Regulatory Considerations for Clinical Decision Support Algorithm Use

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Objectives: Review the following...

- Past regulatory guidance for digital algorithms applied to medicine in the United States
- Current federal law that may apply to CDS algorithms as of May 2019
- OVA-1
- FDA Pilot Pre-Certification Program
- Diagnostic Accuracy and Innovation Act (DAIA)
In the past 12 months, I have not had any significant financial interest or other relationship with the manufacturers of the products or providers of the services that will be discussed in my presentation.

I am employed by NorthShore University Health System (Evanston, IL), which develops and uses clinical decision support tools.

Any opinions expressed in this presentation are my own and do not necessarily reflect the policies of my employer.

I am not a lawyer. Nothing in this presentation should be construed as legal advice.
“sitting in a nondescript office in McNamara's Pentagon, a quiet...civilian is already planning the revolution that will change forever the way computers are perceived. Somehow, the occupant of that office...has seen a future in which computers will empower individuals, instead of forcing them into rigid conformity. He is almost alone in his conviction that computers can become not just super-fast calculating machines, but joyful machines: tools that will serve as new media of expression, inspirations to creativity, and gateways to a vast world of online information."

“Man-Computer Symbiosis.” 1960

“It seems reasonable to envision ... a 'thinking center' that will incorporate ... libraries together with anticipated advances in information storage and retrieval.

The picture readily enlarges itself into a network of such centers, connected to one another by wide-band communication lines and to individual users by leased-wire services...

the cost of the gigantic memories and the sophisticated programs would be divided by the number of users. “

“The main aims are

1) to let computers facilitate formulative thinking as they now facilitate the solution of formulated problems, and

2) to enable men and computers to cooperate in making decisions and controlling complex situations without inflexible dependence on predetermined programs.”

“Lick” Identified the Need to Develop More Useful Data Structures and Programming Languages...

1966-1967: Mass General Hospital Utility Multi-Programming System
1960 to 2007

In many ways, Lick’s visions were realized

Human-computer symbiosis expanded in medicine

But from a regulatory point of view...

– Humans are **Licensed**
– How are the computers / algorithms regulated?
What is a ‘regulated medical device’?

"The term 'device' . . . means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . (2) 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 . . . ."

Section 201(h) Food, Drug and Cosmetic Act

Is the computer side of the human-computer symbiosis a medical device?
2007 FDA Draft Guidance on In Vitro Diagnostic Multivariate Index Assays (IVDMAs)

1) Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a “classification,” “score,” “index,” etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and

2) Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.

Is an IVDMA a regulated medical device?

“An IVDMIA is a device within the meaning of the Act. “

“Some IVDMIAs are laboratory-developed tests (LDTs).”

Is a LDT a regulated medical device?

"clinical laboratories that develop [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the Act," 62 FR 62249

However, the FDA has “generally exercised enforcement discretion over standard LDTs”

What is a “standard” LDT?

• Developed in a single laboratory

• Used in a single laboratory

• LDTs that use primarily analyte specific reagents, general purpose reagents (21 CFR 864.4010), general purpose laboratory equipment (21 CFR 862.2050), other laboratory instrumentation (21 CFR Part 864, subpart D), and controls (21 CFR 862.1660)
Could any IVDMIA be developed as an LDT?

IVDMIAs include elements, as described in the section on "Definition and Regulatory Status of IVDMIAs" of this guidance, that are not among these primary ingredients of LDTs (e.g., complex, unique interpretation functions).

IVDMIAs thus do not fall within the scope of LDTs over which FDA has generally exercised enforcement discretion.”

Why did the FDA care about IVDMIAs?

“IVDMIAs raise significant issues of safety and effectiveness.

These types of tests are developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratorians, and clinicians who order these tests.

Additionally, IVDMIAs frequently have a high risk intended use ... uses to make critical healthcare decisions when FDA has not ensured that the IVDMIA has been clinically validated and the healthcare practitioners are unable to clinically validate the test themselves.

Therefore, there is a need for FDA to regulate these devices to ensure that the IVDMIA is safe and effective for its intended use.”

What was the plan?

“FDA seeks to identify IVDMIAs as a discrete category of device, and to clarify that, even when offered as LDTs, IVDMIAs must meet pre- and postmarket device requirements under the Act and FDA regulations, including premarket review requirements in the case of most class II and III devices.”

Examples of IVDMAs:

Devices classified under 21 CFR 866.6040, Gene expression profiling assay for breast cancer prognosis

A device that integrates quantitative results from multiple immunoassays to obtain a qualitative “score” that predicts a person’s risk of developing a disease or condition.

A device that integrates a patient’s age, sex, and genotype of multiple genes to predict risk of or diagnose a disease or condition.

Examples of things NOT considered IVDMAs:

Devices that combine multiple variables into a single patient-specific result that facilitates an interpretation of the variables that clinicians could otherwise interpret themselves because of extensive experience and training in use of the device (e.g., standard maternal Triple Screen testing—measurement in the second trimester of AFP, hCG, and estriol).

Common, public demographic risk calculations (e.g., Gail Index, Framingham Risk Score)

Devices such as Clinical Decision Support tools that analyze stored clinical information to, for example, flag patient results based on specific clinical parameters (e.g., out of range results, potential drug interactions, opportunities for complementary tests, etc.), create disease registries, summarize patient-specific information in an integrated report, and/or track a patient’s treatment or disease outcome. The analysis performed by these software platforms does not represent a unique interpretation function but rather summarizes standard interpretation of individual variables that clinicians could do themselves.
What happened to IVDMAs and the 2007 Draft Guidance?

IVDIMA 2007 Draft Guidance potential effects:

“Black box” CDS algorithms would be regulated

LDTs with significant “black box” dry lab algorithms would be IVDIMIAs

IVDIMAs would be regulated
2007 to 2016: A Decade of Regulatory Confusion

IVDMIA Draft Guidance was not adopted

Multiple companies developed “IVDMIAs” and submitted them for premarket approval
Example: Ovarian Cancer Screening

7% of woman have a pelvic abnormality on imaging

5-10% of woman in US with have prophylactic surgery for suspected ovarian cancer

Family history, pelvic exam, ascites, evidence of metastases, and CA125 (blood): 47% SN, 77% SP

OVA1™ Test: 510(k) New Device

Type of Test: Software algorithm and 5 immunoassays

Classification: Class II

Intended Use: A qualitative serum test that combines the results of five immunoassays into a single numerical score. It is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist.

The OVA1 Test is an aid to further assess the likelihood that malignancy is present when the physician’s independent clinical and radiological evaluation does not indicate malignancy. The test is not intended as a screening or stand-alone diagnostic assay.

OVA1 is a trademark of Vermillion, Inc.

Reproduced from FDA 510k: k081754
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Device (Assay and Calibrator)</th>
<th>Instrument</th>
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<tr>
<td>CA 125</td>
<td>Elecsys CA 125 II</td>
<td>Roche Elecsys 2010</td>
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<td>CA125 II CalSet</td>
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<td>Prealbumin</td>
<td>N Antisera to Human Prealbumin and Retinal-binding Protein</td>
<td>Siemens BN II</td>
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<td>N Protein Standard SL (human)</td>
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<td>Apolipoprotein A-1</td>
<td>N-Antisera to Human Apolipoprotein A-1 and Apolipoprotein B</td>
<td>Siemens BN II</td>
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<td>N Apolipoprotein Standard Serum (human)</td>
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<td>β₂-microglobulin</td>
<td>Human Beta-2 Microglobulin Latex Enhanced Nephelometric Kit ( Binding Site)</td>
<td>Siemens BN II</td>
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<td>Transferrin</td>
<td>N Antisera to Human Transferrin and Haptoglobin</td>
<td>Siemens BN II</td>
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<td>N Protein Standard SL (human)</td>
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**OvaCalc Software**

Reproduced from FDA 510k: k081754
PRECAUTION: The OVA1™ Test should not be used without an independent clinical/radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of the OVA1™ Test carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.
Risk of Ovarian Malignancy Algorithm (ROMA)

Women with a pelvic mass...
  CA125, HE4, menopausal status -> high or low risk of malignancy

Prospective, multicenter, blinded clinical trial
  472 patients
  SN 93.8%
  SP 74.9%
  NPV 98%

Approved by showing equivalency to OVA1

Amendments to the Food, Drug, and Cosmetic Act (the Act)

Defines how software in medicine can be NOT a ‘device’

‘Devices’ are regulated by the FDA per The Act

“The Act” includes criminal and civil liabilities for violations … whether willful or not
For Software to be NOT a device, It must meet all 4 criteria:

(1) not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system (section 137 520(o)(1)(E) of the FD&C Act);

(2) intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines) (section 520(o)(1)(E)(i) of the FD&C Act);

(3) intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition (section 143 520(o)(1)(E)(ii) of the FD&C Act);

(4) intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient (section 520(o)(1)(E)(iii) of the FD&C Act).
For Software to be NOT a device, It must meet all 4 criteria:

(1) not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system (section 137 520(o)(1)(E) of the FD&C Act);

(2) intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines) (section 520(o)(1)(E)(i) of the FD&C Act);

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Post-21st Century Cures Act

GUIDANCE DOCUMENT

Clinical and Patient Decision Support Software

Draft Guidance for Industry and Food and Drug Administration Staff

DECEMBER 2017
Dec 2017 CDS Draft Guidance

Scope...

(1) clinical decision support software intended for healthcare professionals

(2) patient decision support software intended for patients and caregivers who are not healthcare professionals.

https://www.fda.gov/media/109618/download
Dec 2017 CDS Draft Guidance

Purpose: Identify Software Functions That...

(1) do not meet the definition of a device as amended by the Cures Act;

(2) may meet the definition of a device but for which FDA does not intend to enforce compliance with applicable requirements of the FD&C Act, including, but not limited to, premarket clearance and premarket approval requirements;

(3) FDA intends to focus its regulatory oversight on.

https://www.fda.gov/media/109618/download
Clinical Decision Support (CDS): For the purposes of this guidance, FDA is using the term “CDS” to mean those software functions that meet the first, second, and third criteria of section 520(o)(1)(E) as listed above.

CDS is not always excluded from the device definition by the Cures Act. Only when a CDS function also meets the fourth criterion of section 520(o)(1)(E), which relates to enabling independent review of the basis for recommendations, is the CDS function excluded from the definition of a device.

https://www.fda.gov/media/109618/download
Clinical Decision Support (CDS): For the purposes of this guidance, FDA is using the term “CDS” to mean those software functions that meet the first, second, and third criteria of section 520(o)(1)(E) as listed above.

CDS is not always excluded from the device definition by the Cures Act. Only when a CDS function also meets the fourth criterion of section 520(o)(1)(E), which relates to enabling independent review of the basis for recommendations, is the CDS function excluded from the definition of a device.
International Medical Device Regulators Forum’s (IMDRF)

Software as a medical device (Definition):

software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device

https://www.fda.gov/media/119722/download
FDA’s Current Criteria for SaMD

• Run’s a non-medical purpose computers
• Not necessary for hardware medical device to function
- The “Test Plan”
- Regulatory underpinning
“Non-device” software functions are excluded from the Software Precertification Program:

1. administrative support of a health care facility
2. maintaining or encouraging a healthy lifestyle
3. electronic patient records
4. transferring, storing, converting formats, or displaying clinical laboratory tests or other device data and results, without interpreting or analyzing
5. certain types of limited clinical decision support.

6. Software functions described in final guidance documents that may meet the definition of a device but for which FDA does not intend to enforce compliance with applicable requirements of the FD&C Act are not within the scope of the Software Pre-Cert Program.

https://www.fda.gov/media/119722/download
“For Americans to see the full benefits of digital health products, we need a regulatory framework that accommodates the distinctive nature of digital health technology, its clinical promise, and the compressed cycle of product iterations.

The FDA's traditional approach to medical devices is not well-suited to these products.”

FDA Pre-Certification Pilot Program
Goal?

“FDAs goal with Pre-Cert is to regulate digital health technologies in a way that fosters innovation, the model the agency is piloting is firmly rooted in protecting patient safety.”

FDA Pre-Certification Pilot Program

What?

“a voluntary pathway that embodies a regulatory model more tailored than the current regulatory paradigm to assess the safety and effectiveness of software technologies without inhibiting patient access to these technologies.”

FDA Pre-Certification Pilot Program
Public Feedback

“FDA is seeking public feedback on this version of the working model by March 8, 2019, at https://www.regulations.gov/comment?D=FDA-2017-N-4301-0001.

This feedback will be incorporated into future versions of the program model, which will also be disseminated for public input.”

| Commenters raised the need for a regulatory toolkit or framework to navigate existing FDA policy in the context of the Pre-Cert Program. | FDA intends to develop a decision tree or support tool for organizations to determine:
- whether a SaMD software function meets the definition of device in section 201(h) of the FD&C Act;
- whether a SaMD software function is a function for which FDA has expressed an intent not to enforce compliance to applicable requirements; and
- its applicable risk categorization for Pre-Cert. This extends beyond the scope of the Pre-Cert Program, and FDA will provide its current thinking in a separate document. |
| Commenters provided recommendations for appraisal of organizations using artificial intelligence/machine learning technology. | FDA is considering how organizations that produce software using artificial intelligence or machine learning algorithms may be assessed during an Excellence Appraisal. FDA intends to incorporate the recommendations received as part of the 2019 testing, as needed. |
FDA Pre-Certification Pilot Program Details

- Excellence Appraisal and Precertification
- Review Pathway Determination
- Streamlined Premarket Review Process
- Real-World Performance
12 Appendix – Proposed Organizational Elements to Demonstrate Excellence Principles

FDA intends to evaluate organizational elements based on objective and observable evidence. Although the appraisal method is under development, we expect organizations would provide this evidence as part of the appraisal process, which may include site visits, interviews, or other methods. FDA hopes to implement automation for the acceptance and review of an organization’s demonstration of their elements in future iterations to reduce appraisal burden, increase transparency, and enhance the capability to respond quickly and improve products without reducing public confidence in the program.

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<tr>
<th>Organizational Domains</th>
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<th>Excellence Principle(s)</th>
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<tbody>
<tr>
<td>PS: Product Safety; PQ: Product Quality; ClinR: Clinical Responsibility; CybR: Cybersecurity Responsibility; PC: Proactive Culture</td>
<td>PS</td>
<td>PQ</td>
</tr>
<tr>
<td>Leadership, and Organizational Support</td>
<td>Providing clear accountability and responsibility to address product issues, user issues, constraints, and conflicting priorities throughout the product lifecycle.</td>
<td>X</td>
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<td></td>
<td>Empowering staff to act regarding the decisions or issues impacting users, products, or patient safety.</td>
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<td></td>
<td>Providing the resources and focus to assure important infrastructure and processes to assure patient safety are sustained and improved.</td>
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<tr>
<td>Transparency</td>
<td>Developing and maintaining systems or dashboards where all levels of the organization can rapidly see and understand how they are performing among metrics relevant to the organization.</td>
<td>X</td>
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<tr>
<td></td>
<td>Making defects, deviations, safety issues transparent to internal and external stakeholders, as appropriate.</td>
<td>X</td>
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<tr>
<td></td>
<td>Security and quality issues are communicated with internal and external stakeholders sufficiently to catalyze corrective and preventive action.</td>
<td>X</td>
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<tr>
<td></td>
<td>Buyers and users understand design assumptions about expected operational conditions/environment to use devices safely, securely, and effectively.</td>
<td>X</td>
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Software Precertification Program: Working Model – Version 1.0 – January 2019

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<tbody>
<tr>
<td><strong>People</strong></td>
<td>Developing and maintaining access to highly skilled employees with relevant/applicable clinical knowledge</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>Involving appropriate cross functional subject matter expertise including, engineering, clinical expertise, and user advocates, with frequent engagement and communication in product decisions and potential safety events.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>Continuous development of employees through robust knowledge management, employee development options, coaching, training, and succession planning. This includes keeping updated with the latest clinical developments and patient safety priorities.</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>Developing and maintaining clear and objective employee performance metrics, rewards, and recognitions aligning behaviors to the business goals, values, and rapidly responding to patient safety issues.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Infrastructure and Work Environment</strong></td>
<td>Customer engagement and providing multiple avenues for outreach, feedback, and learning.</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>Implementing the tools, automation, and test environments in development that establish a centralized and visible process.</td>
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<td>Develop and maintain a robust notification and communication framework.</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>Communicate and preserve the relevant results of the activities, processes and expectations related to the SaMD lifecycle processes.</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>Developing and maintaining processes and mechanisms for rapid learning from successes, failures, and near-misses.</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Risk Management: A Patient Safety Focused Process</td>
<td>Regularly questioning how software works by understanding, identifying, and proactively anticipating potential issues and factors that can influence what can go wrong with the software.</td>
<td>X X X X X</td>
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<tr>
<td></td>
<td>Favor rigorously tested software components (i.e. well-vetted cryptographic libraries vs roll your own) or identify risks and mitigations.</td>
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<tr>
<td></td>
<td>Identifying, receiving, and handling vulnerability reports from third parties directly (coordinated vulnerability disclosure) or from public sources, such as vulnerability databases.</td>
<td>X</td>
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<tr>
<td></td>
<td>Accounting for support lifecycles of hardware and software components and dependencies. (i.e. If the SaMD is expected to be used longer than the operating system is supported, how will you continue to address things like security vulnerabilities?)</td>
<td>X</td>
</tr>
<tr>
<td>Configuration Management and Change Control</td>
<td>Source control by establishing mechanisms for initiating, evaluating and controlling changes to software during all lifecycle processes and after deployment.</td>
<td>X X X</td>
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<tr>
<td></td>
<td>Good release management with a secure update process.</td>
<td>X X X X</td>
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<td>The ability to rollback software in the event of an emergency.</td>
<td>X X</td>
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<tr>
<td>Measurement, Analysis, and Improvement of Processes and Products</td>
<td>Responsive issue escalation &amp; resolution.</td>
<td>X X</td>
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<td></td>
<td>Actively monitoring, analyzing, rapidly addressing, and implementing resulting process improvements from user feedback and product issues including safety, cyber or data issues.</td>
<td>X X</td>
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<td></td>
<td>Analyzing and providing the learning collected from real world data back to development teams throughout all lifecycle processes.</td>
<td>X X</td>
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<td></td>
<td>Developing and maintaining process performance metrics that are clear, simple, and actionable across all staff and organizational levels with integrated improvement activities.</td>
<td>X X</td>
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<td>Supporting rigorous interrogation into sources of failure, error, and tampering, including tamper resistant, forensically sound evidence capture and publicly known mechanisms to perform or trigger investigations.</td>
<td>X</td>
</tr>
<tr>
<td>Managing Outsourced Processes, Activities, and Products</td>
<td>Comprehensive risk management of third-party and open source software throughout all lifecycle process and activities.</td>
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<tr>
<td></td>
<td>Avoid third-party software components with known vulnerabilities when less vulnerable alternatives are available.</td>
<td>X</td>
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<td></td>
<td>Maintain and provide traceability and assurance of third-party and open source software throughout the effective lifetime of the software.</td>
<td>X</td>
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<tr>
<td>Requirements Management</td>
<td>Understanding the clinical association between the SaMD output and a clinical condition (i.e., clinical performance) and understanding and updating the priorities, concerns, and value to intended user based on user feedback throughout all lifecycle phases.</td>
<td>X</td>
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<td>Buyers and operators understand the impact of operational isolation (e.g., which features are fully available in standalone/no network mode).</td>
<td>X</td>
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<td></td>
<td>Carefully manage and gate remote access to all device components and dependencies. (e.g. Avoid hardcoded default credentials within the device and enforce secure identity and access management for any provider-operated components like software update distribution servers.)</td>
<td>X</td>
</tr>
<tr>
<td>Design and Development</td>
<td>Secure software development lifecycle, including adversarial resilience analysis and testing, reducing elective attack surface &amp; complexity, and minimizing elective exposure throughout the software lifecycle.</td>
<td>X</td>
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<tr>
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<td>Designing software based on good quality clinical evidence from research and can reference published, peer-reviewed studies that show claimed results.</td>
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<td>Incorporating resilience, containment, and isolation into the design solution so that product fails safely and visibly, continue to perform as expected.</td>
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<td>intended when there are failures in the operating environment, and assures the integrity of data input and storage.</td>
<td>PS PQ</td>
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<tr>
<td></td>
<td>Incorporating anticipated safety risks and mitigations throughout all lifecycle phases and actions taken to prevent recurrence of any unanticipated hazards.</td>
<td>PS PQ ClinR CybR PC</td>
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<td></td>
<td>Reliably identifying and removing code errors at source.</td>
<td>PS PQ ClinR CybR</td>
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<td>Integrating user experience/Human Factors and Good Clinical Practices Human Subject Protection into development in partnership with patients and caregivers.</td>
<td>PS PQ ClinR CybR PC</td>
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<td>Secure, prompt, and agile update mechanism and process, with high rates of prompt update adoption and clear notification and communication to stakeholders.</td>
<td>PS PQ ClinR CybR PC</td>
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<td>Leadership/peer/expert review throughout lifecycle phases and at key milestones.</td>
<td>PS PC</td>
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<tr>
<td>Verification and Validation</td>
<td>Staged release with active user testing.</td>
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<td>Demonstrating software works for intended use / indications for use.</td>
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<td>Measuring quality of the output of the software on the clinical target (intended use, indication of use).</td>
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<tr>
<td>Deployment and Maintenance</td>
<td>Proactive patient and clinical outreach and education including limitations of software and FAQs addressing potential patient safety questions developed as part of release.</td>
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<td>Active control mechanisms to force/push patient safety and security updates.</td>
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<td>Support dependency updates, such as routine operating system upgrades.</td>
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<tr>
<td>Analytic Type</td>
<td>Domain</td>
<td>Value</td>
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</tbody>
</table>
| Real World Health Analytics | Human Factors and Usability Engineering | • Pre-Cert Organization: Support product claims by understanding user ability to comprehend and correctly navigate user interface  
• All stakeholders: Demonstrate continuous improvement in usability engineering to drive health benefits and safety | PQ  PS  ClinR  CybR  PC | User error rate                                    |
| Clinical Safety        | • Pre-Cert Organization: Benefit from early safety signal detection across Pre-Cert organizations  
• All stakeholders: Provide assurance that safety risks are managed and mitigated in a timely way | PQ  PS  ClinR  CybR  PC | Anticipated adverse event rate/severity  
Time to resolve anticipated adverse event  
Unanticipated adverse event rate/severity  
Time to resolve unanticipated adverse event | |
| Health Benefits        | • Pre-Cert Organization: Support product claims and future claim modifications by understanding clinical benefits  
• All stakeholders: Demonstrate positive impact on health outcomes | PQ  PS  ClinR  CybR  PC | Rate of change in targeted health outcome by user demographic | |

PQ: Product Quality; PS: Product Safety; ClinR: Clinical Responsibility; CybR: Cybersecurity Responsibility; PC: Proactive Culture
<table>
<thead>
<tr>
<th>Analytic Type</th>
<th>Domain</th>
<th>Value</th>
<th>Excellence Principle(s)</th>
<th>Example KPIs</th>
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<tbody>
<tr>
<td></td>
<td>User Experience Analytics</td>
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<td>User Satisfaction</td>
<td>• Pre-Cert Organization: Provide insight into brand reputation and</td>
<td>PQ PS ClinR CybR PC</td>
<td>Average user ratings over time</td>
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<td>product performance</td>
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<td></td>
<td></td>
<td>• All stakeholders: Demonstrate excellence in product quality,</td>
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<td>Complaint rates</td>
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<td></td>
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<td>organizational proactivity, and product effectiveness</td>
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<td>Customer survey responses</td>
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<td>Issue Resolution</td>
<td>• Pre-Cert Organization: Build consumer confidence in organization</td>
<td>PQ PS ClinR CybR PC</td>
<td>Time to resolution by clinical/cybersecurity risk category</td>
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<td></td>
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<td>and SaMD product</td>
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<td>Number of open complaints</td>
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<td>• All stakeholders: Demonstrate excellence in safety and product</td>
<td></td>
<td>Time to root cause analysis</td>
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<tr>
<td></td>
<td></td>
<td>quality</td>
<td></td>
<td>Number of repeat issues/complaints</td>
</tr>
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<td>User Feedback Channels</td>
<td>• Pre-Cert Organization: Identify and resolve important user issues</td>
<td>PQ PS</td>
<td>Customer rating of issue resolution</td>
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<td>early and timely</td>
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<td>• All stakeholders: Demonstrate clinical responsibility and</td>
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<td>excellence in product quality by ensuring that user feedback is</td>
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<td>representative of the full user population</td>
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<td>User Engagement</td>
<td>• Pre-Cert Organization: Optimize user experience and meet business</td>
<td>PQ PS</td>
<td>Unique users</td>
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<td>targets for user engagement</td>
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<td></td>
<td></td>
<td>• All stakeholders: Demonstrate product</td>
<td></td>
<td>User retention</td>
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<td>quality, clinical responsibility, and proactivity</td>
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<td>Time in app</td>
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<td>by understanding and continuously improving user experience</td>
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<tr>
<td>Analytic Type</td>
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</tbody>
</table>
| Product      | Cybersecurity| • Pre-Cert Organization: Build consumer confidence in organization and SaMD product  
• All stakeholders: Protect user privacy, ensure product integrity, and maintain system availability | PQ PS ClinR CybR PC     | Number of breaches resulting in loss of user data  
Number of remediated vulnerabilities/ vulnerabilities identified  
System downtime                                                                                     |
| Performance  | Product      | • Pre-Cert Organization: Support product claims and future claim modifications  
• All stakeholders: Demonstrate sustained analytical validity and excellence in continuous improvement in product quality | PQ PS CTX | False positive/false negative rates  
Bug/defect rates  
Version failure rates                                                                                   |
How can the FDA implement Software Precertification without new legislation?

Current Medical Device Classification

Class III: Premarket Approval (PMA) showing Safety and Efficacy

Class II: 510k clearance showing equivalency

Class I: Manufacturer Registers and Lists Product
What if there’s no predicate device?

Prior to 1997: PMA submission

1997: De novo classification as Class I or II possible after 510k submission

2012: De novo classification as Class I or II possible without 510k submission if no predicate device is found by manufacturer

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm
De Novo Classification Process
(Evaluation of Automatic Class III Designation)

Guidance for Industry and Food and Drug Administration Staff


The draft of this document was issued on August 14, 2014.

De Novo Classification Authority and Software PreCert

“FDA intends to utilize the De Novo classification process

... a pathway for certain new types of low to moderate risk devices for obtaining marketing authorization as class I or class II, rather than remaining automatically designated as a class III device that would require premarket approval.”

CDRH. Software Precertification Program Regulatory Framework_January 2019
Who Is Currently Involved in the Pre-Cert Pilot Program?

In September 2017, the FDA selected nine companies out of over 100 applicants to participate in the development of the Software Pre-Cert pilot program:

- Apple
- Fitbit
- Johnson & Johnson
- Pear Therapeutics
- Phosphorus
- Roche
- Samsung
- Tidepool
- Verily

The details of selection criteria for the pilot program were published in the Federal Register notice Software Precertification Pilot Program.

The FDA also hired three Entrepreneur-in-Residence fellows to help support the development of the Pre-Cert Program.
Does self-appraisal make sense?

Why Fixing FAA Aircraft Safety Certification Is Not A Matter Of Money

Marisa Garcia, Contributor at Forbes

During a Senate hearing on Wednesday, Daniel Elwell, the acting administrator of the Federal Aviation Administration, said the FAA Aircraft Certification Service would need 10,000 more employees and $1.8 billion in funding to handle all certifications directly, instead of its current practice of delegating much of the work to designated employees of the companies it regulates.

This would be a significant increase from its 2019 budget of $239 million and 1,300 staff. However, while a larger budget might help the FAA better manage its operations, the FAA’s need for Designees is not an issue of money. It’s an issue of available know-how.

THE DIAGNOSTIC ACCURACY AND INNOVATION ACT
Advancing innovation and safety for patients in diagnostics

In an effort to better protect patients and provide access to innovative diagnostics, the Diagnostic Accuracy and Innovation Act (DAIA) provides a predictable and timely path to market for these increasingly important clinical tests. This legislation has benefited from extensive collaboration with patient groups, researchers, laboratories, diagnostic test developers, innovators, FDA, and others.

The DAIA addresses longstanding concerns with the regulation of diagnostic tests and will bring much needed certainty to the diagnostic industry and its critical role in patient care. This legislation ensures reasonable risk-based regulation, avoids duplicative regulation, advances precision medicine, and applies the same regulatory principles to the same activity regardless of where the test is developed. The DAIA also modernizes the Clinical Laboratory Improvement Amendments (CLIA) program at the Centers for Medicare & Medicaid Services (CMS) to maintain quality laboratory operations. The legislation assigns certain responsibilities to FDA (test development and manufacturing generally) and assigns exclusive jurisdiction over laboratory operations to CMS under CLIA.

SCOPE

The DAIA applies to any in vitro clinical test (IVCT), which includes both finished products (e.g., test kits and platforms) and laboratory test protocols (often referred to in the past as “laboratory develop tests” or LDTs). IVCTs will be a new category and regulatory structure under the Food, Drug, and Cosmetic Act, and will not be regulated as devices, drugs, or biologics. Laboratory operations will be regulated exclusively by CMS/CLIA.

JURISDICTION

The DAIA establishes three distinct, non-overlapping categories of activity and jurisdiction.

- **Test development and manufacturing**, which includes the design, development, and validation of an IVCT as well as the production of an IVCT for distribution to another facility or third-party. FDA will have exclusive jurisdiction over these activities under a new FDA Center devoted to IVCTs.
- **Laboratory operations**, which are all the activities necessary to perform or “run” a developed IVCT, including the preparation of reagents for use in a single CLIA facility, sample preparation, and other pre-analytical processes. CMS/CLIA will have exclusive jurisdiction over laboratory operations.

These things too shall pass ... to whom?

OTHER KEY PROVISIONS

- FDA will have the authority to withdraw IVCTs from the market that present an unreasonable and substantial risk of illness or injury when used as intended.
- FDA and CMS will retain the right to conduct inspections and oversee recalls.
- Third party review processes are encouraged; CMS may delegate inspection and certification.

Summary

• The playing field is shifting for IVDMIA / SaMD / CDS

• The FDA and congress are trying to promote innovation

• Software PreCert program is on interesting legal ground

• Companies are lobbying / commenting / advocating strongly

• Will algorithms empower Laboratory Medicine or commoditize it?