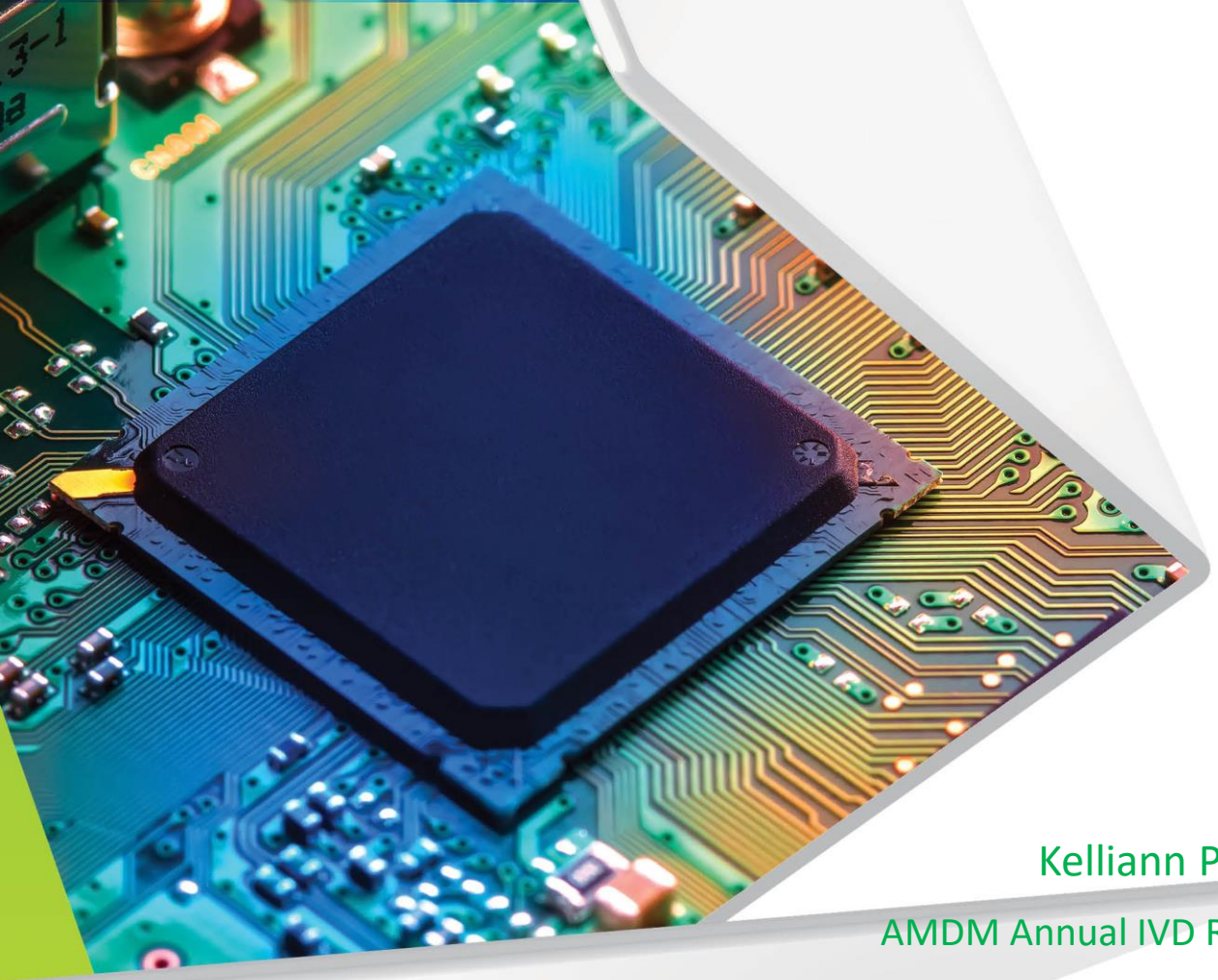

Hogan Lovells

FDA Regulation of Clinical Decision Support Software

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AMDM Annual IVD Regulatory Meeting – April 20, 2023

Agenda

- Overview of FDA Regulation of Software
- What is Clinical Decision Support (CDS) Software?
- Implications of September 2022 Final Guidance
- How to Move Forward

FDA Regulation of Software

How does FDA Regulate Software?

- **Any product *or software function*** may be regulated by FDA if it is an:
  - Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or component that is:
    - Recognized in USP or other compendia,
    - Intended for use in diagnosis of disease or other conditions,
    - Intended for use in the cure, mitigation, treatment, or prevention of disease, or
    - Intended to affect structure or function of the body, and
  - Which does not achieve its primary intended purposes through chemical action on or within the body and which is not dependent on being metabolized.

- **Intended use** is key to whether a product falls within the definition of a device
  - Based on intent of manufacturer
  - Determined from labeling claims, promotional material, oral/written statements by company representatives

21st Century Cures Act Update

- 21st Century Cures Act (2016) excluded certain types of software functions that are considered *low-risk* from the definition of a medical device

- Software functions are no longer subject to FDA regulation if intended for:
  (1) Administrative purposes (e.g., billing, scheduling)
  (2) Health and wellness, unrelated to specific medical purposes (e.g., general fitness)
  (3) Electronic health records created by a health care provider (HCP) and not performing analysis
  (4) Medical device data systems (store, transfer, display, convert formats of device/lab data and HCP findings), without analysis
  (5) *Clinical decision support (CDS) software*, if it meets certain conditions

FDA Regulates Software Based on Perceived Risk

- Degree of impact on the patient
  - Likely actively regulated if it controls the function of another device, or transforms a mobile platform into a regulated device.
- Level of risk it poses to user/patient
  - E.g., type of medical purpose; how results it generates will be used.
- Whether performs patient-specific analysis and/or provides patient-specific output
- Whether used in active patient monitoring
  - If intended to trigger immediate clinical action, regulated unless limited to data transfer/storage/display
- Whether it generates independent analysis or just does a reviewable task for HCP
  - If performs analysis that user could not independently derive, clearance/approval is likely required
  - If assesses patient data/results per established clinical guidelines, likely no longer considered a device

Regulatory Pathways for Digital Health/Software

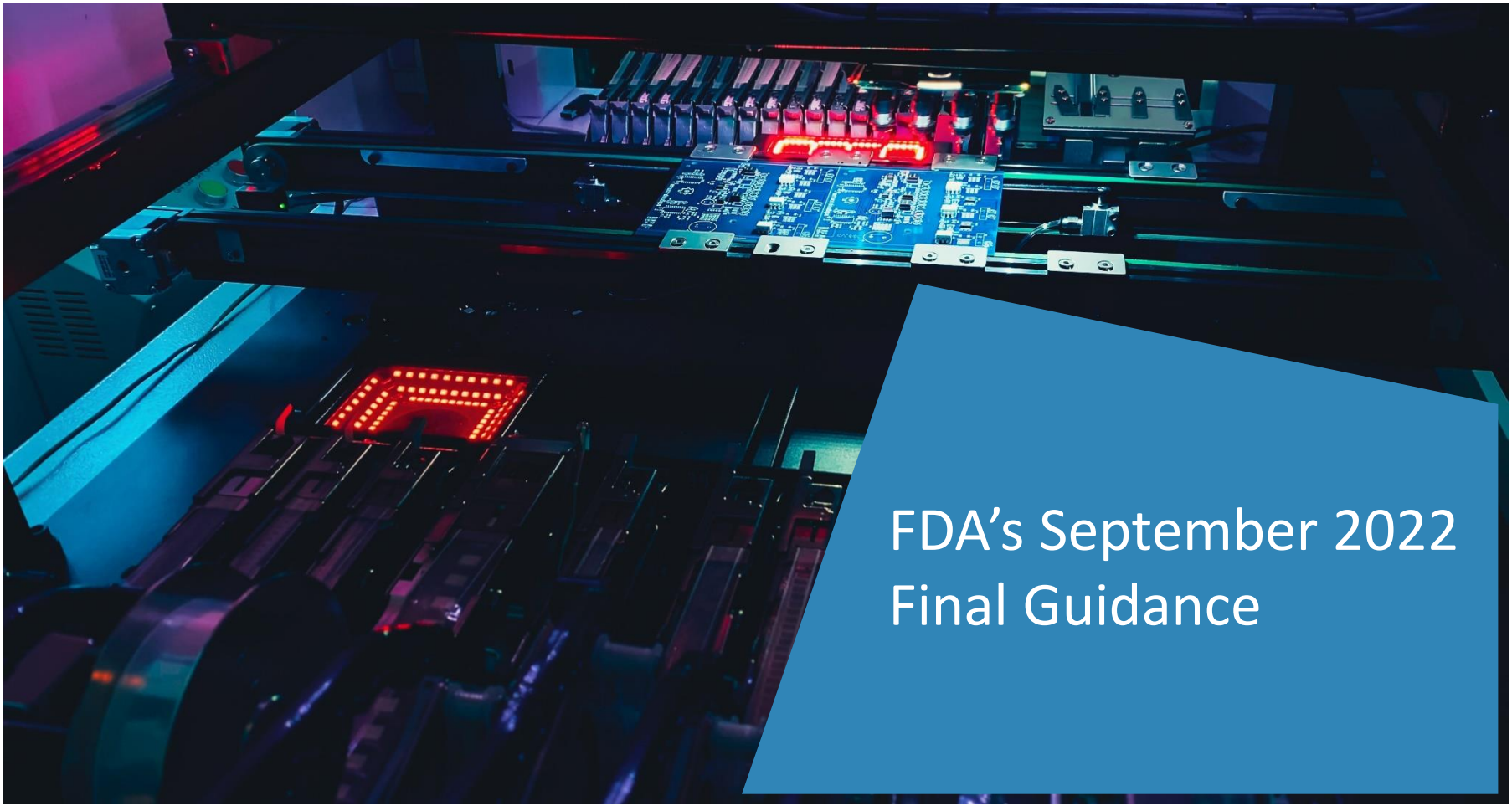
1. Not a medical device (*i.e.*, no FDA regulation)
   - If does not meet the updated definition of a device, considered a consumer product
2. Subject to enforcement discretion (*i.e.*, no active FDA oversight)
3. Actively regulated as a medical device (class I, II or III)
   - Subject to same pre- and post-market regulations as any other device; certain software may have additional requirements
4. Regulated as a combination product (drug, device, and/or biologic)

- Can evaluate FDA precedent for regulation of similar products to help determine the most appropriate regulatory pathway for a new digital health/software product

What is CDS Software?

- Any software function that is intended to support clinical decision-making, such as:
  - Computerized alerts and reminders for HCPs and patients
  - Clinical guidelines
  - Condition-specific order sets
  - Focused patient data reports and summaries
  - Diagnostic support
  - Contextually relevant reference information

- CDS ranges from simple automations of routine clinical calculations to complex, proprietary, machine-learning based algorithms
- With more and more of these products being released, FDA determined a need to clarify which ones are and are not regulated



FDA’s September 2022 Final Guidance

CDS Exclusion under 21st Century Cures Act

- To fall outside the definition of a medical device, CDS software must meet four criteria:
  - (1) *Not* acquire, process, or analyze a medical image, a signal from an IVD, or a pattern or signal from a signal acquisition system
  - (2) *Display, analyze, or print medical information* about a patient or other medical information
  - (3) *Support or provide recommendations* to a HCP about prevention, diagnosis, or treatment of a disease/condition
  - (4) *Enable HCP to independently review the basis* for the software's recommendations so they need not rely primarily on these to make a clinical decision for an individual patient

- To be non-device CDS, the software must be used by an HCP (not a patient/caregiver).

CDS Guidance

- FDA guidance interprets the 4 criteria for "non-device CDS"
- Per draft guidance (2019), significant focus was on Criterion #4 – enabling independent review of the software's recommendations
  - The software must clearly explain:
    - Its purpose or intended use
    - The intended user
    - The inputs used to generate the recommendation
    - The rationale or support for the recommendation (e.g., plain language description of underlying algorithm and its validation)
  - Sources supporting the recommendation or underlying the rationale should be identified, easily accessible, and understandable to the intended user
  - Intended user should be able to reach the same recommendation on their own
    - Essentially precludes proprietary AI algorithms from non-device category ("black box")

Long-Awaited Final CDS Guidance

- The final CDS guidance (September 2022) added clarity while also seeming to bring additional software functions under FDA's regulatory purview
- *Criterion 4* on independent reviewability of the recommendations remains important.
- *Criterion 3:* Must provide condition-, disease-, and/or patient-specific recommendations to enhance, inform and/or influence a decision, while not intended to replace or direct the HCP's judgment
  - Software issuing an output used in time-critical decision-making FAILS
  - Software issuing a specific preventive, diagnostic, or treatment output/directive FAILS

CDS Guidance *(cont'd)*

- FDA considers such software to exceed "supporting or providing recommendations" because of automation bias
  - If only one option provided, insufficient opportunity for HCPs to input their own judgment into the decision-making
  - If situation requires urgent action, insufficient time for HCPs to adequately consider other information

Non-Device CDS Examples Under Current Framework

- Evidence-based order sets for an HCP to choose from, tailored for a particular condition, disease, or clinician preference
- List of preventive/diagnostic/treatment options, based on patient information found in medical record and FDA-approved labeling
  - The list may be prioritized (e.g., based on details of patient's diagnosis)
- Matching patient-specific medical information from records/reports to reference information (e.g., clinical guidelines) routinely used in clinical practice

Non-Device CDS Examples Under Current Framework

- Contextually relevant reference information about a disease/condition (e.g., recommending available treatment options for heart failure patients based on their disease stage and clinical guidelines)
- List of follow-up or next-step options (e.g., after office visit, hospitalization, procedure)
- Drug-drug interaction and drug-allergy contraindication notifications
- Duplicate testing or medication error prevention notifications
  - Flag patient results based on specific clinical parameters in response to a medication order (e.g., out of range test results where reference ranges are predetermined by lab or HCP)
  - *This does not fail Criterion 1 because even if results come from an IVD, they have already been read – the software is just comparing existing results to a set threshold/guideline*

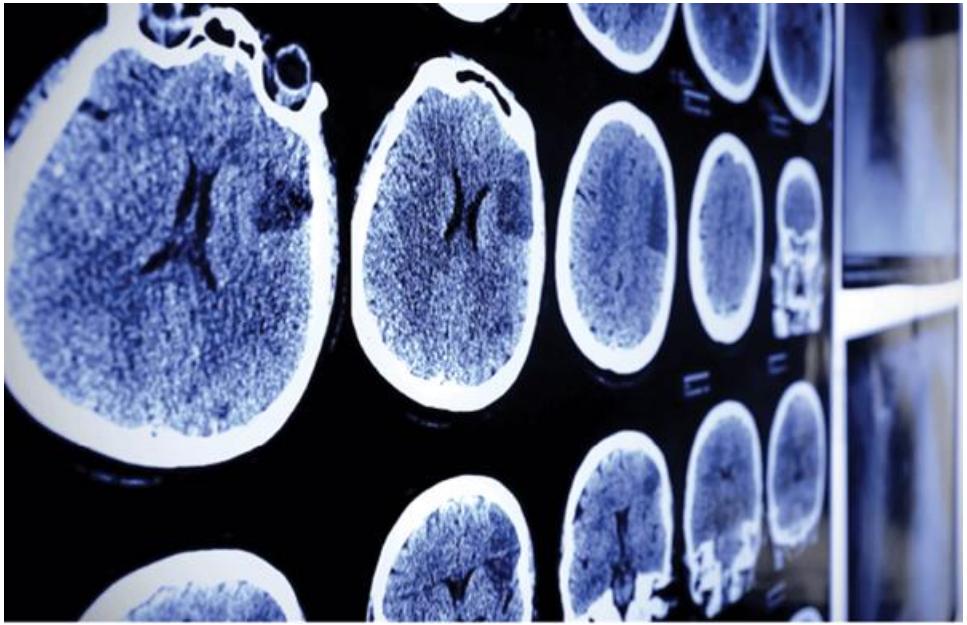
Device CDS Examples Under Current Framework

- Specific preventative/diagnostic/treatment course, or specific follow-up directive
  - e.g., Identify a specific FDA-approved drug based on analysis of patient diagnosis and pathologist-confirmed biopsy results
- Time-critical alarms/alerts intended to trigger potential clinical intervention to assure patient safety
  - e.g., Analyze patient-specific medical information to detect a life-threatening condition (stroke, sepsis) and generate an alarm/alert to notify an HCP
- Many manufacturers used to think these were non-device CDS if the algorithm was explained to user and recommendations are reviewable by HCP

Device CDS Examples Under Current Framework

- Treatment plan for a specific patient's disease or condition
- Information that a specific patient may exhibit signs of a disease/condition, or a risk probability/risk score for a disease/condition
  - e.g., Analyzing patient-specific medical information to predict heart failure hospitalization

Hypothetical #1



A device analyzes CT images with the intended use of differentiating whether the patient has suffered ischemic or hemorrhagic stroke.

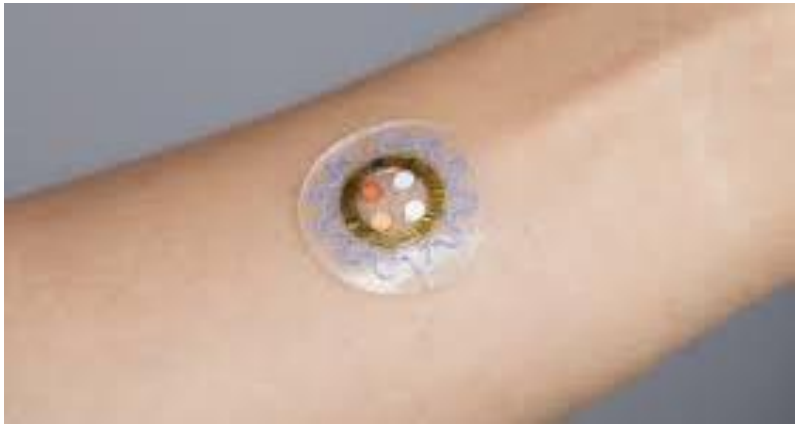
Is this non-device CDS?

Hypothetical #1 – cont'd

- **X** Criterion 1 – The device analyzes a medical image.
- **X** Criterion 2 – The device is not intended to display, analyze, or print medical information – rather, it's intended to display *images* for the purpose of *diagnosing* a patient's condition.
- **X** Criterion 3 – The device provides a specific diagnostic output for a disease/condition.
- **?** Criterion 4 – Unclear whether the software's algorithm is independently reviewable by HCP, but seems unlikely that HCP can fully review how outputs are generated

Hypothetical #2

- Software function analyzes perspiration rate, heart rate, eye movement, and breathing rate from a wearable product
  - Intended use: to monitor if a person is having a heart attack
- ***Is this non-device CDS?***



Hypothetical #2 – cont'd

- **X** Criterion 1 – The device analyzes signals (raw physiological signals).
  - The wearable is a signal acquisition system that measures a parameter by being attached to the body, *for a medical purpose*.
- **X** Criterion 2 – The device is not intended to display, analyze, or print medical information.
- **X** Criterion 3 – The device provides a specific diagnostic output *and* supports time-critical decision-making (limited time to react to mitigate harm if patient is having a heart attack).
- **?** Criterion 4 – Unclear, but seems unlikely that HCP can fully review how the software's outputs are generated.

Hypothetical #3

- AI software function analyzes for risk of C Diff
  - Intended use: to identify potential for C Diff in patient
- ***Is this non-device CDS?***

Hypothetical #3 – cont'd

- √ Criterion 1 – EHR information, such as age, leukocyte count, creatinine levels, inputted into AI software with weights assigned to each input.
- ? Criterion 2 – The device may not be intended to display, analyze, or print a patient's medical information.
  - Unclear if algorithm uses other (non-patient) medical information, such as AI training datasets, etc.
- X Criterion 3 – The device does not meet this criteria of only providing a recommendation to HCP.
  - FDA's guidance explicitly states that a risk score for a particular disease or condition is considered a "specific output" for prevention, diagnosis, or treatment.
- ? Criterion 4 –Unclear but it seems likely that HCP cannot fully review how the software's outputs are generated.
  - One has to question if information is available to HCP to understand key variables that influence the recommendations.

CDS Regulation in Context

- There is still a middle ground
  - *Enforcement discretion* = FDA perceives the product/software to be sufficiently low risk that it does not even determine if it is [not] a medical device, and does not regulate it
    - But the status can change at any time (not binding by statute)

- In a conversation with the Digital Health Center, FDA stressed that the updated CDS guidance is not meant to erase existing enforcement discretion policies under other guidance documents
  - Just meant to track the Cures Act provisions more closely to limit the ability for companies who should be regulated to take advantage of loopholes

- *Recommendation:* Evaluate CDS products that do not qualify as "non-device CDS" under FDA's *Policy for Device Software Functions and Mobile Medical Applications* for potential enforcement discretion

CDS Functions that May Warrant Enforcement Discretion

- FDA will continue to take a risk-based approach in deciding what clinical decision support software to actively regulate
- Enforcement discretion may apply for software that provides singular outputs to guide patient-specific decision-making, but *in accordance with cited, established clinical guidelines*
  - Must be transparent (basis for recommendation is disclosed to HCP)
- *Example:* Software that performs simple calculations routinely used in clinical practice
  - e.g., BMI, APGAR score, NIH Stroke Scale, delivery date estimator

Moving Forward

How to Approach FDA for Clarity

Digital Health Policy Navigator

- Online tool to help determine whether a product's software function may be a focus of FDA regulatory oversight

- https://www.fda.gov/medical-devices/digital-health-center-excellence/step-1-software-function-intended-medical-purpose-0

Feedback for a Future Premarket Submission

- Request a pre-submission outlining the product, proposed regulatory pathway, and data plans
- FDA will schedule a teleconference in 2.5-3 months
- Requests for Feedback on Medical Device Submissions guidance
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program

Interpreting Digital Health Guidance

- Send questions or product description (for initial regulatory assessment) to FDA's Digital Health Center of Excellence at DigitalHealth@fda.hhs.gov.
- FDA usually replies informally in ~2 weeks

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Suzanne assists medical device companies in a wide range of activities across the life cycle of their products, including preparing regulatory submissions for clearance or approval of new devices, advising manufacturers on the lawful promotion and advertising of their devices, and addressing post-market enforcement issues.

Suzanne is well-versed regarding FDA's evolving paradigm for software and digital health products, and she has helped clients determine the appropriate regulatory pathway for products in this space and advocated before FDA for their clearance/approval, where needed.

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Kelliann Payne's science education and background in the medical device industry allow her to quickly understand emerging medical device technology, including digital health products, and informs her current focus on related legal and business issues. Her experience includes the development, regulation, advertising, and litigation of medical devices and digital health products, including machine learning-based clinical decision support software.

Kelliann drafts premarket submissions for diagnostic and therapeutic medical devices, evaluates and formulates applicable regulatory strategies, and reviews the accuracy of marketing claims. She helps companies in their preclinical and clinical programs and leads due diligence reviews for investments and acquisitions.

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Thank you!

Questions?

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