POLMED
OGÓLNOPOLSKA IZBA GOSPODARCZA WYROBÓW MEDYCZNYCH

US Market Entry Considerations

22 June 2021

Rick Proctor

Jeff Smith

BreakThrough Life Science Consulting

AMERICAN CHAMBER OF COMMERCE IN POLAND

THE BRAVEHEART GROUP INC

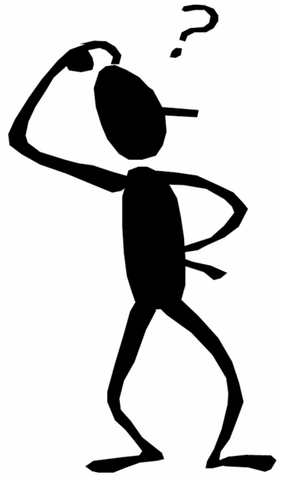
US Market Entry Considerations

A copy of this presentation will be sent to you following the session

QUESTIONS?

Post any questions onto the Webex Chat.

We'll answer them at the end of the session



US Market Entry Considerations

Agenda

- FDA Current Pathways
- Software as a Medical Device (SaMD)
- Mobile Medical Apps
- Laboratory Developed Tests (LDTs)
- Quality Systems - ISO vs. FDA
- Intellectual Property
- US Government Contracting
- Promotional Practices
- Questions

Current Pathways[1]

1. https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/how-study-and-market-your-device

Class I
General Controls

- Feedback Controls - traceability, complaint handling
- No Design Controls
- No 510(k) - product listed w/FDA, begin marketing/ distribution

Class II
General Controls & Special Controls

- Feedback Controls - traceability, complaint handling
- Design Controls - design input/output, verification/ validation
- Clinical Evidence - possible, at FDA discretion, for safety and efficacy
- 510(k) comparing device vs. predicate(s)

Class III
General Controls and Premarket Approval

- Feedback Controls
- Design Controls
- Mfg Controls - supply chain established w/ restrictions on changes
- Clinical Evidence - required for safety and efficacy
- Pre-Market Approval (PMA) - submission + clinical evidence

De Novo

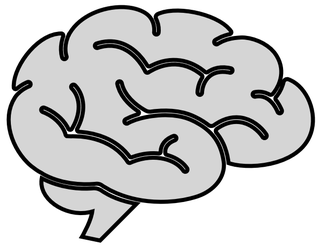
- No predicate, new technology
- Classification/pathway based on risk (None, 510(k) or PMA)

FDA - Device Classification[1]

Classification Panel -
21 CFR 862-892

- OR -

513(g) Request
(fee required)



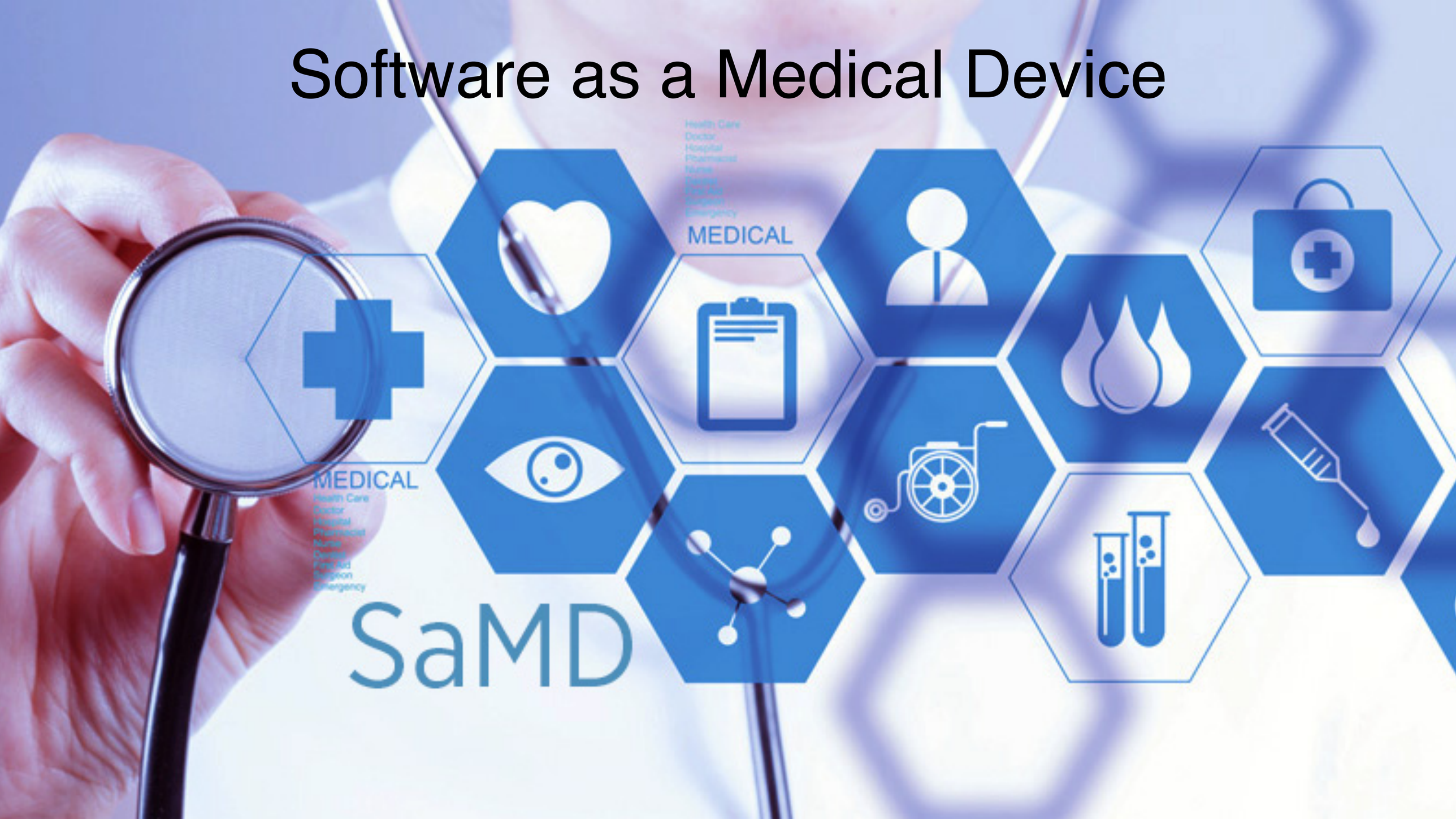
Research

Formal
Request

Follow clearance process outlined in
classification regulation for your device

1. https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/how-study-and-market-your-device

Software as a Medical Device



SaMD Definition

Software[2] intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device[3]

- May be used in combination with other medical devices, other SaMD or general purpose software
- May include in-vitro-diagnostic
- Capable of running on general purpose platforms
- Provide means and suggestions for mitigation of a disease
- Provide information for determining compatibility, detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities
- Aid to diagnosis, screening, monitoring, determination of predisposition; prognosis, prediction, determination of physiological status
- Mobile apps that meet this definition
- May be used in combination with other medical devices, other SaMD or general purpose software

2. IMDRF/SaMD WG/N10FINAL:2013 Software as a Medical Device (SaMD): Key Definitions
3. IMDRF/SaMD WG/N12FINAL:2014 Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations

Examples that ARE SaMD[3]:

Diagnosis of a condition using the tri-axial accelerometer that operates on the embedded processor on a consumer digital camera

Allows a commercially available smartphone to view images for diagnostic purposes obtained from an MRI medical device

CAD - computer-aided detection software running on a general purpose computing platform located in the image-acquisition hardware medical device

Provides parameters that become the input for a different hardware medical device or other SaMD (e.g. treatment planning software that supplies information used in a linear accelerator)

3. IMDRF/SaMD WG/N12FINAL:2014 Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations

Examples that are NOT SaMD[3]:

Used to “drive or control” the motors and the pumping of medication in an infusion pump

Relies on data from a medical device, but does not have a medical purpose (e.g., software that encrypts data for transmission from a medical device)

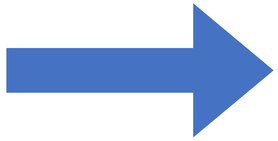
Software that monitors X-Ray tube performance to anticipate the need for replacement

Integrates and analyzes laboratory quality control data to identify increased random errors or trends in calibration on IVDs

3. IMDRF/SaMD WG/N12FINAL:2014 Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations

SaMD

Intended Use/
Intended Purpose



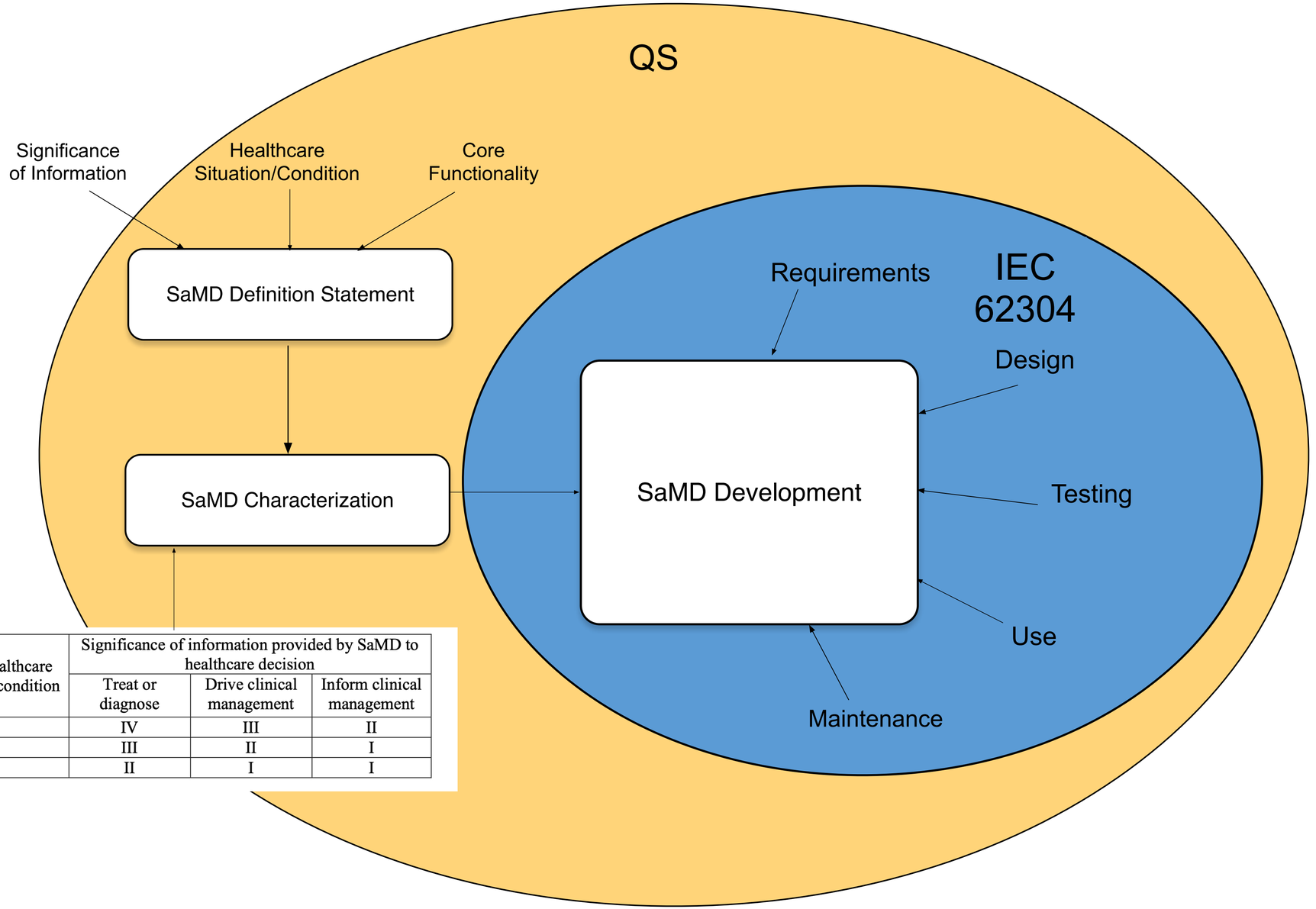
Characterization

Intended Use/Intended Purpose[4]

> The term “intended use / intended purpose” is the objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer

4. GHTF/SG1/N70:2011 “Label and Instructions for Use for Medical Devices”

SaMD[3,5]



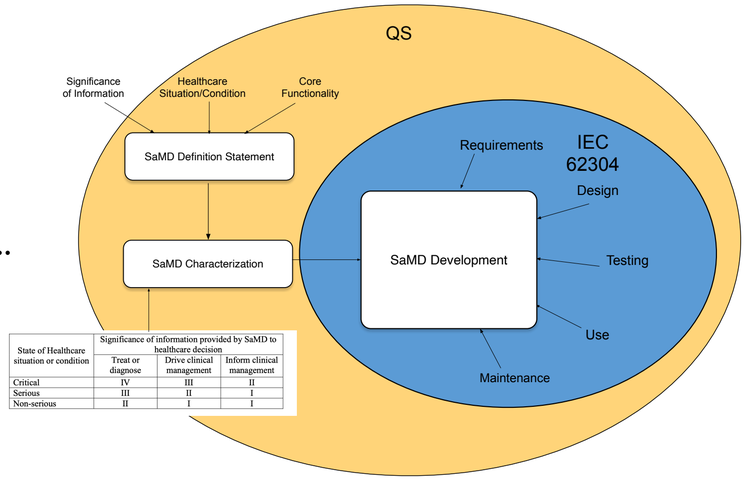
State of Healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

3. IMDRF/SaMD WG/N12FINAL:2014 Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations
5. IMDRF/SaMD WG/N23 FINAL:2015 Software as a Medical Device (SaMD): Application of Quality Management System

SaMD

FDA believes an “agile regulatory paradigm is necessary to accommodate the faster rate of development and potential for innovation in software-based products[6]”

with this...



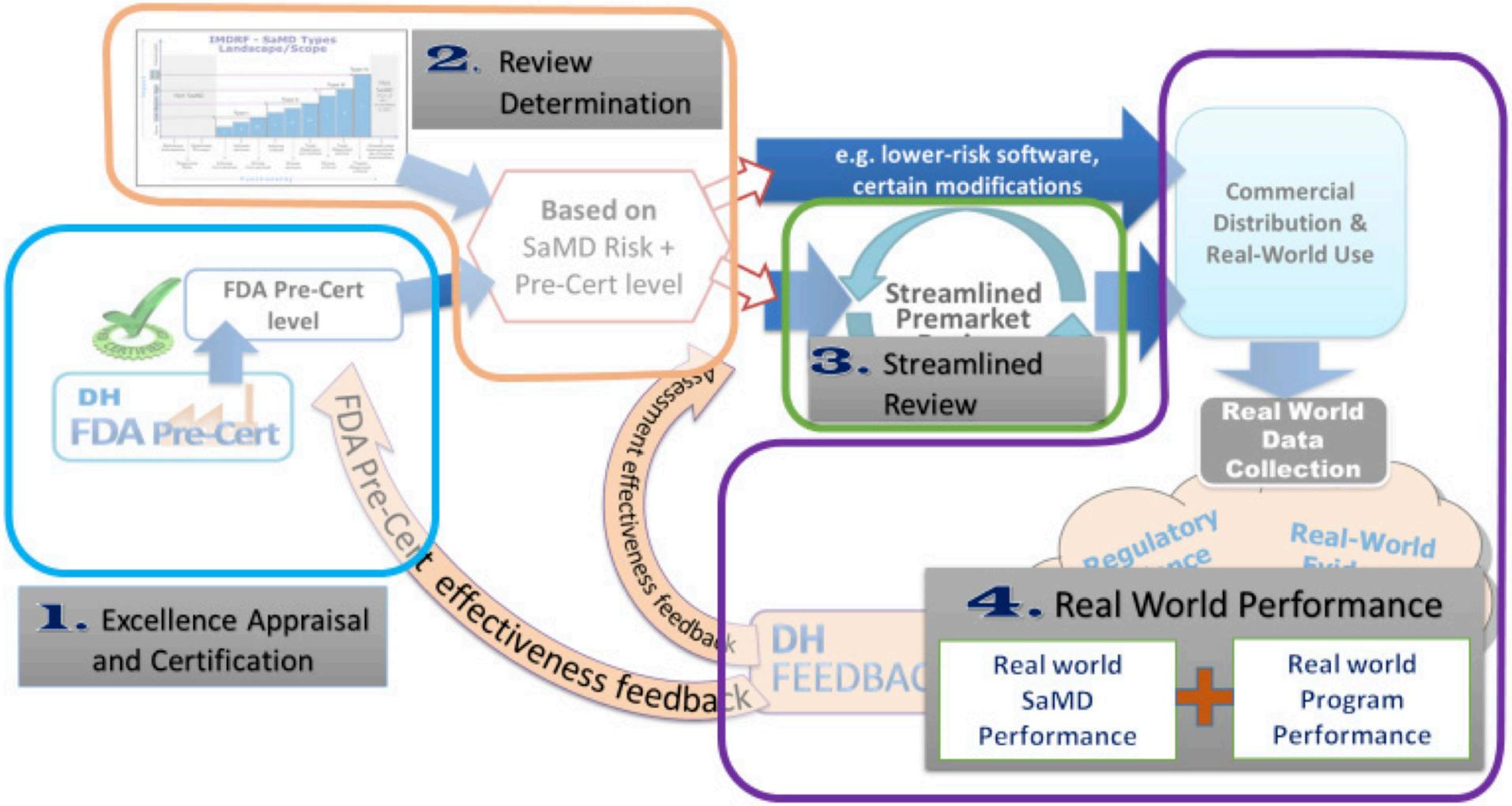
State of Healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

in place...

FDA is establishing a *voluntary* pathway... to assess the safety and effectiveness of software technologies without inhibiting patient access to these technologies.

6. Software Precertification Program: Working Model – Version 0.2 – June 2018

Software Precertification Pilot Program[6]



6. Software Precertification Program: Working Model – Version 0.2 – June 2018

Mobile Medical Applications (MMAs)

Footnote: In 2019 FDA revised guidance language, replacing “mobile applications with “software functions”

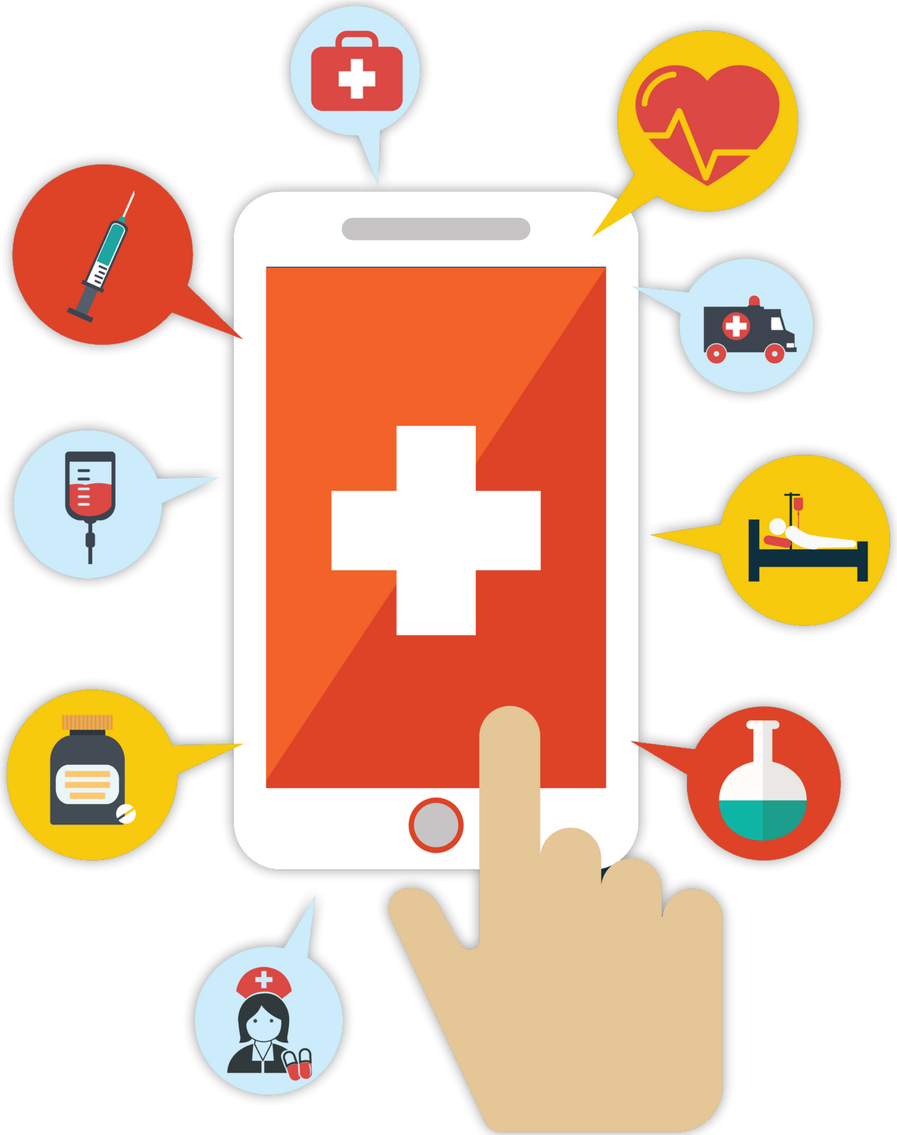
Mobile Medical Applications (MMAs)

FDA guidance first issued 2013, updated 2015 and 2019

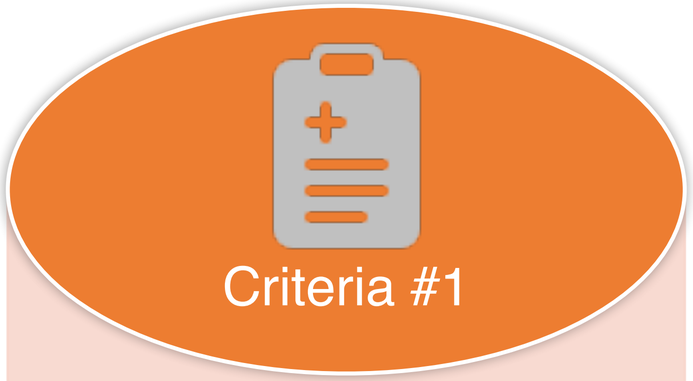
Software that

1. runs on a mobile platform
2. accessed via mobile platform but web-based and runs on a server
3. performs medical device functions

Mobile platform is handheld, off-the-shelf, commercial computing platform, with or without wireless connectivity (smartphone, iPad)



Regulated (Targeted) MMAs



Criteria #1

Meets “function specific” medical device definition below

- Intended for use in the diagnosis or the cure, mitigation, treatment of prevention of disease, *or*
- Affects the structure or any function of the body

Criteria #2

- Used as an accessory to a regulated medical device, *or*
- Transforms a mobile platform into a regulated medical device

Criteria #3

- Functionality could pose a risk to a patient’s safety if the device were to not function as intended

If Regulated MMA…

- Premarket submission required for approval or clearance (510k, De Novo, or PMA)
- Establishing registration and medical device listing
- Studies supporting safety and efficacy
- Quality system regulation
- Product labeling
- Adverse-event reporting

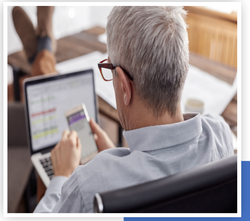
Examples of Regulated MMAs

Apps that control medical devices (Accessories)	Apps that transform a mobile platform into a medical device with attachments, displays, sensors	Apps that provide patient-specific analysis and diagnosis or treatment recommendations
 Controls blood pressure cuff inflation/ deflation and reading	 Attachments to read glucose strips, collect/ monitor ECG	 Calculate dosage for treatment plan
 Control insulin delivery via signal transmission to pump	 Motion sensors to monitor sleep apnea, electronic stethoscopes	 CAD image processing

Enforcement Discretion MMAs

FDA does not intend to regulate these, but can

- Software that helps users self-manage their disease or conditions without providing specific treatment or treatment suggestions
- Software that automates simple tasks for health care providers



Examples

- Coaching software – help users manage conditions like obesity, diabetes, mood disorders
- Practice/treatment guidance for clinicians – matches patient condition to published treatment guidance
- Telemedicine software – facilitates/enhances communication b/w patient and clinician
- Routine calculations – BMI, APGAR

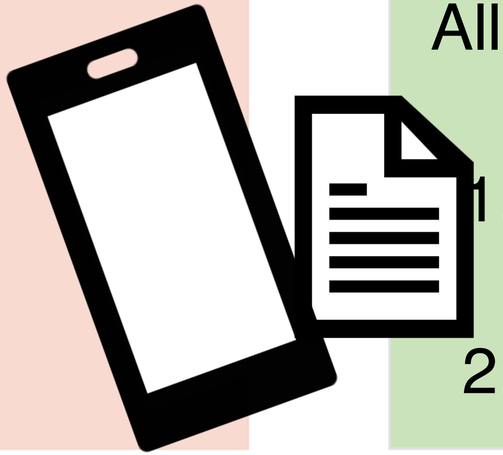
Unregulated (by FDA) Medical Software

Unregulated because it does not meet definition of medical device

- Access copies of reference materials
- Training and education for clinicians
- Patient education
- Office/practice management
- Patient logs, health tracking aids
- Transfer, store, reformat, display data from a regulated MMA without changes

Intended Use Drives Functionality

Intended Use	Labeling
The objective intent of the persons legally responsible for the labeling	All labels, written, printed, or graphic matter 1. upon any article or any of its containers or wrappers, or 2. accompanying such article



- Labeling claims, advertising matter, oral or written statements, sales training materials
- *Your exposure (including criminal charges) is when the device is offered and used for a purpose for which it is neither labeled nor advertised*

Laboratory Developed Tests (LDTs)

Laboratory Developed Tests (LDTs)

Before defining LDTs, you must understand in vitro diagnostic tests (IVDs)

- Reagents, instruments, or systems used to analyze human samples
- Clinicians rely on them to diagnose disease or other conditions, guide treatment, or mitigate/prevent future disease
- IVDs are regulated by the FDA with traditional risk-based approach and pathways

LDTs are a subset of IVDs

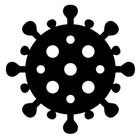
- Designed, manufactured and used within a single laboratory for clinical use
- Used to inform clinicians and patients
- LDTs regulated by Center for Medicaid and Medicare Services (CMS) via Clinical Laboratory Improvement Amendments of 1988 (CLIA)

IVD & LDT Comparison

	IVDs - FDA	LDTs - CMS/CLIA
Who can make them?	Commercial tests, multiple labs, multisource components	Single lab designs, makes, uses, reports results
Use	IVDs used to diagnose, treat, prevent	LDTs can only inform clinicians
Oversight	FDA oversees all medical devices including IVDs (discretion with LDTs)	CLIA oversees labs conducting tests on human samples
Validation standards	Analytical and clinical	Analytical only
Validation method	Risk-based, premarket review	Lab must establish analytical performance
Frequency	Prior to marketing & post market surveillance	Lab inspection very 2 years
Adverse events	Mandatory for manufacturer	Not required
Recall authority	Yes	No

What Has Changed With LDTs

THEN: Low Perceived Risk

Mostly for rare diseases		Many diseases and conditions
Manual analysis and interpretation		Automated processes
Hospital and physician labs		Software, algorithms, AI
Research use only		Being used to diagnose and treat
Not available to consumers		Marketing claims
Single analyte screens		Not single source

NOW: Higher Perceived Risk

Transition to FDA oversight likely: [2014 Draft LDT Guidance]

LDT Enforcement Discretion

FDA Intervention Unlikely

- Did your lab/company develop the test?
- Are all the materials for the test sourced in the same state as the lab is licensed?
- Are you using a single validated CLIA lab to perform test and validate/provide results?

FDA Strict Enforcement

- Are you doing things with your test that put patients/general public at moderate or significant risk?

LDT Selective Interventions

LabCorp

- Ovasure 2008
- Only 1 in 15 + tests accurate
- Ovary removals
- Labcorp did not develop or manufacture
- FDA warning letter, test removed from market

theranos

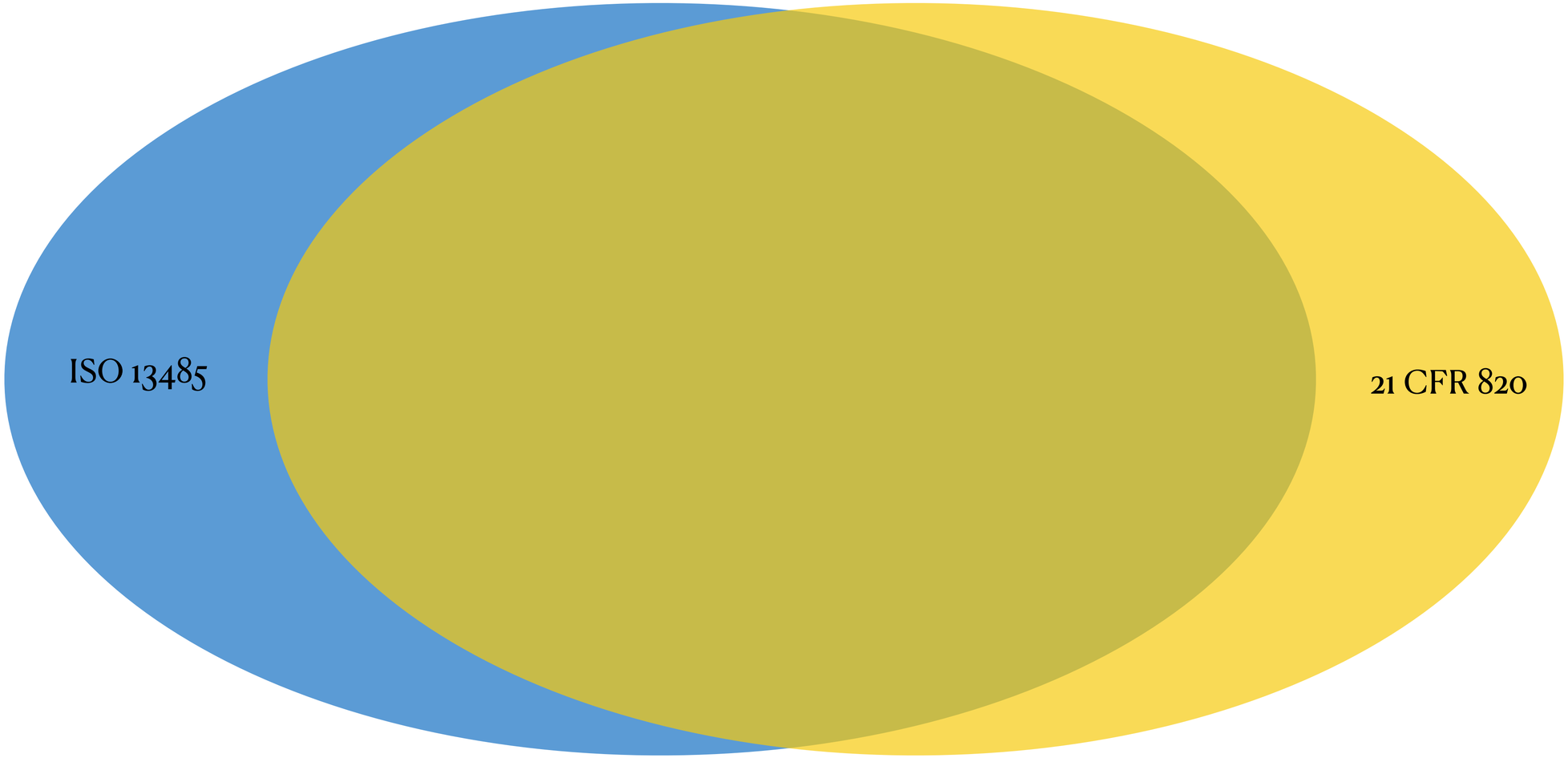
- Raised billion of venture $$$ on premise of revolutionary blood testing tech
- Samples were diluted to run on conventional machines at NJ lab
- FDA cleared HPV test, inspected lab, multiple violations
- Press broke bigger story 2015

23andMe®

- Website:
  “Get personalized genetic insights and tools that can help make it easier for you to take action on your health”

- “ The test is not intended to tell you anything about your current state of health, or to be used to make medical decisions, including whether or not you should take a medication, how much of a medication you should take, or determine any treatment”

Quality Systems - ISO vs. FDA



Quality Systems Comparison[5]

N23	Topic	ISO 13485:2003	Australia	Brazil RDC 16/2013	China MD GMP ([2014]64)	Japan MHLW QMS Ordinance	US 21 CFR
7.2--RISK MANAGEMENT: A PATIENT SAFETY FOCUSED PROCESS	Planning of product realization	7.1	All	2.4	4,38	26-5, 26-6	820.30g
7.3--DOCUMENT CONTROL AND RECORDS	Quality system record		All	3.1.6	24		820.186
	Documentation requirements - General	4.2.1			24	6	820.20e
	Quality manual	4.2.2		2.2.1	24	7	820.20e
	Document control	4.2.3		3.1	25,26	8	820.4
	Control of records	4.2.4		3.1.6.2	27	9	820.18
	Device master record			4.2	50	6-2	820.181
7.4--CONFIGURATION MANAGEMENT AND CONTROL	Document control	4.2.3	All	3.1	25,26	8	820.4
	Control of records	4.2.4	All	3.1.6.2	27	9	820.18
	Control of design and development changes	7.3.7	P1	4.1.10	37	36	820.30i
	Production and service provision - General requirements	7.5.1.1	All	5.1	45,46	40	820.70a,g, I,h
	Identification	7.5.3.1	All	6.4	51	47	820.6
	Traceability	7.5.3.2	All	6.4	53	48	820.65
	Status identification	7.5.3.3	All		52	50	820.86
7.5--MEASUREMENT, ANALYSIS AND IMPROVEMENT OF PROCESSES, ACTIVITIES AND PRODUCT	Measurement, analysis, and improvement	8	All				
	Conformity assurance	8.1		2.2.5.1, 2.2.6	78	54	820.8
	Feedback	8.2.1			66	55	
				7.2	71		820.198
				7.2.1.4, 7.2.1.5	75,76		822
	Internal audits	8.2.2		7.3	77	56	820.22
	Process monitoring	8.2.3		7.3, 2.2.6		57	820.70a
	Product monitoring	8.2.4		7.3, 2.2.6	59,60	58	820.8
	Nonconforming product	8.3		6.5	67-70	60	820.9
	Data analysis	8.4		2.2.6, 9	73	61	820.25
	Improvement	8.5					
	Improvement - General	8.5.1		2.2.1	71,76	62	

5. IMDRF/SaMD WG/N23 FINAL:2015 Software as a Medical Device (SaMD): Application of Quality Management System

Quality Systems Comparison[5]

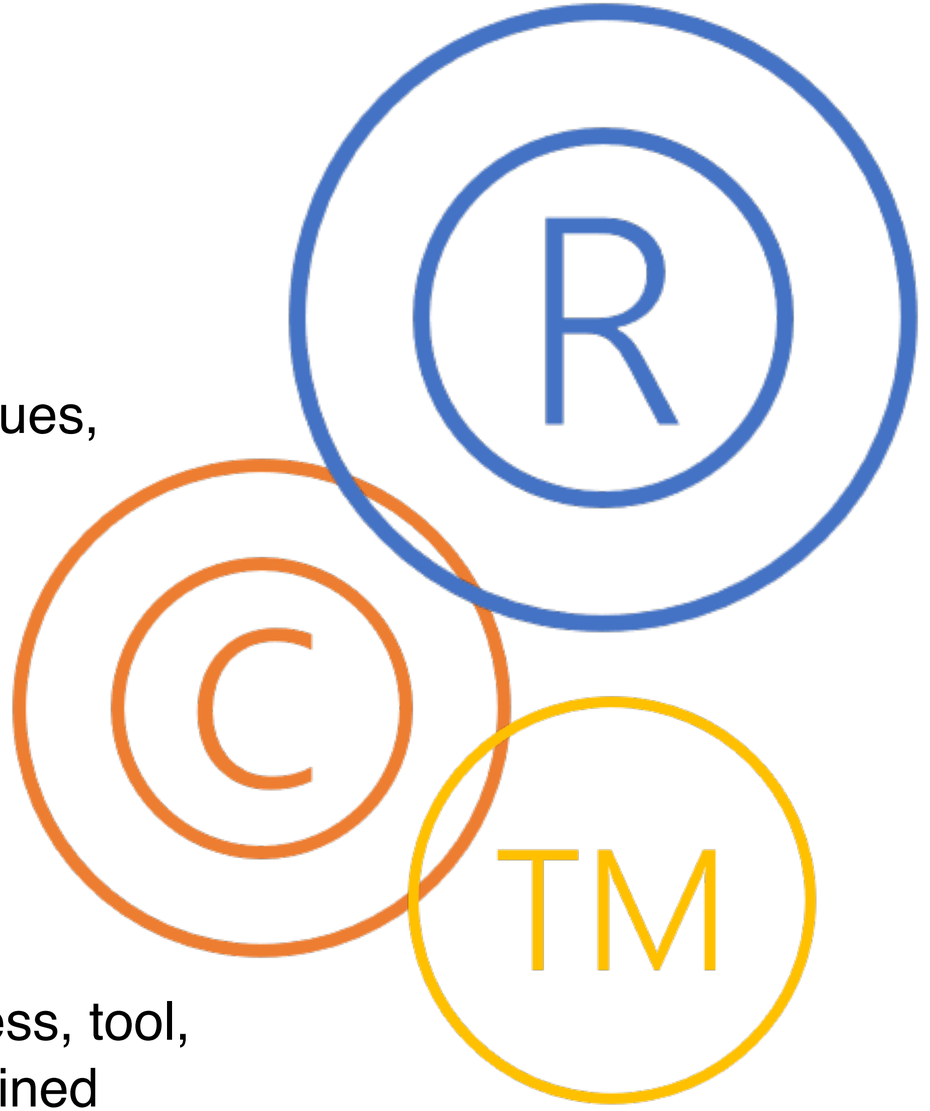
N23	Topic	ISO 13485:2003 [13, 14]	Australia [15]	Brazil RDC 16/2013	China MD GMP ([2014]64)	Japan MHLW QMS Ordinance	US 21 CFR
These Clauses are not specifically addressed by N23	Control of production and service provisions	7.5.1.2	All#		47	41	
	Process validation	7.5.2	P1#, P4#		49	45	820.75
	Traceability documentation	7.5.3.2.1	All#			48	
	Requirements for active implantable	7.5.3.2.2				49	
	Status identification	7.5.3.3	All#			50	
	Device packaging	7.5.5	All#		55	52	820.13
	Handling	7.5.5	All#		55		820.14
	Storage	7.5.5	All#		55		820.15
	Monitoring and measurement	8.2.4.1	All#			58	
	Monitoring and measurement of active implantable	8.2.4.2				59	
	Sterilization records	7.5.1.3				44	820.184
	Production personnel						820.70d
	Production and service provision - General requirements	7.5.1.1	P1#, P4#				820.12
	Issue and implementation of advisory notices		All#				806
	Medical device tracking						821
	Device classification						860
	Label design						801

5. IMDRF/SaMD WG/N23 FINAL:2015 Software as a Medical Device (SaMD): Application of Quality Management System

Software Intellectual Property

Types of IP for Software

- Patent: Protects novel ideas imbedded in software
  - Editing functions, user-interface features, compiling techniques, operating system techniques, program algorithms, menu arrangements, display presentations or arrangements, and program language translation methods
- Copyright: Protection for the particular form in which an idea is expressed (literary work)
  - Source and object code (only registered versions), user interface, how information is displayed
- Trade Secrets: Formula, pattern, compound, device, process, tool, or mechanism not generally known or discoverable, is maintained in secrecy, and gives its owner a competitive advantage
  - Coca Cola formula, software code, concepts and ideas behind code



Example – Smartphone

Trade marks

- NOKIA
- Product "208"
- Start-up tone

Patents & utility models

- Data-processing methods
- Operating system
- Operation of user interface

Design

- Form of overall phone
- Arrangement and shape of buttons
- Position and shape of screen

Trade secrets

- Some technical know-how kept "in-house" and not published

Copyright

- Software
- User manuals
- Ringtones
- Start-up tone
- Images

EUIPO
EUROPEAN UNION INTELLECTUAL PROPERTY OFFICE

AI Regulatory/Intellectual Property Issues

Regulatory

AI can change many technical and performance aspects of regulated devices triggering need for additional approval

2019

FDA issued Proposed Regulatory Framework for Modifications to Artificial Intelligence/ Machine Learning (AI/ ML)-Based Software as a Medical Device (SaMD)

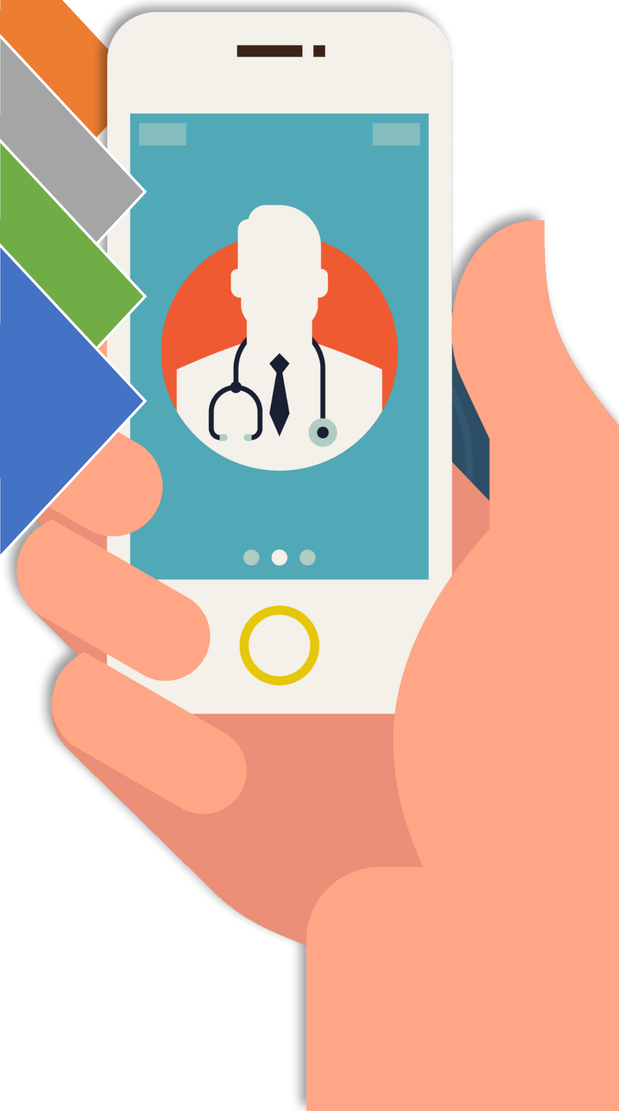
IP

AI patents often describe abstract concepts that are subject to challenge

Above can be overcome by detailing technical improvements to machines/computers that result from AI

2020

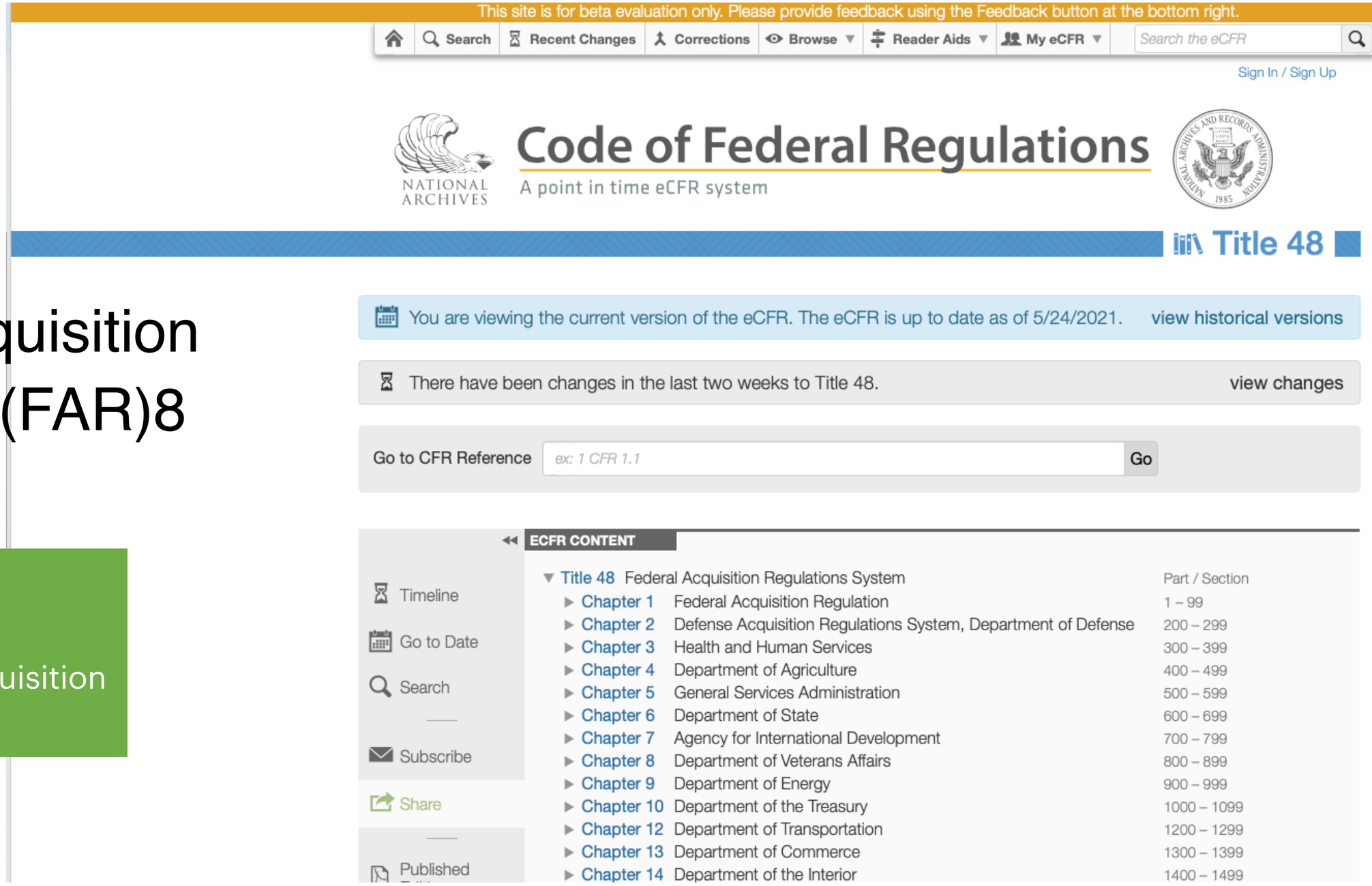
The U.S. Patent and Trademark Office released a report, Inventing AI, providing useful medtech guidance



US Government Contracting

48 CFR - Federal Acquisition Regulation (FAR)8

Governs all US Government procurement/acquisition activities

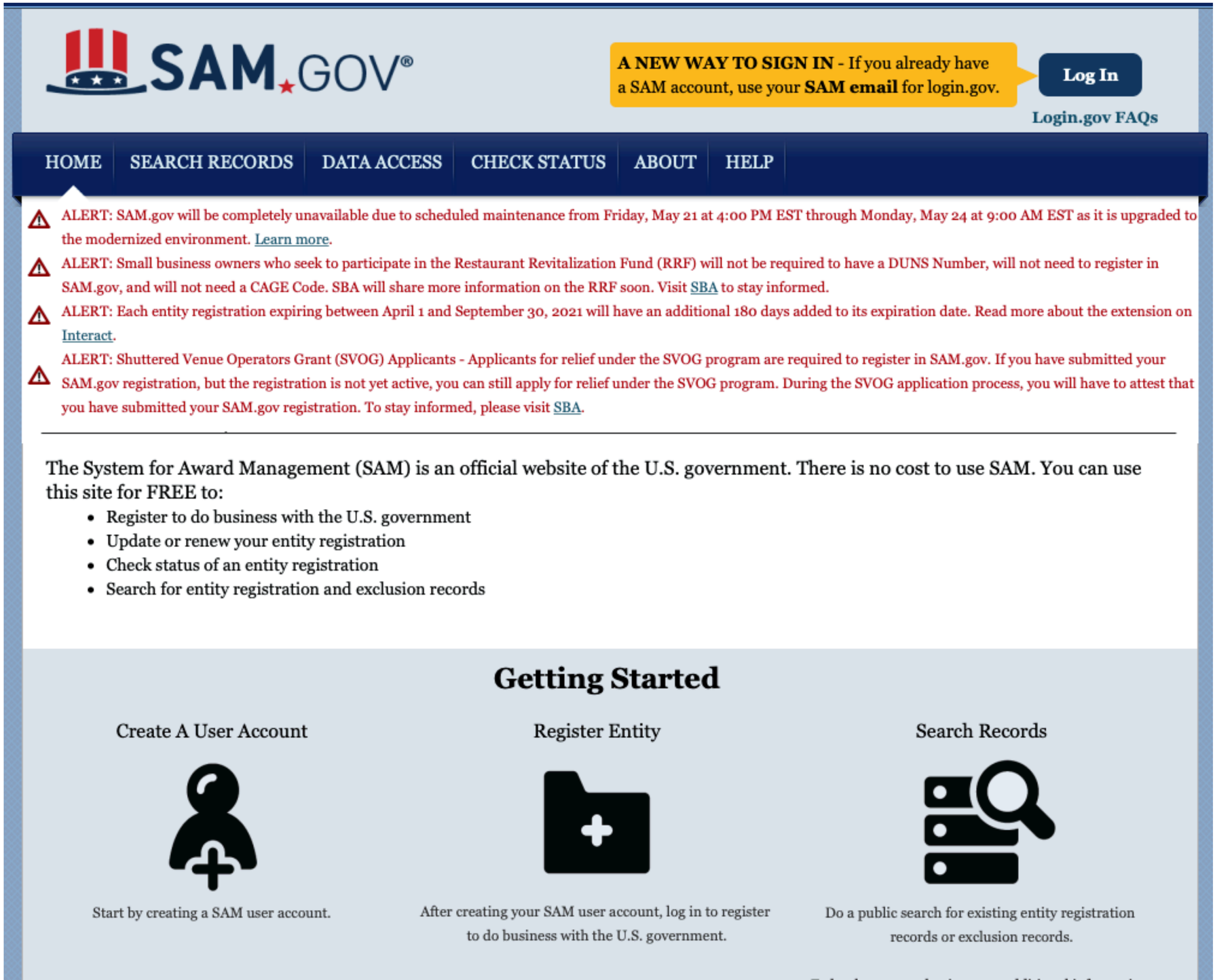


8. https://www.ecfr.gov/

System for Award Management (SAM)[9]

Requires annual registration

- NATO Commercial and Government Entity (NCAGE) Code
- Data Universal Numbering System (DUNS) Number

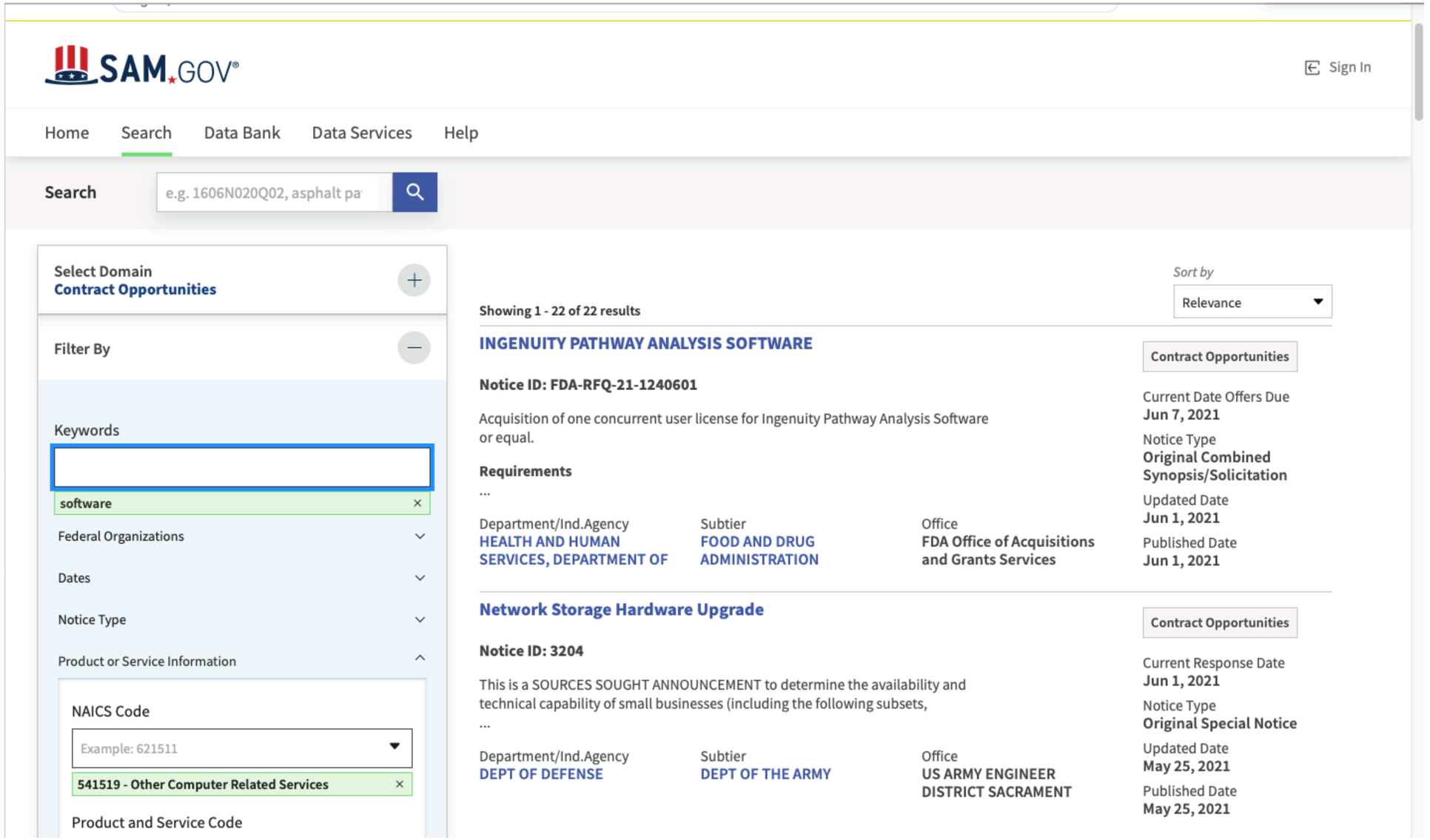


9. https://SAM.gov

System for Award Management (SAM)[9]

Access to contracts

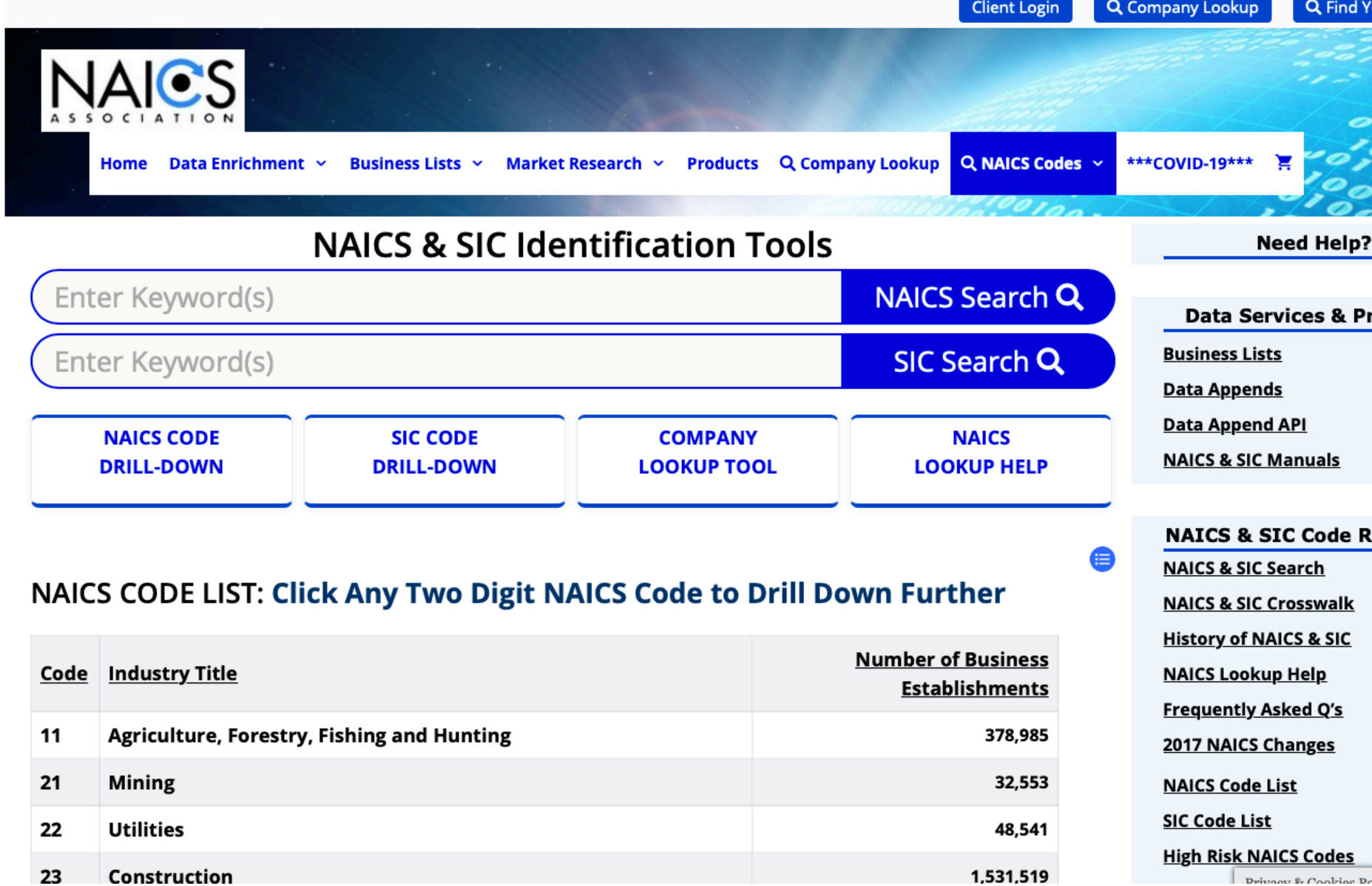
- NAICS Code or Product & Service Code



9. https://SAM.gov

NAICS[10] Code Examples:

- 5415 - Computer System Design & Related Services
- 541511 - Custom Computer Programming Services
- 541715 - Research and Development in the Physical, Engineering, and Life Sciences (except Nanotechnology and Biotechnology)



10. www.naics.com

SAM Registration

↓

Access to contracts

↓

Identify contract opportunities

↓

Submit bid[11]

↓

Selection begins...

11. per 48 CFR

Promotional Claims Exposure

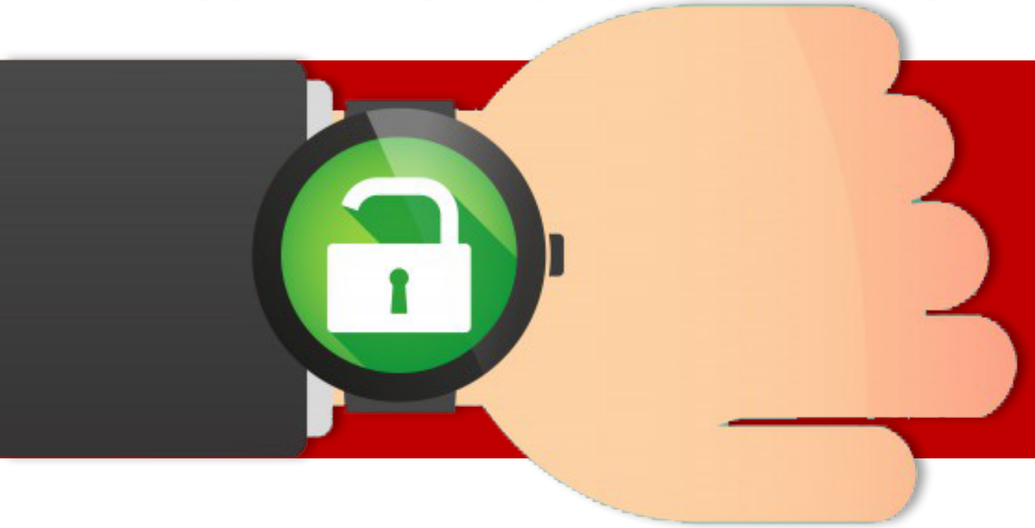
Federal Trade Commission
Enforcement Activity

- 2015
  - “FTC steps up enforcement of misleading software and mobile app promotional claims”
  - Overlapping authority over the advertising and promotion of medical software and MMAs
- ifocus System
  - “Permanently improves children’s focus, memory, attention, behavior, and/or school performance, including ADHD children”
- MelApp and Mole Detective
  - “Increase consumers’ chances of detecting melanoma by analyzing pictures of moles and skin lesions taken with smartphones”

Companies have more latitude with claims for low-risk unregulated apps

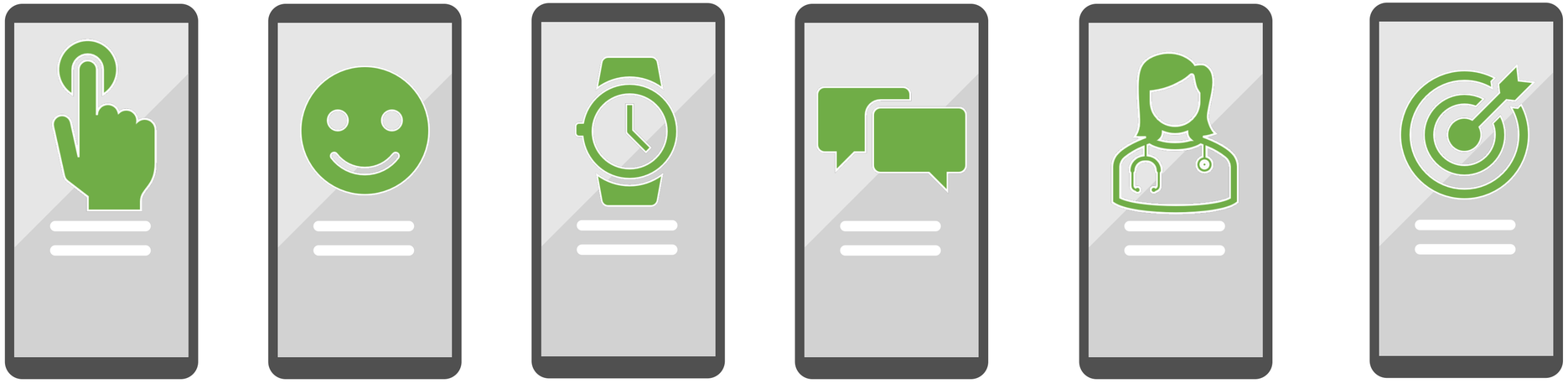
Which US Laws Apply to Your App?

- https://www.ftc.gov/tips-advice/business-center/guidance/mobile-health-apps-interactive-tool
- 10 questions about your MMA
- Health Insurance Portability and Accountability Act (HIPAA)
- The Office for Civil Rights (OCR) within the U.S. Department of Health & Human Services (HHS) enforces HIPAA rules, which protect the privacy and security of certain health information and require certain entities to provide notifications of health information breaches



How you collect and use consumer health information is very sensitive and regulated

What Do Patients Really Want in a Mobile Healthcare App?



Easy to use

Great user experience

Integration with wearables

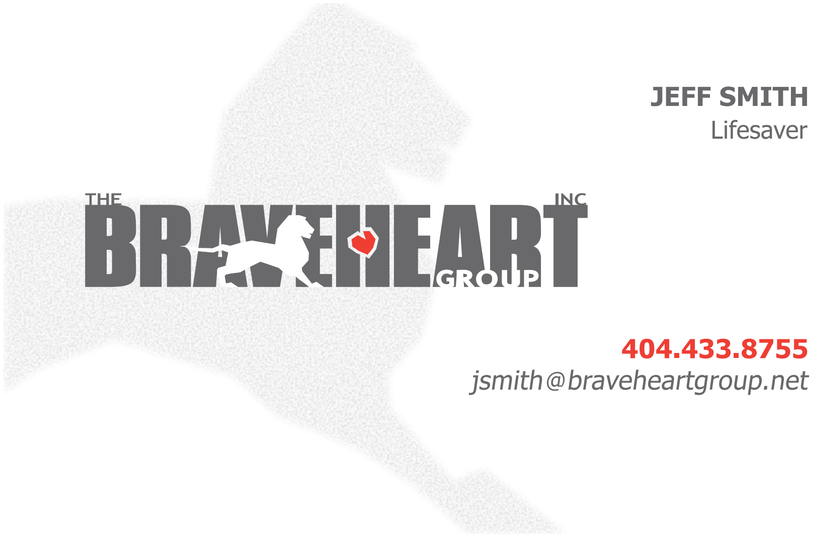
Interact with patient groups

Simple to communicate with HCPs

Actionable information

Questions?


BreakThrough
Life Science Consulting
Rick Proctor
Managing Partner
p: 423-650-3044 | skype: rproctorjr
e: rick.proctor@breakthroughlifescience.com


JEFF SMITH
Lifesaver
THE BRAVEHEART GROUP INC
404.433.8755
jsmith@braveheartgroup.net