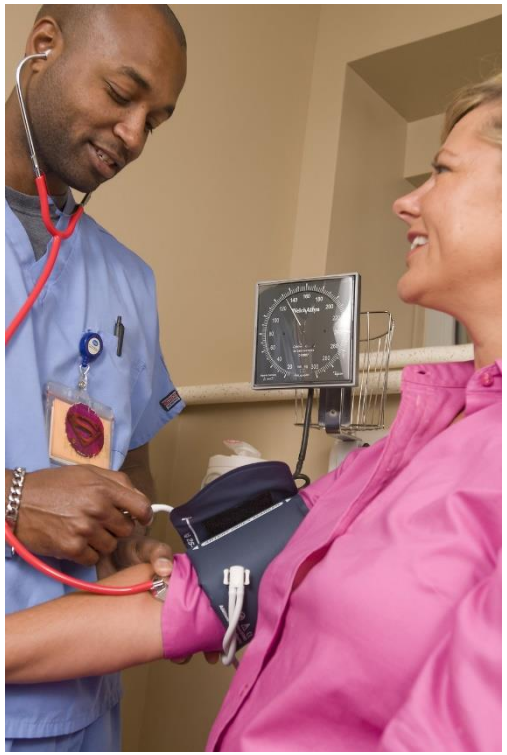
Medical Device Regulation

Impact on in-house manufacturing of medical device software

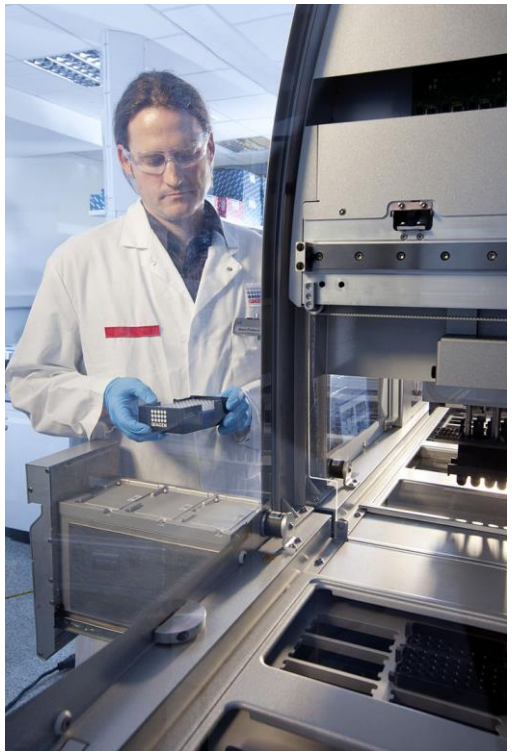
Koen Cobbaert
Expert Regulations, Standards and Quality
Presented for Belgian Hospital Physicists Association
2020-02-07

EU Medical Device Regulations



Medical Device Regulation

Regulation (EU) 2017/745



In Vitro Diagnostic Medical Device

Regulation (EU) 2017/746

Related documents: Implementing and delegated acts, common specifications, device specific guidance

National Provisions

KONINKRIJK BELGIE	ROYAUME DE BELGIQUE
FEDERAAL AGENTSCHAP VOOR GENEESMIDDELEN EN GEZONDHEIDSPRODUCTEN	AGENCE FEDERALE DES MEDICAMENTS ET DES PRODUITS DE SANTE
VOORONTWERP VAN WET BETREFFENDE MEDISCHE HULPMIDDELEN	AVANT-PROJET DE LOI RELATIVE AUX DISPOSITIFS MEDICAUX
FILIP, KONING DER BELGEN,	PHILIPPE ROI DES BELGES,
Aan allen die nu zijn en hierna wezen zullen,	A tous, présents et à venir,
ONZE GROET.	SALUT.
Op de voordracht van Onze Minister van Sociale Zaken en Volksgezondheid,	Sur la proposition de Notre Ministre des Affaires sociales et de la Santé publique,
HEBBEN WIJ BESLOTEN EN BESLUITEN WIJ:	NOUS AVONS ARRETE ET ARRETONS :
Onze Minister van Sociale Zaken en Volksgezondheid is ermee belast het voorontwerp van wet, waarvan de tekst volgt, in Onze naam aan de Wetgevende Kamers voor te leggen en bij de Kamer van volksvertegenwoordigers in te dienen:	Notre Ministre des Affaires sociales et de la Santé publique est chargée de présenter en notre nom aux chambres législatives et de déposer à la Chambre des représentants, l'avant-projet de loi dont la teneur suit :
Hoofdstuk 1 - Toepassingsgebied, definities, bevoegde autoriteit en administratieve bepalingen	Chapitre 1 – Champ d'application, définitions, autorité compétente et dispositions administratives

What software does the regulation affect?

Radiology

Computer aided detection for mammography

Tumor segmentation for diagnostic or treatment purposes

Software intended for daily quality assurance in mammography if it is intended to calibrate or specifically enable or directly assist diagnostic equipment (e.g. monitors, x-ray equipment…) to be used within safe and effective operating conditions.

…

Nuclear medicine

Software that processes data obtained from images to obtain other data (e.g. **converting count to activity**) for use in diagnostic or therapeutic care.

…

Radiotherapy

Software that uses a patient's CT images to estimate proton Stopping Power Ratio (SPR), **predict dose distribution** and plan the patient's treatment with the aim to maximize the tumor control probability while minimizing the normal tissue complication probability.

Modeling and treatment planning software (e.g. 3D CT-based eye-modeling and treatment planning

…

Authorities issued civil and criminal penalties to people that do not comply

The Guardian

International edition

Lifestyle More

sex Health & fitness Home & garden Women Family Travel Money

Lumosity fined millions for making false claims about brain health benefits

The Federal Trade Commission also issued a general warning that it is on the lookout for companies cashing in on the popularity of health-related mobile apps

It seemed like a win-win for fans of the online "brain training" memory game Lumosity - as fun as Candy Crush (almost) but actually good for you: a mind gym to sharpen mental performance and, for older consumers, ward off senility.

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Breast implants: PIP's Jean-Claude Mas gets jail sentence

10 December 2013 Share

The trial of Jean-Claude Mas, seen here arriving at court in Marseille, was one of the biggest trials in French legal history

Penalties are defined through national provisions and are of a often of a criminal nature

Draft Belgian law

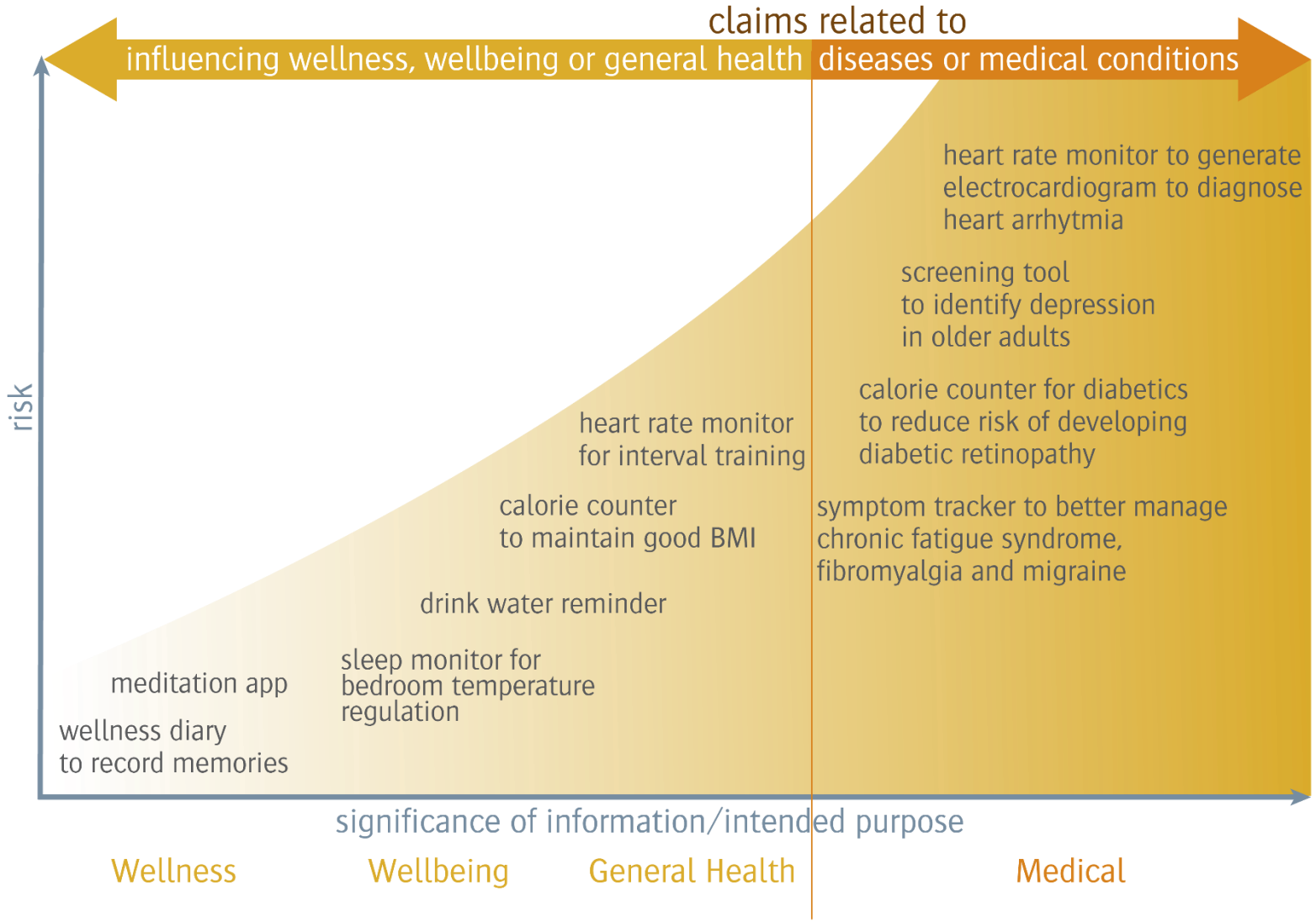
- **Criminal fine 26-600€**: non-compliance with EU MDR, not storing, making available to patient the implant card
- **Criminal fine 200-50.000€ and/or imprisonment of 1 month to 1 year:** not creating and communicating materiovigilance point-of-contact or (also applies to healthcare professionals): not reporting serious incidents to competent authority or using a medical device not in accordance to its instructions for use,
- **Criminal fine 1.000-100.000€ and/or imprisonment of 1 to 3 year:** failure to allow competent authority inspectors on your premises, in rooms or give access to documentation, purposely providing incomplete, false or incorrect information or pieces to competent authorities or obstruct authorities to perform their verification, failure to store UDI
- **Criminal fine 2.000-200.000€ and/or imprisonment of 2-5 year**: not complying with corrective actions imposed by competent authority

The penalty increases one level in case of fraud, a serious incident, criminal organization, repeating the breach in next 5 years or if offering devices/services through means of **mass deployment, e.g. via computer systems or the internet.**

Is it, or is it not a medical device?

Independent of risk

Although there generally is some correlation, whether software is considered a medical device does **not** depend on whether it poses a risk or not, but on whether it meets the definition of a medical device.



Medical Device definition

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,

medical purposes

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- Devices for the control or support of conception
- Products specifically intended for cleaning, disinfection or sterilization of medical devices, accessories of medical devices and products listed in Annex XVI

Diagnosis

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:
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Diagnosis is the process of investigation of the anatomy or morphology, the condition or the functions of the human body irrespective if these are physiological or pathological, **and subsequent interpretation** of this information **with a view to determining possible abnormalities**.

In this context investigation **can include visualisation, detection or measurement**.

Source: draft EC guidance

Excluded: electronic patient records, digital medical handbooks, …

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Qualification does not depend on technical complexity

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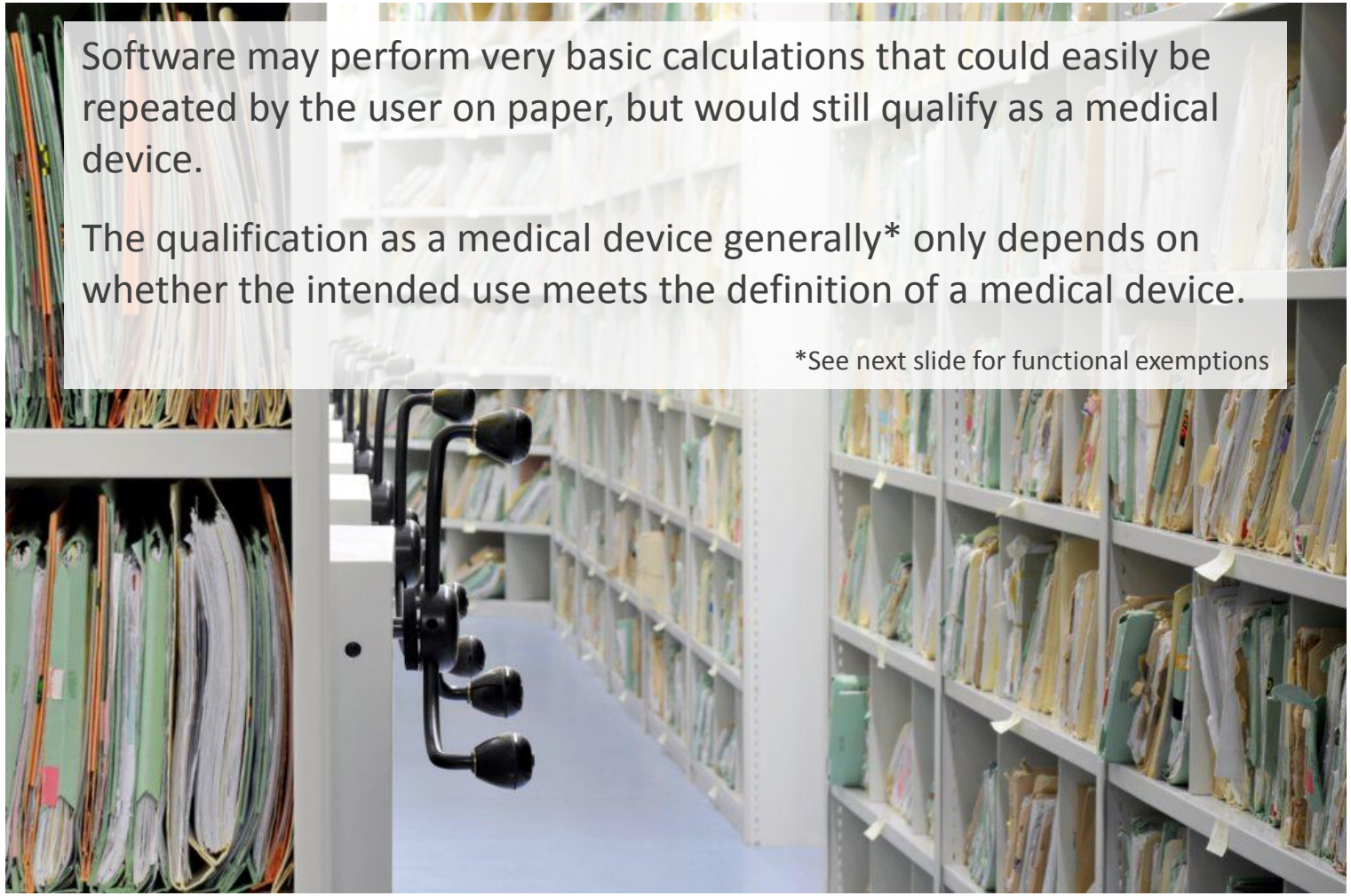
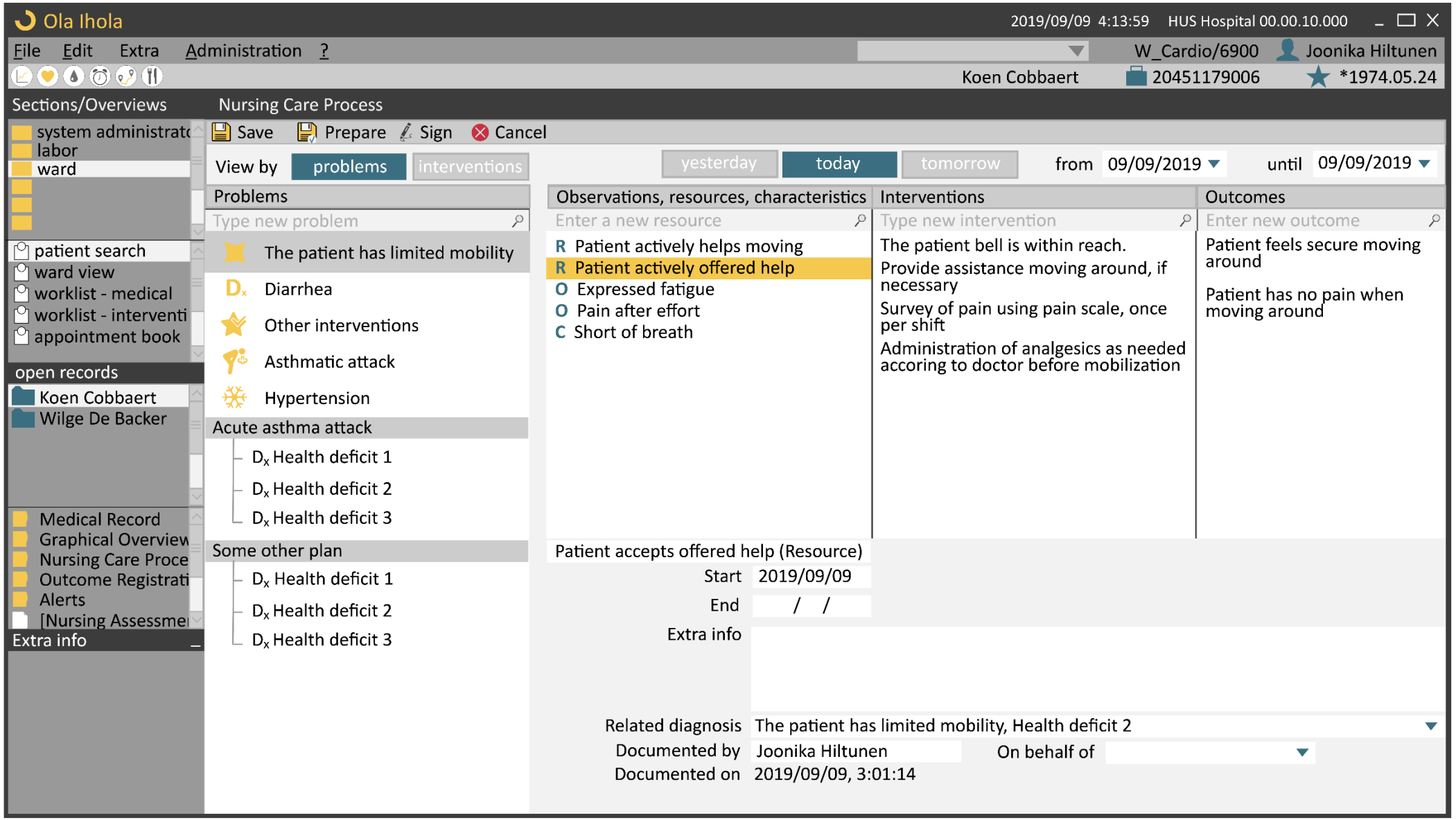


Software may perform very basic calculations that could easily be repeated by the user on paper, but would still qualify as a medical device.

The qualification as a medical device generally* only depends on whether the intended use meets the definition of a medical device.

*See next slide for functional exemptions

Scripts that just parse data in a certain format are not medical devices



Functional Exemptions

Even if the intended use of software is medical,
if it only provides functionality to

1. communicate*
2. store/archive
3. lossless compression**
4. simple search***

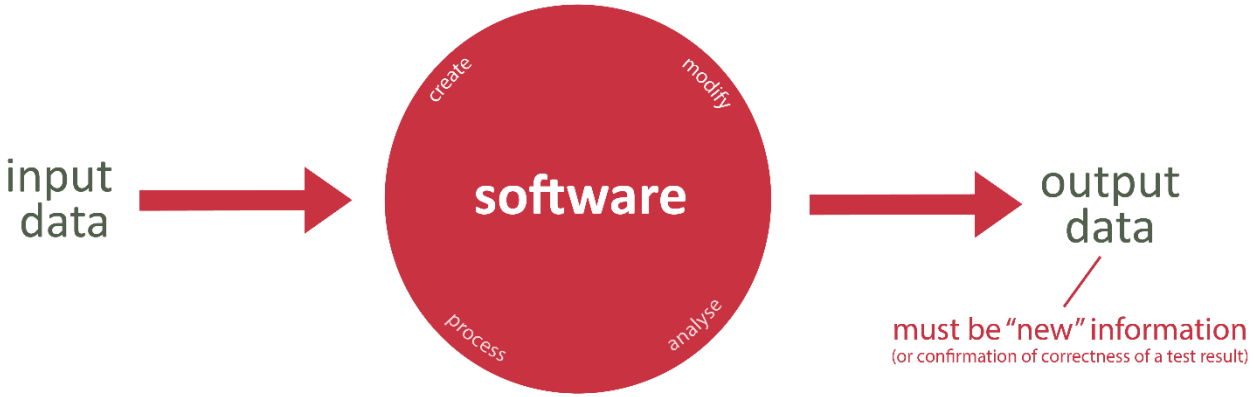
then it **does not qualify as a medical device**.

Source: MDSW Guideline – Guidance on the Qualification and Classification of Software in MDR 2017/745 and IVDR 2017/746 - Decision diagram 1, step 3

* communicate: transfer, data parsing, convert units (pound->kg), alter representation of information for embellishment or compatibility purposes

** lossless compression: compression procedure that allows the exact reconstruction of the original data

***simple search: retrieval of records by matching record metadata against record search criteria or retrieval of information



Software = a set of instructions that processes input data and creates output data

Source: MDSW Guideline – Guidance on the Qualification and Classification of Software in MDR 2017/745 and IVDR 2017/746

SIMPLE SEARCH
retrieval of information or retrieval of records by matching record metadata against record search criteria

Beyond simple search

drug-drug interaction or allergy checks

Fluoxetine + Phenelzine
Warfarin + Diflunisal
Penicillin + allergic patient

The European Court issued a decision in the case C329/16 SNITEM & Philips France vs. the French State that the functionality involved in the drug-drug interaction checks is considered a medical device.

threshold comparisons

Moomin Solidarity Hospital
Lighthouse 12456
Moominvalley
Finland

laboratory report

Name: **Moominpappa**
Date: 2018-02-01 08:22
Doctor: Hammarsten

Patient ID: PAC001
Age: 48y 10m 26d
Sex: Male
Test ID: B165AAF4

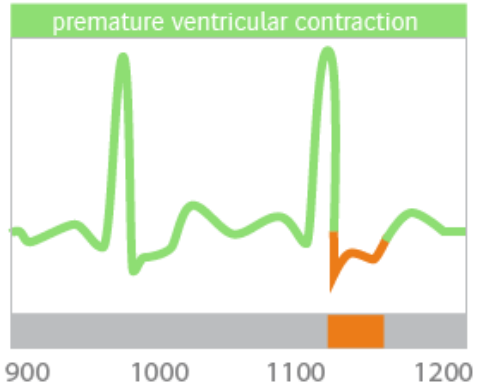
COMPLETE BLOOD COUNT

Test Name	Result	Normal Range	Units
Hemoglobin	12	11.0 - 16.0	g/dL
RBC	3.3	3.5 - 5.50	10^6/uL
HCT	36	37.0 - 50.0	%
MCV	83	82 - 95	fl
MCH	28	27 - 31	pg
MCHC	33	32.0 - 36.0	g/dL
RDW-CV	12	11.5 - 14.5	%
RDW-SD	44	35 - 56	fl
WBC	6.7	4.5 - 11	10^3/uL
NEU%	60	40 - 70	%
LYM%	30	20 - 45	%
MON%	8	2 - 10	%
EOS%	2	1 - 6	%
BAS%	0	0 - 2	%
LYM#	2	1.5 - 4.0	10^3/uL
GRA#	4.7	2.0 - 7.5	10^3/uL
PLT	256	150 - 450	10^3/uL
ESR	2	Up to 15	mm/hr

Digitally signed by:

Dr. Toivo Hammersten
Moomin Public Key: E44311F4
Test id: B165AAF4

signal detection



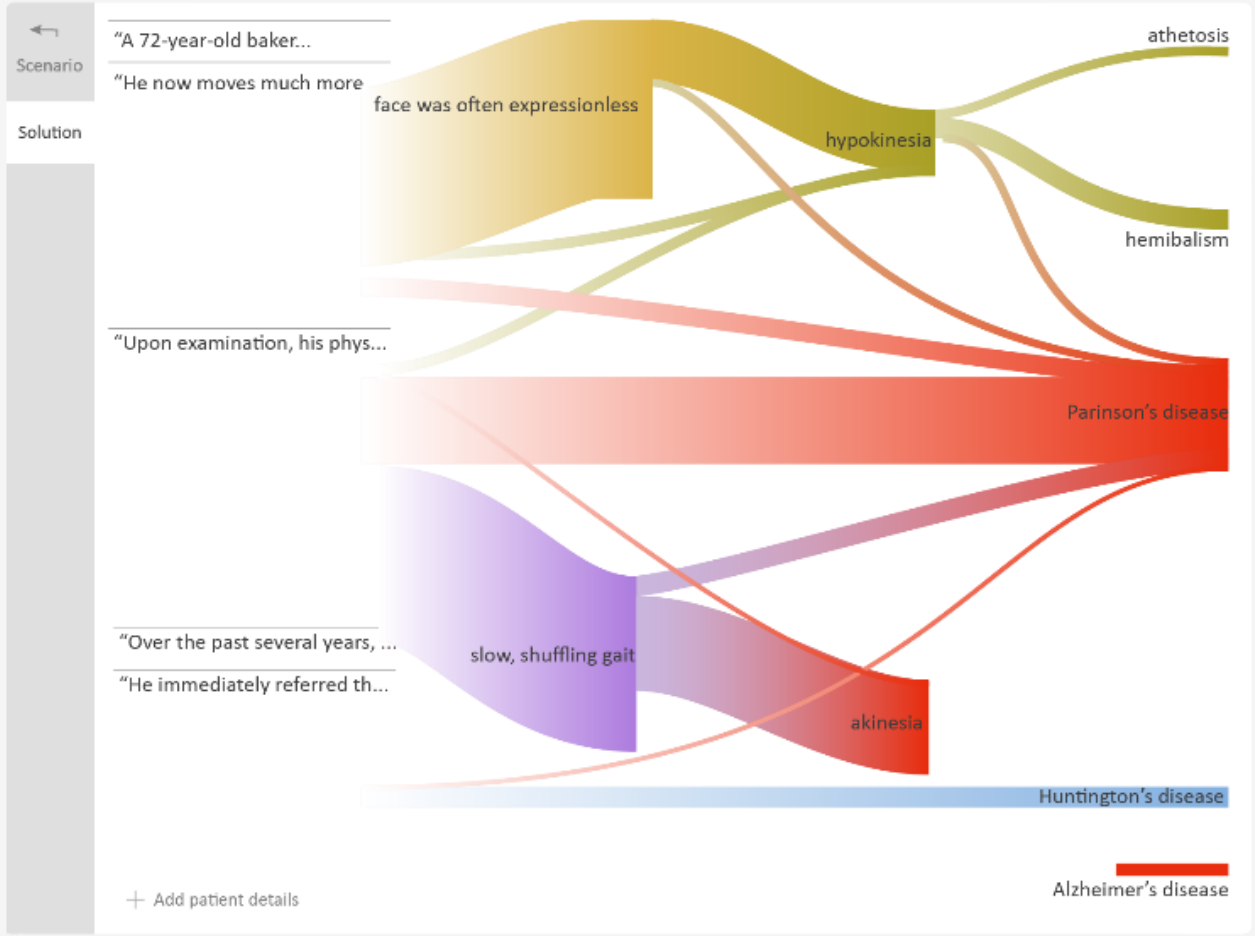
Population Health Software ≠ MD

Clinical decision support = MD

Rules engines, semantic search engines, artificial intelligence or other algorithms that **combine information of an individual patient with scientific/medical guidelines, publications or other knowhow** to provide the user with

- information of options for treating, diagnosing, preventing or mitigating a disease or condition for that specific patient
- Information relevant to that specific patient by aggregating scientific/clinical information about e.g. disease, condition, drugs, medical devices, population, etc.
- Information to guides the user in next diagnostic or treatment interventions

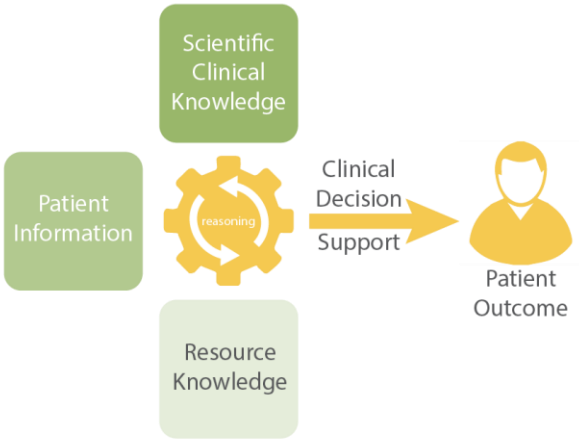
is considered medical device software

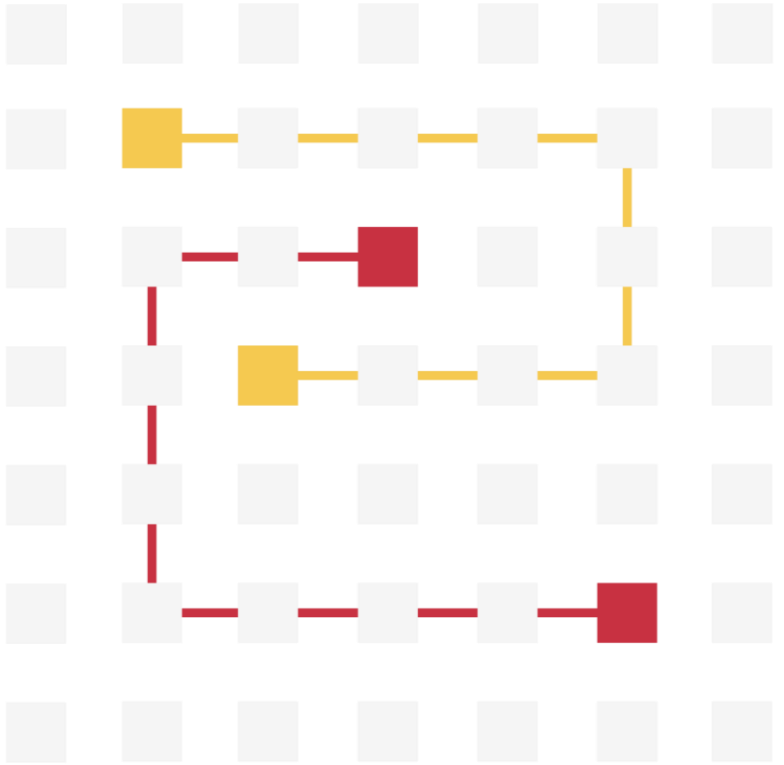


Resource management software and workflow engines

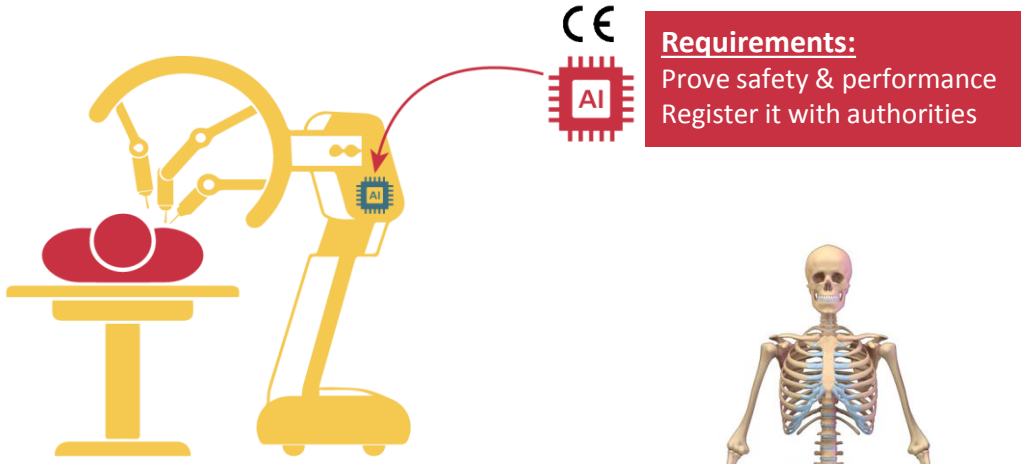
Resource management software intended for scheduling appointments and managing hospital resources efficiently are not medical devices.

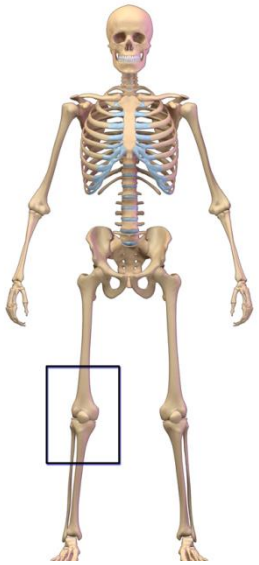
Workflow engines that combine information of an individual patient with scientific/medical guidelines, publications or other knowhow to suggest the next step in the diagnostic or treatment pathway of the patient, or to triage patients, such software is considered decision support software and qualifies as a medical device.





Software upgrades extending the original intended purpose





Manufacturer places a device on the market.

Health Institution changes the device or upgrades a software so that it significantly changes performance, safety or intended purpose. This is also considered in-house manufacturing.

Software accessories

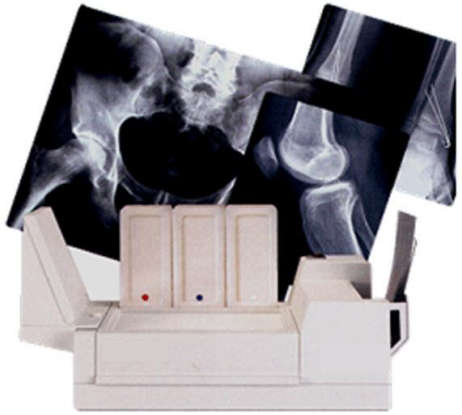
Koen Cobbaert

Accessory

MD

Accessory for a medical device means an article which, whilst not being itself a medical device , is intended by its manufacturer to be used together with one or several particular medical device(s) to **specifically enable** the medical device(s) to be used in accordance with its/their intended purpose(s) or to **specifically and directly assist** the medical functionality of the medical device(s) in terms of its/their intended purpose(s);

Source: MDR Article 2 definitions



A developer specifically enables the x-ray film to fulfill its intended purpose.

- **Medical device**: x-ray film
- **Accessory**: developer

A cushion containing ribs with 3 different dimensions. The cushion enables patients of different height to comfortably lift their legs so that their spine is straightened and the intervertebral disks become clearly visible on the scan, a condition for the scanner to accurately detect the edge of the lumbar vertebrae and measure accurately and precisely.

- **Medical device**: bone densitometer scanner
- **Accessory**: positioning cushion

Calibration of diagnostic monitors or other medical devices: accessories

Software intended for daily quality assurance in mammography if it is intended to calibrate or specifically enable or directly assist diagnostic equipment (e.g. monitors, x-ray equipment…) to be used within safe and effective operating conditions.

Conditions and Requirements for in-house manufacturers

EU MDR/IVDR Article 5(5)

In-house manufacturing: conditions

1. **No equivalent device on market to meet specific needs of target patient population, or not at an appropriate level of performance (document justification)**

   Easy to justify for software. There is always a software feature the commercial solutions don't have.

2. **Device is not manufactured on an industrial scale**

   Even though it can be distributed on an industrial scale, software is only manufacturered once (i.e. compiled). This requirement refers to "manufacturing", not distributing. So, this should never be an issue.

3. **Don't transfer device to other legal entity**

   Don't sell it or give it away to other hospitals or doctors.

   When the software is made by an IT department that is another legal entity of the hospital, consider a sub-contracting relationship …see next slide

Additional Belgian limitation:
In-house manufacturing of devices using **ionizing radiation and implants** is not allowed. This list can be expanded.

Subcontractor control & quality agreements

You remain responsible as in-house manufacturer.
The subcontractor works under your responsibility.

It is essential that you control the subcontractor's influence on the conformity of your device, for example by **auditing** or asking a **quality system that complies with ISO 13485** or **participate in their design review meetings**, or all of the above.

Script a meaningful **supplier quality agreement** that clearly delineates

- Their **role** as subcontractor and your role as in-house manufacturer
- That they are **not to place the device on the market**, not for money, but also not for free
- What **deliverables/documentation** is needed, what is expected in terms of **processes**, identification of **incidents**, **nonconforming product disposition**, **CAPA responsibilities**, **frequency of audits**, IP ownership, **design changes, process changes, material changes**, …

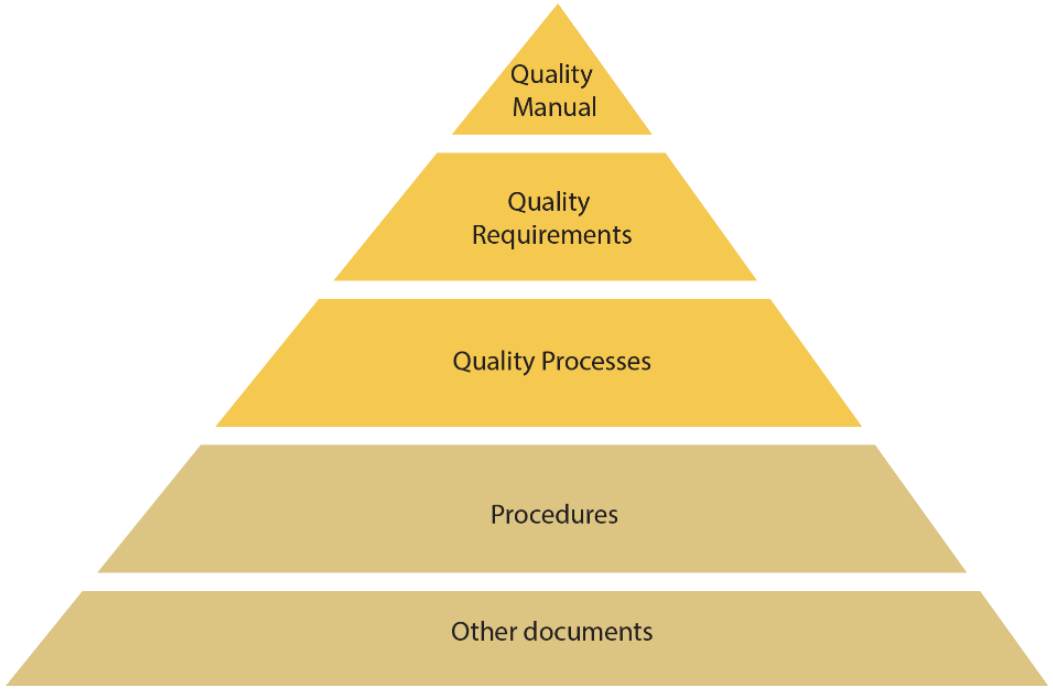
Requirement 1: Cooperate with authorities

Register with FAGG and indicate the type of device you manufacture

Report serious injuries (applicable to all health institutions and healthcare professionals, if applicable: use materiovigilance point)

Be transparent and cooperative when receiving requests for information. Give full access during inspections.

Requirement 2: Manufacture and use occurs under quality management system

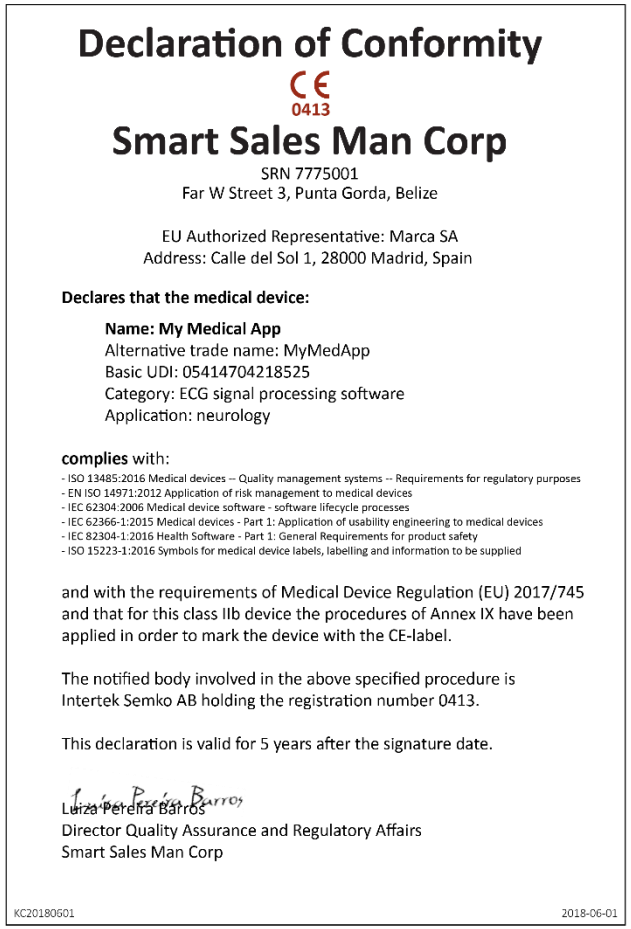


A mature quality system self-identifies and corrects problems, assures a state of control and has a focus on prevention rather than correction, e.g. by monitoring regulatory changes across the world and proactively working towards compliance.

The **ISO 13485** standard is an effective solution to meet the comprehensive requirements for a quality management system for the manufacturing of medical devices. It provides a practical foundation for manufacturers to address the regulations and responsibilities as well as demonstrating a commitment to the safety and quality of medical devices.

ISO 13485 will likely be required in certain countries, but there are no indications that this is the case in Belgium.

Requirement 3: Draft declaration of conformity
Make it publicly available



Declaration of Conformity

CE
0413

Smart Sales Man Corp

SRN 7775001
Far W Street 3, Punta Gorda, Belize

EU Authorized Representative: Marca SA
Address: Calle del Sol 1, 28000 Madrid, Spain

Declares that the medical device:

Name: My Medical App
Alternative trade name: MyMedApp
Basic UDI: 05414704218525
Category: ECG signal processing software
Application: neurology

complies with:

- ISO 13485:2016 Medical devices -- Quality management systems -- Requirements for regulatory purposes
- EN ISO 14971:2012 Application of risk management to medical devices
- IEC 62304:2006 Medical device software - software lifecycle processes
- IEC 62366-1:2015 Medical devices - Part 1: Application of usability engineering to medical devices
- IEC 82304-1:2016 Health Software - Part 1: General Requirements for product safety
- ISO 15223-1:2016 Symbols for medical device labels, labelling and information to be supplied

and with the requirements of Medical Device Regulation (EU) 2017/745 and that for this class IIb device the procedures of Annex IX have been applied in order to mark the device with the CE-label.

The notified body involved in the above specified procedure is Intertek Semko AB holding the registration number 0413.

This declaration is valid for 5 years after the signature date.

Luiza Pereira Barros
Director Quality Assurance and Regulatory Affairs
Smart Sales Man Corp

KC20180601 2018-06-01

The Declaration of Conformity (DoC) is a legally binding document that declares you are in compliance with the applicable legislation necessary to manufacturer and use your product in-house. Specifically, it states that your device conforms with the General Safety and Performance Requirements of the MDR or IVDR.

FAGG has the possibility to define what information such DoC must contain (no specs published today).

On the left is what normal manufacturers use, i.e. not all elements you see in this example apply to in-house manufactuers . There is no mandatory format.

Requirement 4: Draw up technical documentation

Table of Contents

Draws up documentation that makes it possible to have an understanding of the manufacturing facility, the manufacturing process, the design and performance data of the devices, including the intended purpose, and that is sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I to the Regulation are met;

There is no prescribed format. The table of content shown on the left is just one possible example.

Requirement 5:
Ensure device is manufactured in accordance to documentation

i.e. apply design controlled processes

General Safety and Performance Requirements

1. Performance, safety, effectiveness
2. Reduce risks as far as possible
3. Risk management system
4. Risk control measures
5. Use error
6. Lifetime of the device
7. Transport and Storage
8. Known and foreseeable risks, side effects, benefit-risk
9. Devices listed in Annex XV
10. Chemical, physical and biological properties
11. Infection and microbial contamination
12. Devices incorporating a substance considered to be a medicinal product
13. Devices incorporating materials of biological origin
14. Construction of devices and interaction with their environment
15. Devices with a diagnostic or measuring function
16. Protection against radiation
17. Electronic programmable systems
18. Active devices and devices connected to them
19. Particular requirements for active implantable devices
20. Protection against mechanical and thermal risks
21. Protection against the risks posed to the patient or user by supplied energy or substances
22. Protection against the risks posed by medical devices intended by the manufacturer for use by lay persons
23. Label and instructions for use

Source: EU MDR

General Safety and Performance Requirements - Checklist

#	Description	A N/A	Common specification, standard, sub clause or ref.	Complies Yes/No	Reference Justification
Chapter I – General Requirements					
1	Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.	A	IEC 82304 (see table ZZ.1) ISO 14971-1 (see table ZZ.1) EN ISO 60601-1-6 (see table ZZ.1)	Yes Yes Yes	Risk management report (54543654) Clinical evaluation report (54534243) Verification & Validation report (5246866) Summary of safety and clinical performance (5545467)
2	The requirement in this Annex to reduce risks as far as possible means the	A	ISO 14971-1 (see table ZZ.1)	Yes	Risk management report (54543654)

Requirement 6: Review clinical experience from use of device and take all necessary corrective actions

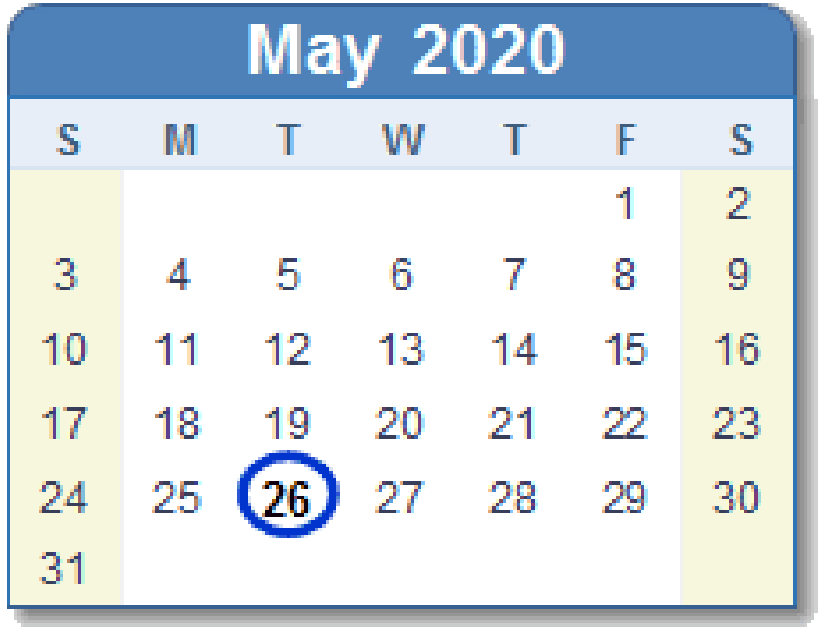
The incident definition does not require that somebody was actually seriously injured, it is sufficient that a serious injury could have happened or can happen if the event occurs again. FAGG can determine content of what you must submit.

Examples of incidents that could be reportable

- An alarm failed to sound.
- Dosages were too fast, too slow or were stopped inconsistent with the data on the display unit.
- Display unit values were inconsistent with other visual outputs of the device, for example, name of patient on screen not correct.
- The system simply stopped.
- The device performed in a manner completely unplanned, when several conditions occurred simultaneously.
- Data were lost or corrupted.
- A calculation or other function was missing, or an instruction was omitted from the user manual.


Justify based on specific needs target population why there is no equivalent device on the market.
Plan risk management and clinical evaluation (identify state of the art, explore what would be considered sufficient clinical data).
Implement quality management system with product design processes.
Perform technical & clinical testing, summative and usability testing.
Review labels and manuals.
Demonstrate compliance with general safety and performance requirements.
Compile technical file, clinical evaluation report, risk management file and design history file.
Review experience gained from clinical use of the devices and take all necessary corrective actions.
Cooperate with authorities.
On request provide them information and allow them to inspect your site.
Research Implement Processes
Product Design & Development
Evidence
Conformity Assessment
Post-Market Surveillance
In-house use
only if no equivalent device exists on the market that meets target patient's population's needs
Perform risk management, requirements engineering, formative usability testing, design, coding, unit testing.
feature complete
code freeze
Write declaration of conformity and make it publicly available.
release

Timeline



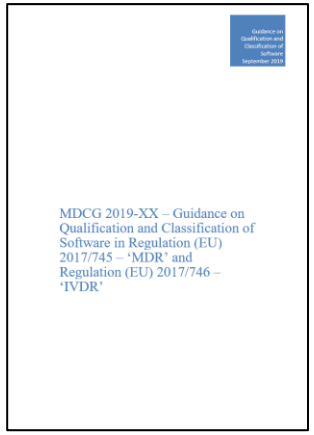
Tuesday, May 26th 2020

As of May 26, 2020 all-in-house manufactured devices that are put into service, must comply.

Devices that were put into service prior to May 26, 2020 must not comply.

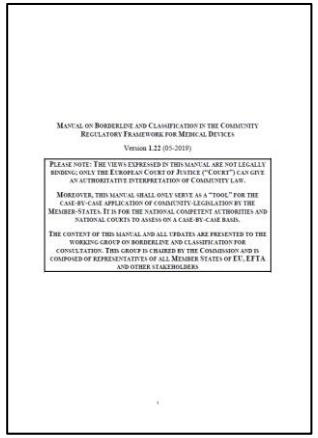
Updates or upgrades to devices put into service prior to May 26, 2020, must comply.

Want to know more?



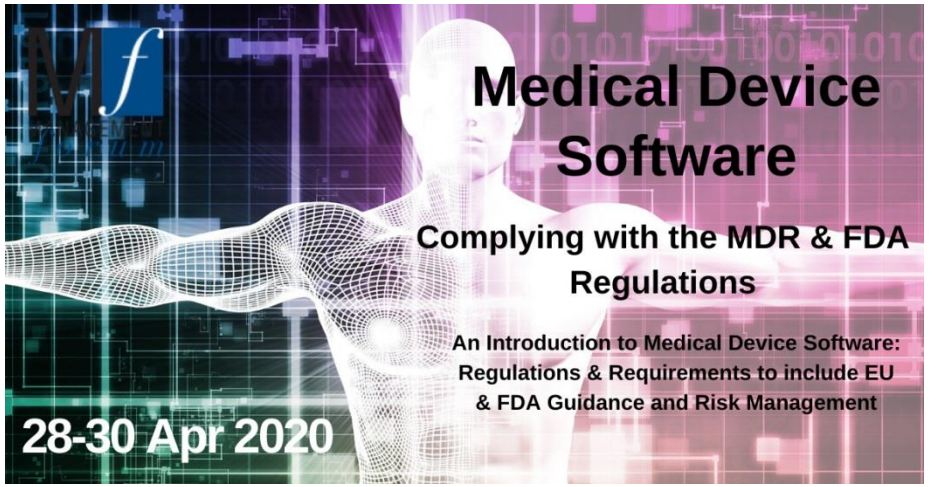
MDCG 2019-11 MDSW Guideline – Guidance on the Qualification and Classification of Software in MDR 2017/745 and IVDR 2017/746

Adopted Oct 2019

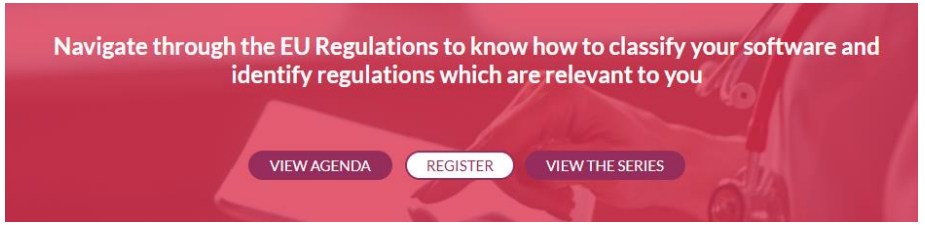


Borderline manual on qualification and classification for MDR 2017/745 and IVDR 2017/746

Adoption date not determined yet



https://management-forum.co.uk/product/details/2149/medical-device-software-complying-with-the-mdr-fda-regulations



http://www.mdti-global.co.uk/event/medicaldevicesoftware

Koen Cobbaert

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