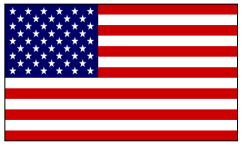
U.S. FDA:n QSR, uusimmat ohjeistukset ja tunnustetut standardit



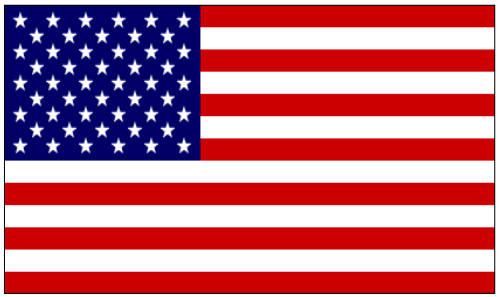
BUSINESS FINLAND

Lääkinnällisten laitteiden regulaatiot – uusimpia tuulia lännestä ja idästä

Health Tuesday, Business Finland
3.5.2022
Tom Ståhlberg

RaLex Partners

USA the biggest MD market and is dominating also worldwide



45 % of global MD markets

10 out of 15 biggest MD companies
25901 MD companies (12891 non-USA)
50 % exported (about 30-40 % to EU)
1/3 global market share

U.S. Department of Health and Human Services
FDA
Food and Drug Administration

CDRH 1802 (+85) persons; total about 20 000 persons

Federal Food, Drug, and Cosmetic Act

Long title	To prohibit the movement in interstate commerce of adulterated and misbranded food, drugs, devices, and cosmetics, and for other purposes.
Acronyms	FFDCA, FD&C Act

Ei protektionismia! Kuluttaja (potilas) keskiössä

FDA Mission

The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

Vaativa, hidas, kaupan este… Onko muuttumassa?

FDA is responsible for **advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable** and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.

Erä 1. USA 1-0.

Isommat ja voimakkaammin kasvavat MD kotimarkkinat
Suuremmat MD valmistajat ja eniten yrityksiä
Suurin MD vienti

Regulatiivinen kulttuuri kypsempi
Regulatiivinen lainsäädäntö ajan tasalla
Viranomaiset iskukykyisiä, MD noin 2000 henkilöä
Kaikki samassa virastossa, noin 20 000 henkilöä
Mahtavan laajat ja hyvät kotisivut
Laaja neuvontatoimintaa
Parempi valmius hoitaa ”emergency use” MD pandemian aikana

Erätauko 1?

Onko lainsäädäntö implementoitu?

Ohjeistukset?

Tunnustetut konsensusstandardit? (Recognized)

Muuta?

Onko lainsäädäntö implementoitu?

Ohjeistukset?

Tunnustetut konsensusstandardit? (Recognized)

Muuta?

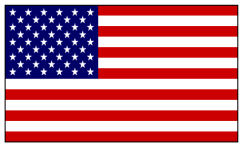
618 MD ohjeistusta (2670 kaiken kaikkiaan)

16 kpl uusi tai päivitetty 2022
40 kpl uusi tai päivitetty 2021
44 kpl draft guidance, toki miinus: 19 kpl 2007-2019!

A-list (2022):
6 final, 10 draft
B-list (2022):
2 final, 5 draft

Päätelmä: Valtava määrä;
sekä ylläpidetään että modernisoidaan

Esim. Cybersecurity – Premarket I. jo 2005!



GUIDANCE DOCUMENT

Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

APRIL 2022

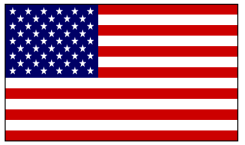
Download the Draft Guidance Document | Read the Federal Register Notice

Draft

Not for implementation. Contains non-binding recommendations.

This guidance is being distributed for comment purposes only.

Esim. Cybersecurity – Postmarket



GUIDANCE DOCUMENT

Postmarket Management of Cybersecurity in Medical Devices

Guidance for Industry and Food and Drug Administration Staff

DECEMBER 2016

Huom.! Pari muutakin ohjeistusta

Onko lainsäädäntö implementoitu?

Ohjeistukset?

Tunnustetut konsensusstandardit? (Recognized)

Muuta?

Recognized = EU:ssa harmonized
EU:ssa Z-liite, täydentää mutta hidastaa oleellisesti

1473 kpl
Linjassa kansainvälisten viimeisten versioiden kanssa
Myös USA-spesifisiä, esim CLSI:n ja 14 muun organisaation

Onko lainsäädäntö implementoitu?

Ohjeistukset?

Tunnustetut konsensusstandardit? (Recognized)

Muuta?

UDI (Unique Device Identification) ja tietokanta GUDID

Luokka III 2014

Luokka I 2020

Tietokantoja

Enforcement etc. 10 kpl

Medical Devices 27 kpl

Huom.! Freedom of Information Act

Erä 2.

…

1906 Food and Drugs Act…

1938 The Federal Food, Drug and Cosmetic Act

21 CFR

51 Muutosta myöhemmin…

1976 Medical Device Amendments

1990 Safe Medical Devices Act

1997 Food and Drug Modernization Act

2002 Medical Device User Fee and Modernization Act (also 2007)

Public Health Security and Bioterrorism Preperedness and Response Act

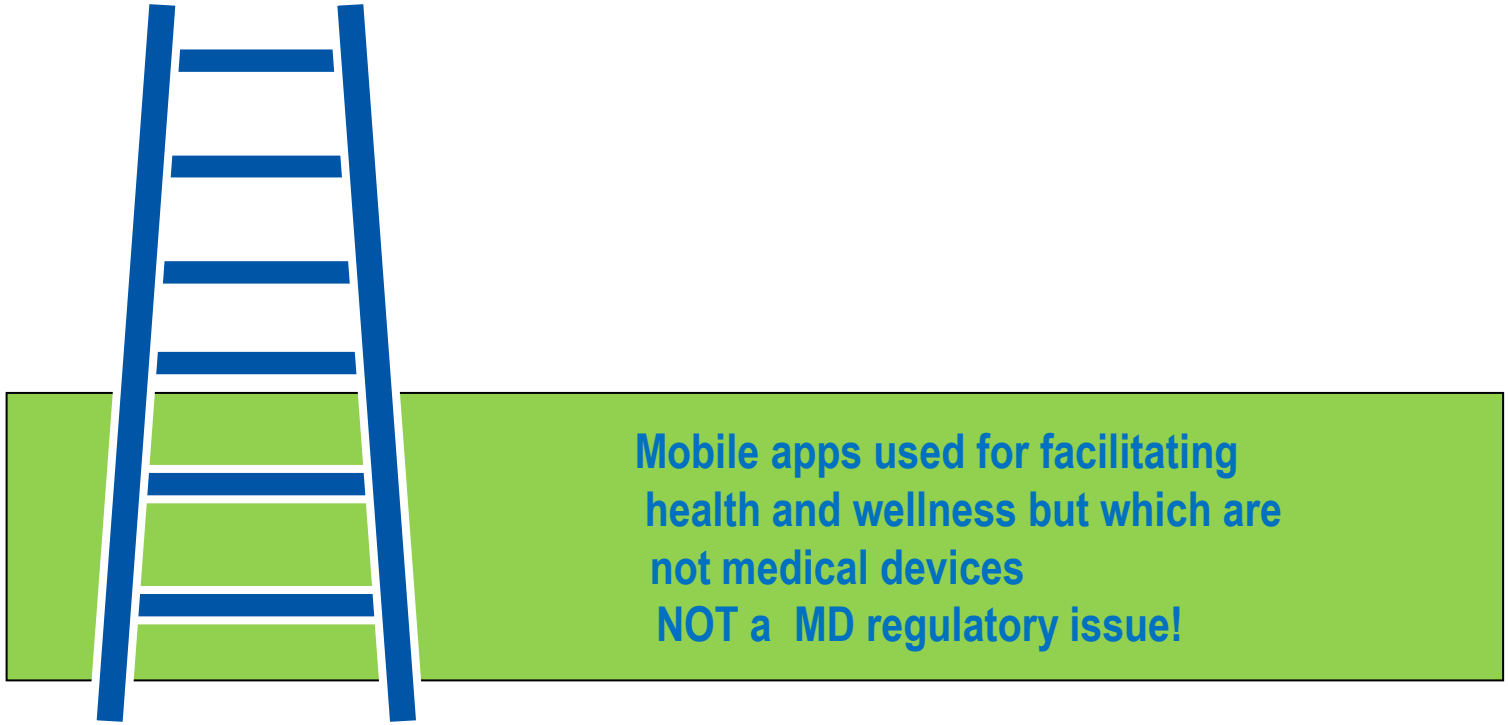
2012 Food and Drug Administration Safety and Innovation Act (FDASIA)

Medical Device User Fee and Modernization Act, also 2017 and coming 2023

2013 Pandemic and All-Hazards Preparedness Reauthorization Act

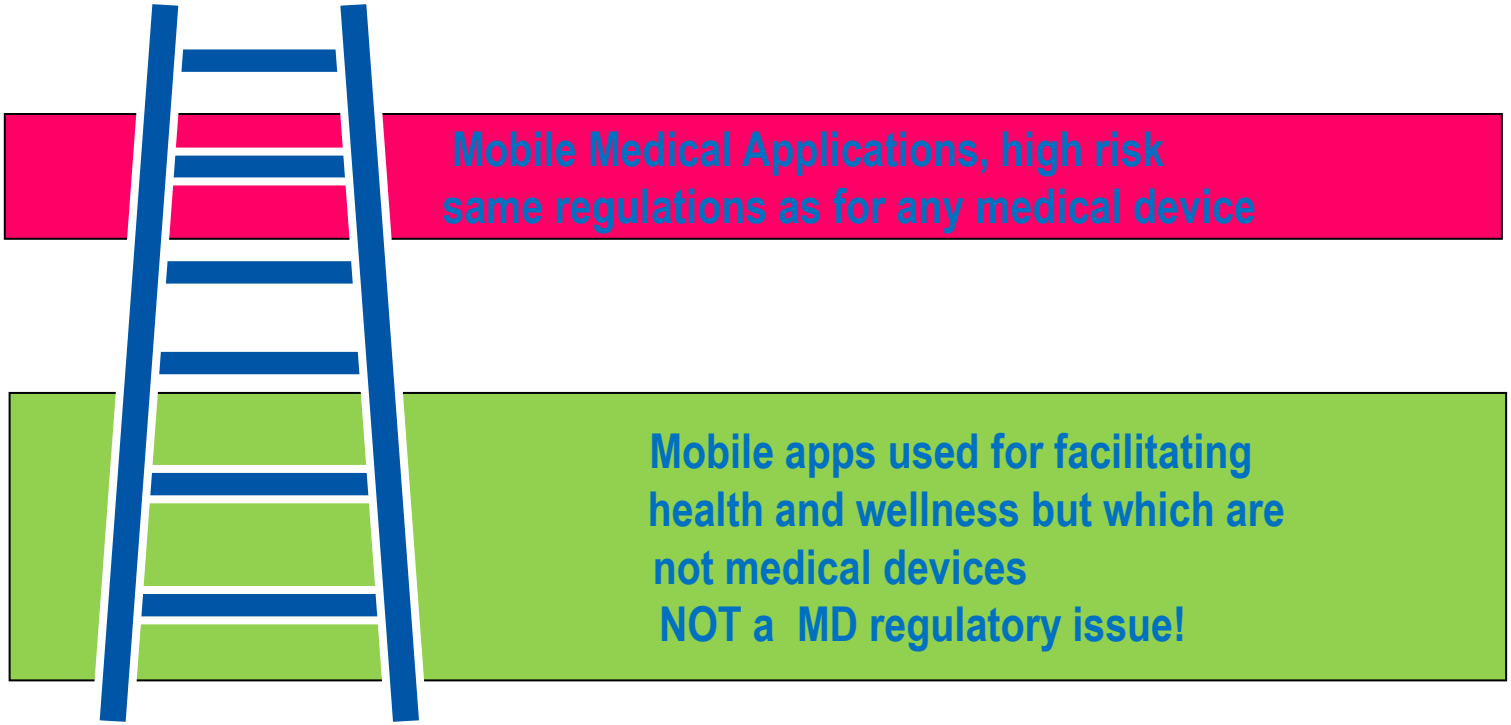
JA 2016 “SUURI MUUTOS”?

Mobile Medical Apps



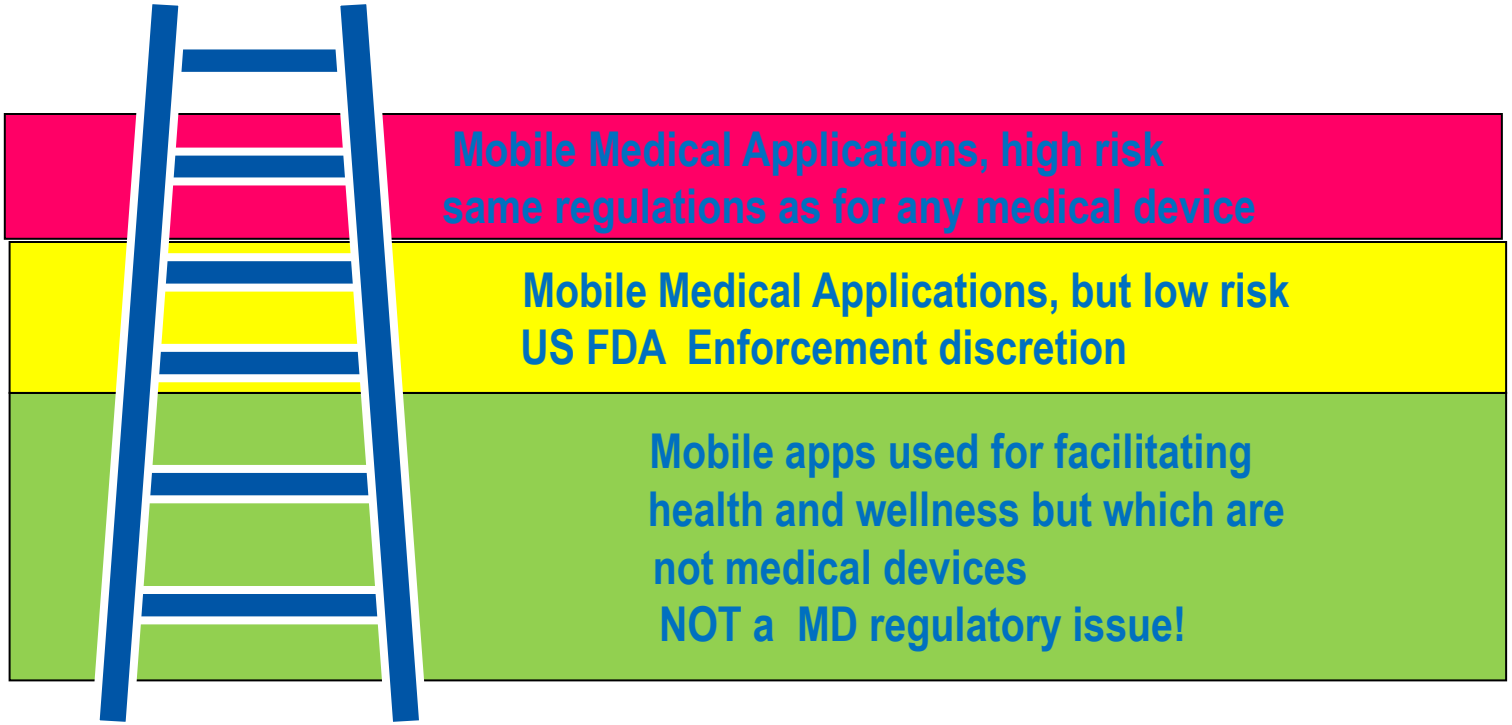
U.S. Department of Health and Human Services
FDA Food and Drug Administration

Mobile Medical Apps



U.S. Department of Health and Human Services
FDA Food and Drug Administration

Mobile Medical Apps



U.S. Department of Health and Human Services
FDA Food and Drug Administration

EU SW Risk classification: Class I gone in practice!

SW are all in demanding risk classes!

State of Healthcare situation or patient condition		Significance of Information provided by the SW to a healthcare situation related to diagnosis/therapy		
		High Treat or diagnose ~ *IMDRF 5.1.1*	**Medium** Drives clinical management ~ *IMDRF 5.1.2*	**Low** Informs clinical management *(everything else)*
	Critical situation or patient condition ~ *IMDRF 5.2.1*	**Class III** *Category IV.i*	**Class IIb** *Category III.i*	**Class IIa** *Category II.i*
	Serious situation or patient condition ~ *IMDRF 5.2.2*	**Class IIb** *Category III.ii*	**Class IIa** *Category II.ii*	**Class IIa** *Category I.ii*
	Non-serious situation or patient condition *(everything else)*	**Class IIa** *Category II.iii*	**Class IIa** *Category I.iii*	**Class IIa** *Category I.i*

Table 1: Classification Guidance on Rule 11

Discrepancy: forerunner, but slow market access

Recognized ”cures”

Exempt	previously mainly Class I proucts, 2017 also about 1000 Class II products (still general requirements apply)
510(k)	
PMA	
De Novo	Strongly recommended by U.S. FDA since 2017
Humanitarian	Exemptions when rare diseases, changed from 4000 to 8000 patients/USA in 2016
Other routes…	

Higher risk classes – market access far too slow!! Some MDs not even available in the USA due to too strong regulations!?
But, also here strong signals.

So what is going on in the USA?

21st Century Cures Act

President Obama, December 13, 2016, …"designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently."

21st Century Cures Act

The 21st Century Cures Act is a first-of-its-kind law. It lays out comprehensive steps designed to increase the pace of approvals.

The act includes a wide range of processes, including the discovery of cures in basic science, streamlining the drug and device development process, and unleashing the power of digital medicine and social media at the treatment delivery phase.

21st Century Cures Act

Low-Risk Medical Devices

The Food and Drug Administration is barred from regulating mobile health apps designed to maintain or encourage a healthy lifestyle if unrelated to the diagnosis, prevention, or treatment of disease. This law will help get more innovative, low-risk technology in patients' hands.

Erä 2. USA 2-0.

Class I and Class II exemptions expanded enormously (still general demands)
Some products totally exempted or enforcement discretion
Humanitarian from 4000/USA to 8000/USA
De Novo route strengthened

21st Century Cure Act revolutionizes the regulatory approaches!

Erätauko 2? Ja erä 3.

Radikaalit uudet tuulet puhaltavat jo ja uusia tulossa!

Breakthrough Devices program
Safer Technologies program (STeP)
Artificial Intelligence and Machine Learning Software as a MD Action Program
Pre-certification Program
From QSR to QSMR

Breakthrough Devices Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 18, 2018.

Replacing previous programs:

- **Expedited Access Pathway**
- **Priority Review**
- **Innovation Pathway**

Quicker routes for: 510(k), De Novo and PMA

The goal

The goal of the Breakthrough Devices Program is to provide patients and health care providers with timely access to these medical devices by speeding up their development, assessment, and review, while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization, consistent with the Agency's mission to protect and promote public health.

First Criterion	The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions

E.g. stroke, cancer, heart attack, ALS, severe trauma

Second Criterion	The device also meets at least one of the following:
	a. Represents Breakthrough Technology
	b. No Approved or Cleared Alternatives Exist
	c. Offers Significant Advantages over Existing Approved or Cleared Alternatives
	d. Device Availability is in the Best Interest of Patients

Breakthrough Device Program Summary

Direct interaction with FDA

Higher priority

Flexibility with regard to clinical studies (if safe, in postmarket)

Dedicated, available, well-trained FDA teams

QMS – less demands

Erätauko 2? Ja erä 3.

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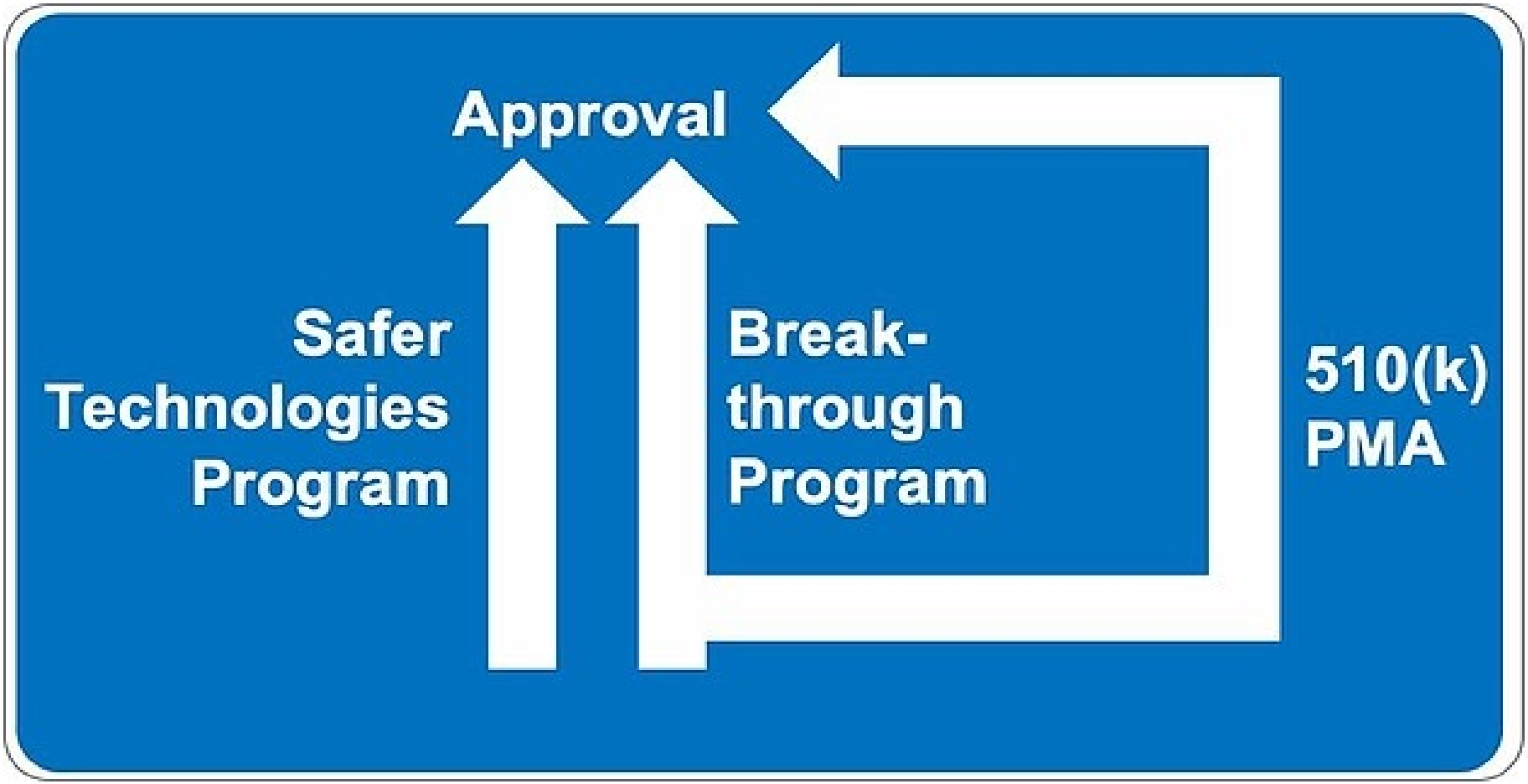

SaferTechnologies Program

Is intended for devices that diagnose or treat less serious diseases and injuries, for example, non-life-threatening or reversible diseases.

Decision within 60 days! Also, the manufacturer has to promise very fast responses in the process!

The company must initiate communication with FDA in early product development.

The goal is to reduce risks merely than to enhance benefits!

SaferTechnologies Program

The device must be innovative in that it improves the risk-benefit profile compared to its alternatives by:

1. **Reducing serious side effects**
2. **Reducing (device) errors**
3. **Reducing use errors of use that can lead to hazards or**
4. **Increasing the safety of another device or procedure, meaning accessories**

Erätauko 2? Ja erä 3.

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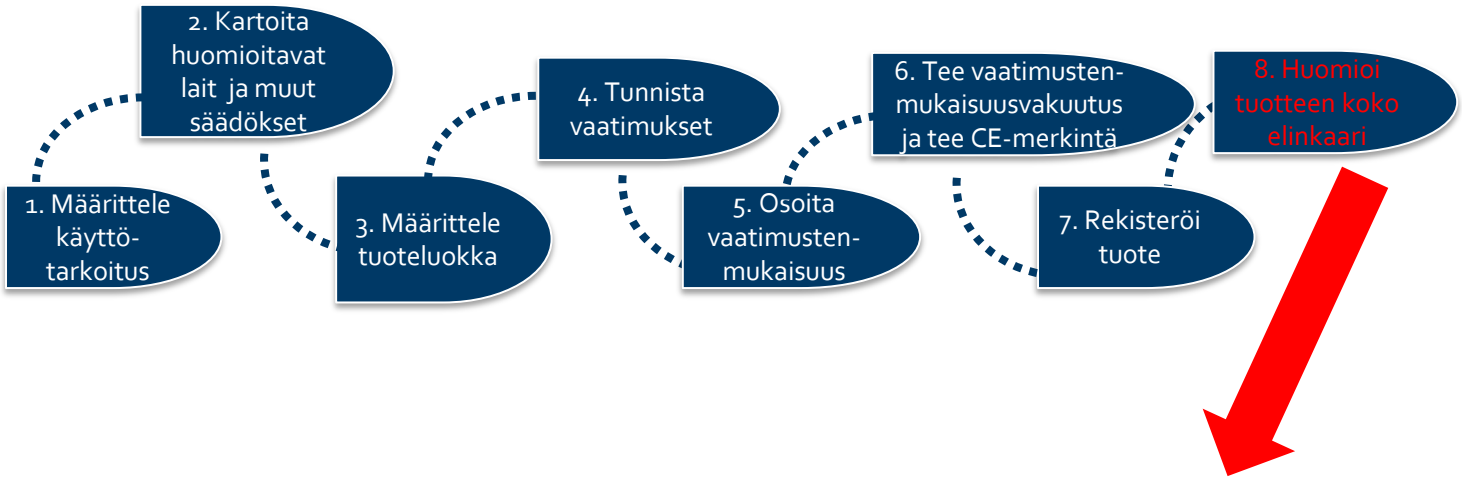
Optimistina uskon, että markkinoille saattamisen asti, AI (itseoppiva) on hoidettavissa ”älykkäästi” soveltaen olemassa olevaa sääntelyä!



Hankala! Lainsäädäntö ei tue/ole valmis hanskaamaan (dynaamista) tekoälyä!

Muutostenhallinta:

Ennen jokaista muutosta arvioitava sen merkitys monelta näkökulmasta (riskienhallinta! vaikuttavuus!) ja päätettävä esim. tarvitaanko uudelleen validointia ja ehkä jopa uudelleen rekisteröintiä – itseoppiva (muuttuva) tekoäly ei oikein istu tähän lähestymistapaan!

Kliininen arviointi – post market clinical follow-up

Riskienhallinnan päivittäminen

Post-market surveillance

Käytettävyysvaatimukset (normal use/abnormal use)

CAPA

Vigilance tilanteet

Statement from FDA Commissioner Scott Gottlieb, M.D. on steps toward a new, tailored review framework for artificial intelligence-based medical devices

2.4.2019

“They include the algorithm’s performance, the manufacturer’s plan for modifications and the ability of the manufacturer to manage and control risks of the modifications.”

“The predetermined change control plan would provide detailed information to the agency about the types of anticipated modifications based on the algorithm’s re-training and update strategy, and the associated methodology being used to implement those changes in a controlled manner that manages risks to patients.“

"…to assure that ongoing algorithm changes follow pre-specified performance objectives and change control plans, use a validation process that ensures improvements to the performance, safety and effectiveness of the artificial intelligence software, and includes real-world monitoring of performance"

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan

January 2021

Erätauko 2? Ja erä 3.

Radikaalit uudet tuulet puhaltavat jo ja uusia tulossa!

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From QSR to QSMR

Digital Health Software Precertification (Pre-Cert) Program

This proposed approach aims to look first at the software developer and/or digital health technology developer, rather than primarily at the product, which is what we currently do for traditional medical devices

In the Pre-Cert program, the FDA is proposing that software products from precertified companies would continue to meet the same safety and effectiveness standard that the agency expects for products that have followed the traditional path to market.

Erätauko 2? Ja erä 3.

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ISO 13485:2012 ja ISO 13485:2016

Quality System Regulation
21 CFR 820
Basic Introduction

Kimberly A. Trautman
FDA's Medical Device Quality Systems Expert

1 + 1 = 2 (QSR + ISO 13485:2016 = QMSR)

”The QMSR draft calls for the current QSR to be withdrawn and replaced by the QMSR, which is shorter in length because much of the QSR’s requirements are already “substantively similar” to what’s found in international quality systems standard ISO 13485:2016. The FDA had been harmonizing its QSR with ISO 13485 since early 2018.” Draft published February, 2022.

Voitte kommentoida < 24.5.2022

Erä 3. USA 3-0.

21st Century Cure Act revolutionizes the regulatory approaches!

Changes throughout to less burdensome approaches

+

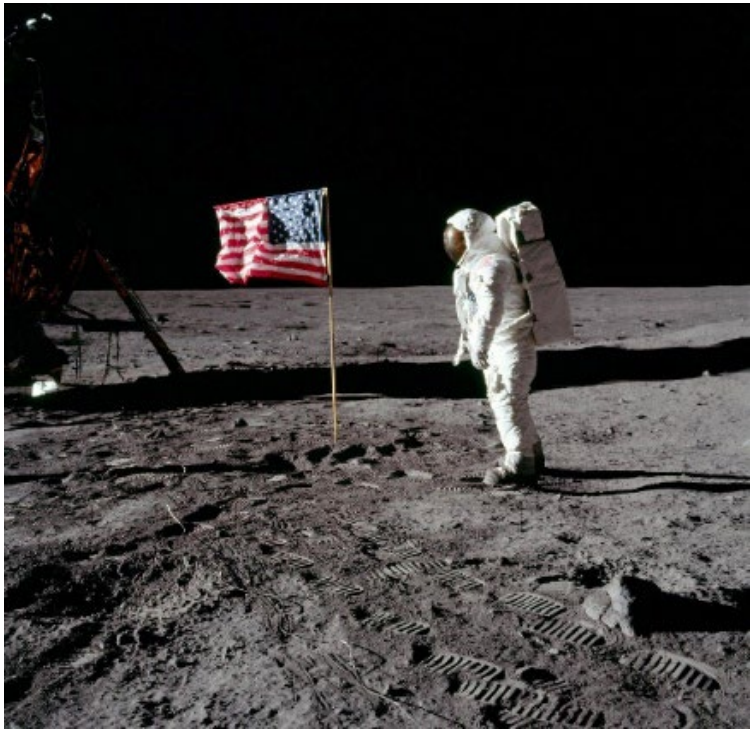
Major new regulatory approaches:

- **Enforcement discretion**
- **Breakthrough Devices program**
- **Safer Technologies program (STeP)**
- **Artificial Intelligence and Machine Learning Software as a MD Action Program**
- **Pre-certification Program**
- **From QSR to QSMR**

I. Ottelu USA 3-0, seuraava ottelu edessä…

Mutta, USA valmistautuu hyvin:

CDRH's Regulatory Science Priorities



CDRH's Regulatory Science Priorities

CONTENTS

Tulevaisuus?

Vapaus ilman vastuuta on kaaosta!

Maa tai yritys joka löytää oikean tasapainon voittaa!

Lääkinnällinen laite on oltava turvallinen ja käyttötarkoitukseensa soveltuva!

"Kaikki me noudatamme lakia voidaksemme olla vapaita." - Cicero

Most competitive regulations:

Mathematical model available will tell who wins…

$$AVE_{js} = \exp\left\{\frac{\mu_{js} - \mu_{*s}}{1-\sigma}\right\} - 1.$$

Still, better outcome evidence: how safe and efficient the medical devices are for real patients!