A Shifting Regulatory Framework for Digital Health: The Impact of Silicon Valley on the FDA's Mission to Promote and Protect the Public Health

M. Jason Brooke, General Counsel and Vice President of Regulatory & Quality, AmalgamRx

Development and Regulation of Innovations: In the Current State of Facts vs. Public Opinions, the Truth Does Not Always Prevail

Nicholas Benetatos, Manager, Exponent, Inc.
Kevin Ong, Principal Engineer, Exponent, Inc.

Discussant: **Nathan Brown**, Partner, Akin Gump Strauss Hauer & Feld LLP
Moderator: **Karen C. Corallo**, Of Counsel, Skadden, Arps, Slate, Meagher & Flom LLP

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M. Jason Brooke, MSE, JD, CSQE

General Counsel and VP of Regulatory and Quality, Amalgam Rx

November 15, 2019

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Agenda

- Overview of Digital Health
- History of Medical Device Regulation
- Silicon Valley's Influence
  - On the Market
  - FDA's Approach to Regulating
- The New Paradigm for Software as a Medical Device
- A Skeptic's View
- Conclusion

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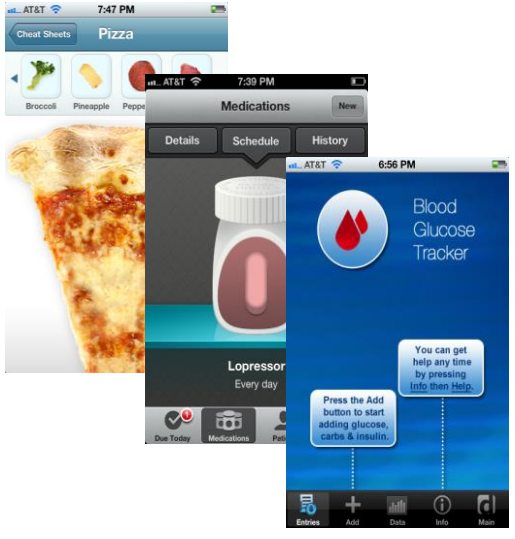
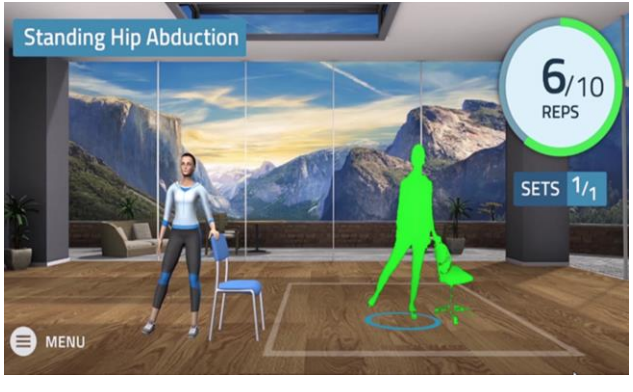
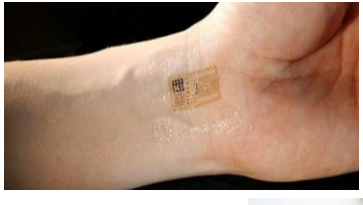
Overview of Digital Health







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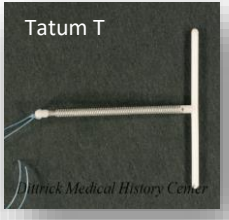
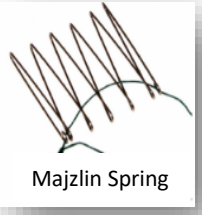
History of Medical Device Regulation

From 1970 to 1974 the A.H. Robins Company marketed an intrauterine device that ultimately resulted in hundreds of septic abortions, killed scores of women, and sterilized more than 10,000.





PUBLIC LAW 94–295—MAY 28, 1976 90 STAT. 539

Public Law 94–295
94th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to provide for the safety and effectiveness of medical devices intended for human use, and for other purposes.

May 28, 1976
[S. 510]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SHORT TITLE AND TABLE OF CONTENTS

Medical Device Amendments of 1976.
21 USC 301 note.

SECTION 1. (a) This Act may be cited as the "Medical Device Amendments of 1976".

(b) Whenever in this Act (other than in section 3(a)(1)(B)) an amendment is expressed in terms of an amendment to a section or other provision, the reference shall be considered to be made to a section or other provision of the Federal Food, Drug, and Cosmetic Act.

21 USC 301.

The Medical Device Amendments Act defined a "device" as:

> [A]n instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . **intended for use in the diagnosis** of disease or other conditions, or in the **cure, mitigation, treatment, or prevention of disease**, in man or other animals, or . . . intended to affect the structure or any function of the body . . . ."

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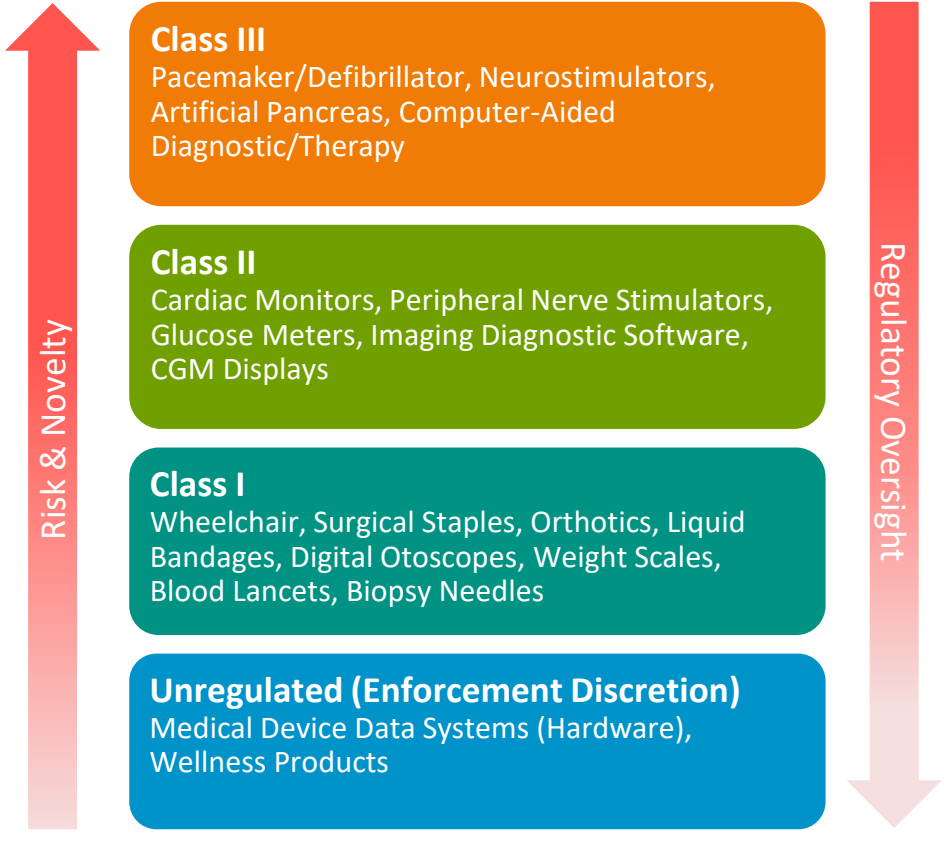
History of Medical Device Regulation



PRE-MARKET REGULATORY OVERSIGHT

- **General Controls**
- Special Controls
- Performance Standards

POST-MARKET REGULATORY OVERSIGHT

- Adverse Event Reporting
- Corrections & Removal
- Inspections

- Prohibition against adulterated or misbranded devices
- **Good Manufacturing Practices (GMPs)**
- Labeling requirements
- **Registration** of manufacturing facilities
- **Listing** of device types
- Record keeping
- Complaint Handling

The FDA has established ~2,000 classification regulations and over 6,000 product codes for medical devices.

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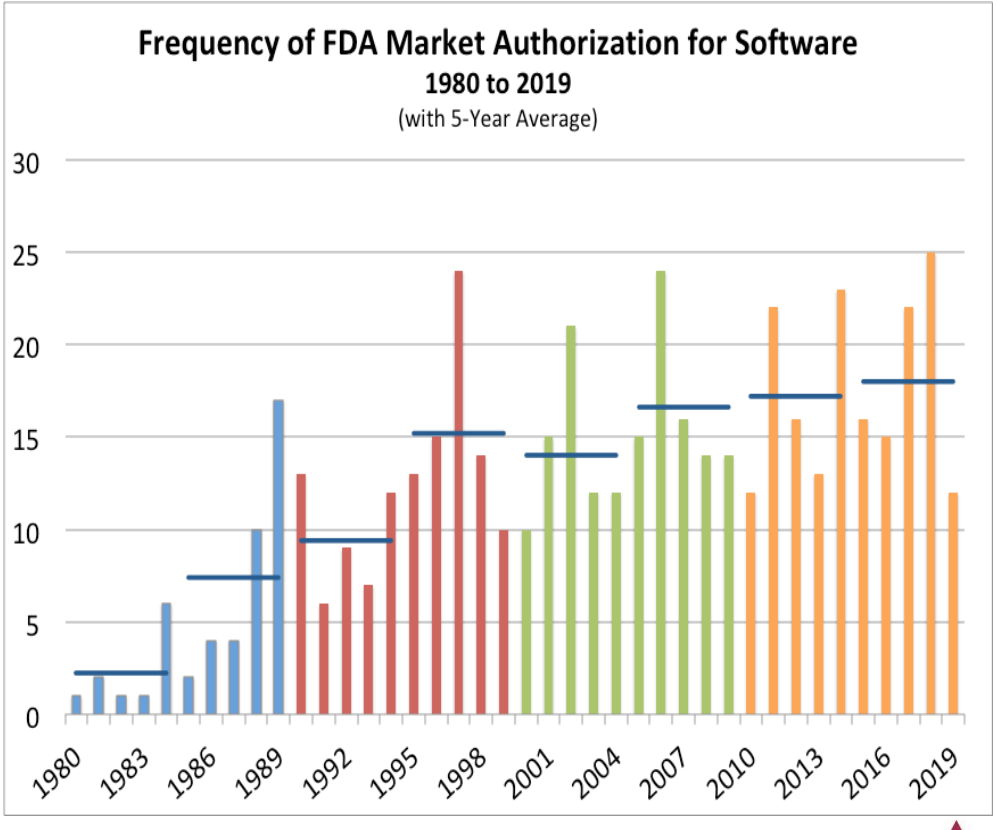
History of Medical Device Regulation

Software has been regulated as a medical device since as early as 1980

Market authorizations from 1980 to 2019 (5-year average)

- 591% increase from early 1980s to 2000
- 18% increase from 2000 to 2019



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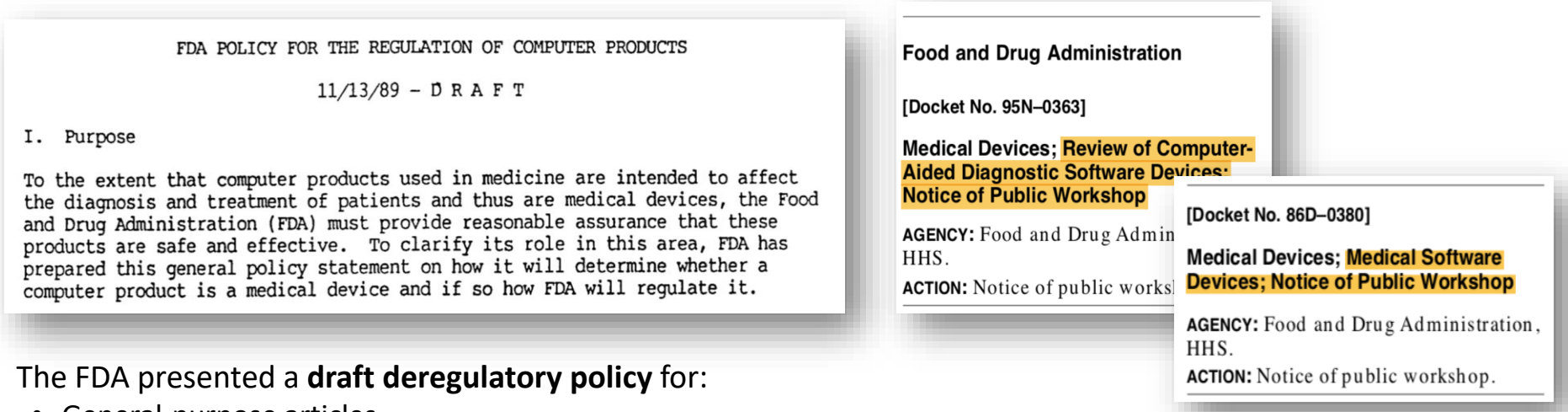
History of Medical Device Regulation



FDA POLICY FOR THE REGULATION OF COMPUTER PRODUCTS

11/13/89 - D R A F T

I. Purpose

To the extent that computer products used in medicine are intended to affect the diagnosis and treatment of patients and thus are medical devices, the Food and Drug Administration (FDA) must provide reasonable assurance that these products are safe and effective. To clarify its role in this area, FDA has prepared this general policy statement on how it will determine whether a computer product is a medical device and if so how FDA will regulate it.

Food and Drug Administration

[Docket No. 95N–0363]

Medical Devices; Review of Computer-Aided Diagnostic Software Devices; Notice of Public Workshop

AGENCY: Food and Drug Admin
HHS.
ACTION: Notice of public works

[Docket No. 86D–0380]

Medical Devices; Medical Software Devices; Notice of Public Workshop

AGENCY: Food and Drug Administration, HHS.
ACTION: Notice of public workshop.

The FDA presented a **draft deregulatory policy** for:

- General-purpose articles
- Products developed by a licensed practitioner
- Products marketed "solely for use in research, teaching, and analysis"
- "[A]rtificial intelligence and other types of decision support systems . . . involv[ing] **competent human intervention**"

FDA attempted to assess the risks of medical software devices and to define **criteria for assessing the impact of product failure**, including:

- **Seriousness** of the disease
- **Time frame for use** of the information
- Concordance with **accepted medical practice**
- **Format** of data and its presentation
- Individualized vs. Aggregate patient care **recommendations**
- **Clarity** of the algorithm

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History of Medical Device Regulation

Food and Drug Administration

21 CFR Parts 808, 812, and 820

[Docket No. 90N–0172]

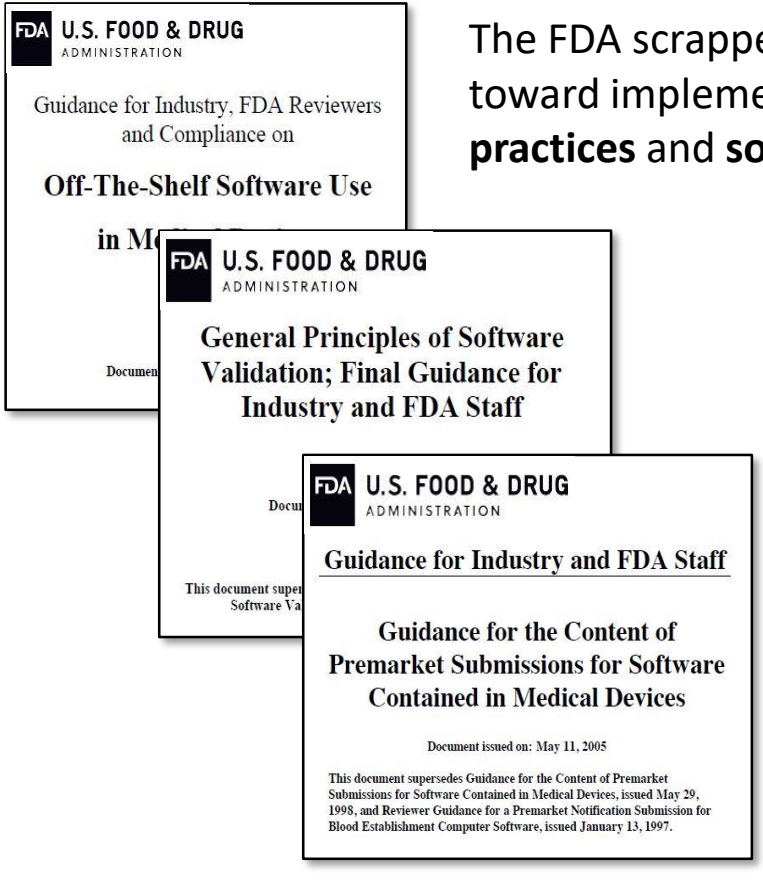
RIN 0910–AA09

Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising the current good manufacturing practice (CGMP) requirements for medical devices and incorporating them into a quality system regulation. The quality system regulation includes requirements related to the methods used in, and the facilities and controls used for, designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use. This action is necessary to add preproduction design controls and to achieve consistency with quality system requirements worldwide. This regulation sets forth the framework for device manufacturers to follow and gives them greater flexibility in achieving quality requirements.



The FDA scrapped the draft policy, shifting instead toward implementation of **good manufacturing practices** and **software-specific guidance**.

GMPs apply "to all medical devices . . . and design controls are of particular relevance to software medical devices, since a study of software-related recalls" from FY1983 to FY1991, "indicated that **over 90 percent of all software-related device failures were due to design-related errors**, generally, the failure to adequately validate software prior to routine production."

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History of Medical Device Regulation

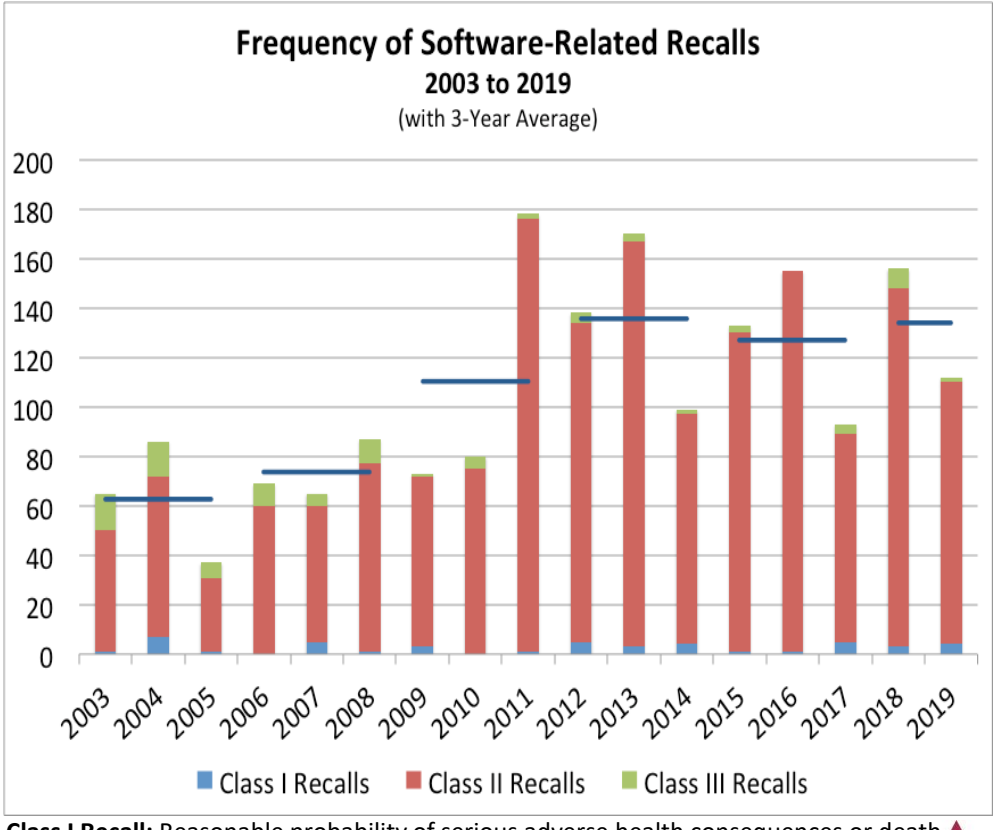
Scores of companies per year are cited for **software-related non-compliance**:

- Validation of device software [was not performed] [is inadequate] [is incomplete].
- Results of the validation of the device software were not [adequately] documented.
- The device master record does not include or refer to the location of device software specifications.

Software-related **recalls went up** in the early 2000s and remained steadily high in the 2010s

- 76% increase from 2003 to 2010
- 21% increase from 2010 to 2019

The vast majority of software-related **recalls are Class II**



Class I Recall: Reasonable probability of serious adverse health consequences or death
Class II Recall: Possible to cause temporary or medically reversible adverse health consequences or remote probability of serious adverse health consequences
Class III Recall: Not likely to cause adverse health consequences.

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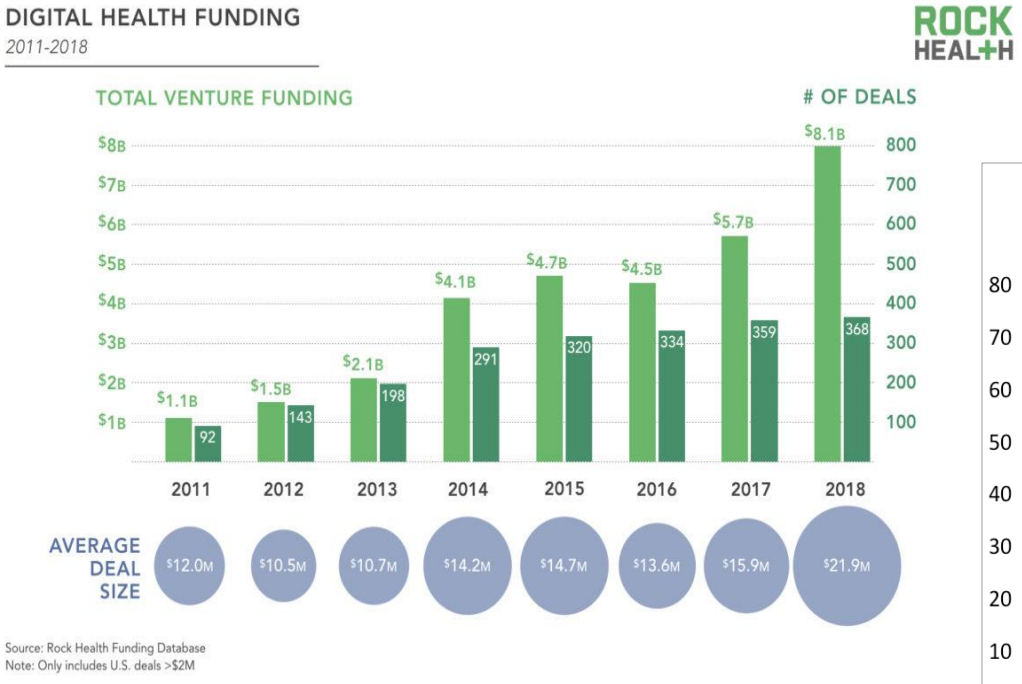
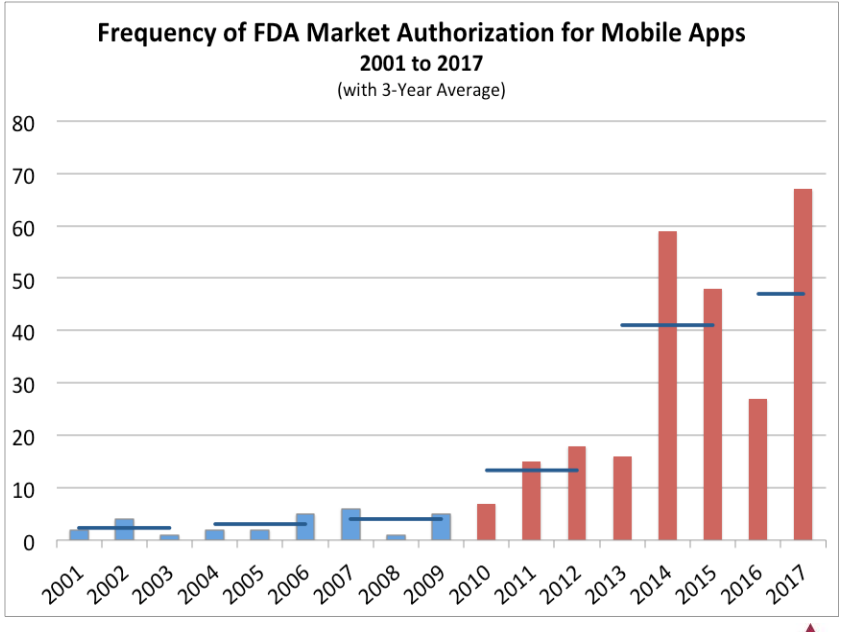
Silicon Valley's Influence



Major investment in the last decade

- Over 2,100 investment deals worth $32B



Dramatic growth in mobile medical apps

- 2-4 per year in 2000s
- 1075% increase on average from 2009 to 2017

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Silicon Valley's Influence

For Release: 09/08/2011

"Acne Cure" Mobile App Marketers Will Drop Baseless Claims Under FTC Settlements

". . . the settlement orders . . . require Koby Brown and Gregory W. Pearson, doing business as DermApps, to pay $14,294, and Andrew N. Finkle, doing business as Acne Pwner, to pay $1,700.

For Release: 9/28/2011

Reebok to Pay $25 Million in Customer Refunds To Settle FTC Charges of Deceptive Advertising of EasyTone and RunTone Shoes

Settlement Order Prohibits Reebok from Making Unsupported Claims that 'Toning Shoes' Strengthen, Tone Muscles

Letter to Biosense Technologies Private Limited concerning the uChek Urine Analyzer

It Has Come to Our Attention Letter

Myshkin Ingawale
C/O Sumit Singh
Biosense Technologies Private Limited
212 Hockney Avenue
MOUNTAIN VIEW, CA 94041
Document Number: GEN1300289

"Urine analysis is a common diagnostic method and is used by clinicians for **up to 25 medical conditions**, including **kidney**, **liver**, **bladder** problems, **urinary tract infections**, **pre-eclampsia** and complications of **diabetes**."

MAR 15 2012

WARNING LETTER

VIA UNITED PARCEL SERVICE

Ely Simon, M.D.
Chief Executive Officer
NeuroTrax Corporation
POB 226
Modiin 71711
Israel

MindStreams®

"MindStreams® will allow a physician or psychologist to assess cognitive deficits earlier in the disease state, before a patient's disease has progressed too far."

Nov 22, 2013

Ann Wojcicki
CEO
23andMe, Inc.
1390 Shoreline Way
Mountain View, CA 94043

Document Number: GEN1300666
Re: Personal Genome Service (PGS)

WARNING LETTER

FEDERAL TRADE COMMISSION
PROTECTING AMERICA'S CONSUMERS

Lumosity to Pay $2 Million to Settle FTC Deceptive Advertising Charges for Its "Brain Training" Program

Company Claimed Program Would Sharpen Performance in Everyday Life and Protect Against Cognitive Decline

FOR RELEASE

January 5, 2016

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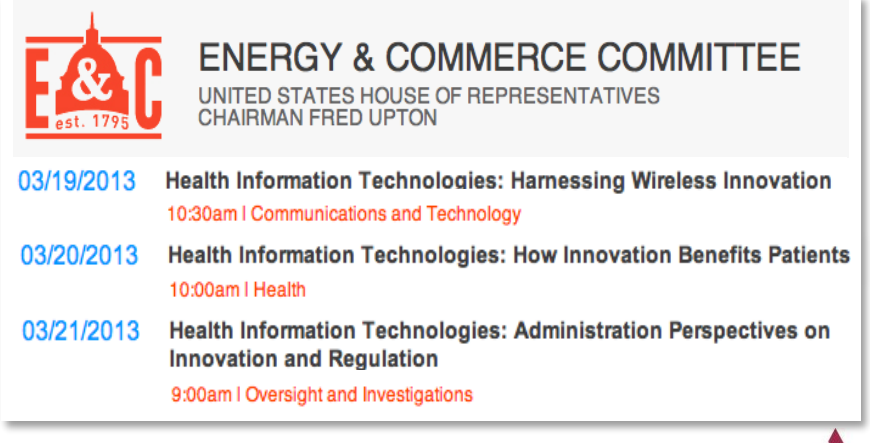
Silicon Valley's Influence

Perpetration of Myths & False Arguments for Deregulation

- Myth #1: The FDA **does not have the authority** to regulate software
- Myth #2: The Food, Drug & Cosmetic Act was **not designed to apply to such innovative technologies** (particularly software)
- Myth #3: The FDA **stifles innovation and prevents investment** by regulating software
- Myth #4: Innovative technology companies have the best engineers so **FDA's oversight is unnecessary**
- Myth #5: FDA regulation **will do more harm than good** due to dysfunction within the agency and—more extreme—bias and corruption
- Myth #6: The FDA should focus only on safety (if anything at all) because the **market will adequately address any ineffective software**
- Myth #7: The FDA **cannot match the pace of software innovation**



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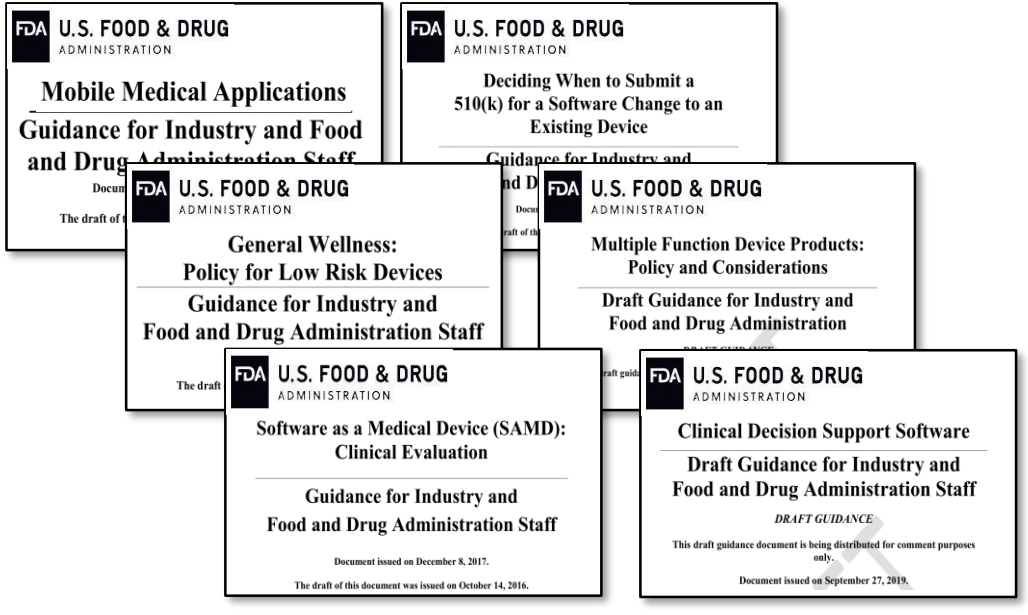
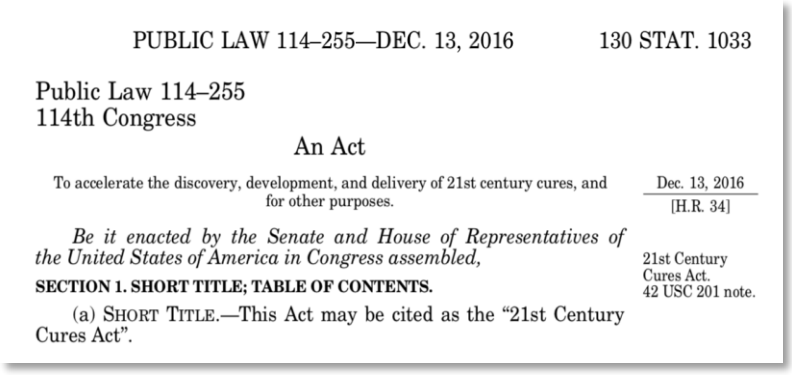
Silicon Valley's Influence

Beginning in ~2010, the FDA embarked on a deregulatory journey in regards to digital health technologies





PUBLIC LAW 114–255—DEC. 13, 2016 130 STAT. 1033

Public Law 114–255
114th Congress

An Act

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

Dec. 13, 2016
[H.R. 34]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

21st Century Cures Act.
42 USC 201 note.

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "21st Century Cures Act".

Medical Device ≠ software that is intended:

1) For **administrative support** of a healthcare facility
2) For maintaining or encouraging a **healthy lifestyle** and is unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition
3) To serve as an **electronic patient record**
4) To serve as a **medical device data system**

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Silicon Valley's Influence

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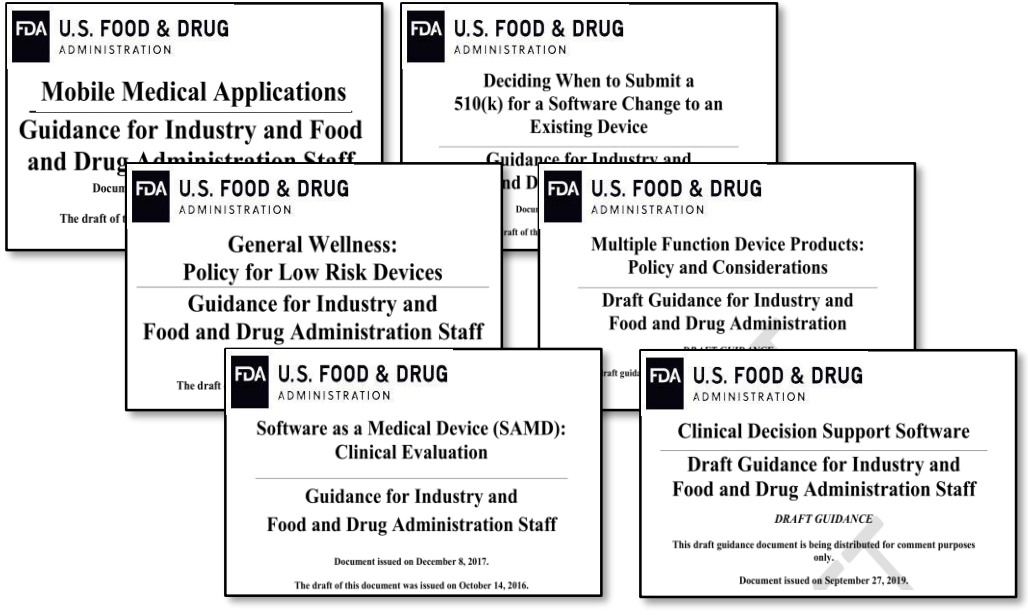

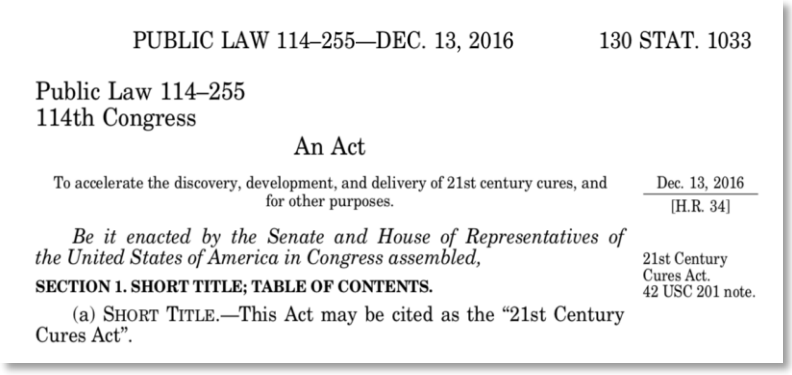

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SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

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Medical Device ≠ software that is intended:

5) a) **Not** to **acquire, process, or analyze** a medical image or a device signal;
b) For **displaying, analyzing, or printing medical information**;
c) For supporting or providing **recommendations to a HCP** about prevention, diagnosis, or treatment; and
d) To enable a HCP to **independently review** the recommendations and, hence, is not intended to for HCP to primarily rely on the recommendations

Requires a modular, risk-based regulatory approach

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The New Paradigm for Software as a Medical Device

Shifting to a Total Product Lifecycle Approach

Post-Market Oversight

Pre-Market Review

Reimagining digital health product oversight

- "FDA intends to develop a precertification program that could **replace the need for a premarket submission** for certain products and allow for decreased submission content and/or faster review of the marketing submission for other products."
- "[C]ollect real-world data postmarket that might be used . . . to affirm the regulatory status of the product, as well as to support new and evolving product functions."
- "[C]onsidering the role of third party certification in facilitating FDA determinations about pre-certification."

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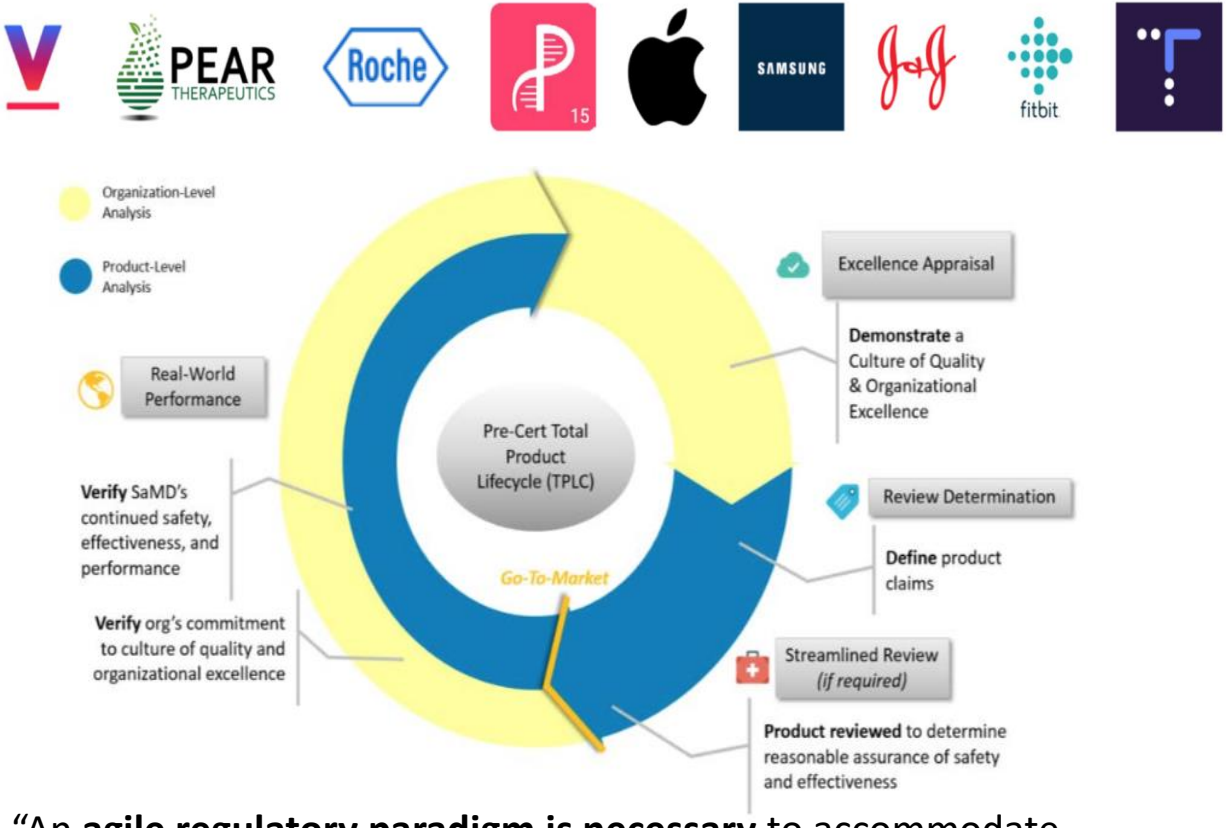
The New Paradigm for Software as a Medical Device

"FDA's **traditional approach** for the regulation of hardware-based medical devices is **not well-suited for the faster, iterative design and development**, and type of validation used for software device functions, including SaMD."



"An **agile regulatory paradigm is necessary** to accommodate the faster rate of development and potential for innovation in software-based products."

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The New Paradigm for Software as a Medical Device

1. Demonstrate a culture of quality and organizational excellence through an **Excellence Appraisal**.
2. Determine the SaMD's required review through **Review Determination**
3. Conduct a **Streamlined Review**
4. Verify a SaMD's continued safety, effectiveness and performance and the organization's commitment to culture of quality through post-market **Real-World Performance**.

- Product Quality – Demonstration of excellence in the development, testing, and maintenance necessary to deliver SaMD products at the highest level of quality.
- Patient Safety – Demonstration of excellence in providing a safe patient experience and emphasizing patient safety as a critical factor in all decision-making processes.
- Clinical Responsibility – Demonstration of excellence in responsibly conducting clinical evaluation and ensuring that patient-centric issues, including labeling and human factors, are appropriately addressed.
- Cybersecurity Responsibility – Demonstration of excellence in protecting cybersecurity and proactively addressing cybersecurity issues through active engagement with stakeholders and peers.
- Proactive Culture – Demonstration of excellence in a proactive approach to surveillance, assessment of user needs, and continuous learning.

Shifting from a product-specific assessment to an **organization-specific analysis**, employing **subjective metrics** that are unpredictable and easily manipulated

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The New Paradigm for Software as a Medical Device

Critical = Life-threatening state of health, including incurable states; requires major therapeutic interventions
Serious = Moderate in progression, often curable; does not require major therapeutic interventions; intervention is normally not expected to be time critical
Non-serious = Slow with predictable progression of disease state; may not be curable; can be managed effectively; requires only minor therapeutic interventions; interventions are normally non-invasive

1. Demonstrate a culture of quality and organizational excellence through an **Excellence Appraisal**.
2. Determine the SaMD's required review through **Review Determination**
3. Conduct a **Streamlined Review**
4. Verify a SaMD's continued safety, effectiveness and performance and the organization's commitment to culture of quality through post-market **Real-World Performance**.

IMDRF Risk Categorization			Level of Review for Level 1 and Level 2 Precertified Organizations' SaMD		
Type	**Subtype**	**Description**	**Initial Product**	**Major Changes**	**Minor Changes**
Type IV	*(9)*	Critical x Diagnose/Treat	Streamlined Review	Streamlined Review	No Review
Type III	*(8)*	Critical x Drive		L1 - Streamlined Review L2 - No Review	
Type III	*(7)*	Serious x Diagnose/Treat			
Type II	*(6)*	Serious x Drive	L1 - Streamlined Review L2 - No Review		
Type II	*(5)*	Non-serious x Diagnose/Treat		No Review	
Type II	*(4)*	Critical x Inform			
Type I	*(3)*	Non-serious x Drive	No Review		
Type I	*(2)*	Serious x Inform			
Type I	*(1)*	Non-serious x Inform			

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The New Paradigm for Software as a Medical Device

Real-World Health Analytics = analyses of real-world clinical outputs and outcomes related to the intended use of the SaMD product
User Experience Analytics = analyses of user experience outputs related to the real-world use of a SaMD product
Product Performance Analytics = analyses of outputs and outcomes demonstrating the real-world accuracy, reliability, and security of a SaMD product

1. Demonstrate a culture of quality and organizational excellence through an **Excellence Appraisal**.
2. Determine the SaMD's required review through **Review Determination**
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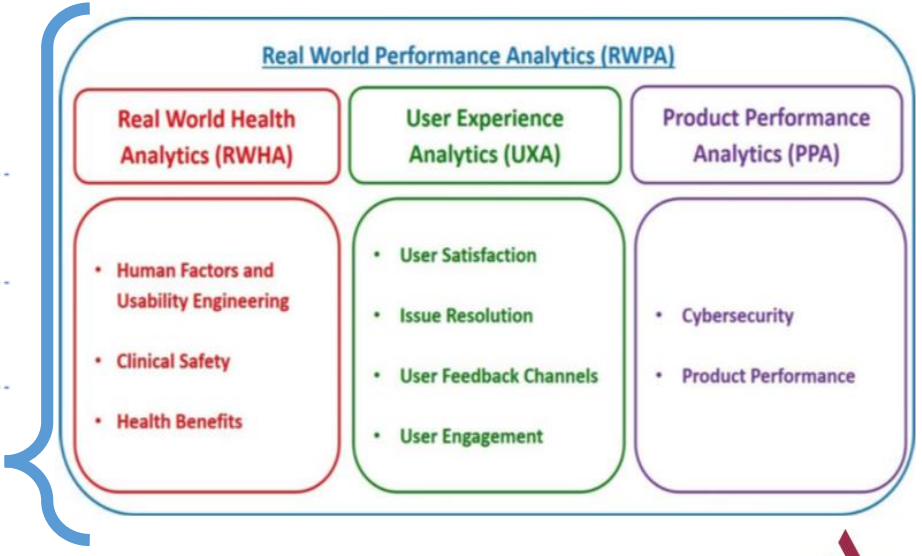

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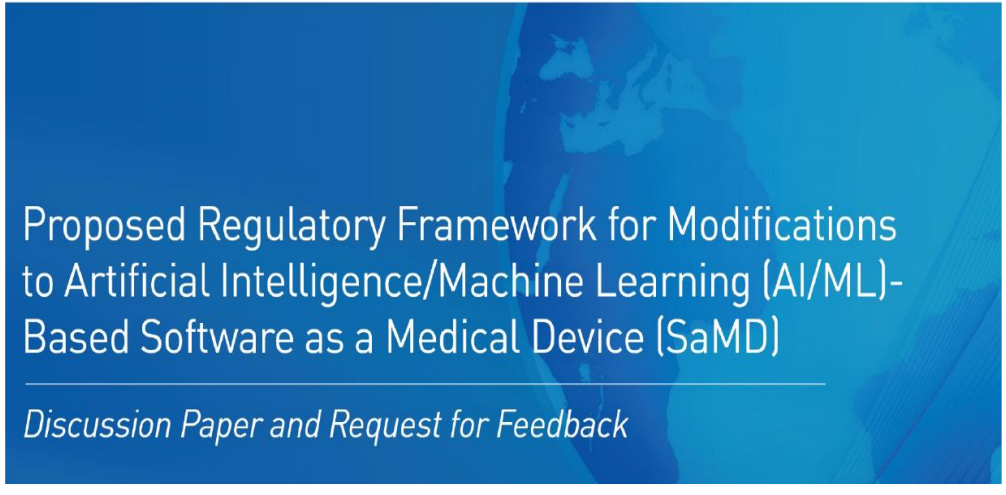
The New Paradigm for Software as a Medical Device

Total Product Lifecycle Approach

- Establish clear expectations on **quality systems** and good ML practices (GMLP)*;
- Conduct **premarket review** and establish clear expectations to continually manage patient risks
- Expect manufacturers to **monitor** the device **and incorporate a risk management** approach in development, validation, and execution of the changes
- Enable **increased transparency** to users and FDA using postmarket **real-world performance reporting**



* GMLP are those AI/ML best practices (e.g., data management, feature extraction, training, and evaluation) that are akin to good software engineering practices or quality system practices.

A Skeptic's View

- Why?
  - What is the trigger for the paradigm shift? On what basis has the FDA concluded that the mission to protect and promote the public health 1) cannot be achieved with the current system or 2) is better achieved through the proposed new paradigm?
    - There is no public health crisis or fundamental flaw in the existing regulatory framework driving this sea change. The interests of "innovators" and mere perception appear to be the drivers.
    - Many of the concepts proposed today were considered in the 1990s and rejected in favor of stricter pre- and post-market controls. The FDA has failed to articulate thorough reasoning to loosen those controls or why a complete overhaul is required as opposed to tweaks to the current framework.
  - To what extent has the FDA evaluated the risk of such a significant change to patients and the public health?
    - Discussion of the proposed new paradigm focuses entirely on the perceived benefits. To the extent a risk analysis has been conducted, no such analysis has been shared with the public.

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A Skeptic's View

- Why?
  - It is not clear that the myths and false arguments about the existing regulatory framework are addressed by the new paradigm.
    - The proposed new paradigm is highly subjective and relies heavily on "trust", undermining the view that the current framework's lack of predictability stifles innovation and investment.
  - From a process perspective, the FDA has not presented the details necessary for stakeholders to fully evaluate and comment in a meaningful way—instead pursuing the Silicon Valley Agile or "fail fast" approach to regulating.
    - The public is being asked to accept a process that increases risk of failure without an opportunity to fully appreciate those risks and to comment accordingly.
    - Such an approach to developing regulations is inconsistent with administrative procedures, which demands notice and an opportunity for the public to comment.
    - Here, the significance of the risk to patients warrants a higher standard. For example, it is not clear to what extent the FDA has engaged with provider associations and patient advocacy groups in developing this new paradigm.
  - The statutory authority for such a program is lacking.

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A Skeptic's View

"[W]e are **concerned that the standards of excellence** the agency is considering **and the process for assessing this excellence may not establish sufficiently rigorous criteria** for qualifying for a streamlined review."

FDA states its "belief that an organization of any size without a medical device or SaMD currently on the market should have the opportunity to deliver products for medical purposes as a pre-certified organization." What is the **public health justification** for that belief?

What is the **public health justification for FDA to abandon its authority** to conduct a full review for a high-risk product?

"We appreciate that FDA speaks to the need for an iterative learning process regarding the parameters of a RWPA framework; however, regulated entities need to have clear rules of the road. **When does FDA expect the iterative process to end and the active regulatory compliance work to begin**?"

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Conclusion

- We should expect products that can significantly influence healthcare decisions—whether a traditional hardware device or SaMD, or if for use by a patient, caregiver, or healthcare provider—are designed and developed to be as safe and effective as reasonably possible and that such products have a reasonably clear and expeditious pathway to the market.
- The current system, albeit not perfect, has proven to balance both aspects of this expectation.
- Driven mainly by outside influences from new entrants to the device industry and their misperceptions of the current regulatory framework, the FDA has proposed to replace a meaningfully effective system with a largely untested one.
- To date, the FDA has not only failed to clearly articulate the proposed approach but has, more importantly, failed to demonstrate its non-inferiority. Until the FDA has provided such clarity and shown such non-inferiority, the new paradigm to regulating software should be viewed with heavy skepticism and significant concern for the well-being of individuals who are making decisions for themselves or others using “innovative” technologies that have not been subject to the existing regulatory framework.

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Development and Regulation of Innovations: In the Current State of Facts vs. Public Opinions, the Truth Does Not Always Prevail

Authors:

Nicholas Benetatos, Ph.D., Kevin Ong, Ph.D., P.E

Michael Frohbergh, Ph.D., Sangeeta Abraham, Ph.D.

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Introduction and Problem Statement(s):

- Recently, the medical device industry along with the perceived role/effectiveness of FDA oversight has come under public scrutiny.
- Often media portrayals contain highly sensationalized and/or individual accounts of negative patient experiences with a medical device product.
- These accounts may not accurately represent the overall performance of these medical devices in the larger population of patients – many of whom gain substantial benefit.
- The extensive regulatory processes and procedures required prior to and after marketing a medical device are also often overlooked by the public.

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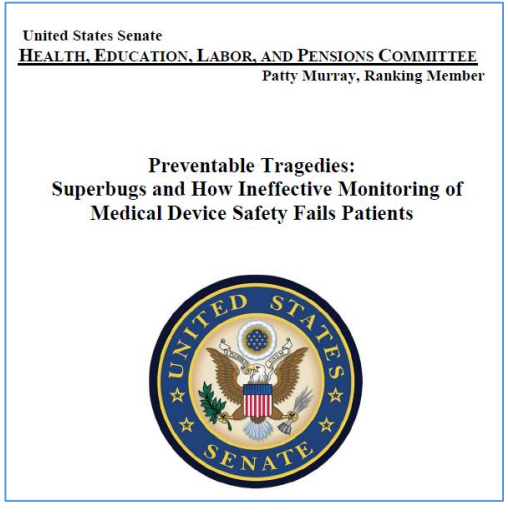
Supporting Evidence and Case Studies:



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Alternative Summary Reporting:

Report: FDA hiding millions of adverse event reports from docs, public

MARCH 7, 2019 BY FINK DENSFORD — LEAVE A COMMENT

JUNE 24, 2019

3 MINUTES

For two decades, the regulator charged with overseeing medical device safety in the United States allowed manufacturers to conceal from public view serious injuries and other malfunctions associated with implants and other medical products, from breast implants to surgical staplers.

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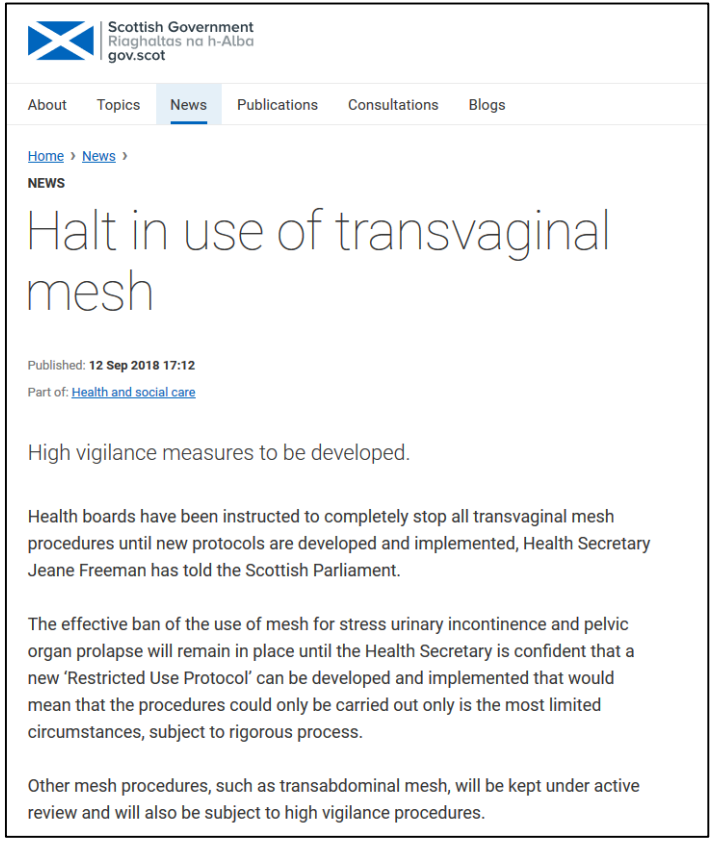
Pelvic Meshes



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NEWS

Halt in use of transvaginal mesh

Published: **12 Sep 2018 17:12**

Part of: Health and social care

High vigilance measures to be developed.

Health boards have been instructed to completely stop all transvaginal mesh procedures until new protocols are developed and implemented, Health Secretary Jeane Freeman has told the Scottish Parliament.

The effective ban of the use of mesh for stress urinary incontinence and pelvic organ prolapse will remain in place until the Health Secretary is confident that a new 'Restricted Use Protocol' can be developed and implemented that would mean that the procedures could only be carried out only is the most limited circumstances, subject to rigorous process.

Other mesh procedures, such as transabdominal mesh, will be kept under active review and will also be subject to high vigilance procedures.

NATIONAL ARCHIVES

FEDERAL REGISTER

The Daily Journal of the United States Government

Rule

Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair

A Rule by the Food and Drug Administration on 01/05/2016

PUBLISHED DOCUMENT

Start Printed Page 364

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Final order.

SUMMARY:

The Food and Drug Administration (FDA or the Agency) is issuing a final order to require the filing of a premarket approval application (PMA) or notice of completion of a product development protocol (PDP) for surgical mesh for transvaginal pelvic organ prolapse (POP) repair.

DATES:

This order is effective on January 5, 2016.

DOCUMENT DETAILS

Printed version: PDF

Publication Date: 01/05/2016

Agencies: Food and Drug Administration

Dates: This order is effective on January 5, 2016.

Effective Date: 01/05/2016

Document Type: Rule

Document Citation: 81 FR 363

Page: 363-370 (8 pages)

CFR: 21 CFR 884

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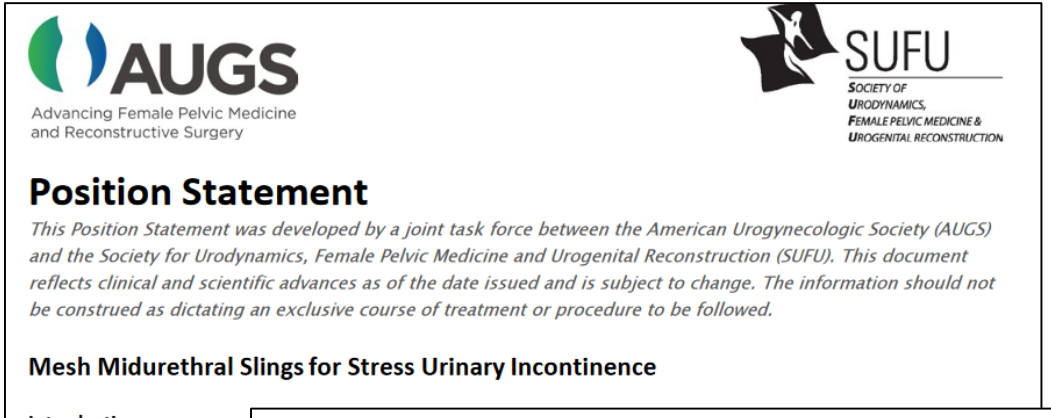
Pelvic Meshes



AUGS
Advancing Female Pelvic Medicine and Reconstructive Surgery

SUFU
Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction

Position Statement

This Position Statement was developed by a joint task force between the American Urogynecologic Society (AUGS) and the Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU). This document reflects clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Mesh Midurethral Slings for Stress Urinary Incontinence

Introduction

The purpose of this positi
Urodynamics, Female Pelv
midurethral sling in the su
associated with coughing,

Developed in the early 19
invasive, generally outpat
polypropylene placed thr
or groin areas.

SUI is a highly prevalent c
associated with coughing,
substantially reduce a wo
behavioral modification a
a more effective treatmer

3. ***Polypropylene mesh midurethral slings are a standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.*** Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain a leading treatment option and current gold standard for stress incontinence surgery.[14] Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members.[15]

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Metal-on-Metal Hips

FDA U.S. FOOD & DRUG ADMINISTRATION

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Advisory Committee Calendar

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- 2011 Advisory Committee Calendar
- 2010 Advisory Committee Calendar
- 2009 Advisory Committee Calendar

June 27-28, 2012: Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee Meeting Announcement

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

This notice has been amended. Please also see June 27-28, 2012: Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee; Amendment of Notice.

Center	Date	Time	Location
CDRH	June 27-28, 2012	7:30 a.m. - 7:00 p.m.	Hilton Washington DC North/Gaithersburg Salons A, B, C, and D 620 Perry Pkwy. Gaithersburg, MD 20877 301–977–8900

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-N-0293]

Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal-register/cfr/ibr-locations.html.*

Issued in Kansas City, Missouri, on February 10, 2016.

Pat Mullen,

Acting Manager, Small Airplane Directorate, Aircraft Certification Service.

[FR Doc. 2016–03307 Filed 2–17–16; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 888

[Docket No. FDA–2011–N–0661]

Effective Date of Requirement for Premarket Approval for Total Metal-on-Metal Semi-Constrained Hip Joint Systems

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final order to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for the hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis; and hip joint metal/metal semi-constrained, with an uncemented acetabular component, prosthesis.

DATES: This order is effective on February 18, 2016.

FOR FURTHER INFORMATION CONTACT: Sergio M. de del Castillo, Center for Devices and Radiological Health, 10903 New Hampshire Ave., Bldg. 66, Rm. 1538, Silver Spring, MD 20993, 301–796–6419.

SUPPLEMENTARY INFORMATION:

144), among other amendments, established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d) of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (generally referred to as preamendments devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices), are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and 21 CFR part 807.

A preamendments device that has been classified into class III and devices

III device may respond to the call for PMAs by filing a PMA or a notice of completion of a PDP. In practice, the option of filing a notice of completion of a PDP has rarely been used. For simplicity, although the PDP option remains available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for the filing of, and obtaining approval of, a PMA.

On July 9, 2012, FDASIA was enacted. Section 608(a) of FDASIA amended section 513(e) of the FD&C Act, changing the process for reclassifying a device from rulemaking to an administrative order. Section 608(b) of FDASIA amended section 515(b) of the FD&C Act, changing the process for requiring premarket approval for a preamendments class III device from rulemaking to an administrative order.

FDA is requiring PMAs for total metal-on-metal (MoM) semi-constrained hip joint systems (heretofore referenced as ''MoM hips''), which include the following two specific preamendments class III devices: Hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis; and hip joint metal/metal semi-constrained, with an uncemented acetabular component, prosthesis.

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) Publication of a proposed order in the **Federal Register**; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payors, and providers. FDA published a proposed order to require PMAs for MoM hips in the **Federal Register** of January 18, 2013 (78 FR 4094), and convened a meeting of a

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Metal-on-Metal Hip Implants

The Journal of Arthroplasty Vol. 27 No. 8 Suppl. 1 2012

Are Metal Ion Levels a Useful Trigger for Surgical Intervention?

William L. Griffin, MD,* Thomas K. Fehring, MD,* James C. Kudrna, MD,†
Robert H. Schmidt, MD,‡ Michael J. Christie, MD,§
Susan M. Odum, MEd,‖ and Anne C. Dennos, BS‖

Abstract: The purpose of this study was to determine if cobalt and chromium ion levels can predict soft tissue damage at total hip revision. This study included 90 metal-on-metal total hip patients with preoperative cobalt and chromium ion levels. Tissue damage noted at revision surgery was graded on a 4-point scale. Sensitivity, specificity, and predictive values were calculated for various threshold values. Receiver operating characteristic analysis was conducted. Using 7 ppb as a threshold, cobalt and chromium ion levels had poor sensitivity and specificity (Co, 65% and 56%; Cr, 29% and 75%). Positive predictive values for cobalt and chromium were only 48% and 26% respectively. The area under the curve was 0.37 for cobalt and 0.44 for chromium. The length of time to revision significantly correlated with tissue damage ($P = .001$). Ion levels are unreliable predictors of periarticular soft tissue damage and should not be used in isolation as surgical intervention triggers. **Keywords:** metal ion levels, total hip revision, cobalt, chromium.

Currently with an arbitrary 7-ppb threshold, patients with a lack of symptoms are being operated on prematurely, and others with significant damage may have a false sense of security from low ion levels. Ion levels should not be used alone to monitor MOM bearings and should not be used in isolation for determining when revision surgery is warranted. Patient history and physical examination with metal ion levels, cross-sectional imaging with ultrasound, or magnetic resonance imaging with metal artifact reduction sequences should be reviewed in combination before considering revision. The possibility of infection must also be considered from the outset in these cases. In this study, we found that tissue damage did positively correlate with time in situ. This would suggest that, in those cases where metallosis is suspected, delaying

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Vaccines

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

The New York Times

How Anti-Vaccine Sentiment Took Hold in the United States

As families face back-to-school medical requirements this month, the country feels the impact of a vaccine resistance movement decades in the making.

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Vaccines

CMAJ NEWS

Lancet retracts 12-year-old article linking autism to MMR vaccines

Published at www.cmaj.ca on Feb. 4

Twelve years after publishing a landmark study that turned tens of thousands of parents around the world against the measles, mumps and rubella (MMR) vaccine because of an implied link between vaccinations and autism, *The Lancet* has retracted the paper.

In a statement published on Feb. 2, the British medical journal said that it is now clear that "several elements" of a 1998 paper it published by Dr. Andrew Wakefield and his colleagues (*Lancet* 1998;351[9103]:637-41) "are incorrect, contrary to the findings of an earlier investigation."

Dr. Richard Horton, editor of *The Lancet*, declined through a spokesperson to speak to *CMAJ* about this issue.

In the original paper, Wakefield and 12 coauthors claimed to have investigated "a consecutive series" of 12 children referred to the Royal Free Hospital and School of Medicine with chronic enterocolitis and regressive developmental disorder. The authors reported that the parents of eight of the 12 children associated their loss of acquired skills, including language, with the MMR vaccination. The authors concluded that "possible environmental triggers" (i.e. the vaccine) were associated with the onset of both the gastrointestinal disease and developmental regression.

In fact, as Britain's General Medical Council ruled in January, the children that Wakefield studied were carefully selected and some of Wakefield's research was funded by lawyers acting for parents who were involved in lawsuits against vaccine manufacturers. The council found Wakefield had acted unethically and had shown "callous disregard" for the children in his study, upon whom invasive tests were performed.

When the original article was picked up by the general media, the findings were fuelled by speeches and public appearances in which Wakefield recommended single vaccines rather than the combined MMR. Many parents seeking a cause for their children's illness seized upon the apparent link between the routine vaccination and autism, say Canadian researchers who laud the retraction.

"I think a lot of families were looking for a reason, so they were extremely vulnerable (to this explanation)," says Jeanette Holden, a geneticist at Queen's University in Kingston, Ontario. Holden, whose brother is autistic, heads the Autism Spectrum Disorders — Canadian–American Research Consortium.

"The problem is that this had dramatic health consequences, which was that people just didn't vaccinate their children," she adds.

In the United Kingdom, the Health Protection Agency attributed a large measles outbreak in 2008 and 2009 to a concurrent drop in the number of children receiving the MMR vaccine. Pockets of measles — which can be fatal — have also cropped up in Canada and the United States as a result of parents' refusal to vaccinate.

"In the course of my discussions with families it's almost invariable that the measles question comes into play," says Dr. Suzanne Lewis, a pediatrician and clinical professor of medical genetics at the University of British Columbia in Vancouver.

"I was quite thankful to see the retraction — it's long overdue," she adds.

Both Holden and Lewis, who is also a member of the Autism Spectrum Disorders — Canadian–American Research Consortium, questioned the article's original heft, given its small sample size.

"Why *The Lancet* published it is completely beyond me," Lewis says.

Dr. Andrew Wakefield speaks to media in London, England on Jan. 28 after the General Medical Council ruled that he acted unethically in doing his research into a link between Measles Mumps Rubella vaccinations and autism.

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to lymphoid obliteration. Histology showed patchy chronic inflammation in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (one). There were no focal neurological abnormalities and CSF and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls (p=0·003), low haemoglobin in four children, and low serum IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351:** 637–41
See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP,), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and bloating and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for a week, accompanied by their parents.

Clinical investigations

We took histories, including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with ICD-10 criteria.[8] Developmental assessment included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[9] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antienteromyseal antibodies and boys were screened for fragile-X if this had not been done

RETRACTED

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Summation and Conclusion

Now more than ever, it is crucial to highlight how the medical device industry operates and is regulated.

Showcasing policies implemented, actions taken, and research conducted to counteract any misguided public perceptions may serve as an important step to advancing technology and furthering the development of innovative, safe, and effective medical products – many of which promise enormous potential to treat previously untreatable diseases.

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A Shifting Regulatory Framework for Digital Health: The Impact of Silicon Valley on the FDA's Mission to Promote and Protect the Public Health

M. Jason Brooke, General Counsel and Vice President of Regulatory & Quality, AmalgamRx

Development and Regulation of Innovations: In the Current State of Facts vs. Public Opinions, the Truth Does Not Always Prevail

Nicholas Benetatos, Manager, Exponent, Inc.
Kevin Ong, Principal Engineer, Exponent, Inc.

Discussant: **Nathan Brown**, Partner, Akin Gump Strauss Hauer & Feld LLP
Moderator: **Karen C. Corallo**, Of Counsel, Skadden, Arps, Slate, Meagher & Flom LLP

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