The new era of digital health - opportunities and regulatory challenges

Nikolas Gregor PTMG@home, 8th October 2020

Agenda

1. The opportunities of digital health
2. Regulatory challenges part I: Qualification as a medical device
3. Regulatory challenges part II: Classification and consequences
4. Regulatory challenges part III: Artifical intelligence and safety assessment
5. Regulatory challenges part IV: Reimbursement
6. A few words on IP

What is digital health?

*"Application of **data** to the delivery of healthcare, using **computational and telecommunications technologies** to support **business** process workflow, **clinical** workflow, and **patient data management**"*

Frost & Sullivan

Practical examples

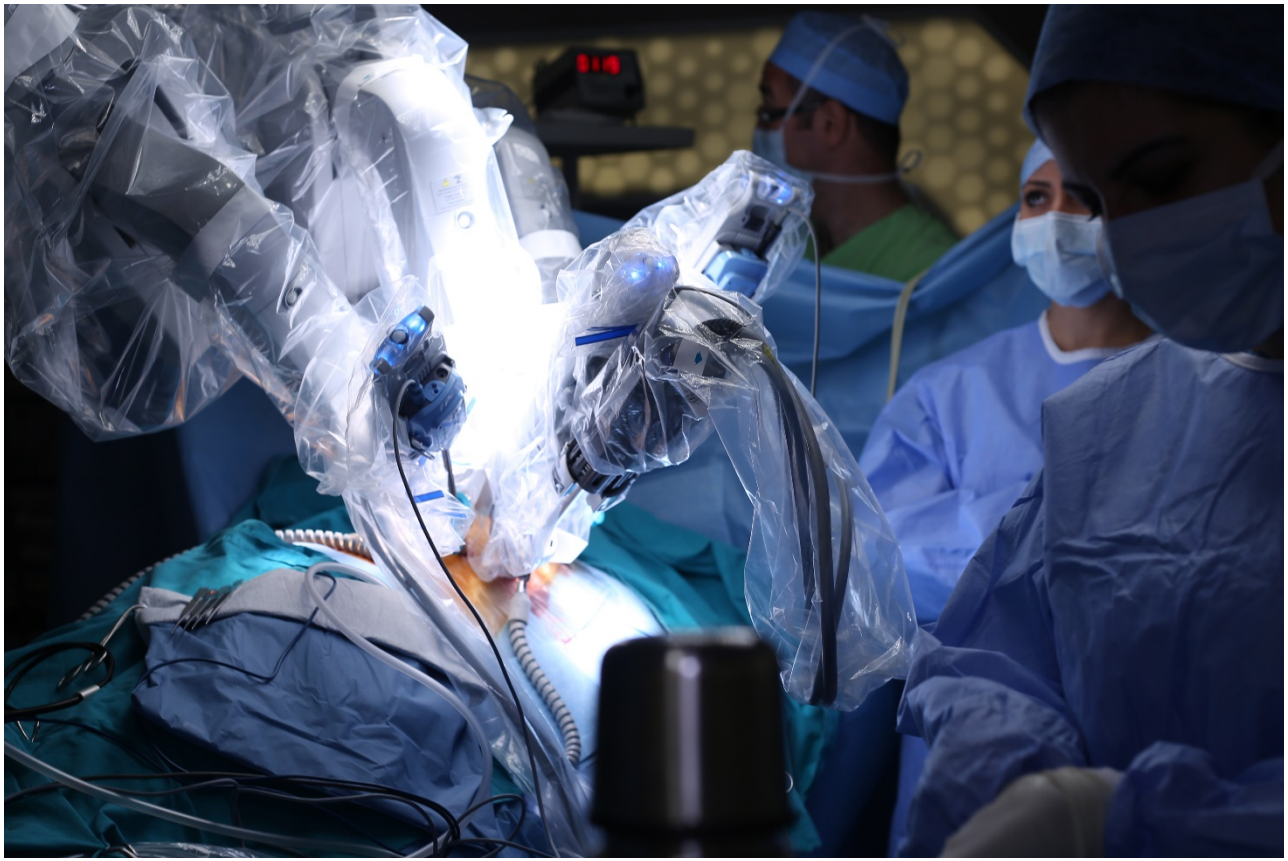
Hospital management software

Practical examples

Electronic health record

Practical examples

Robotics



Practical examples

Telemedicine

Practical examples

Clinical decision support systems (CDSS)

Practical examples

Medical apps

Practical examples

Medical apps: AliveCor

Practical examples

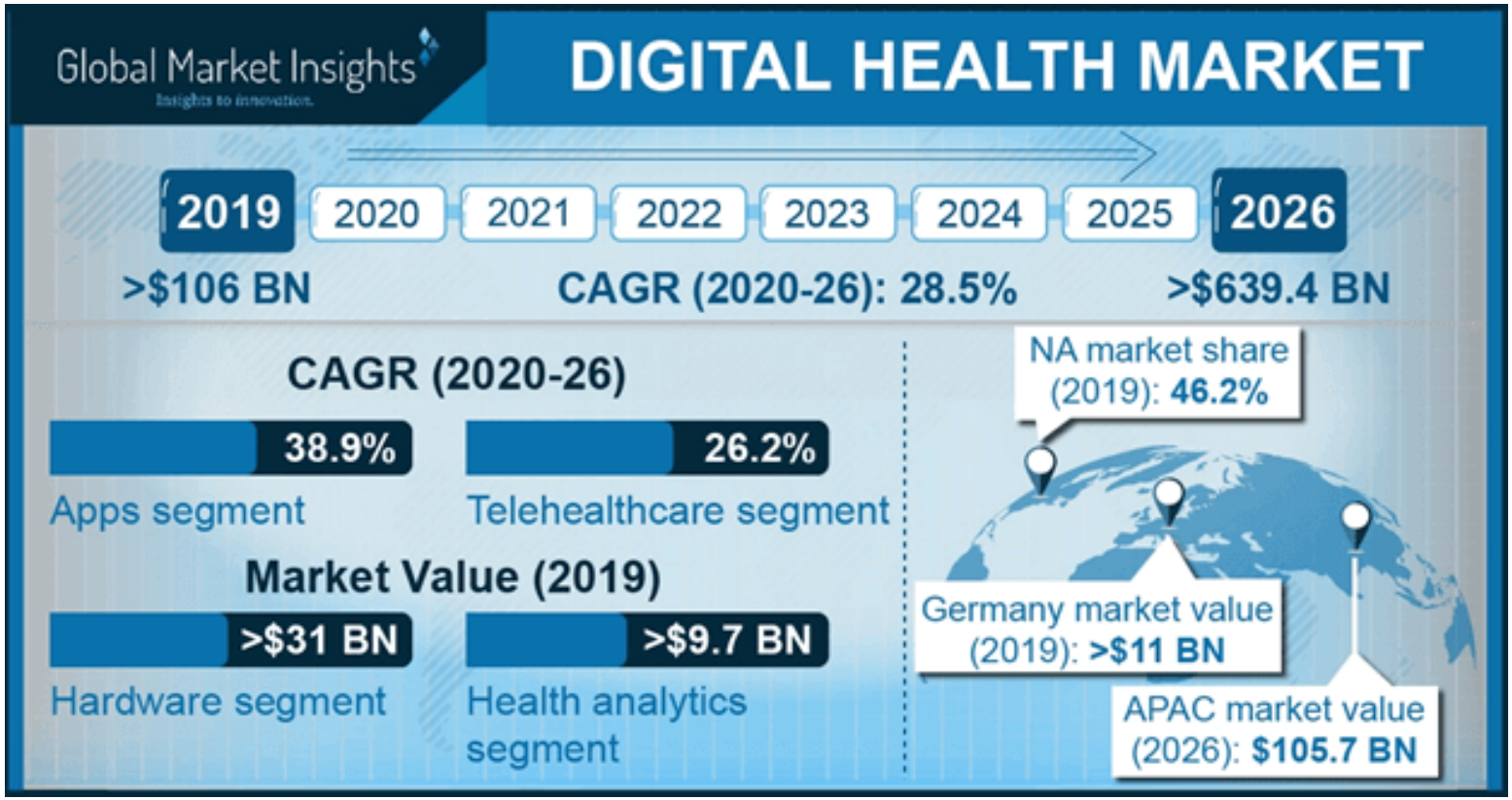
Medical apps: ADA

Hi, I'm Ada.
I can help if you're feeling unwell.

Opportunities of digital health

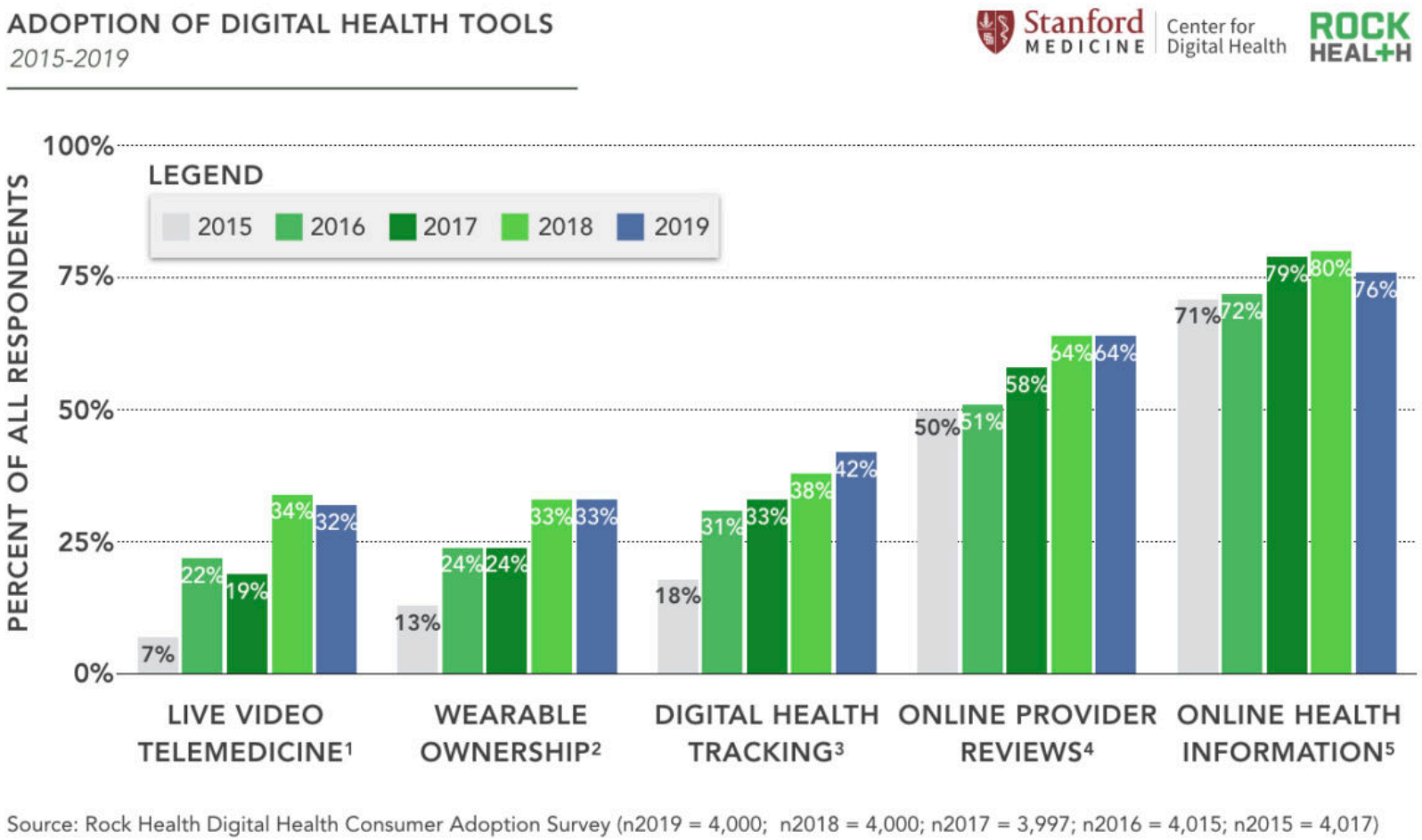
Opportunities of digital health

A field of constant growth…



Source: Ugalmugle/Swain, Digital Health Market Size By Technology, Industry Analysis Report, Global Market Insights, June 2020

Opportunities of digital health



Rock Health and the Stanford Center for Digital Health, *Digital Health Consumer Adoption Report 2019*

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Challenges Part I: Qualification as a Medical Device

Article 1(2)(a) Medical Devices Directive:

"Medical device" means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination (…) **intended by the manufacturer** to be used for human beings **for the purpose of:**

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- **investigation, replacement or modification of the anatomy or of a physiological process**,
- control of conception,

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

Challenges Part I: Qualification as a Medical Device

European Court of Justice, 22 November 2012, C-219/11,
Brain Products vs BioSemi

- **Case:**
  - System ‘ActiveTwo’ to record human brain activity
  - According to manufacturer: No medical purpose
  - But: Use for medical purposes possible

- **Question:**

  *Does a product constitute a medical device only in the case where it intended for a **medical purpose**?*

Challenges Part I: Qualification as a Medical Device

- **Answer: Yes.**

- Recital 6 on software, added in 2007:

    i. Software is a medical device when *intended* by the manufacturer for a medical purpose
    ii. Software for general purposes is not a medical device even if used in a medical context

- 'Non-software devices' and 'software' to be treated equally.

Challenges Part I: Qualification as a Medical Device

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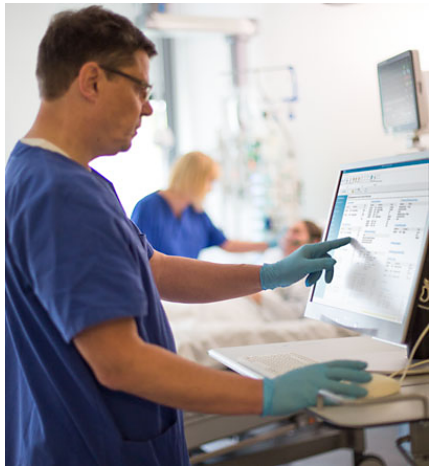
Challenges Part I: Qualification as a Medical Device

European Court of Justice, 7 December 2017, C-329/16, *Philips and Snitem vs France*

- **Case:**
  - Philips' "IntelliSpace Critical Care and Anesthesia": Hospital management software, especially treatment surveillance, for the ICU
  - One function: detection of contraindications, drug interactions and excessive doses

- **Question:**

  Medical device although it does not itself act in or on the human body?



Challenges Part I: Qualification as a Medical Device

- **Answer: Yes.**

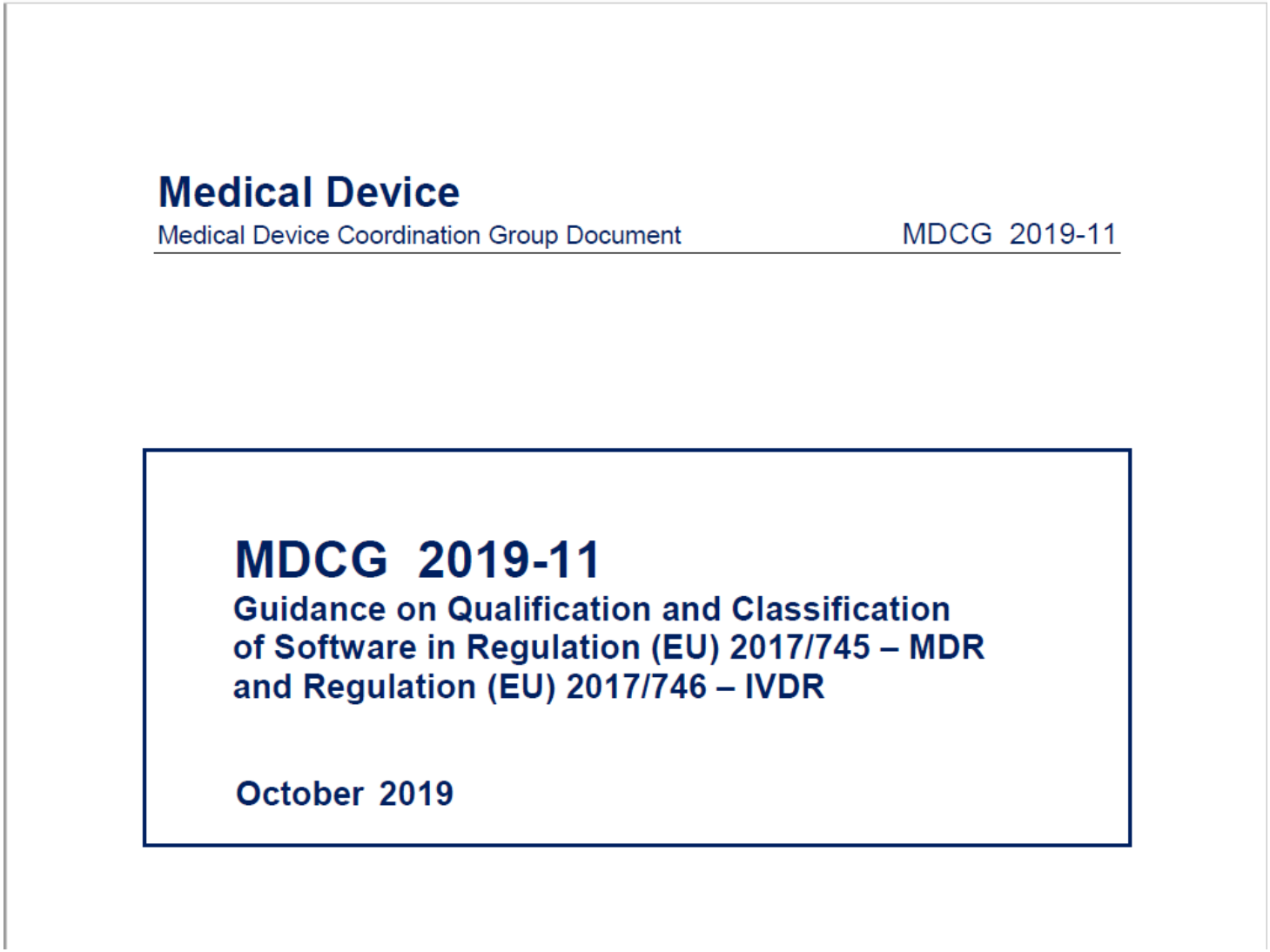
> *"Software, of which at least one of the functions has a medical purpose, is, in respect of that function, a medical device, even if that software does not act directly in or on the human body."*

Challenges Part I: Qualification as a Medical Device

- **Result:**

- Normally: Two cumulative conditions: (1) Objective pursued and (2) action resulting therefrom.
- For software:
  - Only objective is decisive, not the manner in which the effect is being produced (on/in the body or not).
  - Objective must be specifically medical.

Challenges Part I: Qualification as a Medical Device



Medical Device

Medical Device Coordination Group Document MDCG 2019-11

MDCG 2019-11

Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR

October 2019

Challenges Part I: Qualification as a Medical Device

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Guidance:

Medical device stand-alone software including apps (including IVDMDs)

New regulations to replace the current regulatory system have now 'entered into force'. We have produced an Introductory Guide to new medical device regulations:

This guidance applies to the current regulatory framework - new regulations may result in changes to the classification criteria for software medical devices.

Click for next page

For full functionality, this document is best viewed in Acrobat reader.

Challenges Part I: Qualification as a Medical Device

Contains Nonbinding Recommendations

Policy for Device Software Functions and Mobile Medical Applications

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 27, 2019.

Document originally issued on September 25, 2013.

This document supersedes "Mobile Medical Applications" issued February 9, 2015.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Challenges Part I: Qualification as a Medical Device

Standalone software

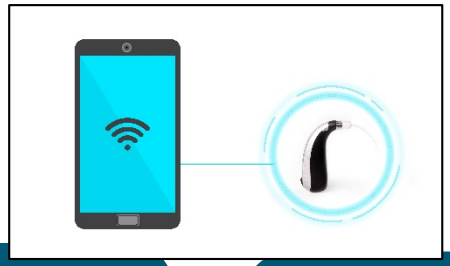
Medical purpose?

Further questions

Software

Incorporated in a medical device

= component



In combination with a medical device

Enables function of device

= accessory

Challenges Part I: Qualification as a Medical Device

Specific medical purpose

vs. medical context

Action on data

vs. storage, communication, simple search

For individual patient?

vs. aggregate population data, epidemiological studies

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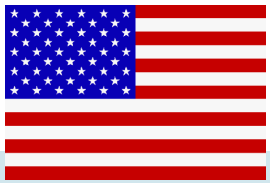
Regulatory challenges part II: Classification and consequences

CE

Directive 93/42/EEC on medical devices

- Registration of manufacturer and device
- Conformity assessment (i) by manufacturer or (ii) by notified body
- Quality management system
- Labeling requirements
- Post-market surveillance



FDA

Federal Food, Drug, and Cosmetic Act

- Establishment registration
- Medical device listing
- (i) Premarket approval or (ii) premarket notification based on substantial equivalence (unless exempt)
- Quality system regulation
- Labeling requirements
- Medical device reporting

Regulatory challenges part II: Classification and consequences

Low risk

High risk

Class I

- Mostly: Non-invasive devices
- EU: Mostly conformity assessment without notified body
- USA: Mostly no premarket notification




Class IIa and IIb

- Mostly: Invasive devices
- EU: Conformity assessment with notified body
- USA: Special controls and premarket notification



Class III

- High risk devices
- EU: Clinical investigation, notified body
- USA: Clinical study, premarket approval


Regulatory challenges part II: Classification and consequences

(MDR)

- Major game changer: **MDR**

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

- In force since 25 May 2017, applicable from **26 May 2021** (postponed by 1 year due to COVID19 pandemic)

Regulatory challenges part II: Classification of medical software

Selection of important areas of change:

- New classification rules
- Vigilance and market surveillance
- Responsible person
- Registration, UDI, EUDAMED
- Clinical evaluation
- UAAs by notified bodies and authorities

Regulatory challenges part II: Classification of medical software

Software under the MDR: "The classification nightmare"

- Current rule:
  - Software = active medical device
  - Roughly: Software is in class IIa/IIb if it is intended to
    - control or monitor the performance of active therapeutic or diagnostic devices in Class IIa/IIb,
    - allow direct diagnosis or monitoring of vital physiological processes,
  - All others: Class I
  - Medical apps: mostly class I

Regulatory challenges part II: Classification of medical software

- **New: Rule 11**
  - Generally: Software intended to provide information used to take decisions with diagnostic or therapeutic purposes = class IIa
  - If decisions have impact potentially causing
    - death or permanent deterioration of health = class III
    - a serious deterioration or surgical intervention = class IIb
  - Monitoring physiological processes = class IIa / class IIb

- **Consequence: All medical apps need conformity assessment by Notified Body**

- Software without certificate under MDD can no longer be marketed. Only software already legally on the market can be sold until 27 May 2025.

Regulatory challenges part II: Classification of medical software

Bottle neck problem:

- So far: 52 notified bodies to certify software
- Under MDR:

Bodies Found : 17

Search criteria :

Legislation : Regulation (EU) 2017/745 on medical devices
Procedure /
Article or annex : ALL
Products : MDA 0315 Software
Horizontal technical competence : ALL

Search

Withdrawn/Expired/Suspended Notifications/NBs are not displayed in this list, you can find them in the Body module under the hyperlink "Withdrawn/Expired/Suspended Notifications/NBs"

Body type	Name	Country
NB 2265	3EC International a.s.	Slovakia
NB 0086	BSI Assurance UK Ltd	United Kingdom
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary
NB 1912	DARE!! Services B.V.	Netherlands
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 2460	DNV GL Presafe AS	Norway
NB 0297	DQS Medizinprodukte GmbH	Germany
NB 0459	GMED	France
NB 0051	IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A.	Italy
NB 2862	Intertek Medical Notified Body AB	Sweden
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0482	MEDCERT ZERTIFIZIERUNGS- UND PRÜFUNGSGESELLSCHAFT FÜR DIE MEDIZIN GMBH	Germany
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany

Regulatory challenges part II: Classification of medical software

FDA approach: Focus of regulatory oversight vs. enforcement discretion

1) Software for supplemental clinical care, by coaching or prompting, to help patients manage their health in their daily environment
2) Software providing easy access to information on patients' health conditions or treatments
3) Software helping patients communicate with healthcare providers
4) Software functions that perform simple calculations routinely used in clinical practice

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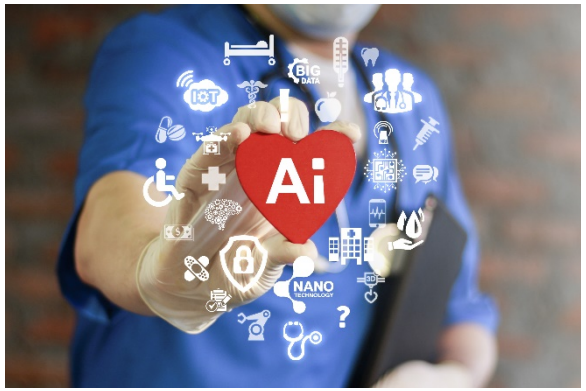
Regulatory challenges part III: Artificial intelligence

What is artificial intelligence?

- Algorithms build their own statistical models based on sample data, known as "training data", by identifying patterns ("machine learning")
- Deductive application of such "machine rules" in order to make predictions or decisions without being explicitly programmed to perform the task
- Programmers cannot predict outcome, "black box"



Regulatory challenges part III: Artificial intelligence and safety assessment

Examples:

1) ADA

- AI based Chatbot
- Poses a series of questions that are personalized by its algorithm based on the responses from each user
- It then uses that information to suggest possible health issues and next steps, e.g. making an appointment

Hi, I'm Ada.
I can help if you're feeling unwell.

Regulatory challenges part III: Artificial intelligence and safety assessment

Examples:

2) Viz.AI Contact

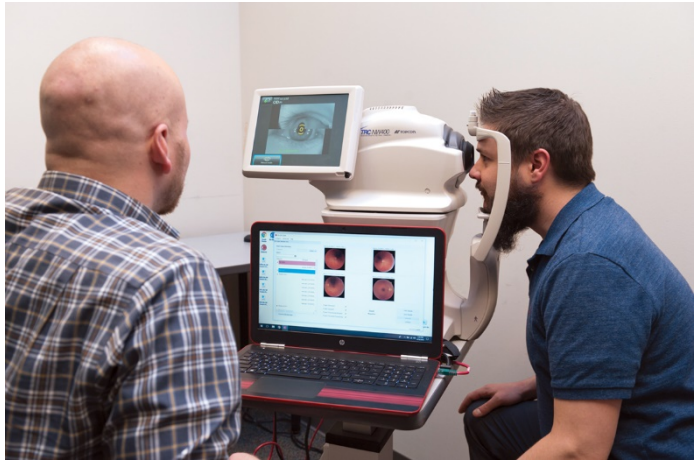
- AI algorithm to analyze CT brain images for indicators of stroke
- Notifies neurovascular specialist with a text message if a large vessel blockage has been identified
- Final diagnosis still made by specialist
- Approved by FDA in February 2018

Regulatory challenges part III: Artificial intelligence and safety assessment

Examples:

3) IDx-DR

- AI algorithm to analyze eye images to detect greater than mild level of diabetic retinopathy (common cause of vision loss of diabetes patients)
- Screening can be made by non-eye specialist
- Screening decision without the need for a clinician to also interpret the image or results
- Approved by FDA in April 2018



Regulatory challenges part III: Artificial intelligence and safety assessment

MDR: Annex I, no. 17

- Software must be designed to ensure repeatability, reliability and performance in line with their intended use
- Software shall be developed and manufactured in accordance with the state of the art, taking into account the principles of development life cycle, risk management, including information security, verification and validation

How can repeatability, reliability and performance as well as verification and validation be ensured for "black box AI"??

Regulatory challenges part III: Artificial intelligence and safety assessment

- Current solution (FDA): **"Locked algorithms"**

- FDA paper of April 2019: **"Total product lifecycle (TPLC) regulatory approach"**
  1) Quality Systems and Good Practices
  2) Initial Premarket Assurance
  3) Approach for modifications after initial review
  4) Transparency and real-world performance monitoring

- EU: **White Paper on Artificial Intelligence**, February 2020
  - Application of the existing legal framework
  - Amending this framework for high-risk applications: training data; data and record-keeping; information to be provided; robustness and accuracy; human oversight; specific requirements for certain particular AI applications, such as those used for purposes of remote biometric identification

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Regulatory challenges part IV: Reimbursement

Medical apps paid by health insurance?

- Germany: Digital Healthcare Act of December 2019
- Reimbursement of digital medical devices (class I and IIa)
- Basic requirements
  - ✓ Inclusion in the directory for digital health applications by BfArM
  - ✓ Prescription (or permission)
- "Live" since April 2020

A "world's first"?

Regulatory challenges part IV: Reimbursement

Digital Healthcare Act of December 2019

- Requirements and process:
  - ✓ Applicant must prove:
    - App's safety, quality and usability
    - Data privacy
    - Positive effects on care
  - ✓ Fast track: Assessment by BfArM within 3 months
  - ✓ If positive effects cannot yet be proven: Preliminary approval for max. 24 months and separate evaluation
  - ✓ In case of definitive inclusion in the list: Price negotiations between manufacturer and the National Association of Sick Funds

Regulatory challenges part IV: Reimbursement

Digital Healthcare Act of December 2019

- Currently: 22 complete applications with BfArM (including ADA)
- First list to be published by the end of September 2020 (?)

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6. **A few words on IP**

A few words on IP

Protection of software and AI inventions

- Software usually protected by copyright (source code)

- Mathematical methods (algorithm) excluded from patentability
- But: If claim relates to a method involving use of a device, invention is of technical nature → causal link to a technical purpose

- Who is the inventor in case of AI-derived inventions?
  - Principle of human creation
  - Change in the law necessary
    - Programmers of AI software?
    - Persons feeding software with data?
    - Company which funded the software? Company which owns it?

A few words on IP

Protection under trade mark law

- Registration for "computer software": Too broad and contrary to the public interest? Bad faith?
- **ECJ, judgment of 29 January 2020, case C-371/18 – Sky vs SkyKick**
  - ✓ Trade mark cannot be declared invalid because of lack of clarity and precision
  - ✓ Bad faith cancellation for lack of any intent to use is (only) possible if apparent that the owner filed with the intention of undermining the interests of third parties, or of obtaining an exclusive right for purposes other than those falling within the functions of a trade mark.

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