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ARTIFICIAL INTELLIGENCE AND CLINICAL TRIALS

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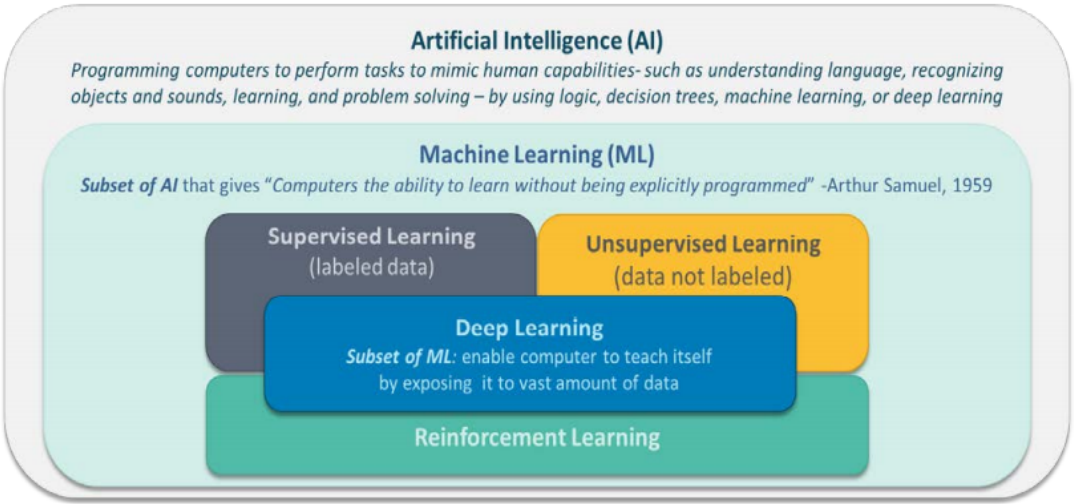
What is artificial intelligence?

- **"[A]ny computer [program] or system that does something we would normally think of as intelligent in humans."**-Deloitte Insights
  - "extracts concepts and relationships form data"
  - Learns from patterns
  - Enhances what humans are able to do
  - Interacts with humans in natural ways



FDA, Artificial Intelligence and Machine Learning in Medical Devices, Executive Summary for the Patient Engagement Advisory Committee Meeting (Oct. 22, 2020)

A variety of AI technologies exist and are being used in biopharma

MACHINE LEARNING
Code or programmes (algorithms) that teach computers things over time through experience. With machine learning technologies, computers can be taught to analyse data, identify hidden patterns, make classifications and predict future outcomes. The learning comes from these systems' ability to improve their accuracy over time without explicitly programmed instructions. There are also subsets of machine learning:

- deep learning: a subset of machine learning based upon a conceptual model of the human brain called 'neural networks'. It's called deep learning because the neural networks have multiple layers that interconnect: an input layer that receives data, hidden layers that compute the data and an output layer that delivers the analysis. Deep learning is especially useful for analysing complex, rich and multidimensional data, such as speech, images and video. It works best when used to analyse large data sets.
- supervised learning: using labelled data to train a machine learning model
- unsupervised learning: algorithms that take a set of data that contain only inputs and finds structure such as grouping or clustering of data points.

SPEECH
A computer system able to understand human speech, including applications such as speech to text and text to speech.

NATURAL LANGUAGE PROCESSING (NLP)
Machines being able to understand and generate natural language in the form of highly unstructured speech or text. NLP powers the voice-based interface for virtual assistants and chatbots.

COMPUTER VISION
The ability to extract meaning and intent from visual elements, whether characters (in the case of document digitisation) or the categorisation of content in images, such as faces, objects, scenes and activities. The technology behind facial recognition—computer vision—is a part of consumers' everyday lives. For example, some mobile phones permit their owners to log in via facial recognition. Computer vision technology "drives" driverless cars and animates cashier-less stores.

PLANNING
A branch of AI that concerns the realisation of strategies or action sequences, typically for execution by intelligent agents, autonomous robots and unmanned vehicles.

EXPERT SYSTEMS
A computer system that emulates the decision-making ability of a human expert.

ROBOTICS
Software that captures and interprets existing IT applications to enable transaction processing, data manipulation and communication across multiple IT systems.

Source: Deloitte analysis.

Necessity of AI/ML in Clinical Trials

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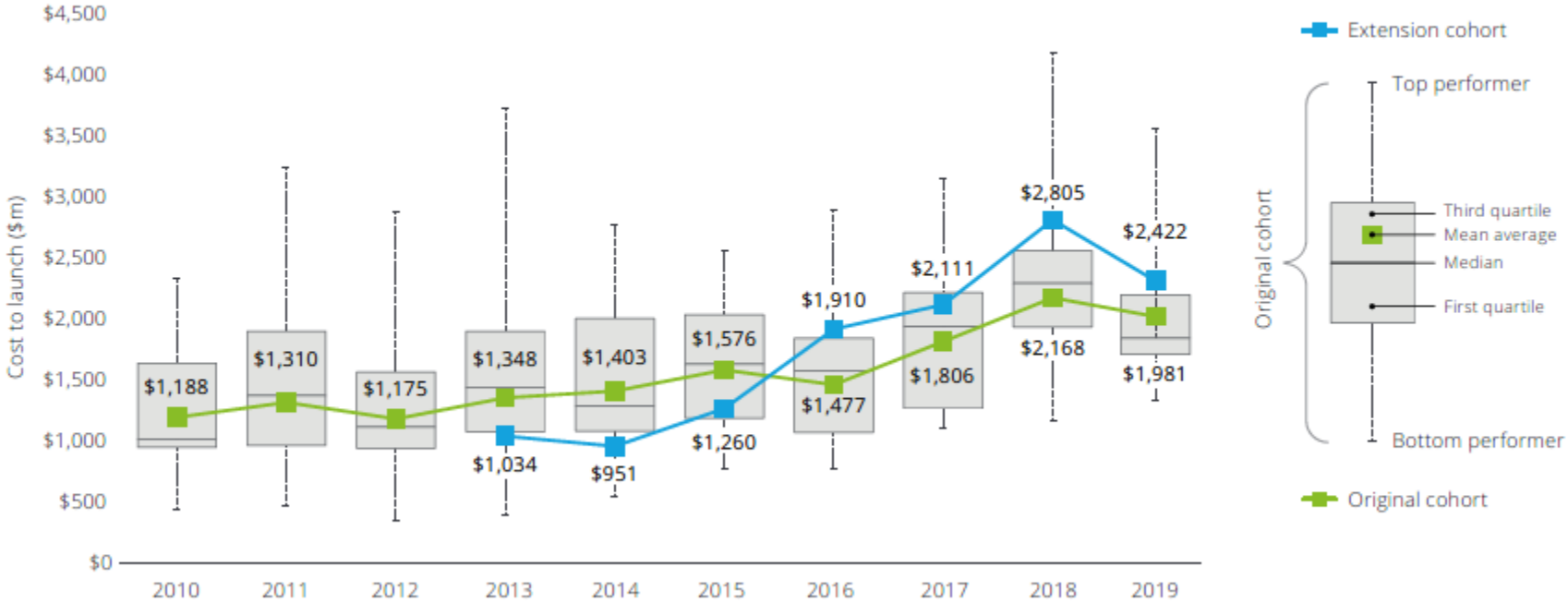
Why now?

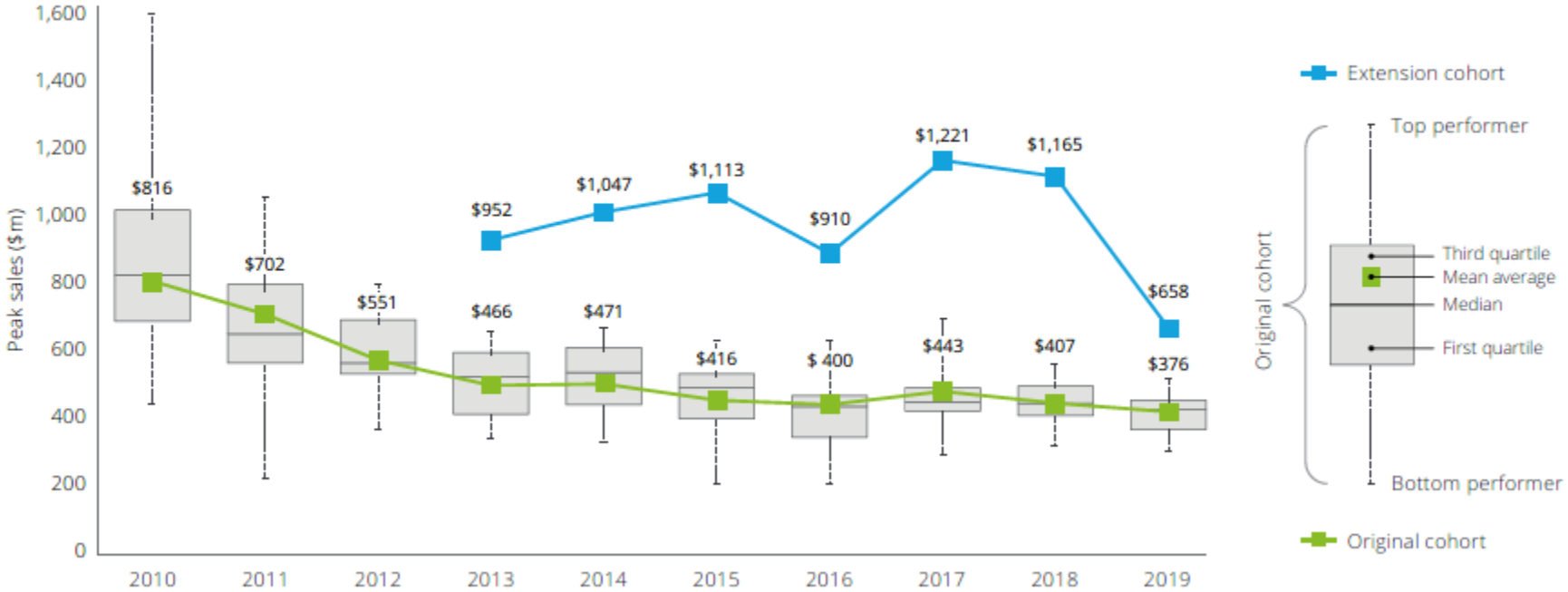
- **Building new efficiencies into drug development is becoming imperative**
  - Increased competition in drug marketing
  - Increasing development time
  - Shorter time in the market/expiring patents
  - Declining peak sales
  - Reimbursement pressures
  - Increasing regulatory compliance costs

Figure 6. Average R&D cost to develop a compound from discovery to launch, 2010-19 – original and extension cohorts



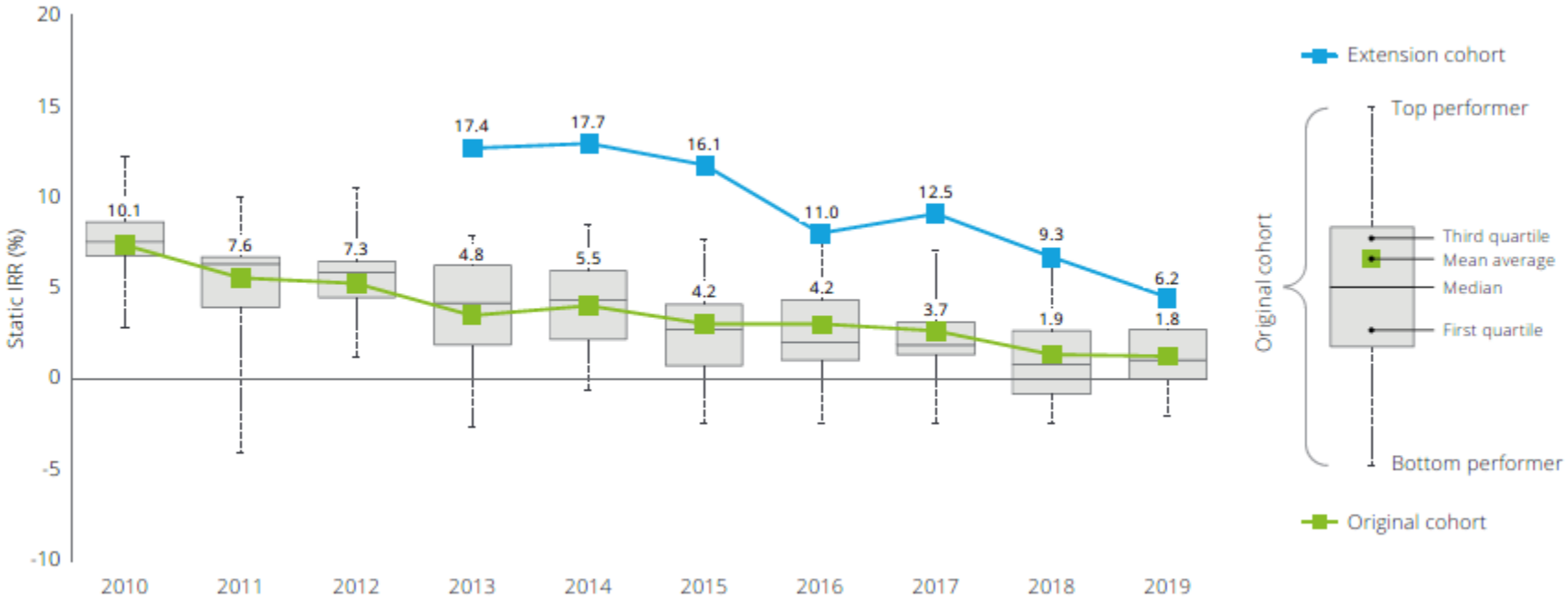
Source: Deloitte LLP, 2019

Figure 7. Average forecast peak sales per pipeline asset, 2010-19 – original and extension cohorts



Source: Deloitte LLP, 2019

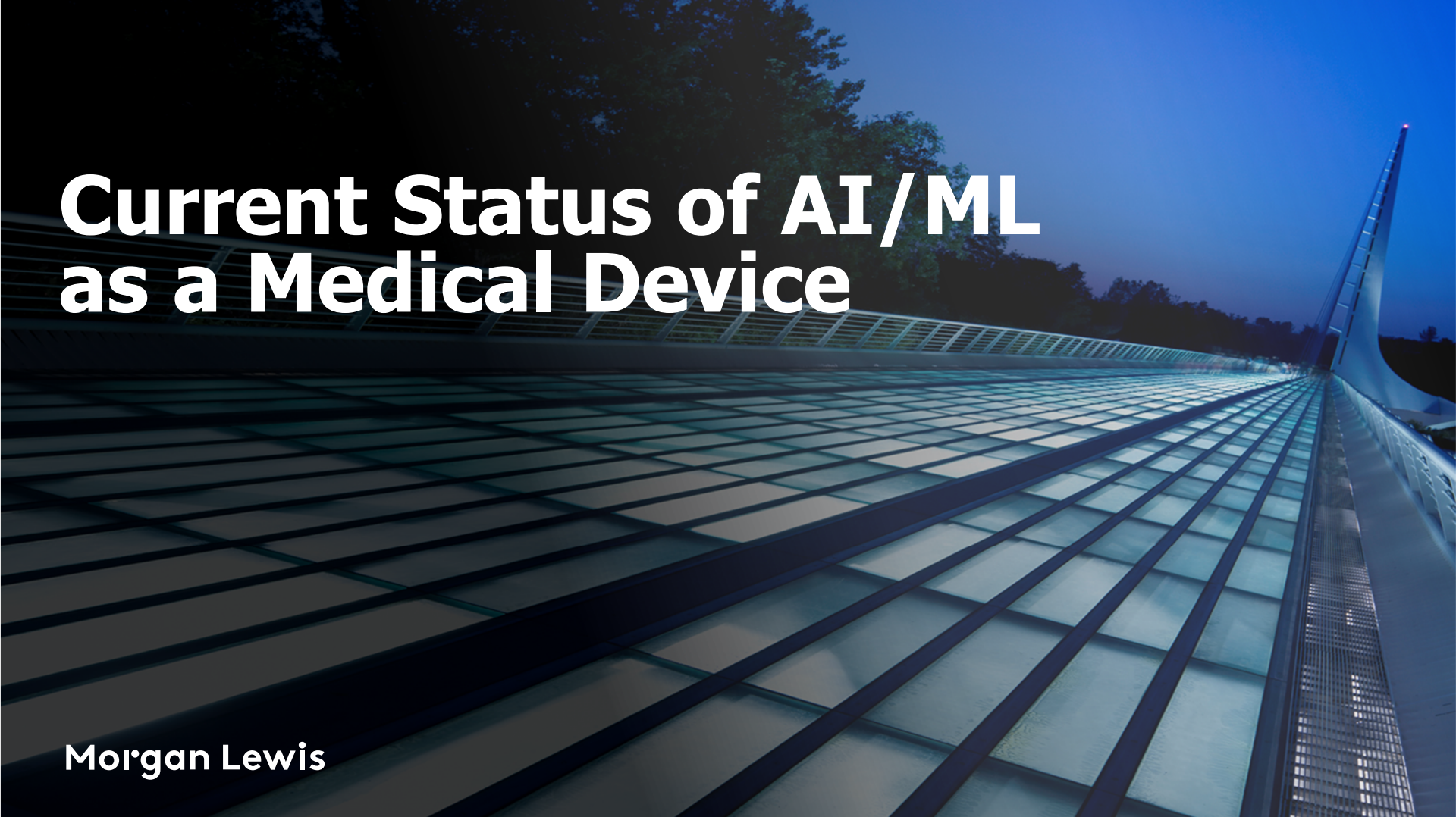
Figure 2. Return on late-stage pipeline, 2010-19 – original and extension cohorts



Source: Deloitte LLP, 2019

Why not?

- For the first time we have access to large amounts of BIG DATA, unlocking potential AI and machine learning uses.
  - *"New streams of real world data (RWD) gathered from electronic health records (EHRs), lab tests, wearable devices, insurance claims, and even social media can provide important evidence on product safety and effectiveness in settings or populations that may be very different than the information gleaned from registrational trials used for approval"*—Dr. Scott Gottlieb (2019)



Current Status of AI/ML as a Medical Device

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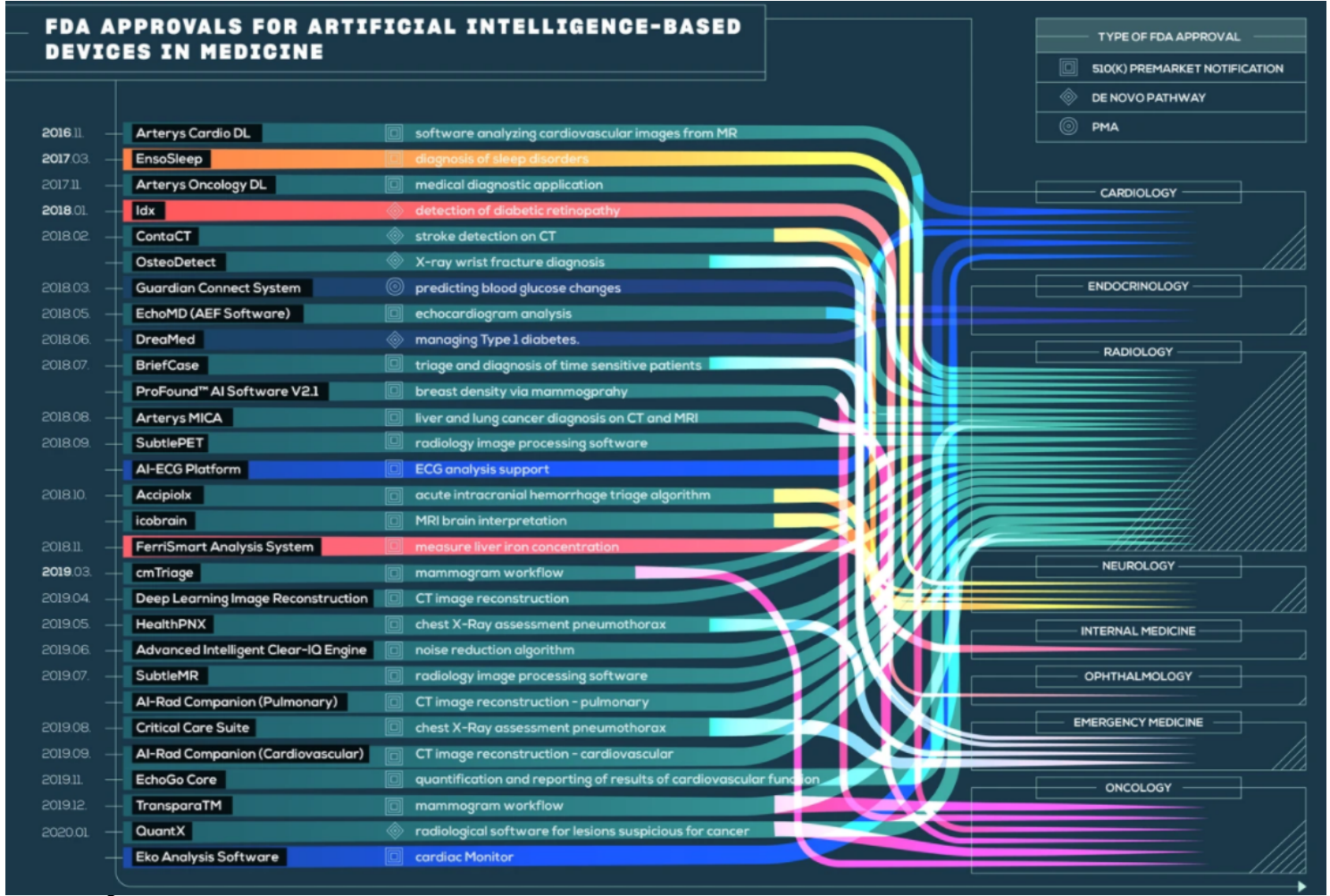


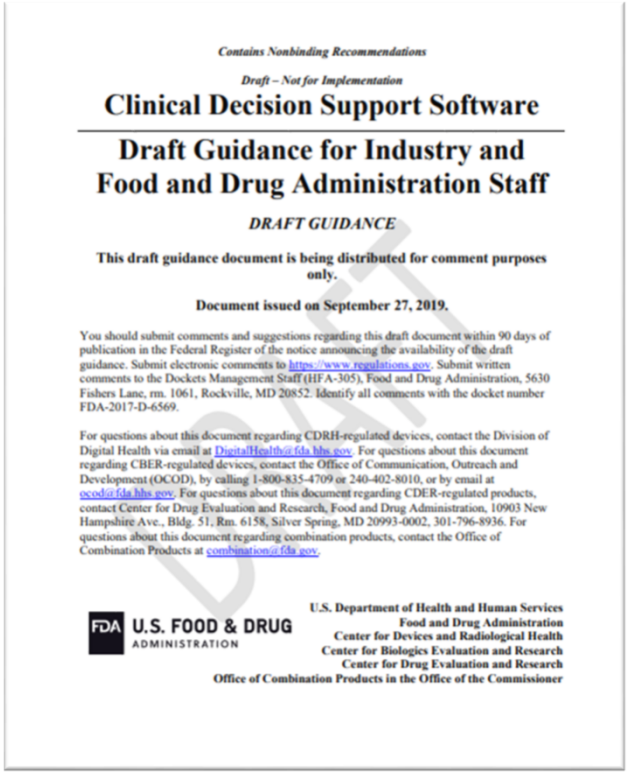
S. Benjamens, et al., The state of artificial intelligence-based FDA-approved medical devices and algorithms: an online database, 3 NPJ Digital Medicine (2020)

Current FDA AI Approach

- FDA released its AI/ML Software as a Medical Device Action Plan in January 2021:
  - Five-part Action Plan:
    - Regulatory framework for AI/ML software – issue a new draft guidance on Predetermined Change Control Plan
    - Encourage harmonization for Good Machine Learning Practice development
    - Promote transparency to users, develop recommendations for AI/ML labeling
    - Support regulatory science efforts to develop methodology for evaluation/improvement of ML algorithms, including efforts to identify and eliminate bias
    - Work with stakeholders piloting real world performance based software
  - Does not provide guidance on when AI/ML software may be subject to FDA oversight
- FDA launched the Digital health Center for Excellence in September 2020

Current FDA AI Approach

- **Clinical Decision Support Software**
  1. Is not "intended to acquire, process, or analyze a medical image or a signal from an *in vitro* diagnostic device or signal acquisition system"
  2. 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)"
  3. 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"
  4. 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"



Contains Nonbinding Recommendations

Draft – Not for Implementation

Clinical Decision Support Software

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on September 27, 2019.

You should submit comments and suggestions regarding this draft document within 90 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 FDA-2017-D-6569.

For questions about this document regarding CDRH-regulated devices, contact the Division of Digital Health via email at DigitalHealth@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD), by calling 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov. For questions about this document regarding CDER-regulated products, contact Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6158, Silver Spring, MD 20993-0002, 301-796-8936. For questions about this document regarding combination products, contact the Office of Combination Products at combination@fda.gov.

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DRAFT

Current Status of AI/ML use with Therapeutics and Clinical Trials

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AI and Biopharmaceuticals

- Current Action Plan is **silent** on AI/ML's application to pharmaceutical/biologic products

Combination Products Coalition

*The scope of applicability of AI/ML to healthcare is not yet known; however, based on industry's early understanding, **we can predict that this technology will have a fundamental impact on how we execute clinical trials, interpret clinical data, and help inform healthcare practitioners of ideal therapies for patients**. ….The CPC further requests that any future discussion papers on AI/ML, as well as any other topic papers or communications related to digital health, **involve [CDER] and [CBER] and include considerations around systems that achieve or influence use of drug and biological products.** The CPC urges FDA to **develop coordinated and consistent digital health policies** across FDA centers to reduce regulatory burdens and support digital health innovation that ultimately helps patients.*

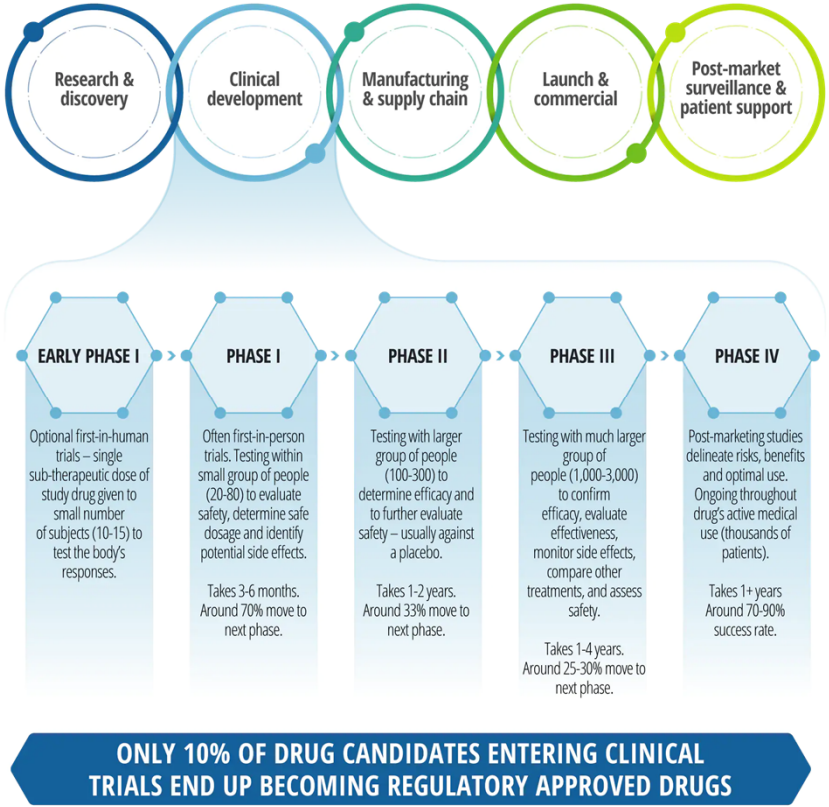
Pharmaceutical Research and Manufacturers of America

*PhRMA urges [CDRH] to **collaborate with [CDER] and [CBER] to develop a coordinated, consistent, and agency-wide approach to regulating AI/ML-based software products**….PhRMA also encourages FDA to develop policies that help facilitate innovation around AI/ML-based software to advance medical research and development and improve health care, including **policies regarding software that relates to prescription drugs, such as software in combination products or software that is not a device**….*

Prescription Drug Use Related Software

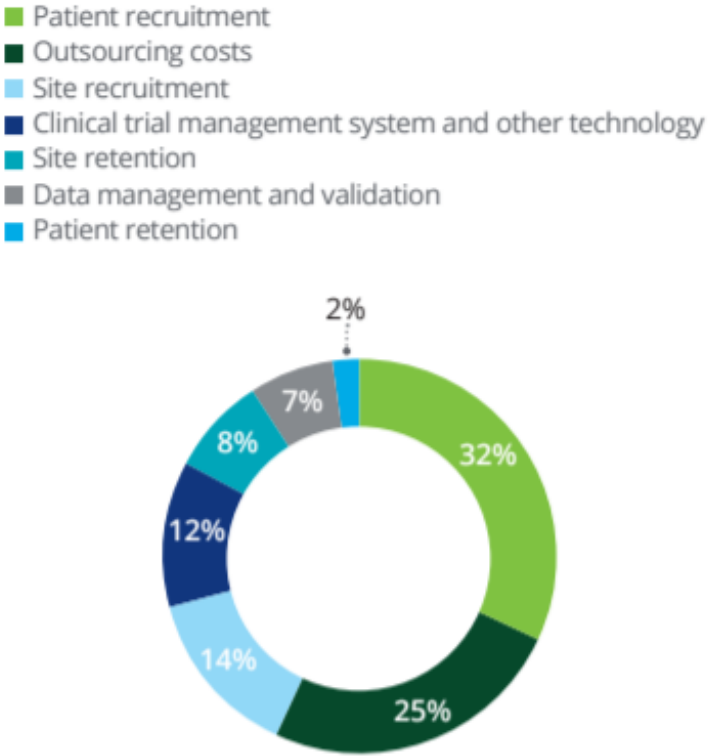
- Nov. 2018 FDA established a docket to solicit comments on a framework for regulating software applications disseminated by or on behalf of drug sponsors for use with prescription drugs.
  - Focuses on software output presented to the end user and not on the software itself
  - Does not address software developed for use with prescription drugs
  - As of 2018, FDA focused on the drug related software as "labeling"/promotional "labeling"
    - *While FDA anticipates that some prescription drug-use-related software will meet the definition of a device, other prescription drug-use-related software will not meet this definition. This proposed framework does not alter the regulatory framework for devices, but focuses on the output of software disseminated by or on behalf of a drug sponsor for use with one or more of its prescription drug(s).*

The traditional approach to clinical development is a lengthy process with only 10 per cent success rate



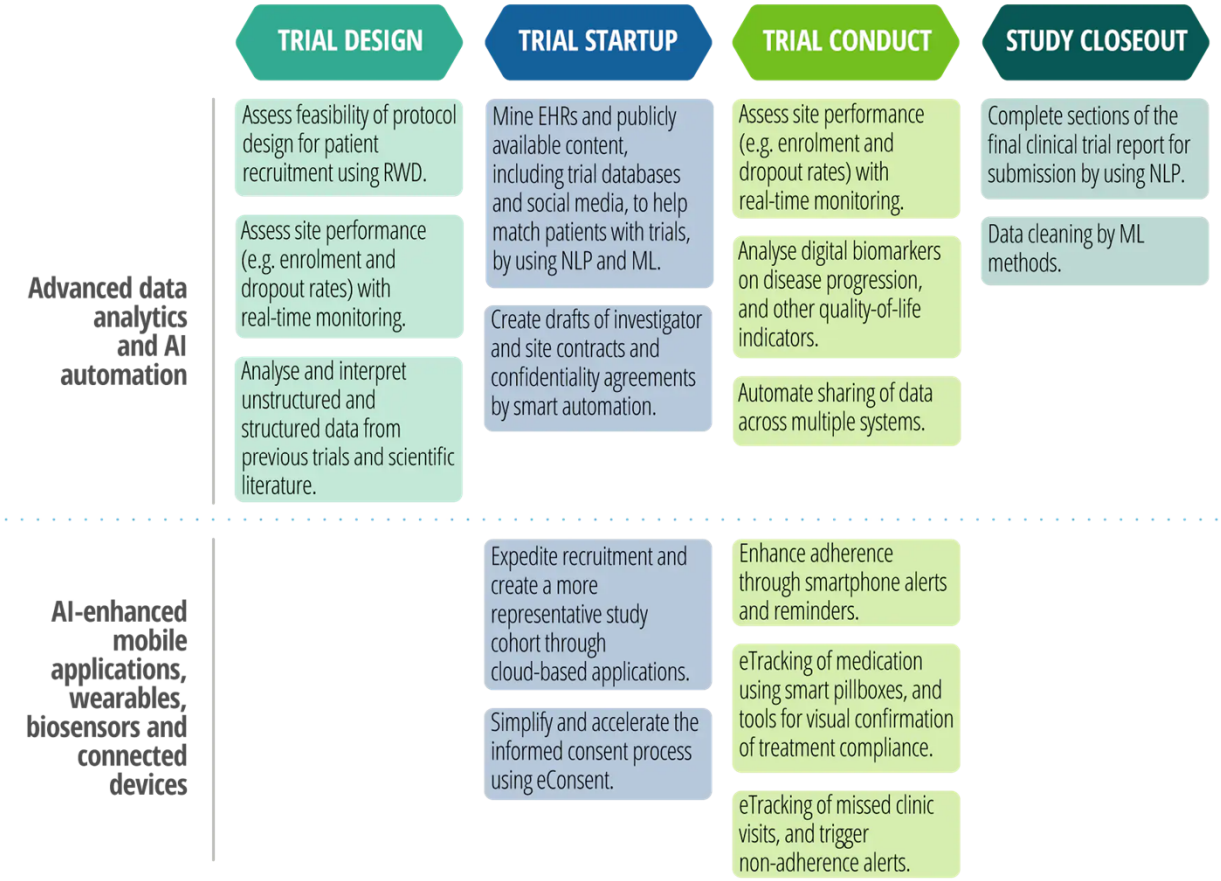
Source: Deloitte analysis.

Cost drivers in clinical trials



Source: Deloitte analysis.

Applications of AI-enabled technology in clinical trials



Source: Deloitte analysis.

Clinical Trial Efficiencies

- Trial Planning and Logistical Monitoring
  - Organize and analyze prior trials to improve the design of future ones
  - In silico modeling of patient responses to inform clinical trial design
    - May allow detection of potential design/product failures before clinical trial enrollment
  - Predictive modeling of trials to identify future challenges and early interventions
- Identification of Appropriate cohorts
  - Use of analytics to combine data with personalization factors and patient records
  - Can be used to identify endpoints/biomarkers and subpopulations
  - Requires OCR and data harmonization among EHR systems
- Cohort Enrichment
  - Decreasing variability
  - Prognostic enrichment
  - Predictive enrichment

Clinical Trial Efficiencies

- Recruitment and Retention
  - Mining available records (e.g., EHRs, insurance claims, etc.) to match the correct patients/sites with the correct trials
  - Mining clinical trial databases to identify potential trials
  - Provide patients with real time feedback to enhance engagement and retention
  - Prediction of patient drop out risk; permitting early intervention
  - Decreased trial size through digital twins
- Monitoring
  - Use of wearable technology, apps, sensors, and biomarkers to provide real-time data and intervention opportunities, if needed
  - Digital monitoring of data to detect site issues

Clinical Trial Efficiencies

- Data Management
  - Automated data capture
  - Real time cleaning of EDC to reduce errors
  - Automated entry of information into dossier/clinical trial report
- Trial Management
  - Algorithms to create protocol based treatment recommendations to decrease protocol deviations
- Trial Accessibility
  - More virtual trials with remote monitoring and visits
  - Use of product candidates under real world conditions
  - More representative trials
  - Learning opportunities from COVID-19

Use of AI/ML in Clinical Development

- Currently very little public information on FDA's approach to the use of AI in clinical trials
- FDA Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot
  - Includes the use of AI to evaluate patients, develop novel endpoints, and inform study design
- FDA pilot program on Model-Informed Drug Development (MIDD)
  - Exposure-based, biological, and statistical models derived from preclinical and clinical data sources
  - Opportunity for sponsors to meet with FDA to discuss MIDD approaches to medical product development
- AltaThera Pharmaceutical's Sotalol IV Artrial Fibrillation approval on alternative dosing strategy
  - *Computer-based simulations incorporating sotalol dose-exposure-QTc relationships were used to derive the intravenous loading doses. Based on these simulations, the intravenous loading dose in a typical patient across each of the renal function categories is expected to achieve steady state concentration faster compared to the conventional oral dosing.*

Legal/Regulatory Considerations for AI/ML in Clinical Trials

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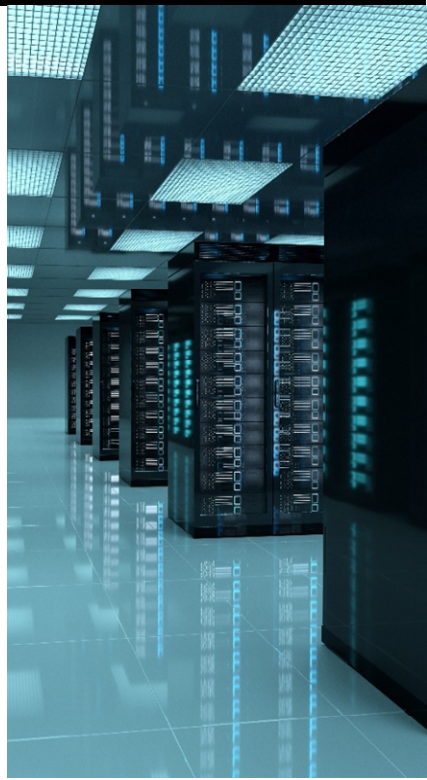
Legal/Regulatory Clinical Trial AI/ML Considerations

- Regulatory status of AI/ML software
  - Use in clinical trials to determine inclusion/exclusion or treatment course may require compliance with FDA's investigational device regulations
    - See e.g., FDA's approach to investigational diagnostics in therapeutic clinical trials
  - If AI is used as part of treatment decision making, will be regulated as a combination product/medical device
- The use of AI/ML may necessitate partnering and the development of internal capabilities, requiring
  - Agreement negotiation
  - Coordination between contracting and regulatory operations
  - Technology and partner diligence (challenging when technology may not be fully transparent)
  - Partner monitoring
- Companies will need to access and maximize large data sets through collaborations, open source platforms, etc.
  - Will necessitate data licensing agreements and data set diligence
  - Will need to ensure dataset compatibility



Legal/Regulatory Clinical Trial AI/ML Considerations

- Securing data against cyber attacks
- Ensuring data use is properly consented and IRB approved
- Validation of the system
  - Do you need to validate?
  - Do you need to provide validation to FDA?
- Introduction of unintended bias
- AI systems may need to be Part 11 compliant
- CDER/CBER staff will need to develop expertise and regulatory framework in AI applications
  - Currently no framework for use of AI in clinical development
  - Companies may need to educate the agency on particular applications, how they work, and GxP controls in place
  - Will require proactive engagement with regulators (both CDER/CBER and CDRH)

How to use AI in FDA regulated clinical trials

- As there is little public information regarding FDA's expectations, the key will be early discussions with FDA to understand the regulatory pathway/approach.
  - How will the AI be used?
    - If used as a subject screening tool, it may not need to be discussed with FDA.
    - If used to measure endpoints, it likely will need to be discussed.
    - What about if used as part of an adaptive clinical trial design?
  - What will FDA require?
    - Will the AI need to be validated and will FDA need to see the validation?
    - Will the AI be classified as a clinical trial tool or a medical device?
  - How much information will FDA want about the AI application?
    - How should this information be shared if the application belongs to another entity?

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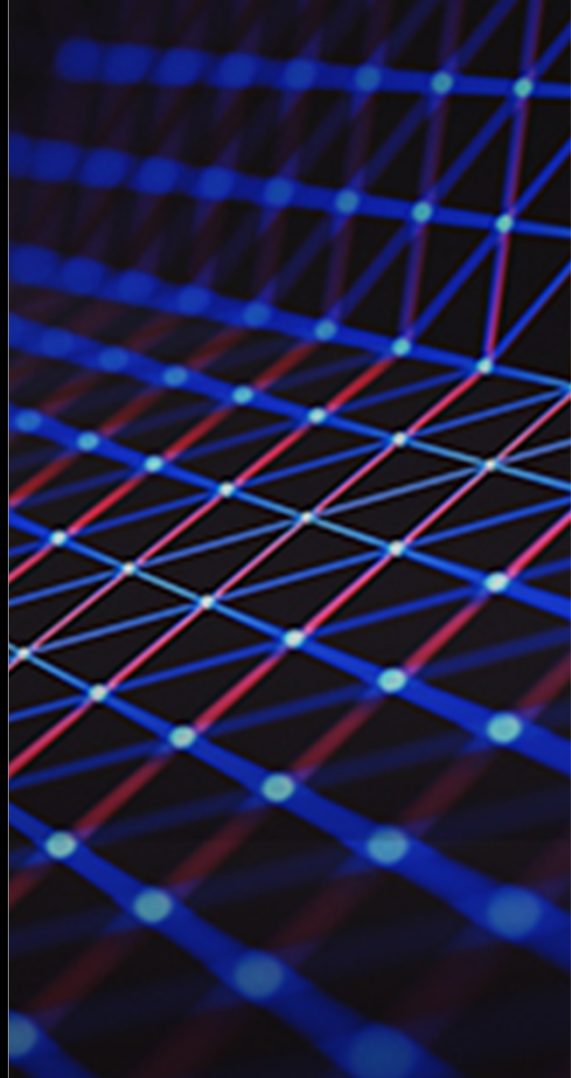
Coronavirus COVID-19 Resources

We have formed a multidisciplinary **Coronavirus/COVID-19 Task Force** to help guide clients through the broad scope of legal issues brought on by this public health challenge.

To help keep you on top of developments as they unfold, we also have launched a resource page on our website at **www.morganlewis.com/topics/coronavirus-covid-19**

If you would like to receive a daily digest of all new updates to the page, please visit the resource page to **subscribe** using the purple "Stay Up to Date" button.



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Biography

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Kathleen M. Sanzo centers her practice on regulatory and compliance issues connected to products regulated by the US Food and Drug Administration (FDA). She leads and counsels clients on matters relating to prescription, OTC drug, and biotechnology products clinical testing; food, dietary supplement, and cosmetic product manufacture, approval, marketing, and distribution; device promotion and labeling issues; food, drug, and device compliance matters; and all consumer product issues regulated by the US Consumer Product Safety Commission (CPSC) and state enforcement agencies.

Biography

Jacqueline Berman
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Jacqueline R. Berman advises companies on US Food and Drug Administration (FDA) regulatory, compliance, and enforcement issues, as well as clinical trials and FDA-regulated product development programs. She also counsels clients on the safety, labeling, and reporting requirements for consumer products under the laws enforced by the US Consumer Product Safety Commission (CPSC), the Federal Trade Commission (FTC), and related state enforcement agencies. Jacqueline's clients include pharmaceutical, device, biologic, dietary supplement, and food/food additive manufacturers.

Jacqueline advises clients on product recalls, marketing applications, labeling, marketing and advertising, and privacy issues. She also works with companies on postmarketing obligations including adverse event reporting and compliance with current good manufacturing practices (cGMP).

Biography

Michele L. Buenafe
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Michele L. Buenafe is a partner in the FDA practice and serves the leader of the firm's digital health initiative. She advises clients on regulatory, compliance, and enforcement issues related to the development, manufacturing, marketing, labeling, and advertising of medical devices, human tissue products, pharmaceuticals, controlled substances, listed chemicals, and combination products. She also advises clients on emerging legal issues relating to digital health platforms such as mobile medical apps, clinical decision support software, telemedicine systems, wearable devices, and other health information technology.

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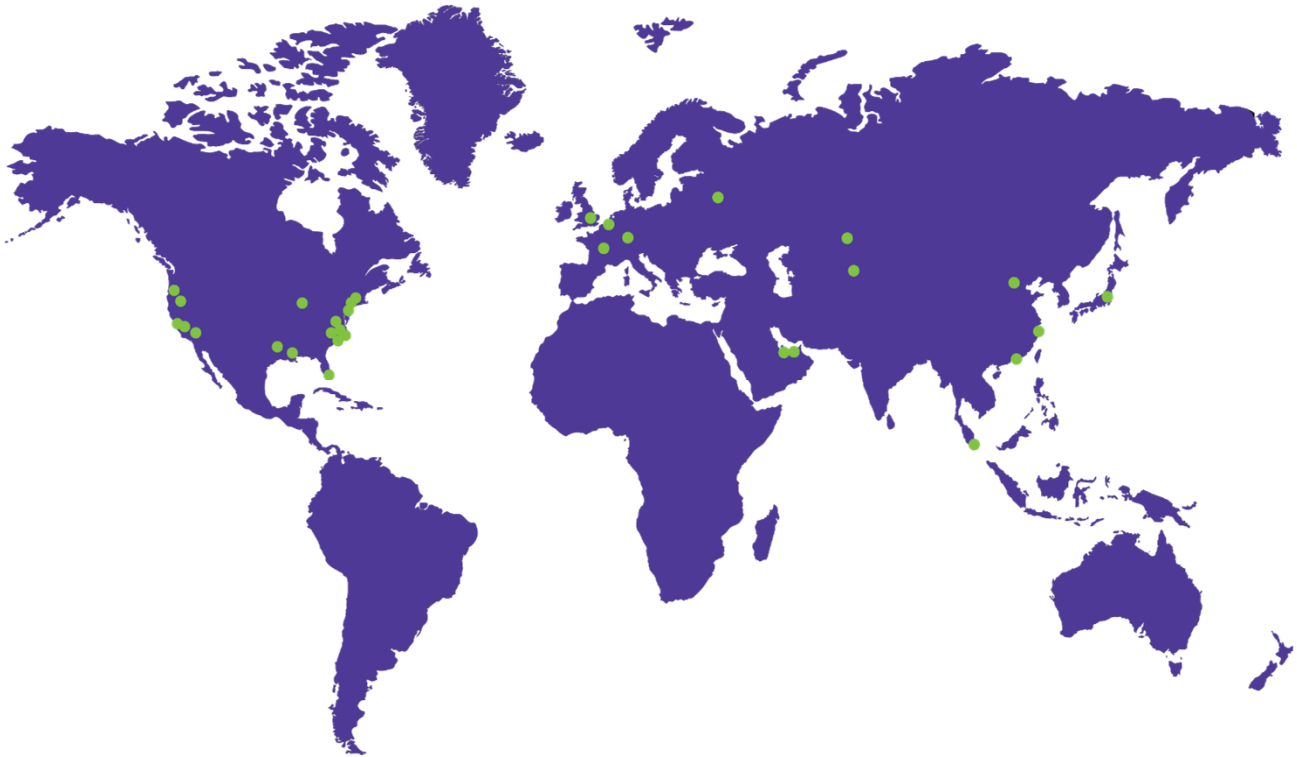

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