Presenter

Michele Buenafe

Morgan Lewis

Agenda

- FDA Regulation of Software and Statutory Exemptions
- FDA's Clinical Decision Support Software Guidance
  - History
  - New Final Guidance
  - Examples
- Related FDA Developments


FDA Regulation of Software and Statutory Exemptions
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Statutory Definition of a "Device"

- FDA regulates software and other digital health technologies that meet the definition of a "device" under the Federal Food, Drug, and Cosmetic Act, which includes
  - Any instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar related article, including any component, part, or accessory
  - Intended for use in the diagnosis of disease or other conditions, or in the cure, treatment, or prevention of disease, or intended to affect the structure or function of the body
  - Which does not achieve its principal purposes by chemical action in or on the body of man or by being metabolized (*i.e.*, not a drug).

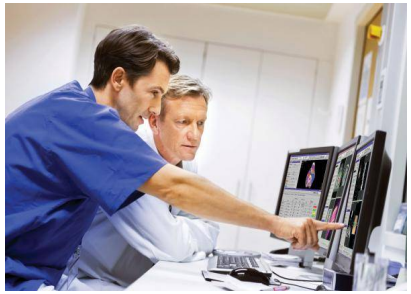
  FFDCA § 201(h), 21 U.S.C. § 321(h)

- VERY broad definition

21st Century Cures Act – Software Carve Outs

- For *administrative support* functions
  - Includes software for "including the processing and maintenance of financial records, claims or billing information, appointment schedules, business analytics, information about patient populations, admissions, practice and inventory management, analysis of historical claims data to predict future utilization or cost-effectiveness, determination of health benefit eligibility, population health management, and laboratory workflow"
  - Not historically regulated by FDA
- For *maintaining or encouraging a healthy lifestyle*
  - Must be unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition
  - FDA Guidance – General Wellness: Policy for Low Risk Devices

21st Century Cures Act – Software Carve Outs



- To serve as *electronic health records*
  - Must meet the following criteria:
    - Such records were created, stored, transferred, or reviewed by health care professionals or by individuals working under supervision of such professionals
    - Certified by ONC per Health IT Certification Program (enforcement discretion for non-certified systems)
    - Not intended for interpretation or analysis of patient records or images for the purpose of diagnosis, cure, mitigation, prevention, or treatment of a disease or condition
- For transferring, storing, converting formats, or displaying *medical device data or results* (including clinical lab test data)
  - Includes "medical device data systems" or "MDDS"
  - FDA Guidance – Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices

21st Century Cures Act – Software Carve Outs

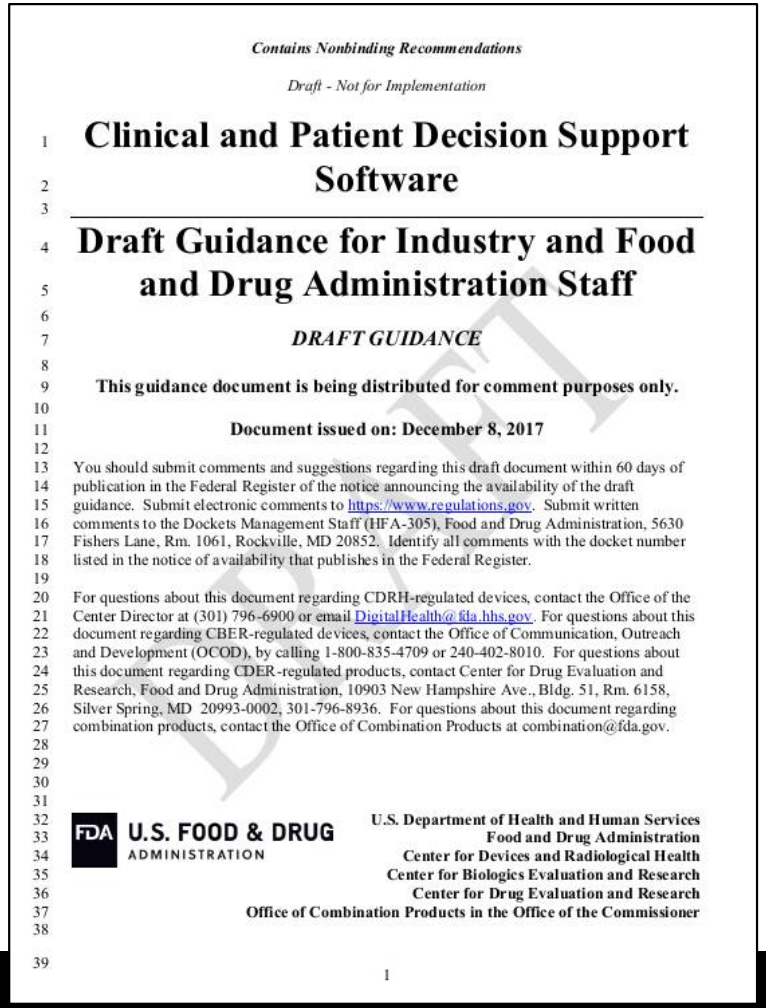
- Medical software exemptions:
  - For *clinical decision support* (CDS) functions that meet the following criteria:
    - Is not "intended to acquire, process, or analyze a medical image or a signal from an *in vitro* diagnostic device or signal acquisition system"
    - Is intended for the purpose of "displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines)"
    - Is intended for the purpose of "supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition"
    - Is 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"
  - The CDS exemption only includes software *intended for use by a health care professional* – not for consumer use

Final Guidance issued Sept. 28, 2022


FDA’s Clinical
Decision Support
Software Guidance
Morgan Lewis

History – 2017 Draft Guidance

- FDA issued first draft CDS Guidance in Dec. 2017
  - Intended to provide guidance on FDA's interpretation of the four statutory criteria
  - Proposed a *policy of enforcement discretion* for "Patient Decision Support Software"
  - Received significant scrutiny by industry and other stakeholders



Contains Nonbinding Recommendations

Draft - Not for Implementation

Clinical and Patient Decision Support Software

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: December 8, 2017

You should submit comments and suggestions regarding this draft document within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

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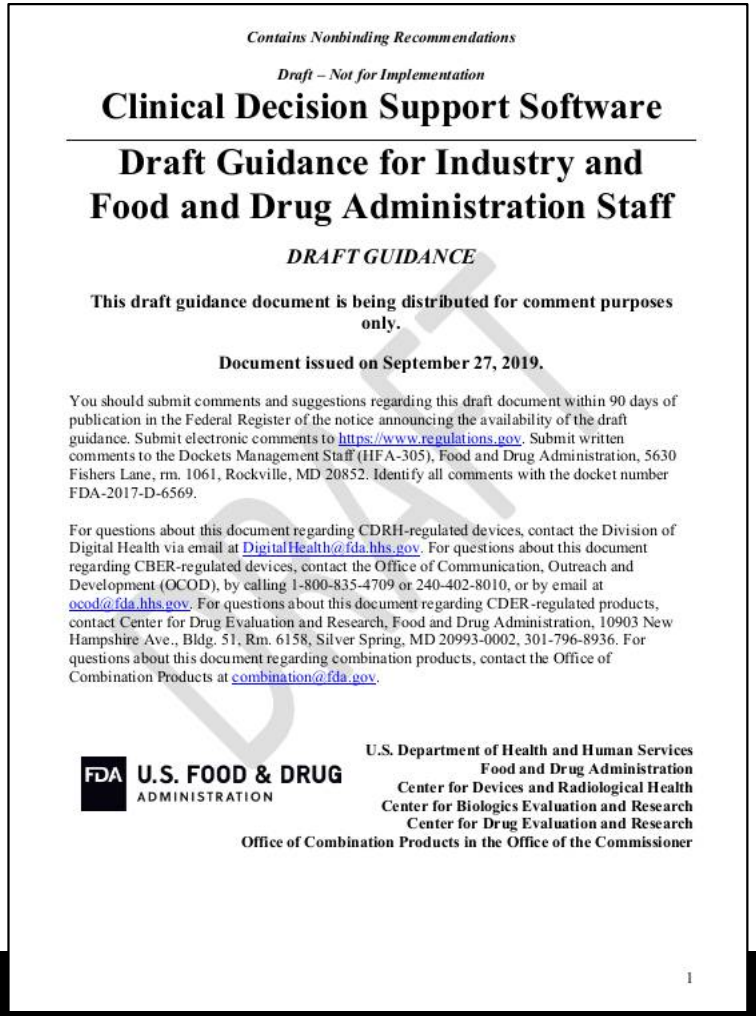
History – 2019 Draft Guidance

- Second draft guidance issued in September 2019
  - New draft guidance divided CDS software into two categories
    - Non-Device CDS
    - Device CDS
  - Proposed *policies of enforcement discretion* based on International Medical Device Regulators Forum (IMDRF) risk categorization framework
  - More lenient than the 2017 draft, but also more complex



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Clinical Decision Support Software

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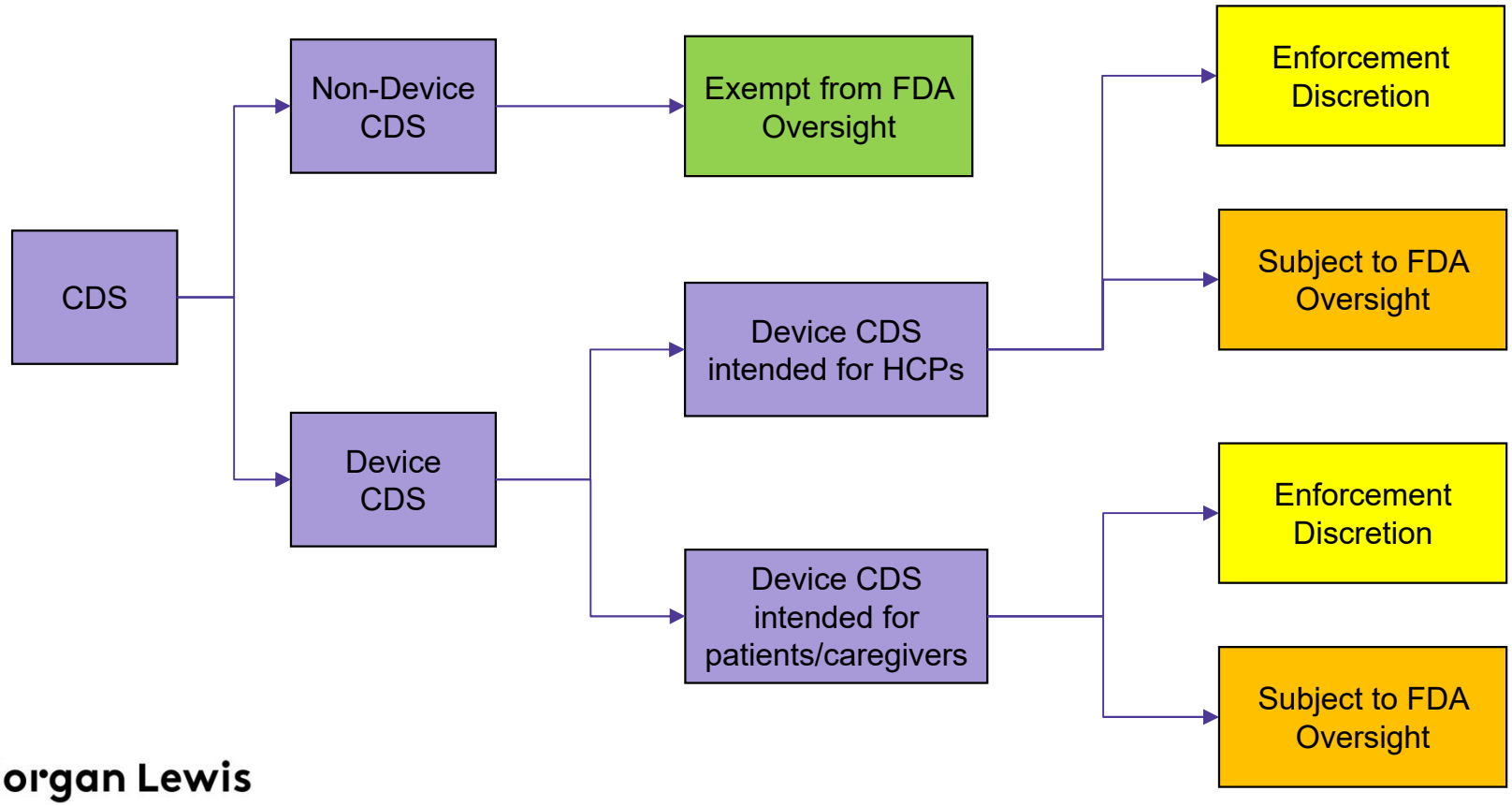
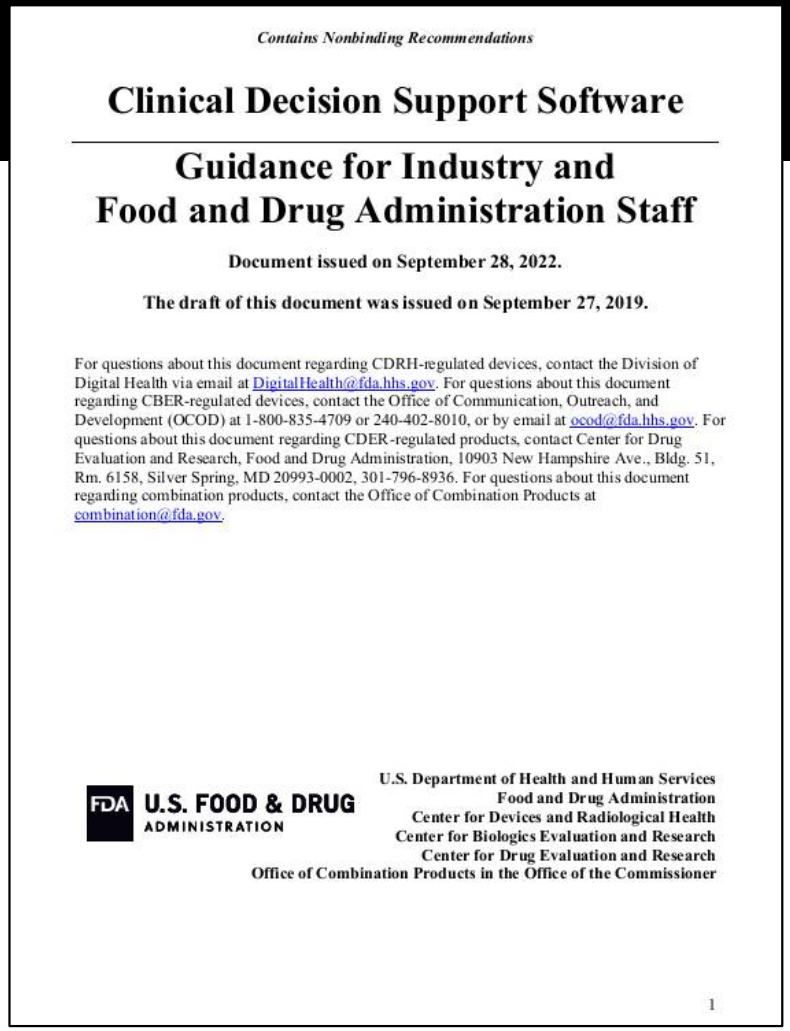
History – 2019 Draft Guidance



2022 Final Guidance

- Describes FDA's current interpretation of the four statutory criteria
- Simpler and more restrictive that the 2019 draft guidance
- No policies of enforcement discretion



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Clinical Decision Support Software

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 28, 2022.

The draft of this document was issued on September 27, 2019.

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2022 Final Guidance – Criterion 1

- Criterion 1 – software function is not "intended to acquire, process, or analyze a medical image or a signal from an *in vitro* diagnostic device or signal acquisition system"
- New guidance state that "FDA considers software functions that *assess or interpret* the clinical implications or clinical relevance of a *signal, pattern, or medical image* to be software functions that *do not meet Criterion 1*"
  - The term *signal* to includes signals that "typically require the use of" an IVD or signal acquisition system
    - A *signal acquisition system* includes devices that "measure a parameter from within, attached to, or external to the body for a medical purpose," which may include use of sensors, collection of samples or specimens, or use of radiological imaging
  - The term *medical image* includes both images generated by use of medical imaging systems and also images that, although not originally acquired for a medical purpose, are processed or analyzed for a medical purpose
  - The term *pattern* is defined to include "multiple, sequential, or repeated measurements of a signal or from a signal acquisition system"

2022 Final Guidance – Criterion 2

- Criterion 2 – the software function is 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)"
  - The term *medical information about a patient* is restricted to information where "the relevance of the information to the clinical decision being made is well understood and accepted" in the practice of medicine, such as test results, symptoms, demographic information, certain medical device outputs (e.g., heart rate or blood pressure readings), and patient discharge summaries
  - The term *other medical information* is restricted to include information "such as peer-reviewed clinical studies, clinical practice guidelines, and information that is similarly independently verified and validated as accurate, reliable, not omitting information, and supported by evidence
- The final guidance requires that medical information be used as an input for the CDS software, which may include a "single, discreet test or measurement result that is clinically meaningful," while "more continuous sampling of the same information […] is a pattern/signal" per Criterion 1
  - Thus, FDA reads into the statute a restriction related to "sampling frequency" for Criterion 2

2022 Final Guidance – Criterion 3

- Criterion 3 – the software function is intended for the purpose of "supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition"
- FDA takes a more restrictive approach to this criterion by limiting scope to include software that generates recommendations intended to "enhance, inform, and/or influence a health care decision" but not intended to "replace or direct the HCP's judgement"
- This *excludes* any software used "in time-critical decision making and in cases where a software function provides a specific preventive, diagnostic, or treatment output or directive"
  - This new exclusion appears to add new restrictions to the language "provides recommendations" from the statute, as anything approaching a definitive recommendation would fall under this new exclusion
  - This includes, for example, software that provides "a specific preventative, diagnostic, or treatment course", indicates "that a specific patient 'may exhibit signs' of a disease or condition", or "identifies a risk probability or risk score for a specific disease or condition

2022 Final Guidance – Criterion 4

- Criterion 4 – software function is 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"
- The final guidance returns to its original 2017 approach to impose new restrictions for CDS software for the purpose of "enabling the HCP to independently review the basis of the recommendations" the software presents
- Provides several labeling recommendations, including:
  - The software or software labeling should include the intended use of the product, which cannot be time critical, the intended HCP user, and the intended patient population
  - The software or software labeling should "identify the required input medical information, with plain language instructions on how the inputs should be obtained, their relevance, and data quality requirements"
  - The software or software labeling should provide a "plain language description of the underlying algorithm development and validation that forms the basis for the CDS implementations"
    - This includes: a summary of the logic or methods relied upon (e.g., statistical modeling or AI/ML techniques), a description of the data relied upon, and a description of clinical validation study results
  - The software output should provide the HCP with "relevant patient-specific information and other knowns/unknowns for consideration (e.g., missing, corrupted, or unexpected input data values)" that will allow the HCP to independently review the CDS recommendations and apply their judgment

Examples – Software that Qualifies as CDS

- Providing evidence-based clinician order sets for an HCP to choose from, tailored for a particular condition, disease, or clinician preference
- Matching patient-specific medical information from records or reports to reference information (e.g., clinical guidelines) that is routinely used in clinical practice
- Drug-drug interaction and drug-allergy contraindication notifications to avert adverse drug reaction
- Prioritized list of preventive, diagnostic or treatment options

Examples – Software that does NOT Qualify as CDS

- Software function that uses a patient's image sets (e.g., CT, magnetic resonance (MR)) to create an individual treatment plan for review by an HCP for patients undergoing radiation therapy treatment with external beam or brachytherapy
- Software function that identifies patients with possible diagnosis of opioid addiction based on analysis of patient-specific medical information, family history, prescription patterns, and geographical data
- Software function that analyzes multiple signals (e.g., perspiration rate, heart rate, eye movement, breathing rate) from wearable products to monitor whether a person is having a heart attack or narcolepsy episode
- Software function that analyzes patient-specific medical information to detect a life-threatening condition, such as stroke or sepsis, and generate an alarm or an alert to notify an HCP
- Software function that analyzes sound waves captured when users cough or recite certainsentences to diagnose bronchitis or sinus infection
- Software function that provides a prioritized list of FDA-authorized depression treatment options to an HCP based on an analysis of reported outcomes in a database of clinical studies using medical information (e.g., diagnosis and demographics) from the patient's medical record

Examples – Analyzing Test Results

- Software that analyzes test results appears to be excluded under Criterion 1
- However, certain examples of in the final guidance of software that qualifies as CDS permit analysis of test results:
  - Software function that flags patient results for an HCP based on specific clinical parameters (e.g., out of range test results where the reference ranges are predetermined by the lab or HCP) in response to a medication order
  - Software function that analyzes blood glucose laboratory test results and pre-diabetes diagnosis from a patient's medical record and provides an HCP with a list of next-step options to consider, such as more frequent office visits or referral to a specialist
  - Software function that analyzes patient-specific medical information (e.g., end stage renal disease (ESRD) diagnosis, lab test results, and patient demographics from the patient's medical record) and provides an HCP with a list of treatment options for ESRD based on implementation of practice guidelines


Related FDA
Developments
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FDA-Related Developments

- FDA updated other guidance documents to align with new CDS Software Guidance
  - Policy for Device Software Functions and Mobile Medical Applications
  - Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act
- Other recent FDA guidance impacting digital health software
  - Computer Software Assurance for Production and Quality System Software – Draft Guidance (Sept. 28, 2022)
  - Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions – Draft Guidance (April 8, 2022)
  - Digital Health Technologies for Remote Data Acquisition in Clinical Investigations – Draft Guidance (Jan. 21, 2022)
  - Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions – Draft Guidance (Dec. 23, 2021)

Artificial Intelligence/Machine Learning Software

- Impact of final CDS Software Guidance
  - Prior 2019 draft guidance included language suggesting certain ML software could either qualify as CDS software or qualify for enforcement discretion
    - ML software could qualify as CDS software if the HCP-user could evaluate the basis of the software's recommendations because the logic and inputs of the ML algorithm were explained and available to the HCP
    - ML software could qualify for enforcement discretion if the software only provides clinical information for non-serious situations or conditions
  - New final guidance does include any examples on AI/ML software and appears to exclude such software from the scope of CDS exemption

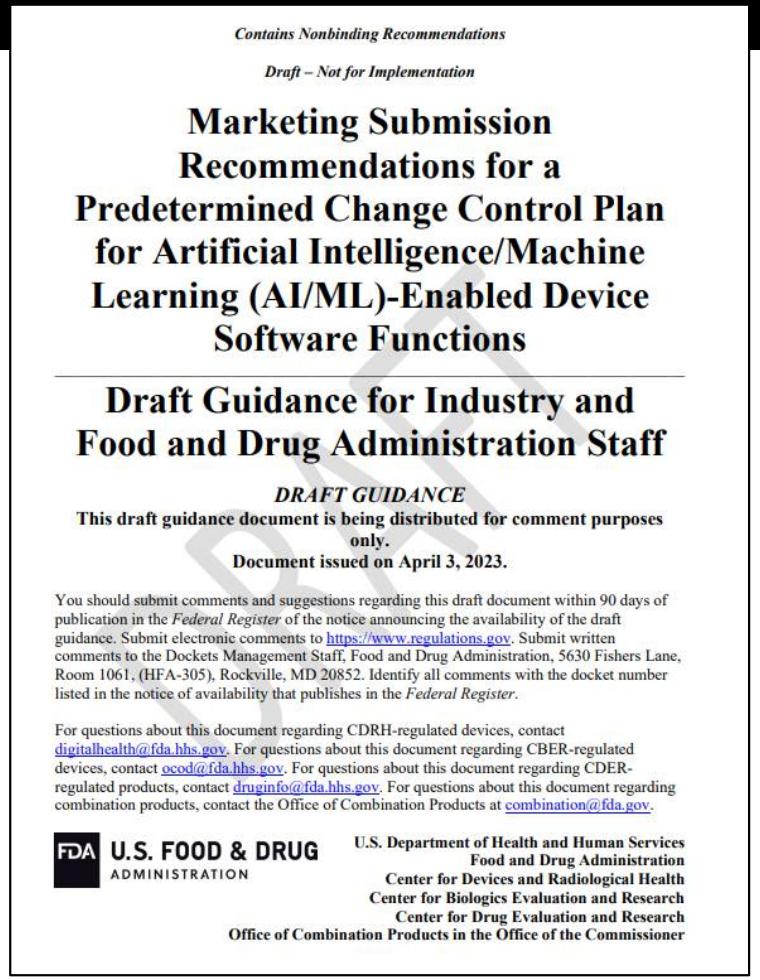
Artificial Intelligence/Machine Learning Software

- April 2019 Discussion Paper - Proposed framework to address how FDA would handle postmarket modifications to AI/ML software devices
  - Existing model requires sponsors to evaluate all device software changes to determine whether the change requires a new submission to FDA
  - May not work for AI/ML software, because such software is intended to continuously evolve
  - Under the proposed framework, AI/ML software developers would include in their initial FDA submissions a *predetermined change control plan*:
    - SaMD pre-specifications (SPS), which define the types of software algorithm changes that are covered/permitted under the plan
    - Algorithm change protocol (ACP), which defines methods to control risks for the permitted changes and how the changes may occur

Artificial Intelligence/Machine Learning Software

- New Draft Guidance for Predetermined Change Control Plans (PCCPs) for ML-enable device software functions, to include:

1. A detailed description of the specific, planned device modifications
2. The associated methodology to develop, validate, and implement the modifications in a manner to ensure continued safety and effectiveness
3. An Impact Assessment to describe the assessment of the benefits and risks of the planned modifications and risk mitigations



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Draft – Not for Implementation

Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions

Draft Guidance for Industry and Food and Drug Administration Staff

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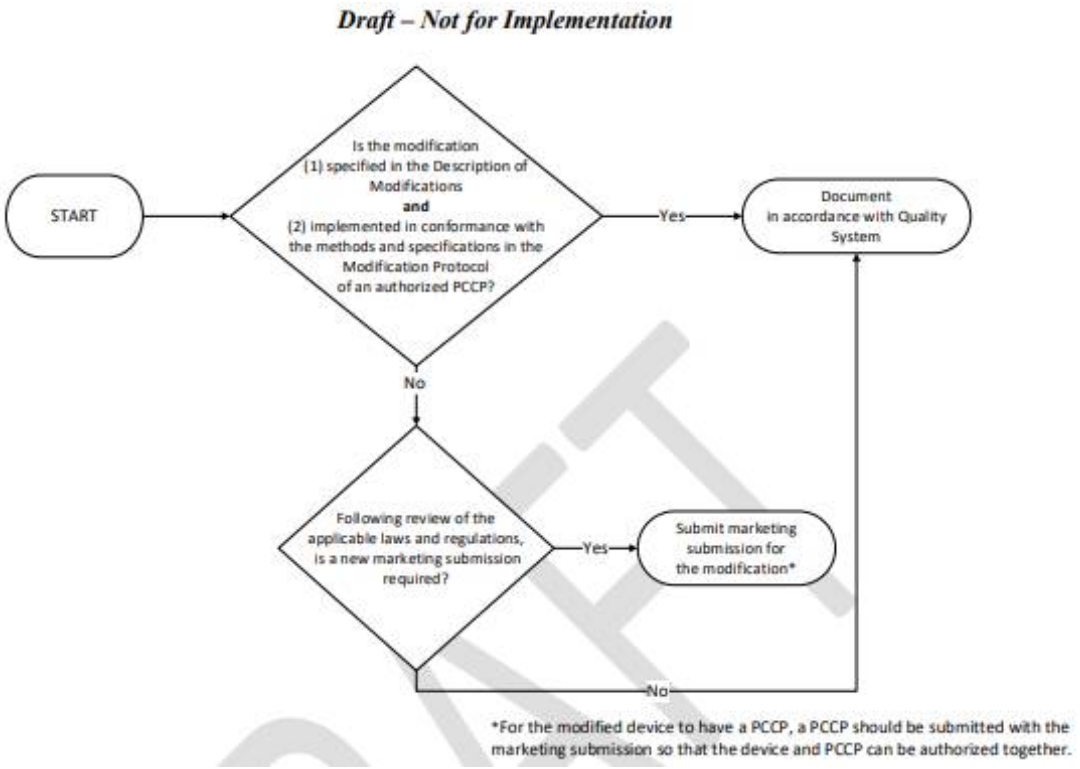
Artificial Intelligence/Machine Learning Software



- Modifications consistent with the authorized PCCP would not require a new premarket submission
- Modifications outside the scope of the PCCP would need to be assessed per existing laws and regulations
- Modification of the PCCP itself generally would require a new premarket submission

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Morgan Lewis

Biography

Michele L. Buenafe
Washington, DC
+1.202.739.6326
michele.buenafe@morganlewis.com

Michele L. Buenafe counsels clients on US Food and Drug Administration (FDA) compliance and enforcement matters related to medical devices, combination products, and digital health technologies, such as software as a medical device (SaMD), telemedicine systems, clinical decision support software, wearable devices, artificial intelligence systems, and mobile medical apps. She also advises on US Drug Enforcement Administration (DEA) and state regulatory issues for controlled substances and medical products, including both drugs and devices. Michele serves as the leader of the firm's digital health team and as co-leader for the firm's cross-practice healthcare industry team.

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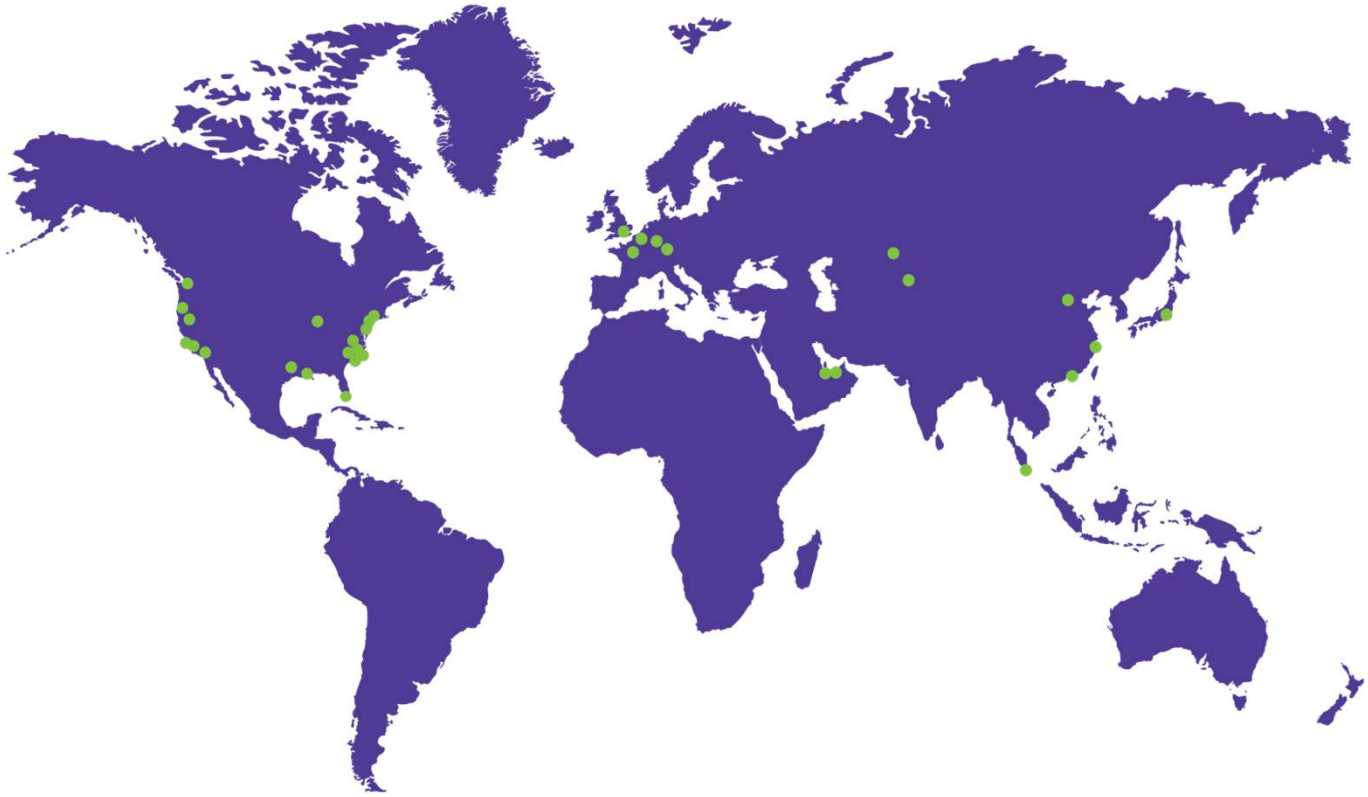

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