HITRI plus
Heavy Ion Therapy Research Integration

Certification Aspects of heavy ion therapy machines

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

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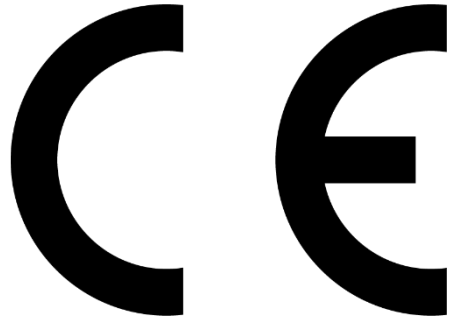
"This material was prepared and presented within the HITRIplus **Specialised Course on Heavy Ion Therapy Research,** and it is intended for personal educational purposes to help students; people interested in using any of the material for any other purposes (such as other lectures, courses etc.) are requested to please contact the authors (Muhamed Junuzovic muhamed.junuzovic@medaustron.at)

Heavy ion therapy machines

Once we have developed a beautiful and powerful device, what is required to bring it to market as a medical device… how can we prove that a patient will not be harmed during irradiation… can the operating and service personnel use the device in a safe way… are the operating environment and the neighborhood affected by electromagnetic field and radiation…?

What is CE marking?



- The Conformité Européenne (CE) Mark is defined as the European Union's (EU) mandatory conformity marking for regulating the goods sold within the European Economic Area (EEA) since 1985.
- The CE Marking serves as a declaration from the manufacturer that their product complies with **the essential requirements of the relevant European health, safety and environmental legislation** laid out in the different product directives.
- Once a product has been awarded the CE Marking, then it is able to move freely within the European Free Trade Association (EFTA) and the European Union (EU).

Manufacturers

- Manufacturers play a crucial role in ensuring that products placed on the extended single market of the European Economic Area (EEA) are safe.
- They **are responsible** for checking that their products **meet** EU **safety, health, and environmental protection** requirements.
- It is the manufacturer's responsibility to carry out the conformity assessment, set up the technical file, issue the EU declaration of conformity, and affix the CE marking to a product. Only then can this product be traded on the EEA market.

Manufacturer data sheet

Manufacturer Data Sheet for the medical device: / Herstellerinformationen für das Medizinprodukt:

MedAustron Particle Therapy Accelerator MAPTA

(01)UDI-DI(21)UDI-PI:	(01)9120111630017(21)V.1.03
Version:	V.1.03
Copyright:	2012 - 2022 www.medaustron.at

MedAustron

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Österreich

2022

CE 0483

What is a legal basis for CE marking of a medical device?

- EU Regulations
  - They are directly applicable
  - Example: MDR has to be applied for (new) Medical Devices latest from the end of transition period.
- EU Directives
  - They need to be implemented via national laws
  - Example: LVD is implemented by Austrian Elektrotechnikgesetz

Applicable Legal Regulations and Directives

- **European Medical Device Regulation (EU) 2017/745 (MDR)**
  - Set of regulations that governs the production and distribution of medical devices in Europe.
  - Compliance with this regulation is mandatory for manufacturers that want to market or sell their products in the EEA.
- **European Low Voltage Directive 2014/35/EU (LVD)**
  - Ensures that electrical equipment provides a high level of protection for European citizens, and benefits fully from the single market.
  - Outlines essential safety requirements for electrical equipment operating with a voltage of 50 -1000 V for alternating current and 75-1500V for direct current.

Applicable Legal Regulations and Directives #2

- **Directive for electro-magnetic compatibility 2014/30/EU (EMC)**
  - ensures that electrical and electronic equipment does not generate, or is not affected by, electromagnetic disturbance.
- **Machinery Directive 2006/42/EC (MD)**
  - defines essential health and safety requirements of general application (permits the free movement of machinery).
  - Applicable for machinery; interchangeable equipment; safety components; lifting accessories; chains, ropes and webbing; removable mechanical transmission devices; partly completed machinery…

Applicable Legal Regulations and Directives #3

- **European Directive for protection against the dangers arising from exposure to ionising radiation 2013/59/EURATOM**
  - establishes uniform basic safety standards for the protection of the health of individuals subject to occupational exposures, besides the medical and public exposures against the dangers arising from ionising radiation.
- **Directive on restriction of hazardous substances 2011/65/EU (RoHS)**
  - Set of rules on the restriction of the use of hazardous substances in electrical and electronic equipment (EEE) with a view to contributing to the protection of human health and the environment, including the environmentally sound recovery and disposal of waste EEE

Application of / Compliance to Standards

- Compliance to standards is not legally required, but
  - Standards reflect the state of the art in their field of concern.
  - Application of standards makes technical solutions and processes comparable.
  - Compliance to standards is commonly accepted as precondition for approval of compliance to legal regulations.

Classes/Types of Standards

- process standards: „good practices“ for management processes (e.g. IS0 9001, ISO 13485, ISO 14971, IEC 62304 etc.)
  - ensuring that the result of a process fulfills defined requirements
- technical standards: defining state of the art (e.g. DICOM-standards)
  - ensuring interoperability, compatibility, comparability
  - often linked to safety aspects
- safety standards: definition of safety requirments (e.g. IEC 60601 - series)
  - technical implementation of a requirement = “appropriate risk mitigation measure”
  - compliance to a requirement = „acceptable residual risk“
- testing standards: definition of standardized test specifications (e.g. IEC 62353)
  - common acceptance of test results

Quality management system & ISO 13485

- A medical device quality management system (QMS) covers all aspects of medical device's life cycle. The purpose of QMS is to improve the quality of the medical device and related services.
- The ISO 13485 standard lays down the requirements for QMS for medical devices.
- QMS processes to be established:

  Development; Production; Service delivery; Risk management; Document control; Internal audits; Management reviews; Corrective and preventive actions; Handling of resources (human resources, infrastructure, equipment, locations); Communication with customers.

				
Audits	*Selection of Suppliers and Subcontractors*	*Provision of Resources*	*Purchasing*	*Configuration Management*
				
Data Analysis	*Identification and Traceability of Assets*	*Customer Feedback and Complaint Handling*	*Control of Defective Assets*	*Control of Technical Documentation*
				
Control of Documents and Records	*Control of nonconforming products*	*Control of Corrective and Preventive Measures*	*Control of Measuring Equipment*	*Process Management*
				
Management Review	*Personnel Competence*	*Post-Market Surveillance*	*Product Change*	*Product Release*
				
Product Realization	*Risk Management*	*Service*	*Software Validation*	*Measurement of the Product*
				
Vigilance				

Product testing and conformity check

- The process of demonstrating that the device will reliably and safely perform in use.
- Extensive design validation testing - performance testing, toxicity and chemical analysis, and sometimes human factors or even clinical testing.
- Conformity assessment is a procedure that determines whether the requirements of the MDR for the medical device have been met. It must be performed with a positive result before placing a medical device on the market.

MAPTAv1-182 - Validation of Summary Test Reports — Passed — Nir Kahn — yes

	#	Step	Step Description	Expected Result	Actual Result
✔	1	**Summary Test Report on Compatibility for MAPTA**	Verify that the document Summary Test Report on Compatibility for MAPTA is released in DMS.	Summary Test Report on Compatibility for MAPTA is released in DMS.	v10.0
✔	2	**Summary Test Report on EN 60601-2 for MAPTA**	Verify that the document Summary Test Report on IEC 60601-2-64 for MAPTA is released in DMS.	Summary Test Report on IEC 60601-2-64 for MAPTA is released in DMS.	v10.0
✔	3	**Summary Test Report on Validation of MAPTA**	Verify that the document Summary Test Report Validation of MAPTA is released in DMS.	Summary Test Report Validation of MAPTA is released in DMS.	v13.0
✔	4	**Summary Test Report on Verification of MAPTA**	Verify that the document Summary Test Report on Verification of MAPTA is released in DMS.	Summary Test Report on Verification of MAPTA is released in DMS.	v10.0 in Polarion, v11.0 in DMS
✔	5	**Overview on test reports regarding Risk Management performed at MedAustron**	Verify that the document Overview on test reports regarding Risk Management performed at MedAustron is released in DMS.	Overview on test reports regarding Risk Management performed at MedAustron is released in DMS.	v13.0
✔	6	**Summary test report risk mitigation measures**	Verify that the document Summary test report risk mitigation measures is released in DMS.	Summary test report risk mitigation measures is released in DMS.	v15.0
✔	7	**Compliance statements to selected requiements of IEC 60601-2-64**	Verify that the document Compliance statements to selected requirements of IEC 60601-2-64 are released in DMS.	Compliance statements to selected requirements of IEC 60601-2-64 are released in DMS.	DD080_MAPTA_1606280, v2.0
✔	8	**Beam related information**	Verify that the document Beam related information is released in DMS.	Beam related information is released in DMS.	v7.0
✔	9	**Summary Test Report on EN 60601-1 for MAPTA**	Verify that the document Summary Test Report on EN 60601-1 for MAPTA is released in DMS.	Summary Test Report on EN 60601-1 for MAPTA is released in DMS.	v8.0
✔	10	**Summary Test Report on Functional Safety Concept for MAPTA**	Verify that the document Summary Test Report on Functional Safety Concept for MAPTA is released in DMS.	Summary Test Report on Functional Safety Concept for MAPTA is released in DMS.	v11.0
✔	11	**Summary Test Report on MAPTA IT**	Verify that the document Summary Test Report on MAPTA IT is released in DMS.	Summary Test Report on MAPTA IT is released in DMS.	v4.0
✔	12	**Risk Management Report MAPTA**	Verify that the document Risk Management Report MAPTA is valid and released in DMS.	Risk Management Report MAPTA is valid and released in DMS.	v21.0
✔	13	**Functional Safety Concept MAPTA**	Verify that the document Functional Safety Concept MAPTA is released in DMS.	Functional Safety Concept MAPTA is released in DMS.	v7.0
✔	14	**Test report for TC_MAPTA_I_000512**	Verify that there is a valid test report for TC_MAPTA_I_000512 is released in DMS.	A valid test report for TC_MAPTA_I_000512 is released in DMS.	See summary test reports.
✔	15	**Summary Test Report of IR1**	Verify that the document Summary Test Report of IR1 is released in DMS.	The document Summary Test Report of IR1 is released in DMS.	v1.0

Technical documentation (according to MDR)

- A general description of the product, including any planned variants along with its intended use;
- The design specifications, including the standards which will be applied and the results of the risk analysis, and a description of the solutions adopted to fulfill the essential requirements, which apply, if the standards referred to in Article 5 are not applied in full;
- The techniques used to control and verify the design, the processes, and the systematic measures which will be adopted during the design phase;
- Compatibility and interoperability reports;

Technical documentation #2

- The solutions adopted in accordance with Annex I Chapter I Section 2;
- The preclinical evaluation;
- The clinical evaluation referred to in Annex X of;
- The draft label;
- Instructions for use.

- **MedAustron techfile index - 500 pages!**

KapitelNo ChapterNo.	Kapitel-Titel Chapter Title			
DokNo. DocNo.	Dokumententitel Document Title in grau: obsoletes Dokument / in grey: obsolete document	Date added	Vers.	Vertraulichkeit Confidentiality
1	**1_Device Description and Specification**			
ZA000_11100_1505131	Glossar	2021-09-22	12.0	restricted
ZC000_30400_2007133_MSM (previously ZC000_30400_2007133)	Readme Chapter 1 TechFile MAPTA	2020-10-12	2.0	restricted
1.01	**1.01 General description of the device, its variants and its intended purpose**			
FS-121015-a-PGR	Intended Use MAPTA	2020-10-12	2.0	restricted
DB010_MAPTA_1603221	Normal Use MAPTA	2016-04-14	1.0	restricted
DB010_MAPTA_1409151	Produktbeschreibung MAPTA	2021-09-01	3.0	restricted
130010/0	Produktliste Medizinprodukte mdc	2022-01-11	3.0	restricted
BE030_30500_1307091	Responsibility Deliv-Accept-Comm MAPTS	2015-01-27	4.0	restricted
1.1.1	**1.1.1 Name and address of the manufacturer**			
DA010_MAPTA_1607241	Manufacturer Data Sheet MAPTA	2022-01-29	34.0	open
1.1.2	**1.1.2 Overview of devices, device groups or device types...including UDI - DI (if applicable)**			
FA000_30400_2006241_ABU	Overview Structure of Technical File MAPTA acc to MDR	2021-09-22	3.0	restricted
1.1.3	**1.1.3 Trade Names under which the device is placed on the market**			
0107085	Medical Devices Registry Confirmation MAPTA	2021-06-16	3.0	restricted
1.1.4	**1.1.4 Description and specification of the device including its intended purpose, indication(s), contraindication(s) and warnings**			
DD082_MAPTA_1404021	Clinical Evaluation MAPTA	2020-10-13	3.0	restricted
DC030_MAPTA_1903211	Gebrauchsanweisung MedAustron Particle Therapy Accelerator V.1.02 und V.1.03	2021-12-22	12.0	restricted
FS-121015-a-PGR	Intended Use MAPTA	2020-10-12	2.0	restricted
DD080_MAPTA_1607251	MAPTA - Compatibility Documentation	2022-01-29	34.0	restricted

Notified Body

- Notified bodies are government accredited, mostly private companies that take over sovereign tasks on behalf of national authorities.
- According to the MDR, medical device manufacturers have to involve notified body in the conformity assessment process.
- Typical tasks of notified bodies:
  - Certification of QMS according to ISO 13485 and to the Annexes of MDR
  - Review of technical files such as risk management files, software files and usability files, and checking compliance with legal requirements
  - Assessment of clinical evaluations

CE mark and EU Declaration of Conformity

- **There is no CE Certification!** There is no agency like the FDA or the European Medicine Agency approving or certifying medical devices.
- The **EU declaration of conformity** is an important legal document in which the manufacturer declares the conformity of their medical device.
- The declaration of conformity must contain:
  - Information about the device
  - Information on the conformity of the device
  - Information about the manufacturer
  - Other information (place and date of issue, name and function of the person signing the declaration, signature)

CE mark and EU Declaration of Conformity

EBG MedAustron GmbH
Marie Curie-Straße 5
A-2700 Wiener Neustadt
Österreich
Tel. +43 2622 26 100

MedAustron

Declaration of Conformity

Product details:

Product name	MedAustron Particle Therapy Accelerator MAPTA
UDI-DI	912011163MAPTAZ5
Type	V.1.03
Classification according to (EU) 2017/745 Annex VIII	Class IIb; rule 9

Manufacturer details:

SRN	AT-MF-000002630
EBG MedAustron GmbH	A-2700 Wiener Neustadt Marie Curie-Straße 5

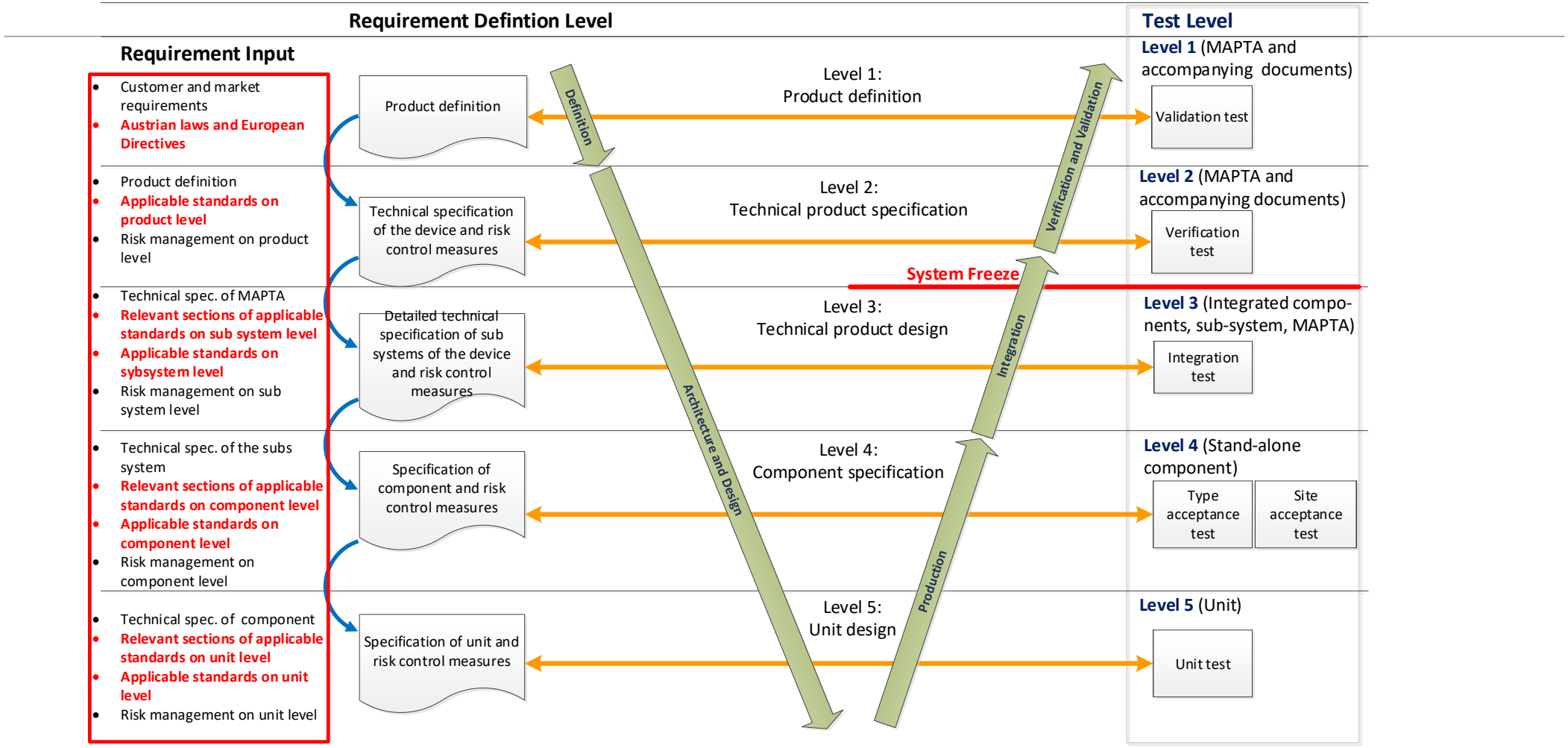
Assessment details:

Notified body	mdc medical device certification GmbH Kriegerstraße 6 70191 Stuttgart; Germany
Route of directive (EU) 2017/745	Annex IX, EC DECLARATION OF CONFORMITY
Certificates	D4000600006

The manufacturer declares under sole responsibility that the products described above are in compliance with the requirements of regulation (EU) 2017/745. The products are CE-marked.

CE 0483

Example of design and verification using V-model



EU vs FDA approval process

CE Mark

- Main function is to assess the safety and efficacy of new devices
- Obtained through a clinical evaluation of published data for existing equivalent devices
- Requires a postmarket clinical follow-up study once the CE Mark is obtained
- Valid in all EU countries and recognized almost globally

FDA Approval

- Main function is to assess the safety and efficacy of new devices
- Requires a full clinical trial or trials
- Narrow approved range of parameters
- Valid only in the United States

EU vs FDA approval process

CE Mark

- Puts more onus on and endues a greater amount of trust to the manufacturer and to the physician
- Allows new technology to more quickly become available to patients
- Leaves safety and efficacy of the surgical procedure that is performed by the device to the responsibility of the physicians and surgeons who use the device

FDA Approval

- More expensive to obtain, as the documentation required from investigators is much less efficient, the review cycle is about three times longer, and there are almost always more rounds of questions
- Indicates that strict criteria have been met, signifying that clinical application of a drug or device will be safe and effective

Questions & Discussion