to be acquainted with the MDR by studying the technical documentation needed to obtain a CE mark, setting the general requirements regarding design and construction, providing the necessary standards and presenting relevant evidence that all the requirements are met by standards. The new regulation is more challenging for the manufacturers as there are more requirements that need to be considered, different classification system, pre-clinical and clinical testing to be done and more documentation to be prepared. For all medical devices, MDR provides detailed instruction on the minimum content and the necessary elements to be included in the technical documentation which is clearly stated in Annexes II and III of the MDR (Table 3). Annex VIII of the MDR determines the device's classification to be I, IIa, IIb or III. Classification is risk-based which means that the higher the risk the medical device introduces to the patient, the higher the class will be. Clinical electroporator is considered to be an active, therapeutic and high-voltage medical device which is classified as class IIb medical device by Annex VIII of the MDR. The pulses are delivered to the tissue by electrodes as a necessary but separate medical device. If the electrodes are placed on the patient's skin, they are considered to be non-invasive medical accessories, classified as class I. If the electrodes are intended to be placed inside the patient's body, they are considered to be invasive medical accessories, classified as class III.

Table 3. Technical documentation's content

	(a) Annex II – Technical Documentation:
1.	Device description and specification, including variants and accessories
	1.1 Device description and specification
	1.2 Reference to previous and similar generations of the device
2.	Information to be supplied by the manufacturer
3.	Design and manufacturing information
4.	General safety and performance requirements
5.	Benefit – Risk analysis and risk management
6.	Product verification and validation
	6.1 Pre-clinical and clinical data
	6.2 Additional information required in specific cases
	(b) Annex III – Technical Documentation on Post-Market Surveillance:
1.	The Post-Market Surveillance Plan
2.	Periodic Safety Update Report
3.	Post-Market Surveillance Report

Within technical documentation, manufactures must present suitable evidence to show that the device fulfills the requirements detailed in Annex I in consideration with the related standards. At the beginning of the process, quality management system has to be implemented in compliance with the standard EN ISO 13485:2016/AC:2016. Emphasis is put on the safety of the patient due to the high voltage pulse generator that should not be hazardous for patients as well as for operators. In this respect, clinical electroporators should meet the standard for risk analysis EN ISO 14971:2012 and the general standard for basic safety and essential performance of medical devices EN 60601-1:2006/A1:2013 to prove that the

benefits for the patient always outweigh the risks incorporated with the device. Clinical electroporators must also meet collateral standards such as EN 60601-1-2:2015 for electromagnetic disturbances and EN 60601-1-6:2010 for usability, which has to be followed by EN ISO 62366:2008. Since clinical electroporators are programmable medical devices, standards, such as EN ISO 62304:2006/AC:2008 and IEC 80002-1:2009 for medical device software should be considered. For battery powered clinical electroporators the standard for safety requirements for secondary cells and batteries, IEC 62311:2019 should be taken into consideration. The electrodes are medical devices which will be used as accessories together with the clinical electroporator and are in direct contact with the patient's skin. However, certification should be done separately. As stated in EN 60601-1:2006/A1:2013, medical electrical equipment or system and their parts or accessories intended to come into direct or indirect contact with biological tissues, cells or body fluids shall be assessed and documented according to the guidance and principles given in the ISO 10993 series of standards. Therefore, the most important standards to be considered are the standards for biological evaluation of medical devices EN ISO 10993:2009 (parts: -1, -5 and -10) as non-invasive or invasive electrodes are considered to be medical devices to be put on patient's skin or inside the patient's body respectively.

4 Conclusions

Electrical safety is a topic of very high importance in medical device quality assurance. Applying the principles and requirements described by the safety standards is important and should be considered from the beginning of the design for every medical electronic device. It is important for the device to pass all electrical safety tests in order to be accepted for further testing by relevant standards and certification. Medical device regulation and applicable standards are there to help the designer develop a device that will provide benefits to the patient while reducing foreseeable risks.

When it comes to electrical safety and certification of a clinical electroporator currently, we have to consider all previously mentioned standards and medical device regulation to assure safety of the device, since a particular standard for clinical electroporator does not exist. We have to make sure to choose the proper insulation, limit the leakage currents, voltage and energy within the limits allowed by the standard EN 60601-1:2006/A1:2013, meet the requirements for electromagnetic compatibility presented in the collateral standard EN 60601-1-2:2015, follow all device's relevant standards and consider the fault operations while maintaining quality assurance, efficiency and smooth operation of the device. The manufacturer has to carry out the conformity assessment, prepare the required technical documentation to include the elements set out in Annexes II and III and continuously ensure that the technical documentation is up to date.

As the clinical electroporators market grows, having a particular standard can speed up this process and enable the harmonization of all commercial, certified clinical electroporators to improve the safety, quality and efficiency of these devices in order to provide even more effective treatment.

Acknowledgements

This study was supported by the Slovenian Research Agency (ARRS) (MRIC UL IP-0510, P2-0249). The investment is co-financed by the Republic of Slovenia and the European Regional Development Fund.

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