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MEDICAL DEVICE REGULATORY REQUIREMENTS

Report

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AUTHORS

Name	Organization
Sandra Balseiro	IPN
Ana Brito	IPN
João Quintas	IPN
Margarida Realinho	IPN

PEER REVIEWERS

Name	Organization
Catarina Ruano	NIV
Cristiana Fernandes	CFRT

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Executive Summary

This document summarizes the main information and considerations that govern the regulatory aspects of ORACIA. The work carried out in “Task 1.1 – Regulatory pathway” will continue throughout the majority of the timeline of the project to allow the consortium to proceed with due diligence in terms of ethical and legal clearance as needed.

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1. Introduction

Aphasia is an acquired disorder of language that affects an individual's comprehension and expression across the range of modes of communication (listening, reading, speaking, writing, gesture and calculation). This is common in older adult patients in the context of vascular or neurodegenerative disorders.

ORACIA will develop a solution to support home and technology-based rehabilitation for people with Aphasia. The main objective and technical advance will be the development of an Information and Communication Technology-based (ICT-based) platform that will promote the extension of the rehabilitation intervention performed in-clinic to the community setting (e.g., patient home, home care center).

ORACIA addresses rehabilitation in a holistic perspective (speech and language therapy, physical therapy and cognitive training) with an intensive, high-repetition, task-oriented and task-specific therapy approach.

Thus, given that ORACIA has a well-defined clinical purpose, namely: "rehabilitation for people with Aphasia", and that its mode of action does not use pharmacological, immunological or metabolic means, ORACIA qualifies as a medical device. Therefore, to enter the European Union (EU) market, ORACIA needs to comply with the requirements of the Regulation EU 2017/745 (Medical Devices Regulation - MDR) in order to obtain the CE marking. The regulatory framework of ORACIA will be explored in the following sections.

2. Medical devices regulation

2.1. Regulatory

"Medical devices have a fundamental role in saving lives by providing innovative healthcare solutions for the diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease. The EU has a competitive and innovative medical devices sector, characterised by the active role of small and medium-sized enterprises. It is supported by a regulatory framework that aims to ensure the smooth functioning of the internal market, taking as a base a high level of health protection for patients and users. The medical devices sector is essential to the provision of healthcare to citizens and is an important player in both the European and global economy." (Source: https://ec.europa.eu/health/md_sector/overview_en).

Medical devices (MDs) are subject to regulation to guarantee their safety and effectiveness. It's not unexpected that the MD regulation, as well as the bodies involved in that same regulation, differ from one geographical area to another. For example, in the United States, MDs are regulated by the Food and Drug Administration (FDA), in Brazil by the Brazilian Health Regulatory Agency (Anvisa), in Canada by Health Canada and in Japan by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). It is therefore crucial that all individuals and organizations involved in the design, development and manufacture of medical devices are aware of these differences and follow the regulations of the territories where they aim to sell these devices.

Specifically, all MDs marketed in the European Union, with the exception of *in vitro* diagnostic medical devices (IVDs), shall comply with the requirements of the Regulation EU 2017/745 (MDR).

According to the MDR, medical device "means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability;
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state;
- providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body."

It is necessary to clarify that software itself, when specifically intended to be used for one or more of the medical purposes described above, qualifies as a medical device.

ORACIA will develop a solution to support home and technology-based rehabilitation for people with Aphasia. Specifically, it will be developed an ICT-based platform to support home and technology-based rehabilitation for people suffering from this condition. This solution will promote the extension

of the rehabilitation intervention performed in-clinic to the community setting (e.g., patient home, home care center). ORACIA addresses rehabilitation in a holistic perspective (speech and language therapy, physical therapy and cognitive training) with an intensive, high-repetition, task-oriented and task-specific therapy approach.

Aphasia is an acquired disorder of language that affects an individual's comprehension and expression across a range of modes of communication (listening, reading, speaking, writing, gesture and calculation). It is common in older adult patients in the context of vascular or neurodegenerative disorders.

Therefore, based on the definition of a medical device presented in the MDR, as well as the intended use and mode of action of ORACIA, it can be concluded that ORACIA qualifies as a medical device. This means that, in order to be marketed in the EU, ORACIA must bear the CE mark, and for that, it must comply with the applicable requirements of the MDR.

A question arises: Is it enough to comply with the MDR to commercialize medical devices, and in particular ORACIA, in the EU market?

The answer is "**NO**". To bring a MD to market in the EU it is necessary to be aware of the MDR, as well other applicable Union harmonisation legislation and related guides. In this context, for example, in addition to MDR, some ISO/IEC standards, Medical Device Coordination Groups (MDCGs) and Medical Device guidance documents (MEDDEVs) are also relevant when bringing MDs to market in EU.

These other standards and guides provide a set of technical specifications and orientations on the design, manufacture, risk assessment, testing, and other lifecycle stages of medical devices, and can help ensure that MDs meet the requirements set forth by the MDR. Regarding the ORACIA project, it is imperative to consider the standards and guidelines listed in Table 1.

TABLE 1 - STANDARDS AND GUIDES APPLICABLE TO ORACIA

Subject / Area	Applicable standards or guides
Quality Management System (QMS)	ISO 13485:2016 - Medical Devices – Quality management systems – Requirements for regulatory purposes ISO/TR 80002-2:2017 – Medical device software — Part 2: Validation of software for medical device quality systems
Risk Management	ISO 14971:2019 - Medical Devices – Application of risk management to medical devices ISO/TR 24971:2020 – Medical devices — Guidance on the application of ISO 14971 IEC/TR 80002-1:2009 – Medical device software — Part 1: Guidance on the application of ISO 14971 to medical device software
Usability	IEC 62366-1:2015 - "Medical Devices - Application of usability engineering to medical devices"

Software Development and Validation	IEC 62304:2006 – Medical device software — Software life cycle processes IEC 82304-1:2016 - Health software — General requirements for product safety
Cybersecurity	IEC 62443-4-1:2018 – Security for industrial automation and control systems - Part 4-1: Secure product development lifecycle requirements IEC 62443-4-2:2018 – Security for industrial automation and control systems, Part 4-2: Technical security requirements for IACS components IEC 81001-5-1:2021 – Health software and health IT systems safety, effectiveness and security — Part 5-1: Security — Activities in the product life cycle MDCG 2019-16 Rev.1 – Guidance on Cybersecurity for medical devices
Electrical Safety	IEC 60601-1-11:2015 – Medical electrical equipment — Part 1-11: General requirements for basic safety and essential performance — Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment
Clinical Investigation	ISO 14155:2020 - Clinical investigation of medical devices for human subjects – Good clinical practice

It must be considered that this list is not closed. Specifically, concerning MDCG and MEDDEV, it is advisable to frequently visit the pages "MDR guidance documents" and "MEDDEV Guidance List", respectively, where new and updated documents are continually published.

2.2. CE Marking

CE marking is a mandatory conformity mark on certain products placed on the market within the European Economic Area (EEA). It indicates that the product is in compliance with the relevant EU legislation. The CE marking is a symbol that the product has been evaluated and meets the necessary standards, and allows for free movement of goods within the EEA. CE marking is mandatory for a wide range of products, including electronics, machinery, medical devices, and toys.

In the case of medical devices, and according to MDR: "'CE marking of conformity' or 'CE marking' means a marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in this Regulation and other applicable Union harmonisation legislation providing for its affixing".

The following diagram (Figure 1) summarizes the main steps required to obtain CE marking for a medical device, which involve:

1 – Qualification the product as a medical device, according to the definition presented in the MDR (see previous section);

2 – MD classification based on its risk level (classes I, IIa, IIb, and III) using the MDR annex VIII classification rules;

3 – General Safety and Performance Requirements (GSPR) checklist elaboration;

4 – Identification of applicable standards and guidelines (see previous section);

5 – Testing and verification of the MD as applicable, its risk class and typology;

6 – Performing the Clinical Evaluation, including, if applicable, a Clinical Investigation;

7 – Performing the Risk evaluation;

8 – Technical Documentation compilation and Quality Management System (QMS) implementation.

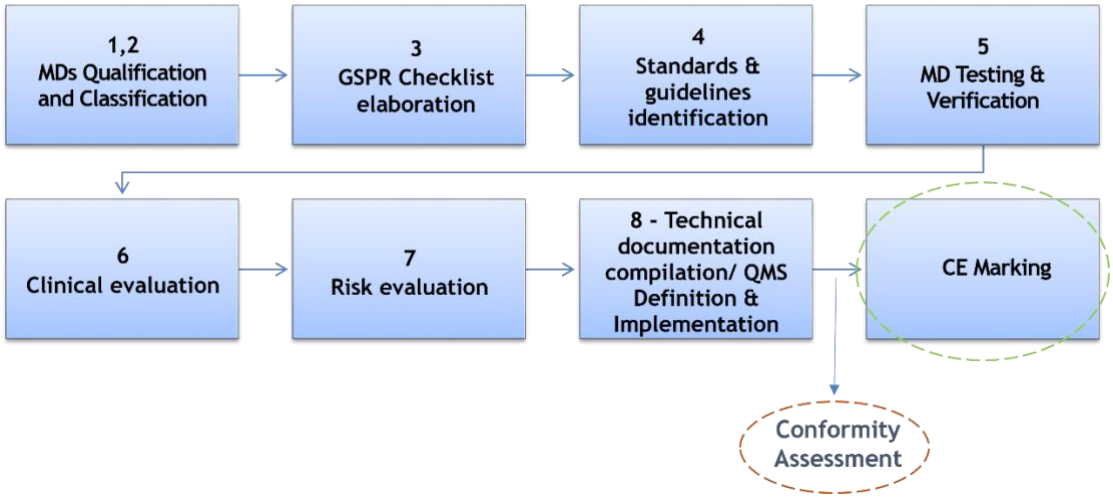

FIGURE 1- ROADMAP TO OBTAIN CE MARKING FOR MEDICAL DEVICES

Once all the preceding steps (1 to 8) have been accomplished, a conformity assessment must be conducted to demonstrate compliance with the MDR requirements. Affixing the CE marking to the medical device can only take place after a successful conformity assessment.

There are different procedures to demonstrate conformity with the MDR. These assessment procedures differ for different medical device risk classes. It is therefore important to correctly classify the medical device.

Regarding ORACIA, its classification will depend on the tools/functionalities that it will provide. If the present MD only allows patients and caregivers access to rehabilitation exercises, then according to rules 11 and 13 of annex VIII of the MDR, ORACIA will be a class I medical device. If, on the other hand, the device gives information to the patient or caregiver, which can be used to readjust therapy, according to the same rules (11 and 13), the device is classified as IIa.

For Class I device, with exemption of Class I sterile, reusable and with measurement functions, the involvement of the notified body is not required, and the device can be placed on the market based on the self-Declaration of Conformity (MDR - Annex IV) that is issued by the manufacturer, in addition to Maintenance of Technical Documentation according to Annex II & III (Figure 2).

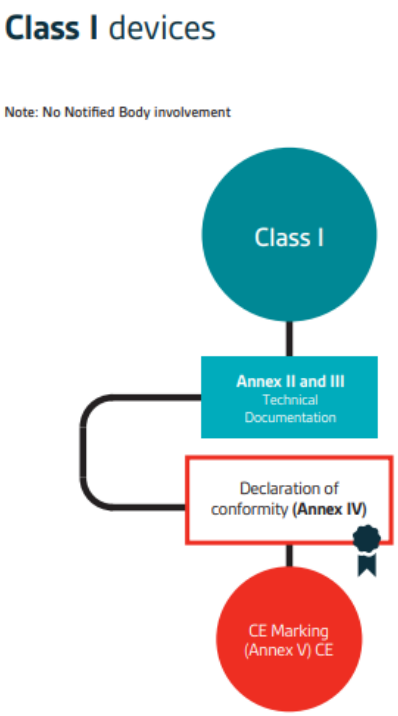

FIGURE 2 - CONFORMITY ASSESSMENT FOR CLASS I MEDICAL DEVICES
(adapted from: MDR Conformity Assessment Routes Notified Body Assessments – BSI)

For class IIa devices it is valid the QMS route according to Annex IX, (chapter I and III) as well as the assessment of the technical documentation (chapter II). Alternatively, it is possible to apply the Annex XI Part A – Production Quality Assurance or Part B – Product Verification in addition to Technical Documentation as per Annex II & III (Figure 3). In both scenarios, the participation of a Notified Body is necessary.

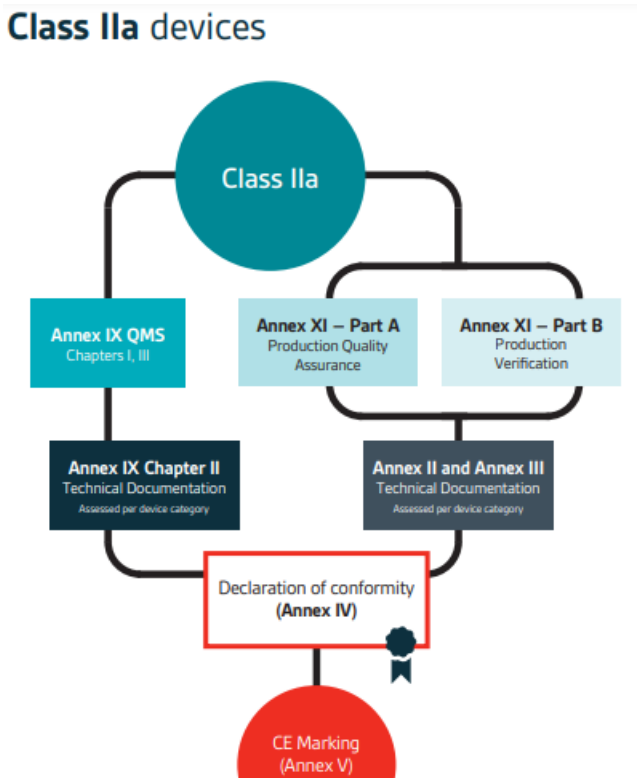

FIGURE 3 - CONFORMITY ASSESSMENT FOR CLASS IIA MEDICAL DEVICES
(adapted from: MDR Conformity Assessment Routes Notified Body Assessments – BSI)

The list of Notified Bodies designated under MDR can be found in the Nando (New Approach Notified and Designated Organisations) Information System.

3. Conclusion

Considering its intended use and mode of operation, it is confirmed that the ICT-based platform ORACIA qualifies as a medical device. Thus, and depending on the territory where it is intended to be marketed, ORACIA will be subject to different regulations.

For an MD to be marketed in the EU, it must comply with the applicable requirements of the Regulation EU 2017/745 (MDR) and other applicable Union harmonization standards. Depending on the risk class, different procedures can be adopted for conformity assessment and subsequent affixing of the CE marking. According to the MDR, and depending on the functionalities that will be assigned to the device, ORACIA may be classified as a MD class I or class IIa. It should be noted that if ORACIA is classified as a Class IIa medical device, the involvement of a Notified Body in this process will be necessary, which will not occur if it is classified as Class I.

Finally, it must be considered that, to place a product on the EU market, one must take into account not only the MDR, but also other relevant standards and guidelines such as ISO standards, MDCG, and MEDDEV. The MDR establishes the legal framework for the regulatory oversight of MDs in the EU, while ISO standards provide guidance on various aspects of the device development, production, and performance. The MDCG provides guidance and advice on the interpretation and application of the MDR, and MEDDEV provides guidance on specific aspects of medical device regulation.

4. References

IEC 60601-1-11:2015 – Medical electrical equipment — Part 1-11: General requirements for basic safety and essential performance — Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

IEC 62366-1:2015 - "Medical Devices - Application of usability engineering to medical devices"

IEC 62304:2006 – Medical device software — Software life cycle processes

IEC 62443-4-1:2018 – Security for industrial automation and control systems - Part 4-1: Secure product development lifecycle requirements

IEC 62443-4-2:2018 – Security for industrial automation and control systems, Part 4-2: Technical security requirements for IACS components

IEC/TR 80002-1:2009 – Medical device software — Part 1: Guidance on the application of ISO 14971 to medical device software

IEC 81001-5-1:2021 – Health software and health IT systems safety, effectiveness and security — Part 5-1: Security — Activities in the product life cycle

IEC 82304-1:2016 - Health software — General requirements for product safety

ISO 13485:2016 - Medical Devices – Quality management systems – Requirements for regulatory purposes

ISO 14155:2020 - Clinical investigation of medical devices for human subjects – Good clinical practice

ISO 14971:2019 - Medical Devices – Application of risk management to medical devices

ISO/TR 24971:2020 – Medical devices — Guidance on the application of ISO 14971

ISO/TR 80002-2:2017 – Medical device software — Part 2: Validation of software for medical device quality systems

MDCG 2019-16 Rev.1 – Guidance on Cybersecurity for medical devices

Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR)

https://health.ec.europa.eu/medical-devices-sector/overview_en

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https://ec.europa.eu/growth/tools-databases/nando/