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FDA Perspective on the Regulation of Artificial Intelligence in Health Care and Biomedicine

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IMPORTANCE Advances in artificial intelligence (AI) must be matched by efforts to better understand and evaluate how AI performs across health care and biomedicine as well as develop appropriate regulatory frameworks. This Special Communication reviews the history of the US Food and Drug Administration's (FDA) regulation of AI; presents potential uses of AI in medical product development, clinical research, and clinical care; and presents concepts that merit consideration as the regulatory system adapts to AI's unique challenges.

OBSERVATIONS The FDA has authorized almost 1000 AI-enabled medical devices and has received hundreds of regulatory submissions for drugs that used AI in their discovery and development. Health AI regulation needs to be coordinated across all regulated industries, the US government, and with international organizations. Regulators will need to advance flexible mechanisms to keep up with the pace of change in AI across biomedicine and health care. Sponsors need to be transparent about and regulators need proficiency in evaluating the use of AI in premarket development. A life cycle management approach incorporating recurrent local postmarket performance monitoring should be central to health AI development. Special mechanisms to evaluate large language models and their uses are needed. Approaches are necessary to balance the needs of the entire spectrum of health ecosystem interests, from large firms to start-ups. The evaluation and regulatory system will need to focus on patient health outcomes to balance the use of AI for financial optimization for developers, payers, and health systems.

CONCLUSIONS AND RELEVANCE Strong oversight by the FDA protects the long-term success of industries by focusing on evaluation to advance regulated technologies that improve health. The FDA will continue to play a central role in ensuring safe, effective, and trustworthy AI tools to improve the lives of patients and clinicians alike. However, all involved entities will need to attend to AI with the rigor this transformative technology merits.

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Novel technologies are often prematurely anointed as transformative forces in health care. Although many general-purpose tools, such as electronic health records (EHRs), digital health technologies, and telemedicine platforms, have been touted as revolutionary, artificial intelligence (AI) has surpassed them all in terms of hopes, expectations, and concerns.[1] The US Food and Drug Administration (FDA) has long been preparing for the incorporation of AI into biomedical product development and health care. However, AI continues to present unique challenges and opportunities. This Special Communication reviews the history of the FDA's regulation of AI in the industries it oversees and 10 concepts that deserve consideration as the regulatory system adapts to address this rapidly evolving technology.

The FDA's History of Regulating AI-Enabled Medical Products

AI is a machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or virtual environments.[2,3] AI systems use machine- and human-based inputs to perceive real and virtual environments, abstract such perceptions into models through analysis in an automated manner, and use model inference to formulate options for information or action.[2,3] In reality, AI spans applications ranging from simple algorithms to machine learning (ML) approaches to enormously complex transformer models and generative AI tools. These differences in complexity require flexible, risk-based regulatory schemes in these various dimensions.[4]

The FDA's first approval of a partially AI-enabled medical device took place in 1995, when the FDA approved PAPNET, a software that used neural networks to prevent misdiagnosis of cervical cancer in women undergoing Papanicolaou tests. Although PAPNET was shown to be more accurate than human pathologists, it was not adopted in clinical practice due to inadequate cost-effectiveness.[5] Since then, the FDA has authorized approximately 1000 AI-enabled medical devices, with their most common use being in radiology, followed by cardiology (**Figure 1**).[6]

The FDA has also received hundreds of regulatory submissions for drugs that included the use of AI in their discovery and development.[7]

Figure 1. Artificial Intelligence–Enabled Medical Devices Authorized for Marketing by the US Food and Drug Administration, by Year

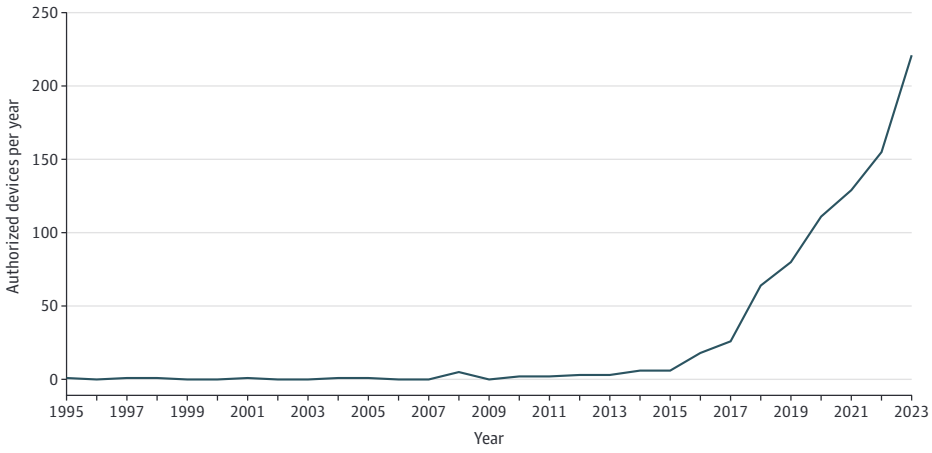

Figure 2. Total Product Life Cycle Approach to Artificial Intelligence (AI)

This diagram maps the phases of a traditional software development life cycle to AI. It highlights systematic methods related to data and model evaluation during the data collection and management and model building and tuning phases. It also illustrates monitoring AI software postdeployment in the operation and monitoring and real-world performance evaluations phases. Additional details are available via the US Food and Drug Administration.

In 2021, 132 such applications were received, a 10-fold increase from 2020. The most common applications of AI in drug development include enhancing drug discovery and repurposing, clinical trial design elements, dose optimization, adherence to drug regimens, end point and biomarker assessment, and postmarket surveillance. Although AI in drug development is most commonly used in oncology, it is followed by mental health—a field that may particularly benefit from digital health technologies.

The FDA regulates 20% of the US economy and must continuously evolve to oversee the safe and effective use of AI across regulated industry, ensuring compliance while fostering innovation. In January 2021, the FDA shared a 5-point action plan to advance AI- and ML-enabled software,[6,8] which included a commitment to further a tailored regulatory framework for AI-enabled medical devices. This remained aligned with a later Congressional request for the FDA to issue draft guidance that provided a pathway for developers to respond to AI's continuous evolution without unduly having to return to the FDA for approval.[9] In 2022, the FDA also published final guidance pertaining to clinical decision-support software,[10] one of several guidances written to describe the FDA's policies as they relate to the device definition amended by the 21st Century Cures Act and the resulting effect the amended definition had on the FDA's oversight of certain medical device software, which included AI applications.[11] More recently, the FDA's medical product centers described 4 areas of focus with regard to the development and use of AI in medical products: (1) fostering collaboration to safeguard public health; (2) promoting development of harmonized standards, guidelines, best practices, and tools; (3) advancing development of regulatory approaches that support innovation; and (4) supporting research related to evaluation and monitoring of AI performance.[3]

Concepts Pertinent to Regulation of AI by the FDA

AI Regulation Within the Broader US Government and Global Context

The FDA's approach is grounded in laws and appropriations from Congress and informed by broader US government interests.[2] The FDA regulates industries that manufacture and distribute products in global markets; therefore, it is important that US regulatory standards are compatible with global standards to the fullest extent possible. The FDA co-leads an AI working group of the International Medical Device Regulators Forum to promote global harmonization of AI best practices. The FDA is also leading working groups within the International Council for Harmonisation to modernize clinical trial design and conduct by incorporating advanced and proportionate approaches to data management that would appropriately accommodate AI in clinical trials.

Keeping Up With the Pace of Change in AI

The broad scope of AI and the pace of change in its development and adoption raise questions about the appropriate regulatory frameworks for AI as well as whether sufficient staff are available to efficiently process the large volume of AI-enabled submissions to the FDA. Development, deployment, and use of AI-enabled products will thus require an adaptive, science-based regulatory scheme to prevent harm while also supporting innovation that optimizes their benefits.

The FDA has already laid out the groundwork for such a scheme for medical devices, which use a total product life cycle approach (**Figure 2**).[12] The FDA has shown openness to innovative programs for emerging technologies, such as the Software Precertification Pilot Program. However, as that program demonstrated, successfully developing and implementing such pathways may require the FDA to be granted new statutory authorities.[13] The sheer volume of these changes and their impact also suggests the need for industry and other external stakeholders to ramp up assessment and quality management of AI across the larger ecosystem beyond the remit of the FDA.

Flexible Approaches Across the Spectrum of AI Models

Congress has specified different levels of regulation for medical devices, which allows for regulation of AI-enabled medical devices in a risk-based approach. On one end of the spectrum are models supporting healthy behavior and administrative functions that are not regulated by the FDA, eg, some AI applications that automate general health care office operations. On the other end are models embedded in traditional medical devices, such as cardiac defibrillators, which are clearly regulated. Models used for clinical decision support fall in the middle where the degree of risk informs the FDA's application of regulatory requirements, particularly when the basis for the algorithm's output cannot be deciphered into a mechanistic explanation by a clinician.[10] These risk-based regulatory approaches will need careful consideration and adaptation.

A practical application of this schema involves the marketing authorization granted to Sepsis ImmunoScore (Prenosis, Inc), an AI algorithm granted de novo classification as a Class II device.[14] The software identifies patients at risk for having or developing sepsis using 22 predetermined inputs from EHRs to generate a risk score, although it should not be used as the sole basis to determine the presence or risk of sepsis. Given potential risks, including algorithm failure, model bias, clinician overreliance, incorrect interpretation, or poor input, special controls were established to provide reasonable assurance of its safety and effectiveness. These mitigation measures included clinical and nonclinical performance testing, software verification, validation and hazard analysis, labeling, human factors assessment, technological characteristics, and postmarket management, including ongoing performance evaluation.

The Use of AI in Medical Product Development

The potential of AI to inform multiple aspects of medical product development is profound and already underway (**Box 1**).[22] Although not specifically endorsing any particular practice, the FDA sees great potential in the application of AI in drug development and clinical research. Just as with any medical product, a key element of regulation is that the final product intended for use must be evaluated in adequate and well-controlled clinical studies to demonstrate empirically that the product's benefits outweigh its risks for that intended use. FDA reviewers must have a deep understanding of the discipline to be able to appropriately review applications that are submitted for marketing approval, eg, applications where AI-assisted target selection or intervention strategies are submitted for approval. Therefore, maintaining a workforce with technical expertise and insight into progress in AI will be crucial to the agency's ability to provide useful and timely guidance to industry as products are developed.

Box 1. Select Current and Potential Uses of Artificial Intelligence (AI) in Drug Development

Drug Target Identification, Selection, and Prioritization
- Analyze complex and disparate data sources to inform biological target selection.[15]
- Mine and analyze large multiomics and other data sets to provide information on the structure and function of targets to predict their role in disease pathways.[16,17]

Screening and Designing Compounds
- Predict efficacy and adverse events based on compounds' specificity and affinity for a target.[18,19]
- Predict classes of drugs potentially interacting with the same targets or with a similar mechanism of action, which could help predict molecule toxicity.
- Aid drug repurposing by analyzing data from a variety of sources (eg, electronic health records, registries, and digital health technologies) to identify previously unknown effects of drugs on disease pathways.[20]

Modeling Pharmacokinetics and Pharmacodynamics
- Analyze time series data to complement pharmacokinetic and pharmacodynamic models.[21]
- Aid in dose optimization in special populations with limited data (eg, rare disease, pediatric, and pregnant populations).

Advanced Pharmaceutical Manufacturing
- Optimize process design and implement advanced process control, smart monitoring, and maintenance and trend monitoring.

Additional details are available via the US Food and Drug Administration.

The role of AI in medical product development is not just limited to the premarket setting, but also includes clinical research as well as postmarket surveillance and evaluation (**Box 2**).[22,40,41] By analyzing vast amounts of real-world data, AI systems can detect patterns and anomalies that may improve the ability to find potential safety issues, unexpected benefits, or performance inefficiencies. Such a proactive approach may enable quicker identification of adverse events, leading to timelier interventions and corrections. Additionally, AI can synthesize analysis of clinical trials, postmarket surveillance, and patient feedback, providing a comprehensive overview of a product's life cycle across areas that have previously been separate. This could enhance patient safety while accelerating medical product innovation.

Preparing for the Unknowns of Large Language Models and Generative AI

Applications of generative AI, such as large language models (LLMs), present a unique challenge because of the potential for unforeseen, emergent consequences; the FDA is yet to authorize an LLM. However, many proposed applications in health care will require FDA

Box 2. Select Current and Potential Uses of Artificial Intelligence (AI) in Clinical Research

Participant Recruitment
- Mine data from clinical trial databases, trial announcements, social media, medical literature, registries, and structured and unstructured data in registries and electronic health records to match individuals to trials.[23]
- Ensure adequate representation of populations likely to use the medical product (eg, by gender, race and ethnicity, etc) as matching algorithms are created and to confirm achievement of equitable inclusion.

Selection and Stratification of Trial Participants and Sites
- Predict an individual participant's clinical outcome based on baseline characteristics to enrich clinical trials,[24,25] reduce variability, and increase study power.[26]
- Stratify patients into different groups and monitoring strategies based on predicted probability of serious adverse events.
- Evaluate site performance and determine which may run behind based on prior data.

Adherence and Retention
- Improve adherence during a clinical trial through tools such as smartphone alerts and reminders, eTracking medication (eg, smart pillboxes and tools for visual confirmation), and missed clinical visits, which trigger nonadherence alerts.[27]
- Use digital biomarkers (eg, facial and vocal expressivity) to monitor adherence remotely.
- Improve participants' access to trial information by enabling tools such as AI chatbots, voice assistance, and intelligent search.
- Reduce participant burden by using passive data collection and extracting more information from available data generated during clinical practice or through study activities.[16]

Clinical Trial Data Collection, Management, and Analysis
- Identify new characteristics of conditions[28] or predict status of and response to treatment of a chronic disease.[29]
- Evaluate multimodal data and composite measures.[30]
- Harmonize data cleaning, duplicate detection, controlled terminology, and imputation.[31]
- Enhance data curation via masking and deidentification of personal identifiable information, metadata creation, and search and retrieval of stored data.
- Evaluate drug candidates and outcomes using virtual cohorts with variability of traits representing desired population.[32]
- Use digital twins to generate simulated clinical records to predict placebo group response.
- Detect symptom clusters to identify safety signals.[33,34]

Postmarket Safety Surveillance and Evaluation
- Detect and evaluate adverse event associations from medical literature and social media.[35,36]
- Identify adverse events for individual case safety report submissions.
- Determine case validity by assessing minimum reporting requirements and assisting in case prioritization by expectedness.[37]
- Code individual case safety reports to structured medical dictionaries.[38]
- Classify probability of a causal relationship between drugs and adverse events.[35]
- Facilitate aggregated individual case safety reporting.[39]

Additional details are available via the US Food and Drug Administration.

oversight given their intended use for diagnosis, treatment, or prevention of diseases or conditions. Even "AI scribes" meant to summarize medical notes can hallucinate or include diagnoses not discussed in the visit. The complexity of LLMs and the permutations of outputs necessitate oversight from individuals and institutions in addition to regulatory authorities. Because we cannot unduly burden individual clinicians with such oversight,[42] there is a need for specialized tools that enable better assessment of LLMs in the contexts and settings in which they will be used. Such tools could be developed from scratch or adapted from existing LLM evaluation tools, eg, DeepEval and MLflow. As applications of LLMs move into decision support for clinicians but also patients[43,44] carrying significant risk, it may be wise to start with areas with the deepest body of evidence supporting clinical decision-making, eg, cardiology, oncology, and in lower-risk clinical workflows where there is time to evaluate their outputs. LLMs also carry great potential to elevate the usefulness of existing technologies, such as EHRs[45] and wearable digital health technologies.[43] Therefore, there is a need for regulatory innovation in this space to enable both analysis of these information sources and integration into clinical decision-making. Proactive engagement among developers, clinicians, health system leaders, and regulators on platforms such as the FDA's Digital Health Advisory Committee will be critical.

The Central Importance of AI Life Cycle Management

Given the capacity for "unlocked" models to evolve and AI's sensitivity to contextual changes, it is becoming increasingly evident that AI performance should be monitored in the environment in which it is being used. This need for postmarket performance monitoring of AI has profound implications for the management of information by health systems and clinical practices. To meet the moment, health systems will need to provide an information ecosystem much like that monitoring a patient in the intensive care unit. The tools and circumstances of this ongoing evaluation must be recurrent and as close to continuous as possible, and the evaluation should be in the clinical environment in which it is being used. Concepts such as external assurance laboratories[46] or site-specific localized validation[47] have promise, but, given the complexity of the issue, more approaches and tools are needed to further refine AI evaluation because an unmonitored AI system deployed in practice could do significant harm.

The Responsibilities of Regulated Industries

Industries regulated by the FDA must comply with all applicable laws and requirements of the regulatory framework administered by the agency. Further interpretation is provided by guidances, which reflect the current thinking of the agency but are not binding on the FDA or the public. At its core, FDA regulation begins with voluntary compliance by the regulated industries themselves. For example, the FDA reviews studies typically funded by industry but does not conduct clinical trials. Therefore, the concept that regulation of AI in medical product development and application for products that the FDA oversees begins with responsible conduct and quality management by sponsors does not fundamentally differ from the FDA's general regulatory regime.

In addition to safety assessment, it is important to evaluate whether health benefits of AI applications accrue to patients when they are being used to inform, manage, or treat patients. Even

clinical decision support, if systematically biased, can either improve or reduce the accuracy of clinical decision-making.[48] Currently, however, neither the development community nor the clinical community is fully equipped for the recurrent, local assessment of AI throughout its life cycle. Health systems could fill this role, but currently their clinical information systems are unable to monitor the ongoing and long-term safety and effectiveness of these interventions. Accurate assessment of model performance in a medical product after deployment requires similar rigor as premarket evaluation. For example, this includes diligent follow-up of the relevant patient population because valuable information is typically found in those patients lost to follow-up due to death or other adverse outcomes.

The evolution of AI illustrates a major quality and regulatory dilemma. Since the safety and effectiveness of many AI models depends on recurrent evaluation of their operating characteristics, the scale of effort needed could be beyond any current regulatory scheme. For traditional medical products, which generally remain the same no matter where they are distributed, appropriately robust studies for a specific indication can provide assurance of safety and effectiveness of the product for the US population, but this may not necessarily be the case for many AI-enabled medical products given their contextual sensitivity. Therefore, this is an important area necessitating close scrutiny as AI becomes more routine.

Maintaining Robust Supply Chains

AI models are likely to play a crucial role in managing supply chains, but could also be vulnerable to outages and shortages themselves. Thus, considering their dual role in supply chains is critical. Supply chains for all FDA-regulated products have become increasingly complex, global, and focused on efficiency, defined by attributes such as "just-in-time" delivery and minimal inventory. This system works well when the situation is stable, but demand or supply shocks caused by natural disaster, war, economic difficulty, or manufacturing uncertainty create shortages, with little resiliency in the system to enable rapid recovery. Although elements of supply chain inventory and flow are kept as proprietary information, when shortages occur, the FDA and other government entities struggle to make connections among competitors to provide needed supplies. The use of sophisticated AI models and plugging the holes in data to anticipate or rapidly respond to shortages could ameliorate both shortages in generic drugs and the quality and supply stability of low-cost devices. Further, minimizing vulnerability to cybersecurity threats and developing resilient backups in the event of technology outages must be integral to these technologies.

Finding the Balance Between Big Tech, Start-Ups, and Academia

The field of commercial AI products, especially generative AI, is dominated by big tech companies that have the capital, computational resources, and expertise needed for their development. At the same time, many start-ups and entrepreneurs are entering the field, while academic institutions are flush with ideas that could contribute to progress. This also pertains to the diversity of sites where AI might be used. Among numerous challenges will be the daunting task of determining ways for all developers, including small entities, to ensure that AI models are safe and effective across the total product life cycle in diverse settings. Most current FDA programs have special initiatives to support small business and academia that would also apply to AI.

The Tension Between Using AI to Optimize Financial Returns vs Improving Health Outcomes

When institutions and health systems purchase or invest in the development of AI technology, return on investment is understandably a key consideration. Unfortunately, the relationship between optimizing finances and improving health outcomes for patients and communities is complex and at times at odds. Because of potentially conflicting incentives, optimizing decisions for better patient outcomes could result in a financial disadvantage to health systems, provider organizations, or insurance companies.

Although the FDA does not regulate the practice of medicine, it has a strong mission to both advance public health and biomedical innovation. Therefore, there is concern that a disproportionate focus of AI applications on financial return on investment could harm patient outcomes and reduce acceptance and trust in this technology. Many AI innovations that could benefit patients may come at the price of traditional jobs, capital structures, and revenue streams in health care. Yet too many US residents live in health care deserts,[49] with primary care shortages even in many physician-dense areas, and AI algorithms could point to more preventive services that currently are not profitable. Furthermore, AI could significantly improve the efficiency of clinical services, thereby freeing clinicians to do the one thing that ultimately no machine can: forge a human connection with the patient.[50] However, care is needed to ensure that AI's ability to optimize processes is not used to further reduce human interaction by compressing patient-clinician interaction even further. Clinicians are the bridge between this technology and patients, and can play an important role in advocating for high-quality evidence for health benefits that inform the clinical application of AI.

An intentional focus on health outcomes will be necessary to overcome the pressure to emphasize practices that lead to suboptimization of the health care system,[51] the adverse risks of financialization,[52] and data blocking. The mandate for the FDA to safeguard and promote the health of individuals and public health will apply pressure to the system, but the need for a broad collaboration for responsible collective advancement extends beyond the FDA.

Conclusions

Historic advances in AI applied to biomedicine and health care must be matched by continuous complementary efforts to better understand how AI performs in the settings in which it is deployed. This will entail a comprehensive approach reaching far beyond the FDA, spanning the consumer and health care ecosystems to keep pace with accelerating technical progress. If not, there is a risk that AI could disappoint similar to other general-purpose technologies deployed in health care settings or even create significant harm if untended models' performance deteriorates or focuses on financial return without adequate attention to impact on clinical outcomes.

Strong oversight by the FDA and other agencies aims to protect the long-term success of regulated products by maintaining a high grade of public trust in the regulated space. It is in the interest of the biomedical, digital, and health care industries to identify and deal with irresponsible actors and to avoid misleading hyperbole.

Regulated industries, academia, and the FDA will need to develop and optimize the tools needed to assess the ongoing safety and effectiveness of AI in health care and biomedicine. The FDA will continue to play a central role with a focus on health outcomes, but all involved sectors will need to attend to AI with the care and rigor this potentially transformative technology merits.

ARTICLE INFORMATION

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