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REGULATING THE USE OF AI IN DRUG APPROVALS

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ABSTRACT

This comprehensive Article explores the evolving role of artificial intelligence (AI) in the drug validation process within the U.S. Food and Drug Administration (FDA). By examining historical practices alongside emerging trends, the study assesses the legal implications and challenges associated with the integration of AI technology in pharmaceutical regulation. The exploration commences with an overview of traditional FDA validation techniques which provides a strong foundation for understanding the pre-AI regulatory framework. Through extensive analysis of case studies and empirical evidence, the Article establishes how AI enhances efficiency, accuracy, and decision-making processes in drug validation. Furthermore, the legal aspects section scrutinizes key issues encompassing transparency, cybersecurity, data protection, intellectual property rights, and regulatory decision-making, with particular emphasis on the principle of nondelegation. In addition to examining FDA advisories on AI implementation, the study suggests enhancements to optimize the application of AI within the existing regulatory framework. The conclusion

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emphasizes the significance of proactive measures in refining current legal structures and establishing comprehensive industry guidelines that effectively address the transformative potential of AI in drug validation. By elucidating the benefits and challenges of AI adoption, this research contributes to the ongoing discourse surrounding the appropriate utilization and regulation of AI in the field of drug validation.

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Introduction

As the integration of artificial intelligence (AI)technology becomes increasingly prevalent in various industries, its implications in the field of drug validation have garnered significant attention.[1] This Article aims to delve into the intricate guidelines surrounding the use of AI by the Food and Drug Administration (FDA), examining its traditional approaches and identifying emerging trends. By investigating the potential legal dilemmas and constraints inherent in the application of AI in drug validation this study contributes to the ongoing discourse on the appropriate regulation of AI in the pharmaceutical domain.

The first section provides a historical overview of the techniques traditionally employed by the FDA in the drug validation process. Through an examination of established practices, this section establishes a foundational understanding of the FDA's regulatory framework prior to the introduction of AI technology. Building upon this foundation, the second section explores the progressive integration of AI in drug validation practices. By exploring case studies and empirical evidence, this section highlights the transformative impact of AI in enhancing efficiency and accuracy in the decision-making processes within the FDA's purview. Delving into the multifaceted legal aspects surrounding AI implementation, the third section scrutinizes pertinent legal clauses that are particularly relevant to the FDA's use of AI technology in drug validation. Key legal dilemmas discussed include the challenges pertaining to transparency due to the intricate nature of AI algorithms, concerns

[1] *See* Stan Benjamens, Pranavsingh Dhunnoo & Bertalan Meskó, *The State of Artificial Intelligence-Based FDA-Approved Medical Devices and Algorithms: An Online Database*, 3 Npj Digit. Med. 118 (2020), https://doi.org/10.1038/s41746–020–00324–0; Urs J Muehlematter, Christian Bluethgen & Kerstin N Vokinger, *FDA-Cleared Artificial Intelligence and Machine Learning-Based Medical Devices and Their 510(k) Predicate Networks*, 5 Lancet Digit. Health e618 (Sept. 2023), https://doi.org/10.1016/S2589–7500(23)00126–7; *How FDA Regulates Artificial Intelligence in Medical Products*, Pew (July 2021), https://pew.org/3yglbCS; Jodie Tillman, *FDA Looks to Help Shape AI's Growing Role in Drug Development,* ASHP News Ctr., (Dec. 4, 2023), https://news.ashp.org/News/Midyear/2023/12/04/ai-and-machine-learning; Joanne S. Eglovitch, *FDA Sees Rapid Uptick in Drug and Biologic Submissions with AI/ML Components*, Reg. Focus a RAPS Pub. (July 12, 2023), https://www.raps.org/News-and-Articles/News-Articles/2023/7/FDA-sees-rapid-uptick-in-drug-and-biologic-submiss.

regarding cybersecurity and data protection, intellectual property claims arising from AI-generated innovations, and the principle of nondelegation in regulatory decision-making. In the final section, this Article evaluates the advisories issued by the FDA in response to the utilization of AI in drug validation. By critically analyzing the effectiveness and limitations of these advisories, this section explores potential enhancements that could further optimize the application of AI within the FDA's regulatory framework.

This Article concludes by emphasizing the inadequacies of the current legal framework governing the use of AI in FDA drug validation and underscores the need for proactive measures to refine existing legal structures and establish more comprehensive industry guidelines. By shedding light on the transformative potential of AI and its impact on regulatory processes, this study aims to contribute to the ongoing discourse surrounding the appropriate utilization and regulation of AI in the field of drug validation.

I. How Did the FDA Approve Drugs in the Past?

This Part offers a chronological overview of significant historical events that have shaped the FDA's development, highlighting its evolving focus in response to changing social, political, and economic landscapes. As a public health agency, the FDA plays a crucial role in safeguarding public health by ensuring the safety, efficacy, and security of medical products and devices.[2] It is important to note that products under the FDA's supervision account for approximately 20 percent of household expenditure in the US, making the agency not only critical for public health but also a driving force behind the national economy.[3]

A. The predecessor (pre-1906)

Before the Food and Drug Act of 1906, there was minimal federal regulation on drugs and food.[4] The first of such regulation

[2] *What We Do*, U.S. Food & Drug Admin. (Nov. 21, 2023), https://www.fda.gov/about-fda/what-we-do.

[3] the Off. of the Comm'r, *FDA at A Glance* (Nov. 2021), https://www.fda.gov/media/154548/download#:~:text=FDA%20oversees%20the%20safety%20of,dollar%20spent%20by%20U.S.%20consumers.

[4] John P. Swann, *How Chemists Pushed for Consumer Protection: The Food and Drugs Act of 1906*, 24 Chem. Herit. 6 (2006).

occurred in 1862, when President Lincoln established a Bureau of Chemistry in the US Department of Agriculture.[5] Though numerous bills on regulatory regimes were proposed during 1879 and 1906, none resulted in regulatory power for the Bureau over the safety and efficacy of drugs.[6] The only notable regulation at the time occurred in 1905, unrelated to any government agency, when the American Medication Association (AMA) initiated a requirement that drug companies present proof of effectiveness for products to be advertised in the AMA and related journals.[7] However, there remained no government regulation of the area until the passage of the Food and Drug Act in 1906.[8]

B. The modern era of the FDA (post-1906)

In response to growing public concern, President Roosevelt signed the Food and Drug Act (known as "the Wiley Act") in 1906, which empowered the Bureau of Chemistry to prohibit misbranded and adulterated food and drugs in interstate trade.[9] The agency's initial tasks included regulating only the accurate labelling of products rather than pre-market approvals[10] and only prevented misleading or false statements on the identity and composition of drugs rather than its therapeutic effects.[11] In 1911, the first major case involving the Wiley Act, *U. S. v, Johnson* upheld these limits to the Act's scope.[12] In *U. S. v. Johnson*, the Court questioned the legality of worthless drugs with misleading statements on their labels.[13] The Supreme Court held that misleading statements on the curative effects of a drug do not fall within the scope of the Wiley

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[5] U.S. Food and Drug Admin., https://www.fda.gov/ (last visited Aug. 30, 2023).

[6] Stephen Daily, *A Brief History of the FDA*, Cataract & Refractive Surgery Today (Oct. 2011), https://crstoday.com/articles/2011-oct/a-brief-history-of-the-fda.

[7] U.S. Food & Drug Admin., A History of the FDA and Drug Regulation in the United States 1.

[8] Daily, *supra* note 6.

[9] *Id.*

[10] Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, 40 FDA Consumer Mag. 14, 16 (2006).

[11] Mason Marks, *Automating FDA Regulation*, 71 Duke L. J. 1207, 1215 (2022).the Food and Drug Administration ("FDA"

[12] *United States v. Johnson*, 221 U.S. 488, 498 (1911).

[13] *Id.*

Act.[14] In 1912, in response to the judicial ruling, Congress passed the Sherley Amendments to add restriction of false therapeutic claims with the intent of fraud to the Bureau's authority.[15] Although the burden to prove intent in these cases remained challenging for the Bureau, seizure of misbranded drugs increased dramatically in the 1920s and 1930s.[16]

While the *Wiley Act* set the foundation for drug regulation, the regulation had major gaps.[17] Though the Bureau recommended a complete revision of the law in 1933,[18] the proposed bill did not pass until 1938, a year after the tragedy of Elixir Sulfanilamide, which killed more than 100 people, most of whom were children.[19] In 1938, President Roosevelt signed the new law, the Federal Food, Drug, and Cosmetic Act (FDCA), which created the FDA and assigned it more responsibility than the Bureau of Chemistry previously had.[20] Filling one of the gaps of the Wiley Act, the FDCA introduced the mandatory requirement of evidence of safety before drugs could be marketed.[21] Though the law expressly required firms to undertake all necessary studies to prove the safety of the drugs, there were no specific instructions on the testing methodology.[22] Despite the FDA's attempt to standardize clinical research through the publication of a 1944 article about experimental design, proper clinical trial methods, and data analysis methods on JAMA, a study conducted in 1951 estimated that 45 percent of all clinical trials lacked a control group. The absence of a control group significantly decreases the accuracy of the results.[23]

Shortly after the approved drug Thalidomide caused undesirable effects on patients in 1961, the Kefauver-Harris Amendment was passed to demand evidence of both safety and efficacy which

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[14] *Id.*
[15] Meadows, *supra* note 10, at 16.
[16] Daily, *supra* note 6.
[17] *Id.*
[18] *Id.*
[19] *Id.*
[20] Marks, *supra* note 11, at 1215.
[21] *Id.*
[22] Suzanne W. Junod, *FDA and Clinical Drug Trials: A Short History*, 2008 FDLI Update 55, 55 (2008).
[23] *Id.*

were not explicitly mandated in the original FDCA.[24] It also added the requirement for the FDA to approve a drug's marketing application before it can be marketed.[25]

Although the statutory language was still ambiguous as to the actual meaning of 'substantial evidence' to pass the new efficacy test, the drug industry interprets the term to constitute "adequate and well-controlled studies" which use at least control groups, random allocation of patients, and techniques to minimize bias.[26] The modern model of the three-phased trial was gradually developed to fit this requirement, recognizing that a poorly-designed trial not only wastes resources, but also poses risks to patients.[27]

Phase 1 aims to evaluate the safety of the drug using a small-scale trial that involves drug testing in a smaller number of healthy volunteers, usually ranging from twenty to one hundred, and lasts for several months.[28] Phase 2 requires more participants and longer duration to evaluate both effectiveness and safety.[29] The final phase includes participants with specific health conditions to simulate the effects of the drugs in real-life scenarios.[30] This trial usually involves many more participants and lasts longer, with a typical duration ranging from one to four years.[31] Then, if the drug is approved after submission, the FDA requires an additional phase involving constant monitoring of the drug's public uses.

C. Developments along the way

Although the three-phase procedure provided for increased reliability in the FDA, among some obvious obstacles was the length of time required for drugs to get approved.[32] Delays could be caused by disagreement between the FDA and the industry, long-winded chemistry reviews, waiting periods for FDA feedback,

[24] Daily, *supra* note 6.
[25] Meadows, *supra* note 10.
[26] Junod, *supra* note 22, at 56.
[27] Marks, *supra* note 11, at 1215–16.
[28] Marks, *supra* note 11, at 1216.
[29] .
[30] *Id.*the Food and Drug Administration ("FDA"
[31] *Id.*
[32] Murray Grant, Address Presented to 25th. Annual Educational Conference by the Food and Drug Law Institute: Progress and Problems in FDA's Drug Approval Process 4 (Dec. 15–16, 1981).

and the resolution rate of identified deficiencies by the drug firms.[33] These delays can be detrimental to patients and companies, especially for imperative drugs.[34] Apart from the lengthiness of the procedure, clinical trials using unapproved drugs can be unpredictable, exposing participants to the risk of physical and psychiatric injuries.[35]

Considering these limitations, the FDA introduced four measures to speed up the process: (1) priority review, (2) accelerate approval, (3) fast track designation, and (4) breakthrough therapy designation.[36] Evidently, these efforts have successfully reduced the average time for FDA drug approval.[37] However, this update came with the costs of post-market surveillance, as 79 percent of budget for the FDA's Center for Drug Evaluation was spent on new drug reviews, compared to 53 percent in 1992.[38] This imbalance led to increasing reliance on the industry to detect risks after the drug was sold on the market, aligning the FDA's interests more with the firms.[39]

Further, the FDA's shift towards surrogate evidence, meaning the use of laboratory data instead of direct evidence, in accelerated pathways was problematic and criticized as eroding the evidentiary threshold.[40] The shift away from clinical evidence was also seen as the result of increasing collaboration between the FDA and the regulated firms.[41] Consequently, changes created doubts as to the credibility of the evaluation system and concerns that the adoption of AI may further exacerbate these existing issues, which will be discussed in Part II.

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[33] .

[34] *Id.*

[35] Marks, *supra* note 11, at 1217.

[36] *Id.*the Food and Drug Administration ("FDA"

[37] Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *New FDA Breakthrough-Drug Category—Implications for Patients*, 370 New Engl. J. Med. 1252, 1253–55 (2014).

[38] Will Wang & Albert I. Wertheimer, *History, Status, and Politicization of the FDA*, 18 Rsch. Soc. & Admin. Pharm'y 2811, 2812 (2022).

[39] *Id.*

[40] Marks, *supra* note 11, at 1218; Darrow, Avorn, and Kesselheim, *supra* note 35, at 1255; Lucija Tomljenovic & Christopher A. Shaw, *Too Fast or Not Too Fast: The FDA's Approval of Merck's HPV Vaccine Gardasil*, 40 J.L. Med. & Ethics 673, 675 (2012).

[41] Marks, *supra* note 11, at 1218.

II. The Digital Era of the FDA

A. The trend of automated state agencies

With the rapid development and expanding capabilities of AI technology, government agencies in the US have begun to incorporate AI into various aspects of their work, including enforcement, regulatory tasks, adjudication, public services and engagement, and internal management.[42] The 2020 report drafted for the Administrative Conference of the United States (AUCS) shows that among sixty-four agencies in the US, the FDA holds the fourth-highest ranking in terms of AI use cases .[43] Surprisingly, among all AI uses discussed in the report, 53 percent were developed in-house, followed by private contracting.[44] In fact, the FDA has been devoted to developing AI capacity itself.[45] In 2019, former FDA Commissioner Scott Gottlieb submitted a request to Congress for approximately $70 million to fund the Digital Health Centre of Excellence focused on AI research.[46] Because the FDA is responsible for formulating many public health policies and overseeing medical products that may affect every household in the United States, it is crucial to consider the implications of the agency's move towards adopting AI.

B. What is AI?

Before delving into a detailed examination of the FDA's applications of AI, this section provides an overview of AI technology potentially utilized by the agency, along with a discussion of its limitations. Modelling and simulation, which the FDA uses, solve problems of complex systems when no easier solutions are available.[47] To undertake assessment on a system that is made up of a

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[42] David Freeman Engstrom, Daniel E. Ho, Catherine M. Sharkey & Mariano-Florentino Cuéllar, Government by Algorithm: Artificial Intelligence in Federal Administrative Agencies 10 (2020), https://www.ssrn.com/abstract=3551505.

[43] *Id.* at 16.

[44] *Id.* at 18.

[45] *Id.* at 54.

[46] *Id.*

[47] William A. Menner, *Introduction to Modeling and Simulation*, 16 Johns Hopkins APL Tech. Dig. 6, 6 (1995).

collection of entities, models are constructed with several inputs, outputs, and conditions.[48] Simulation can then be achieved by adjusting the variables and tuning the conditions to observe different outcomes.[49]

Simulation and modelling take priority in the FDA's AI strategy, as they aim to replace conventional clinical trials with the use of virtual patients.[50] The Director of the Office of Regulatory Science and Innovation at the FDA hopes that AI can play an integral role in regulatory decision making, although this has not yet been achieved.[51] The issues around the credibility of models have been recognized by the FDA. Many existing or proposed models have not been delicately evaluated so their credibility is unknown.[52] There is also insufficient data for model development and validation, along with a lack of adequate analytical methods.[53] Further, the lack of good practices of computational modelling simulation across the applications and credibility assessment tools is problematic.[54]

Another type of relevant AI technology is machine learning (ML). ML has a high risk of bias, which could be introduced by developers during the selection of training data, labelling of the data to make it more readable by the system, selection of models, or interpretation of the results.[55] If the model is trained on datasets that underrepresent certain populations, it may result in inaccurate and biased predictions for these groups.[56] As racial bias is already

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[48] *Id.* at 7.

[49] Nat'l. Inst.of Biomedical Imaging and Bioengineering, Computational Modeling (2018), https://www.nibib.nih.gov/science-education/science-topics/computationalmodeling.

[50] *Credibility of Computational Models Program: Research on Computational Models and Simulation Associated with Medical Devices*, U.S. Food & Drug Admin. (Nov. 16, 2023), https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/credibility-computational-models-program-research-computational-models-and-simulation-associated.

[51] *See* Marks, *supra* note 11, at 1222–23.

[52] *Credibility of Computational Models Program*, *supra* note 50, at 2.

[53] *Id.*

[54] *Id.*

[55] Marks, *supra* note 11, at 1226.

[56] *Id.* at 1224.the Food and Drug Administration ("FDA"

problematic in the health care sector, similar bias may be built into or even exemplified by the health care algorithms.[57] For example, a risk-assessment algorithm used in guiding clinical decision-making has produced biased predictions which state that White patients given the same predicted risk score tend to be healthier than the Black patients.[58] This bias is found to be produced by mainly by the initial labels used in the training.[59] The system also erred in predicting future health care costs due to the use of a systematic bias that Black patients historically spend less on health care than the White counterparts.[60]

The last relevant AI technology is AI that uses deep learning, an algorithmic system of deep neural networks that remains obscure or concealed from human understanding.[61] Deep learning algorithms that cause transparency issues are intrinsically present. This is usually referred to as the 'black box' problem, which is still pending comprehensive solutions despite some progress.[62] The black box problem is urgent because the accompanying lack of understanding creates a lack of trust as more decision-making processes are delegated to AI in healthcare sectors.[63]

C. Use of AI by FDA

Among all AI technologies adopted by the FDA, the following discussion summarizes four of the major implementations: (1) the Federal Adverse Event Reporting System ('FAERS'); (2) the Public Health Assessment via Structural Evaluation ('PHASE'); (3) virtual humans and patient-specific models; and (4) simulated clinical trials.

1. *FAERS*. In addition to rulemaking and guidance, the FDA employs a combination of pre-market approvals and post-market surveillance to ensure the safety of pharmaceuticals and medical

[57] Danton S. Char, Nigam H. Shah & David Magnus, *Implementing Machine Learning in Health Care—Addressing Ethical Challenges*, 378 New Engl. J. Med. 981, 981 (2018).
[58] Pranav Rajpurkar, Emma Chen, Oishi Banerjee & Eric J. Topol, *AI in Health and Medicine*, 28 Nat. Med. 31, 36 (2022).
[59] *Id.*
[60] *Id.*
[61] Warren J. von Eschenbach, *Transparency and the Black Box Problem: Why We Do Not Trust AI*, 34 Phil. & Tech. 1607, 1607 (2021).
[62] *Id.* at 1608.
[63] *Id.*

equipment.[64] FAERS is one of the databases used for post-market surveillance. It contains voluntary submissions of feedback from patients, caregivers, and healthcare professionals, and mandatory submissions from manufacturers.[65] These include information on adverse event reports, mediation error reports, and product quality complaints resulting in adverse events.[66] While this is a useful channel for the FDA to receive concrete feedback from the market, there are limitations in the system due to the substantial quantity of information, duplicative reports, reports of differing quality and thoroughness, and unqualified data.[67] In response, the FDA has used AI to streamlined methods of extraction and utilization of the data.[68]

One pilot effort undertaken by the FDA is to use natural language process ("NLP") to convert the unstructured data flowing into FAERS into structured data, subsequently establishing connections between drugs and a specific medical condition, hepatic failure.[69] Another initiative led by FDA scientists in collaboration with researchers from Stanford University employed comparable techniques but with a slightly different analytical strategy.[70] These efforts have achieved success to some degree, uncovering previously undetected connections between liver failures and particular drug combinations.[71] The collaboration between the FDA and Stanford scientists has resulted in the production of a tool that promises to be pivotal in creating a system designed to efficiently allocate scarce resources towards improving post-market product surveillance and the safety issue identification.[72]

However, there are drawbacks in the method, primarily the difficulty to recognize the causal relationship between the drugs

[64] *Guidance, Compliance, & Regulatory Information*, U.S. Food & Drug Admin. (2023), https://www.fda.gov/drugs/guidance-compliance-regulatory-information.
[65] Engstrom et al., *supra* note 42, at 55.
[66] *Id.* (quoting *Questions and Answers on FDA's Adverse Event Reporting System (FAERS)*, U.S. Food & Drug Admin. (June 4, 2018), https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers).
[67] *Id.*
[68] *Id.*
[69] *Id.*
[70] *Id.*
[71] *Id.* at 56.
[72] *See id.*

and hepatic failure.[73] FEARS consists of data only on adverse events, meaning the model is trained exclusively on negative outcomes, which results in challenges when inferring the specific drug that causes the hepatic failure.[74] Also, the use of NLP on unstructured data may exacerbate the causal inference challenges, which can be dangerous, as inaccurate predictions could result in life-or-death consequences.[75] FDA officials, in acknowledgement of this weakness, conceded that the pilot project did not successfully produce results that are accurate enough to be deployed in practice.[76] Apart from focusing on algorithmic development to enhance the system, the FDA can also approach the issue from the origin, requiring manufactures to submit structured data so that NLP can produce more precise predictions.[77]

These initiatives have demonstrated the change in thinking of the regulatory framework from pre-market approvals to post-market surveillance accelerated by the development of AI. Historically, the FDA has been devoted in minimizing "Type I" errors, which involve approval of drugs that results in safety issues, at the expense of allowing corresponding "Type II" errors, caused by withholding drugs that may provide net safety benefits to the patients.[78] Post-market surveillance may uncover risks that are neglected in clinical trials, meaning Type II errors can be reduced without worsening Type I errors.[79] Consequently, the public may benefit from the improved product quality arising from the AI's constant monitoring of the firms.[80] Also, the use of this technology could foster innovation while encouraging institution participation in regulatory framework in post-market surveillance regime.[81]

2. *PHASE*. The PHASE protocol developed by the FDA serves as a method for characterizing newly discovered substances that

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[73] *Id.*
[74] *Id.*
[75] *Id.*
[76] *Id.*
[77] *Id.*
[78] Catherine M. Sharkey & Kevin M. K. Fodouop, *AI and the Regulatory Paradigm Shift at the FDA*, 72 Duke L.J. Online 86, 99 (2022).
[79] *See id.* at 105.
[80] *Id.* at 98.
[81] *Id.* at 97–98.

lack *in vitro* and *in vivo* data.[82] It is a computational model that was originally developed for characterizing fentanyl analogs and helps to assess risk of public safety that may be introduced by drugs.[83] The method can readily generate *in silico* binding profiles of any drugs and is comprised of three components that: (1) measure how the structural similarity of a compound to another controlled substance, (2) forecast the likely biological targets of a compound, and (3) provide an estimation of the compound's binding affinity at the receptor(s) of interest.[84] Due to the significant deficiency in *in vitro* or *in vivo* data on kratom, the *in silico* data generated by PHASE can prioritize compounds of concern and provide guidance on which biological targets should be tested initially *in vitro*, avoiding the expensive and time-consuming processes of testing all suspect compounds against all potential biological targets.[85]

In 2018, the FDA published a statement from Commissioner Gottlieb on the scientific evidence generated from PHASE analysis on kratom, a botanical substance, that has caught the FDA's attention due to the presence of opioid compounds.[86] The FDA has always aimed to tackle the issues of misuse and abuse of opioid drugs.[87] On February 4, 2016, the Opioid Action Plan was initiated in response to the growing concerns of opioid abuse while ensuring appropriate access to pain medications.[88] The plan includes broadening availability of abuse-resistant versions of opioid medications, authorizing more effective approaches for addressing opioid

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[82] Christopher R. Ellis et al., *Assessing the Structural and Pharmacological Similarity of Newly Identified Drugs of Abuse to Controlled Substances Using Public Health Assessment via Structural Evaluation*, 106 Clin. Pharmacol. & Ther. 116, 116 (2019).

[83] *Id.*

[84] *Id.* at 117–18.

[85] *Id.* at 119; Christopher R. Ellis et al., *Evaluating Kratom Alkaloids Using PHASE*, PLOS ONE, Mar. 3, 2020, at 1–2, https://doi.org/10.1371/journal.pone.0229646.

[86] Press Release, U.S. Food & Drug Admin., *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse* (Feb. 6, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds.

[87] *Opioid Medications*, U.S. Food & Drug Admin., https://www.fda.gov/drugs/information-drug-class/opioid-medications (Mar. 29, 2021).

[88] Ellis et al., *supra* note 82, at 116.

use disorder, preventing overdoes fatalities, and implementing measures to mitigate the surplus of opioids susceptible to misuse.[89]

The other chemical noted is kratom, a tropical tree native to Southeast Asia that has leaves that are chewed on or consumed as tea.[90] Currently, the FDA has approved no prescriptions or over-the-counter drug products containing kratom or two of its main chemical components, mitragynine and 7-hydroxymitragynine (7-OH-mitragynine)[91] While kratom has been identified as a potential therapeutic agent for a range of conditions such as pain, coughing, diarrhea, anxiety, depression, opioid use disorder, and opioid withdrawal symptoms,[92] its recreational use is prevalent in both the European Union and the United States. [93] In these regions, individuals commonly seek out kratom to attain a state of legally permissible euphoria, despite the inherent risks associated with its consumption..[94] Due to the risk of serious adverse events that could from consuming kratom, including liver toxicity, seizures, substance use disorder ("SUD"), and, in some rare cases, death, the FDA has consistently opposed its consumption.[95]

Nevertheless, there is insufficient scientific knowledge on kratom and have been few well-designed scientific studies involving the testing of kratom on humans.[96] There have only been some animal studies with kratom extracts containing mitragynine or 7-OH-mitragynine.[97] An interest in studying kratom has led the FDA's efforts in supporting related research for which development of PHASE represents a tremendous advance in this field.[98] PHASE offers a deeper understanding of the molecular structure of the chemical constituents of substances found in kratom, their behaviors

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[89] *Id.*

[90] Christopher R. Ellis et al., *Evaluating Kratom Alkaloids Using PHASE*, PLOS ONE, Mar. 3, 2020, at 2, 2 & 17 n.14, https://doi.org/10.1371/journal.pone.0229646.

[91] *FDA and Kratom*, U.S. Food & Drug Admin., https://www.fda.gov/news-events/public-health-focus/fda-and-kratom (Feb. 22, 2024).

[92] *Id.*

[93] Ellis et al., *supra* note 90, at 2.

[94] *Id.*

[95] *See FDA and Kratom*, *supra* note 91.

[96] *Id.*

[97] *Id.*

[98] *See* U.S. Food & Drug Admin., *supra* note 86.

inside the body and their potential effects on the brain.[99] In short, PHASE applies each of its components to *para*-fluoroisobutyryl fentanyl (FIBF), a synthetic opioid, of which overdose is associated with various deaths.[100] Further, the FIBF was provisionally classified as a schedule I substance under the Controlled Substances Act (CSA) on May 3, 2017, reflecting its high risk of abuse[101]

The first component of PHASE detects any structural similarity of the new drug with current schedule drug substances.[102] If the new drug is found to be "substantially similar" to a controlled substance in schedule I of II of the CSA, it is to be treated as a schedule I substance under the Federal Analogue Act.[103] Information on manually curated chemical structures of currently scheduled drugs are recorded in FDA's database, allowing street-drugs that may use multiple names or do not follow the naming conventions to be detected.[104] Results showed that the chemical structures of the 25 most prevalent compounds in kratom are structurally similar to the controlled opioid analgesics, such as morphine derivatives.[105] Next, the biological target prediction uses two software programs, SEAware and Clarity, to predict the potential binding targets of the 25 kratom alkaloids by adopting approaches, including ML techniques, such as random forest, support vector machine, and artificial neural networks.[106] Researchers concluded that 22 (including mitragynine) of the 25 compounds in kratom bind to mu-opioid receptors, which confirms that two of the five most prevalent compounds (including mitragynine) readily activates opioid receptors.[107] Researchers also found that some kratom compounds may bind to transporters and receptors that cause cardiovascular and neuropsychiatric responses.[108] This corroborates the FDA's

[99] *Id.*
[100] *See* Ellis et al., *supra* note 82, at 117.
[101] *Id.* at 116–17.
[102] *Id.* at 117.
[103] Controlled Substance Analogue Enforcement Act of 1986, 21 U.S.C § 813; Controlled Substances Act, 21 U.S.C. § 802(32)(A)(i).
[104] Ellis et al., *supra* note 82, at 117–18.
[105] U.S. Food & Drug Admin., *supra* note 86, at 3.
[106] Ellis et al., *supra* note 82, at 118; Ellis et al., *supra* note 90, at 4.
[107] U.S. Food & Drug Admin., *supra* note 86, at 3; *see also* Ellis et al., *supra* note 90, at 7–11 (discussing study findings in detail).
[108] Ellis et al., *supra* note 82, at 119.

previous warning of kratom's side effects, including seizures and respiratory depression.[109] The third component, prediction of binding affinity, uses molecular docking that is a type of virtual screen that analyzes the intermolecular interactions with a substance and the active site of the biological target.[110] Results confirmed that kratom has a strong binding affinity to mu-opioid receptors that is comparable to scheduled opioid drugs.[111] Based on this evidence, the FDA again justified its objection to kratom, stating confidently that compounds found in kratom can be called opioids.[112]

Nonetheless, critics of the FDA's continuing opposition to kratom argue that it is a safer substitute than opioid drugs, while others doubt the validity and credibility of evidence presented by PHASE.[113] More specifically, Marks argued that PHASE omitted some of the critical factors in determination of drug effects and potential for harm, including the phrase absorption, distribution, metabolism, and excretion.[114] Thus, just like how facial features and behaviors are not reliable factors in predicting future likelihood of committing criminal acts in police force, predictions based on chemical structures and binding affinity can be unreliable in predicting drug effects.[115] Further, it was argued that one of the software used in PHASE, Clarity, is trained on datasets that may contain bias, which could undermine the accuracy and credibility of the conclusions.[116] Marks pointed out that PHASE is not an adequate substitute for the eight-factor analysis which FDA traditionally adopted, including "complex historical epidemiological, and psychological factors"[117]

Acknowledging that the analysis is incomprehensive, it should be noted that these factors can always be added to the model along

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[109] U.S. Food & Drug Admin., *supra* note 86, at 3.
[110] Ellis et al., *supra* note 82, at 119.
[111] U.S. Food & Drug Admin., *supra* note 86, at 3.
[112] *Id.*
[113] *See* Maia Szalavitz, *The FDA Shouldn't Support a Ban on Kratom*, Sci. Am. (Aug. 12, 2021), https://www.scientificamerican.com/article/the-fda-shouldn-rsquo-t-support-a-ban-on-kratom/; Marks, *supra* note 11, at 1228.
[114] Marks, *supra* note 11, at 1229.
[115] *Id.* at 1230.the Food and Drug Administration ("FDA"
[116] *Id.* at 1231–32.the Food and Drug Administration ("FDA"
[117] *Id.* at 1231.the Food and Drug Administration ("FDA"

developments.[118] Thus, it may be too abrupt to discount the significance of PHASE, as it secures a means to provide rapid evaluation on newly identified drugs that lacks *in vitro* and/or *in vivo* data, preventing the public from potential risks to health.[119] Also, the PHASE protocol may be generalized to all types of drugs, though it was originally designed in the context of opioids and fentanyl derivatives.[120] Further, the protocol may serve as a seminal tool along the path of integrating AI into the hybrid human-machine review process, which may be more accurate and reliable than the traditional approach.[121]

3. *Virtual Family and Virtual Patients.* The twentieth century has presented the FDA with evolving challenges, including the changing threats to the public, rapidly developing and emerging cutting-edge technologies that create new safety risks, globalization of the public health sector, and the need to provide prompt and valuable feedback to consumers in an era characterized by an overwhelming volume of information.[122] In 2011, the FDA published a strategic plan that stated eight priority areas, of which four are associated with computational modelling and one focused on stimulating innovation in the sector titled "Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes."[123] In the statement, the FDA acknowledged the role of computational modelling in lowering evaluation costs for medical devices and enhancing the simulation of scenarios that might be impractical or dangerous for human testing.[124] The FDA Office of Science and Engineering Laboratories (OSEL) is devoted to transforming computational modelling from a scientific tool into a regulatory tool.[125]

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[118] *Cf.*
[119] *Id.*
[120] *Id.*
[121] Sharkey & Fodouop, *supra* note 78, at 93.
[122] Tina M. Morrison, Pras Pathmanathan, Mariam Adwan & Edward Margerrison, *Advancing Regulatory Science with Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories*, Frontiers Med., Sept. 25, 2018, at 1, 2.
[123] U.S. Food and Drug Admin., Advancing Regulatory Science at FDA 3 (2011), https://www.fda.gov/media/81109/download.
[124] *See id.* at 7–9.
[125] Morrison et al., *supra* note 122, at 2.

In pursuit of supporting the innovation of Digital Health Technologies (DHT), the FDA issued the AI/ML-Based Software as a Medical Device Action Plan in 2021 that presented a comprehensive approach to AI-enabled medical devices (a subset of DHT).[126] Recently, the FDA published another framework regarding the implementation of DHT in drug development where it expressly pointed out that AI and ML hold the promise of revolutionizing healthcare by extracting fresh and significant insights from the extensive data produced by other DHT.[127] Generally, the application of AI software can be sorted into two categories: those regulated as medical devices and those used to evaluate the safety and efficacy of other medical products.[128]

Examples of approved AI-enabled medical devices on patient-specific cardiovascular models include HeartFlow, which produces a 3D representation of patient coronary arteries and simulates blood circulation to forecast the fractional flow reserve.[129] Another example is the CardioInsight Mapping System that models patients' hearts and torsos to simulate electrical activity on the heart based on body surface recordings.[130] Also, in 2020, the FDA approved Caption Guidance, the first cardiac ultrasound software that utilizes AI to assist users in capturing images of patients' hearts that is eligible for diagnostic quality.[131] When mishandled or misunderstood, patient-specific models have the potential to subject individuals to unnecessary interventions or lead them to avoid life-saving procedures.[132] HeartFlow forecasts the outcomes of high-risk procedures that might otherwise be conducted if they

[126] U.S. Food and Drug Admin., Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan (2021), https://www.fda.gov/media/145022/download.

[127] U.S. Food and Drug Admin., Framework for the Use of Digital Health Technologies in Drug and Biological Product Development 10 (2023), https://www.fda.gov/media/166396/download?attachment.

[128] Marks, *supra* note 11, at 1237.

[129] Morrison, Pathmanathan, Adwan & Margerrison, *supra* note 122, at 6–7.

[130] *Id.* at 6.

[131] Press Release, U.S. Food & Drug Admin., FDA Authorizes Marketing of First Cardiac Ultrasound Software That Uses Artificial Intelligence to Guide User (Feb. 7, 2020), https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-first-cardiac-ultrasound-software-uses-artificial-intelligence-guide-user.

[132] Marks, *supra* note 11, at 1237.

were less expensive, less intricate, or safer.[133] The lack of safer alternatives likely justifies the use of HeartFlow in these cases .[134]

Conversely, models of virtual heart are also integrated into assessing the safety and effectiveness of medical devices, which speeds up the approval processes.[135] Since 2014, the FDA has devoted itself to research aimed at developing a human heart model that can be incorporated into evaluations of new medical devices and therapies through an ongoing collaboration with the French software company, Dassault Systèmes.[136] The SIMULIA Living Heart model designed by Dassault Systèmes includes clearly delineated anatomical features, encompassing internal structures like a heart valve as well as coronary arteries and veins, along with the nearby vascular system.[137] The model has been used to test the effectiveness of a virtually implanted medical device designed for the purpose of treating mitral valve regurgitation.[138]

Another virtual model that has wide application in the operation of the FDA is the Virtual Physiological Human (VPH), which has been in development since 2007 as a European Commission supported project,[139] and was included in the FDA's strategic plan.[140] VPH can be employed in two distinct areas. First, VPH can assist the fundamental understanding of physiology and its dysfunction. Second, VPH can help facilitate the individualization of medical decisions and development of new medical products by producing in silico methods.[141] Medical device regulatory evaluation usually involves review of scientific evidence from four models: animal data, laboratory data, human data, and data from computational

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[133] *Id.*

[134] *Id.*the Food and Drug Administration ("FDA"

[135] Brandi Vincent, *FDA Seeks Virtual Heart to Test Medical Devices*, Nextgov/FCW (Aug. 5, 2019), https://www.nextgov.com/emerging-tech/2019/08/fda-seeks-virtual-heart-test-medical-devices/158946/.

[136] *Id.*

[137] Karl D'Souza, *Technology to Transform Lives: The SIMULIA Living Heart Model*, NAFEMS BENCHMARK, July 2015, at 3, https://www.3ds.com/fileadmin/Industries/life-sciences/pdf/NAFEMS-Benchmark-Technology-to-Save-Lives-LHP-07–01–15.PDF.

[138] Marks, *supra* note 11, at 1237–38.

[139] *Id.* at 1236.the Food and Drug Administration ("FDA"

[140] U.S. Food & Drug Admin., *supra* note 123, at 13.

[141] .

modelling.[142] The FDA endeavors to cut reliance on animal and human data by using more data generated from virtual patients.[143] As of 2017, the Virtual Family has been used in over 160 FDA medical device submissions.[144]

The first Virtual Family initially published by the FDA online consists of highly detailed and anatomically correct whole-body models of an adult male, an adult female, and two children, developed on magnetic resonance imaging data of healthy volunteers.[145] They were intensively used in medical device submissions to analyze the amount of energy absorption in patients receiving Magnetic Resonance Imaging ("MRI").[146] An expanded version of the Virtual Family is the Computable Virtual Population developed collaboratively by the FDA and research groups all around the world, which consists of seventeen virtual humans varying in age from eight weeks to eighty-four years.[147]

Although virtual human models currently face certain limitations relating to blood vessels and nerve tissues, these issues will inevitably be perfected with the FDA's continued development efforts, and the benefit of the technology outweighs these limitations.[148] The application of Virtual Family allows manufacturers to run thousands of simulations with slight variations on innovative medical devices to capture different responses, which is unrealistic with traditional clinical trials due to the significant costs.[149] Apart from cost-saving, Virtual Family also benefits the agency because

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[142] Tina M. Morrison, Regulatory Advisor, U.S. Food & Drug Admin., Address at the FDA Science Writers Symposium: Using Modeling and Simulation for Medical Device Innovation - Virtual Patients for Regulatory Decision Making 7 (Sept. 18, 2015), https://www.fda.gov/files/science%20%26%20research/published/Using-Modeling-and-Simulation-for-Medical-Device-Innovation—Virtual-Patients-for-Regulatory-Decision-Making-by-Tina-M.-Morrison.pdf.

[143] *Id.*

[144] Marks, *supra* note 11, at 1238.

[145] U.S. Food & Drug Admin., *supra* note 141.

[146] Morrison, *supra* note 142, at 9.

[147] *Computable Virtual Population: Resolution at Its Limit*, IT'IS Found., https://itis.swiss/virtual-population/virtual-population/vip3 (last visited Mar. 9, 2024).

[148] *See* Andreas Christ et al., *The Virtual Family—Development of Surface-Based Anatomical Models of Two Adults and Two Children for Dosimetric Simulations*, 55 Physics Med. & Biology. N23, N35 (2010).

[149] Morrison, *supra* note 142, at 9.

it allows testing to be run under worst-case or difficult scenarios, augmenting the safety assessment of products.[150] Recognizing these advantages, the FDA is committed to developing and improving the virtual human models to create a future dominated or replaced with simulated clinical trials.

4. In Silico Clinical Trials ("ISCT"). With the development of the aforementioned VPH which is a critical component of ISCT, the FDA is heading towards a more AI-integrated regulatory framework. The exploration with ISCT began as early as 2011, when the VPH Institute introduced ISCT as a replacement for patient-specific models.[151] Later, the Avicenna Initiative, which established an extensive consensus-building process engaging academic, industrial, and regulatory experts, defined ISCT as "the use of individualized computer simulation in the development or regulatory evaluation of a medical product or medical device/medical intervention."[152] The consensus discussed the applications of *in silico* technologies in three macro-phases: design/discovery, pre-clinical assessment, and clinical assessment.[153]

The first case where the FDA approved the adoption of *in silico* simulation to replace animal testing occurred in 2008 when it approved an experiment that substituted dogs with a type I diabetes simulator to enhance the safety assessment of new artificial pancreas technologies.[154] Since then, the JDRF Artificial Pancreas Consortium, which initiated the project, has utilized it as a primary platform for testing new closed-loop control algorithms.[155] Another advancement was the mock submission to the FDA started by the Medical Device Innovation Consortium.[156] They formed a working group called "Clinical Trails Informed by Bench and Simulations,"

[150] Morrison, Pathmanathan, Adwan & Margerrison, *supra* note 122, at 6.
[151] Francesco Pappalardo, Giulia Russo, Flora M. Tshinuna & Marco Viceconti, *In Silico Clinical Trials: Concepts and Early Adoptions*, 20 Briefings in Bioinformatics 1699, 1700 (2019).
[152] Marco Viceconti, Adriano Henney & Edwin Morley-Fletcher, *In Silico Clinical Trials: How Computer Simulation Will Transform the Biomedical Industry*, 3 Int. J. Clin. Trials 37, 41 (2016).
[153] *Id.*
[154] *See* Eleni Bekiari et al., *Artificial Pancreas Treatment for Outpatients with Type 1 Diabetes: Systematic Review and Meta-Analysis*, 361:k1310 Brit. Med. J. at 1–2 (2018).
[155] Pappalardo, Russo, Tshinanu & Viceconti, *supra* note 151, at 1702.
[156] *Id.*

that consists of members from the industry and the FDA to construct a mock submission presenting and evaluating the virtual patient model.[157] The virtual patient model was used in a theoretical clinical study where the primary endpoint was a 5% failure rate within a 2-year period.[158] The study also assessed type I error and statistical power across various scenarios.[159] Another example is FDA's support of conducting safety assessments of MRI compatibility of pacemakers *in silico* since the approval of Medtronic Revo MRI pacemaker system in 2011.[160]

ISCT plays a critical role in enhancing the efficiency and effectiveness of each phase in clinical trials through optimizing drug dosage and safety assessments. Phase I trials serve two primary purposes: first, to assess the safety of the drug and second, to determine the appropriate dosage using a method known as "dose escalation."[161] This process aims to identify the optimal dosage that provides the desired therapeutic effect while avoiding potentially harmful levels of toxicity.[162] ISCT is useful here as it predicts the optimal dosage using mathematical approaches so that dosage escalations do not follow the traditional "trial and error" method.[163] The traditional Phase I trial usually involves few participants and thus raises issues with the biological variability of the tested subjects.[164] The adoption of ISCT would tackle this issue while highlighting particular issues related to particular diseases through reproduction.[165] Thus, ISCT enhances drug safety profiles and optimizes therapeutic effects by refining dosage levels.[166]

Phase II trials are aimed at confirming effectiveness of the drug, monitoring side effects, and further evaluating safety though experiments conducted on a larger group of volunteers with the

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[157] *Id.*
[158] *Id.*
[159] *Id.*
[160] Owen Faris & Jeffrey Shuren, *An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials*, 376 N. Engl. J. Med. 1350, 1351 (2017).
[161] Pappalardo, Russo, Tshinanu & Viceconti, *supra* note 151, at 1703.
[162] *Id.*
[163] *Id.*
[164] *Id.* at 1703–04.
[165] *Id.* at 1704.
[166] *Id.*

medical condition that the drug is designed to treat.[167] However, the number of enrolled patients is still relatively limited making it challenging to reveal common adverse effects.[168] In this context, ISCT could be employed to identify virtual patients that could serve as representative examples displaying adverse effects.[169] Such an approach could facilitate the detection of potential concerns prior to embarking on a comprehensive Phase III trial.[170] Due to the primarily mechanistic and subject-specific nature of ISCT models, they possess significant explanatory capabilities, aiding in the identification of strategies to advance drug development.[171]

Phase III trials are designed to assess the effectiveness of a new drug and its clinical practice value.[172] This phase is conducted at a larger scale and as a result is potentially the most expensive, time-consuming, and challenging phase.[173] First, introducing ISCT assists in reducing, refining, and partially replacing animal and human experimentation.[174] When adopted together with imaging and sensing, ISCT produces surrogate measurements to provide informative assessment on biomedical that would be impossible to obtain directly without invasive means.[175] Second, ISCT could reduce the number of animals or humans required in the experimentation while cutting the duration of such involvement.[176] For example, if the surrogate measurement enhances the experimental consistency of the *in vivo* study, the necessary sample size needed to achieve statistical significance would be reduced.[177] Third, ISCT adoption could partially replace animals or humans in a trial which is illustrated in the example of FDA approval on artificial pancreas technologies.[178] Lastly, a potential use of ISCT could be relevant

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[167] *Id.*
[168] *Id.*
[169] *Id.*
[170] *Id.*
[171] *See id.*
[172] *Id.*
[173] *Id.*
[174] Viceconti, Henney & Morley-Fletcher, *supra* note 152, at 41–42.
[175] *Id.* at 42.
[176] *Id.*
[177] *Id.*
[178] *Id.*

in situations where conventional clinical trials may be too risky.[179] To illustrate, osteogenesis imperfecta appears in one in 20,000 newborns in the United States, which is 200 OI patients per year.[180] Thus, to conduct Phase III clinical trials on 2000 osteogenesis imperfecta patients of the same age would be unsustainable and risky, but it could be achieved with ISCT.[181]

In addition to ISCT's benefits for the technical dimensions of clinical studies, the application of this technology offers advantages that extend well beyond the immediate trial framework. The replacement of the control arms with ISCT eliminates the need to give participants placebos, so every volunteer can be assigned to the intervention arm receiving experimental therapy.[182] The suggestion to employ simulated trials for both the control and intervention groups may, paradoxically, limit the opportunities available to patients. In addition, using simulated control groups can address the issue of unblinding, where study participants realize they were given placebos.[183]

The use of simulated trials may also contribute to racial equity.[184] Over time, racial minorities have suffered mistreatment and exploitation in the realm of scientific study.[185] These groups may not have been adequately represented in clinical experiments, leading to ongoing inequalities in modern healthcare and medical research.[186] This absence of diversity is not only unjust, but it also compromises the validity of trial outcomes, limits the applicability of the findings, and poses risks to patients.[187] Besides, simulated trials could enhance studies involving human participants by using

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[179] *Id.*

[180] *Id.* Osteogenesis imperfecta is an uncommon genetic disorder affecting the bones that could last lifelong, characterized by patients having bones that are either too soft, abnormally shaped, or accompanied by additional complications. See *Osteogenesis Imperfecta in Children*, University of Rochester Medical Center: Health Encyclopedia, https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=85&contentid=p00123 (last visited Mar. 9, 2024).

[181] Viceconti, Henney & Morley-Fletcher, *supra* note 152, at 42.

[182] Marks, *supra* note 11 at 1239.

[183] *Id.*the Food and Drug Administration ("FDA" at 1240.

[184] *Id.*

[185] *Id.*

[186] *Id.*the Food and Drug Administration ("FDA" at 1240–41.

[187] *Id.*the Food and Drug Administration ("FDA" at 1241.

virtual human counterparts, which would be especially beneficial for research on rare diseases further enhancing the generalizability of the results because finding individuals with required conditions can be difficult.[188] However, it should be noted that utilizing algorithmic forecasts in lieu of clinical information may give rise to novel forms of prejudice and engender unforeseen hazards.[189]

Another major obstacle to simulated trials is the use of surrogate endpoints, which would substantially undermine their credibility. Endpoints are measurements of clinical trial efficacy that are categorized into true endpoints and surrogate endpoints. True endpoints include health status, survival, and cost, while surrogate endpoints are measurements including physiological, laboratory, or test results that predict events.[190] Consequently, even significant medical occurrences like myocardial infarctions and strokes can be viewed as surrogate indicators given that their indirect impact on key health outcomes such as overall well-being, longevity, and associated expenses.[191] As surrogate endpoints serve as a readily quantifiable metric that can be observed within a relatively brief period, they are employed as a substitute for the actual endpoints of interest, which creates uncertainty regarding the causal relationship between the occurrence of an event and an outcome.[192]

A legitimate surrogate marker ought to exist within the causal trajectory leading to a genuine endpoint.[193] Ascertaining causality demands an in-depth comprehension of the disease's pathophysiology, representing a more stringent requirement than merely identifying a correlation.[194] Should a correlation exist without underlying causation, the connection between the surrogate and the outcome could be subject to confounding variables.[195] The Bradford Hill criteria for establishing causality consists of nine factors,

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[188] *Id.*
[189] *Id.*
[190] William S. Weintraub, Thomas F. Lüscher & Stuart Pocock, *The Perils of Surrogate Endpoints*, 36 Eur. Heart J. 2212, 2212 (2015).
[191] *Id.*
[192] *See id.*
[193] *Id.* at 2214.
[194] *Id.*
[195] *Id.*

including the temporal relationship requirement that a cause must come before the effect.[196] Thus, surrogate variables are only reliable when situated along a causal pathway before the intervention that elicits observable effects on both the surrogate and the endpoint.[197]

The FDA officially recognizes both blood pressure and low-density lipoprotein (LDL) cholesterol as surrogate endpoints in clinical trials, commonly used to forecast the effectiveness of a particular treatment in reducing the occurrence of cardiovascular diseases.[198] Nonetheless, a multitude of cases demonstrate contrary outcomes.[199] Specifically, studies targeting cholesterol levels reveal that elevations in high-density lipoprotein (HDL) cholesterol are inversely associated with cardiovascular events that can lead to increased mortality rates.[200]

Consequently, the relationship between real-world surrogate markers and clinical endpoints frequently entails a degree of uncertainty.[201] This issue could be further exacerbated when dealing with virtual endpoints as they are algorithmically derived and serve as surrogates for their real-world counterparts. Accordingly, the epistemological validity of virtual endpoints is constrained.[202] ISCT has been criticized for its failure to formulate novel causal principles in and of themselves, although it can leverage existing knowledge of established causal laws to provide insights into the variability of results.[203] A primary reservation pertains to the foundational information upon which ISCT is built and the stability of such knowledge.[204]

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[196] *Id.*
[197] *Id.* at 2215.
[198] *Id.* at 2214.
[199] AIM-HIGH Investigators et al., *Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy*, 365 New. Engl. J. Med. 2255, 2255 (2011); Stephan Fichtlscherer et al., *Differential Effects of Short-Term Lipid Lowering with Ezetimibe and Statins on Endothelial Function in Patients with CAD: Clinical Evidence for "pleiotropic" Functions of Statin Therapy*, 27 Eur. Heart J. 1182, 1182 (2006).
[200] Weintraub, Lüscher & Pocock, *supra* note 190, at 2214.
[201] *Id.* at 2216–17.
[202] Marks, *supra* note 11, at 1244.
[203] Barbara Osimani, Marta Bertolaso, Roland Poellinger & Emanuele Frontoni, *Real and Virtual Clinical Trials: A Formal Analysis*, 38 Topoi 411, 420 (2019).the results of a Randomised Clinical Trial (RCT
[204] *Id.* at 421.the results of a Randomised Clinical Trial (RCT

A further impediment to the credibility of simulated trials stems from the absence of universally accepted guidelines or benchmarks within the industry.[205] This issue is compounded by the inherent conflicts of interest that arise when industry participants develop computational models primarily to substantiate the safety and effectiveness of their own offerings.[206] Insofar as computer algorithms remain proprietary and opaque, with manufacturers withholding access to source code and training data, such obscurity could potentially mask biases that benefit industry participants.[207]

After discussing the technologies and identifying potential risks associated with their use, the next section addresses how administrative law principles apply to the FDA's development of computational models and simulations.

III. Problems on Existing Regulatory Oversight

A. The Black Box Issue

As automation of conventional decisions intensifies and is supported by an ever evolving and intricate data infrastructure, apprehension regarding the reliability of these mechanisms is heightening.[208] Some academics contend that escalating reliance on data-decision making could culminate in an "algocracy," where algorithm-driven processes inherently limit human involvement and understanding in public decision-making processes.[209] This apprehension is magnified in the context of deep learning (DL), a subset of AI rooted in profound neural networks, which remains enigmatic and beyond the realm of human apprehension.[210] This is referred to as the black box problem, which potentially leads to the issue of opacity in the process of administrative decision making. Scholars perceive the "black box" issue as one of the "triple

[205] Marks, *supra* note 11, at 1245.
[206] *Id.*the Food and Drug Administration ("FDA"
[207] *Id.*the Food and Drug Administration ("FDA"
[208] Von Eschenbach, *supra* note 61, at 1608.
[209] John Danaher, *The Threat of Algocracy: Reality, Resistance and Accommodation*, 29 Phil. Tech. 245, 246 (2016).
[210] Von Eschenbach, *supra* note 61, at 1608.

barriers" impeding public accountability, standing alongside trade secrets, nondisclosure agreements, and intricate technicalities.[211]

Opponents of this idea consider this phenomenon as an inherent characteristic of algorithmic forecasts that does not warrant alarm.[212] Some even posit that algorithms enhance organizational transparency.[213] They argue that by standardizing agency procedures, algorithms offer a more consistent approach compared to the often capricious nature of human decision-making, thus rendering the system more discernible and foreseeable.[214] While it may be acknowledged that governmental transparency is not universally favorable[215], past apprehensions, multiple instances of algorithmic prejudice, and prevalent disparities in social and healthcare realms underscore the crucial need for championing transparency in algorithms within the public health sphere.[216]

The healthcare industry has been historically marred by racial disparities.[217] Imbalances stemming from flawed data collection methodologies rooted in racial injustice can introduce potential biases in the data employed for model training.[218] This peril is termed by Deborah Hellman as the "compounding injustice principle."[219] Ultimately, these apprehensions underscore the demand for transparency within the system.

In the United States, issues relating to transparency are often governed by the Freedom of Information Act (FOIA)[220] and some sections of the Administrative Procedure Act (APA).[221] Collectively,

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[211] Marks, *supra* note 11, at 1247.
[212] *See id.*the Food and Drug Administration ("FDA"
[213] *Id.* at 1247.the Food and Drug Administration ("FDA"
[214] *Id.*the Food and Drug Administration ("FDA" at 1247–48.
[215] *See, e.g.,* Rishma R. Vedd, H. Drew Fountaine, David Liu & Anne Wu, *FDA Drug Approval and Its Relation to a Pharmaceutical Company's Stock Price*, 24 J. Fin. & Acct. 1, 3 (suggesting it could be favorable to keep information about FDA drug approvals confidential until official announcements in order to minimize the potential for insider trading).
[216] Marks, *supra* note 11, at 1250–51.
[217] Deborah Hellman, *Big Data and Compounding Injustice*, 21 J. Moral Phil. (forthcoming 2024).
[218] *See id.*
[219] *Id.*
[220] Freedom of Information Act, 5 U.S.C. § 552 (1967).
[221] Administrative Procedure Act, 5 U.S.C. § 500 (1946).

these laws establish a foundational mechanism enabling citizens to understand the actions and intentions of the government. Specifically on the issue of transparency, agencies are required to clearly articulate their decisions, provide reasons behind such decisions, and ensure that evidence underpinning these decisions is available to the public.[222] However, the inherent obscurity of FDA decision making based on "black box" software models could potentially reverse progress and introduce obfuscation.

Under APA, an arbitrary and capricious criterion mandates that government agencies provide a cogent justification for its decisions, establishing a logical link between the facts underlying the resultant decision.[223] The test for "arbitrary and capricious" is well established in the 1983 Supreme Court case *Motor Vehicle Manufacturers Association v. State Farm*.[224] As scholars have noted, when computational systems operationalize a model, the law still demands a cogent rationale to guarantee that the "ultimate responsibility for the policy decision remains with the agency rather than the computer."[225] However, subsequent cases suggest that when courts scrutinize such scientific judgments, in contrast to basic factual determinations, they should exercise deference and restraint.[226] Certainly, the PHASE protocol has faced criticism.[227] Detractors contend that while its methodology may appear advanced and commendable on the surface, deeper investigation reveals limited depth.[228] Such mistrust towards algorithmic determinations could jeopardize public health.[229]

Beyond the requisite provision of comprehensive justifications to pass the "arbitrary and capricious" scrutiny, agencies face additional standards that emphasize the necessity to unveil the

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[222] Cary Coglianese & David Lehr, *Regulating by Robot: Administrative Decision Making in the Machine-Learning Era*, 105 Geo. L.J. 1147, 1205–06.
[223] *Id.* at 1207.
[224] Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 42–43 (1983).
[225] Coglianese & Lehr, *supra* note 222, at 1208.
[226] *Id.*
[227] Marks, *supra* note 11, at 1209.
[228] *Id.* at 1249.the Food and Drug Administration ("FDA"
[229] *Id.*the Food and Drug Administration ("FDA"

analytical foundation behind their determinations.[230] The Office of Management and Budget issued the Circular A-4 which establishes guidelines for undertaking regulatory impact assessments, mandating agencies to "meticulously record the assumptions and methodologies employed in the analysis, address the uncertainties tied to the estimates, and make available to the public the pertinent data and foundational analysis".[231] However, it offers leeway for circumstances where "it may often be impractical or even impermissible or unethical to apply the reproducibility standard to [certain] data." This exception is also seen in FOIA as the law allows agencies to withhold data that falls under the category of trade secrets or confidential business information, as well as information gathered for law enforcement purposes.[232]

Presumably, these exceptions would permit the FDA to retain confidential data, given that their role falls under the purview of law enforcement, encompassing regulatory inspections and audits of administrative infractions.[233] The FDA's data might also qualify for protection under trade secrets and confidential business information provisions, especially if the program is developed in collaboration with a private company under contract.[234] Considering these exemptions, several agencies have proactively endeavored to enhance the transparency of their algorithmic forecasts.[235] Clearly, the U.S. Patent and Trademark Office (PTO) has demonstrated its aversion to "black box" algorithms.[236] For example, the PTO decided to not renew a contract with AI Patents, a company that creates patent search algorithms, due to disputes concerning complete transparency.[237] Another agency, the Environmental Protection Agency (EPA), has adopted a molecular modeling platform akin to the FDA's, called ToxCast.[238] The EPA has a marked preference

[230] Coglianese & Lehr, *supra* note 222, at 1209.
[231] *Id.*
[232] *Id.* at 1210.
[233] *Id.* at 1210–11.
[234] *Id.*
[235] Marks, *supra* note 11, at 1252–53.
[236] *Id.*the Food and Drug Administration ("FDA"
[237] *Id.*the Food and Drug Administration ("FDA"
[238] *Id.* at 1208.the Food and Drug Administration ("FDA"

for employing nonproprietary computer models when possible.[239] And contrary to the FDA, the EPA makes its models accessible to the public and provides an "owner's manual" to aid users in understanding and operating the system.[240]

Moreover, while the APA aims to bolster transparency in decision-making via the notice-and-comment provision,[241] certain agency publications might sidestep this process, given that not all agency activities fall under the legislative category. The FDA is notably adept at circumventing the process by primarily releasing recommendations in the form of industry guidance, which is, on the surface, nonbinding.[242] This approach enables the agency to promulgate de facto regulations while eluding specific procedural checks and balances.[243] While the Food and Drug Modernization Act of 1997 mandates public involvement when the FDA releases significant guidance, there isn't a compulsory stipulation for the FDA to address public feedback.[244] Former FDA commissioner Gottlieb's pronouncement regarding the PHASE protocol could potentially fall under the classification of guidance, particularly if it pertains to the design and testing of regulated products and/or the assessment or approval of associated submissions.[245] Nevertheless, the FDA could contend that Gottlieb's declaration does not qualify as guidance, positioning it as press materials, editorial content, or general information disseminated to consumers—categories which are exempted from the agency's prescribed definition of guidance.[246]

As agencies navigate into the era of machine learning, they may continue to make use of these established exemptions, even in scenarios beyond the realm of algorithmic predictions.[247] Consequently, there is a pressing need for legal frameworks to

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[239] *Id.*the Food and Drug Administration ("FDA"

[240] *Id.*the Food and Drug Administration ("FDA"

[241] *See* Cary Coglianese, Heather Kilmartin & Evan Mendelson, *Transparency and Public Participation in the Rulemaking Process: Recommendations for the New Administration*, 77 Geo. Wash L. Rev. 924 (2009).

[242] Marks, *supra* note 11, at 1254.

[243] *Id.*the Food and Drug Administration ("FDA"

[244] *Id.*the Food and Drug Administration ("FDA"

[245] *Id.* at 1254–55.the Food and Drug Administration ("FDA"

[246] *Id.* at 1255.the Food and Drug Administration ("FDA"

[247] Coglianese & Lehr, *supra* note 222, at 1213.

evolve, ensuring agencies remain bound, or at minimum, strongly encouraged, to release an adequate amount of information.[248] Such disclosures are pivotal to demystifying what might initially be perceived as an enigmatic analytical approach, guaranteeing alignment with the current principles of open and transparent governance.[249]

Beyond the realm of federal statutes, the judiciary holds significant importance, as courts are poised to address the myriad ways agencies utilize algorithms. The APA empowers courts with the discretion to review final agency actions.[250] It mandates that the agency should review the pertinent data and provide a coherent justification for its decisions, ensuring a logical link between the evidence gathered and the decisions taken.[251] Scholars such as Danielle Citron have expressed concern regarding the judiciary's inability to adapt to agencies that increasingly use algorithms in their decision making.[252] Specifically, courts might struggle to identify the precise rules being implemented in particular cases.[253]

Fortunately, the emergence of "explainable AI" (xAI) holds promise in addressing the challenges posed by the black box nature of certain algorithms. xAI represents a variety of initiatives aimed at elucidating or assisting humans in understanding the manner in which a specific machine learning model arrives at its conclusion.[254] xAI can be constructed utilizing the exogenous approach, which offers pertinent details to users about the model's

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[248] *Id.*the Food and Drug Administration ("FDA"

[249] *Id.*the Food and Drug Administration ("FDA"

[250] 5 U.S.C. § 702 (2012).

[251] Ashley Deeks, *The Judicial Demand for Explainable Artificial Intelligence*, 119 Colum. L. Rev. 1829, 1839–40 (2019).

[252] *See* Danielle Keats Citron, *Technological Due Process*, 85 Wash. U. L. Rev. 1249 (2008).2024

[253] Deeks, *supra* note 251, at 1840–41.

[254] *Id.* at 1834." making it difficult to identify how and why the algorithms reach particular decisions, recommendations, or predictions. Yet judges are confronting machine learning algorithms with increasing frequency, including in criminal, administrative, and civil cases. This Essay argues that judges should demand explanations for these algorithmic outcomes. One way to address the "black box" problem is to design systems that explain how the algorithms reach their conclusions or predictions. If and as judges demand these explanations, they will play a seminal role in shaping the nature and form of "explainable AI" (xAI

functionality through external, independent methods.[255] Alternatively, there is the decompositional approach which endeavors to clarify or emulate the model's inherent reasoning process.[256] . Given this context, courts, as crucial participants within the legal system, play a pivotal role in influencing the development and implementation of xAI, including decisions about when, how, and in what manner it should be deployed.[257] Moreover, it's vital for these judicial entities to proactively support the adoption of xAI in relevant cases, thereby ensuring that AI's decision-making processes are transparent and accountable, particularly in legal contexts where understanding the rationale behind AI-generated outcomes is essential for fairness and justice.[258]

Moreover, recent research has pioneered novel methodologies that convert the opaque nature of deep neural networks into their shallower, transparent counterparts.[259] These white-box networks are more intelligible to humans, offering an opportunity to enhance the decision-making process by shedding light on the inherent logic behind them. The finding introduces an algorithmic method to determine the weights of values, thus elucidating the precise, localized functional correlation between the input and output

[255] *Id.* at 1834–35." making it difficult to identify how and why the algorithms reach particular decisions, recommendations, or predictions. Yet judges are confronting machine learning algorithms with increasing frequency, including in criminal, administrative, and civil cases. This Essay argues that judges should demand explanations for these algorithmic outcomes. One way to address the "black box" problem is to design systems that explain how the algorithms reach their conclusions or predictions. If and as judges demand these explanations, they will play a seminal role in shaping the nature and form of "explainable AI" (xAI

[256] *Id.*" making it difficult to identify how and why the algorithms reach particular decisions, recommendations, or predictions. Yet judges are confronting machine learning algorithms with increasing frequency, including in criminal, administrative, and civil cases. This Essay argues that judges should demand explanations for these algorithmic outcomes. One way to address the "black box" problem is to design systems that explain how the algorithms reach their conclusions or predictions. If and as judges demand these explanations, they will play a seminal role in shaping the nature and form of "explainable AI" (xAI

[257] Marks, *supra* note 11 at 1837.

[258] Deeks, *supra* note 250 at 1834.

[259] Mattia Jacopo Villani & Nandi Schoots, *Any Deep ReLU Network Is Shallow*, 1 (2023), http://arxiv.org/abs/2306.11827 (last visited Mar. 19, 2024).

variables.[260] While there are current constraints limiting its adaptability primarily to smaller models, ongoing advancements may soon make it universally applicable across all model sizes.[261] This has the potential to address the foundational challenge of transparency in neural networks.

B. Emphasis on Cybersecurity and Privacy

In this rapidly advancing technological era, the interrelated issues of cybersecurity and privacy have become increasingly pronounced. For instance, if a cybercriminal successfully breaches a hospital's medical system, gaining access to confidential patient information, they could potentially monetize this data by selling it or use it to extort the hospitals.[262] An April 2020 study by the International Criminal Police Organization (Interpol) highlighted that the vulnerabilities were further amplified during the COVID-19 pandemic, given the critical role hospitals play in patient care during such crisis.[263] Another peril linked to the cybersecurity of medical devices is the potential for hackers to endanger patients directly, either by manipulating the dosage of medications or by tampering with electric currents.[264] The interconnectedness and interoperability of medical devices in healthcare environments such as hospitals imply that a compromise in one system could likely lead to disruptions in others, potentially causing serious disruptions to the entire health system.[265] At the 2015 BlackBerry Security Summit, an ethical hacker named Graham Murphy vividly demonstrated this risk by successfully hacking into a LifeCare PCA

[260] *Id.* at 9.
[261] *Id.*
[262] Peter Littlejohns, *The Challenge of Embedding Security and Privacy into a Medical Device*, NS Med. Devices (Nov. 12, 2020), https://www.nsmedicaldevices.com/analysis/medical-device-security-challenge/..
[263] *Id.*
[264] *Id.*
[265] David DiMolfetta, *FDA Shores up Cybersecurity Requirements for Medical Devices*, Wash. Post (May 18, 2023, 6:51 AM), https://www.washingtonpost.com/politics/2023/05/18/fda-shores-up-cybersecurity-requirements-medical-devices/.12,9]]},"issued":{"date-parts":[["2023",5,18]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

pump, and administering a lethal dose of morphine into an empty glass for the audience to see.[266]

Following this demonstration, the FDA became acutely aware of the potential risks and has since been proactively working to bolster the cybersecurity measures surrounding medical devices; [267] however, as the devices grow in complexity, they become more susceptible to cyberthreats. [268] In 2016, FDA promptly issued guidance directed at medical device manufacturers, urging them to tackle cybersecurity concerns.[269] The FDA also released the "Medical Device Cybersecurity Regional Incident Preparedness and Response Playbook," which provides healthcare organizations with guidelines to enhance their readiness for such incidents.[270] Additionally, the FDA offers manufacturers avenues to address patient safety concerns on a broader scale.[271] The FDA has also collaborated with other institutions such as the International Medical Device Regulators Forum (IMDRF) in publishing guidance to manufacturers on cybersecurity, and the Healthcare and Public Health Sector Coordinating Council (HSCC) in the development of the Medical Device and Health IT Joint Security Plan.[272]

A notable initiative to address cybersecurity concerns was the amendment of the FDCA, incorporating section 524B, titled "Ensuring Cybersecurity of Devices. This addition was facilitated through the passage of the Consolidated Appropriations Act, 2023.[273] The Act's comprehensive legislation codifies the FDA's prior guidelines for medical device firms into statutory requirements and allocates $5 million to the FDA for the recruitment of personnel for its enforcement.[274] Prior to the amendment, the FDA had merely provided guidelines which were not binding. However,

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[266] Littlejohns, *supra* note 262.

[267] *Cybersecurity*, U.S. Food & Drug Admin., https://www.fda.gov/medical-devices/digital-health-center-excellence/cybersecurity (last visited Mar. 2, 2024).

[268] DiMolfetta, *supra* note 265 ("Medical devices face potentially greater cyberthreats as the devices become more complex").

[269] U.S. Food & Drug Admin., *supra* note 267..

[270] *Id.*

[271] *Id.*

[272] *Id.*

[273] Pub. L. No. 117–328 136 Stat. 4459 (2022).

[274] DiMolfetta, *supra* note 265.

after the amendment, in March 2023, the FDA instituted a binding requirement mandating that all new medical device submissions incorporate a plan addressing the "surveillance, identification, and resolution" of cybersecurity issues.[275] Additionally, manufacturers must establish a mechanism ensuring "adequate confidence" in the safety of the respective device.[276] Manufacturers are also required to submit a software bill of materials, detailing the code, tools, processes, and other components that constitute the software.[277]

While the FDA has adopted this new protocol for regulatory decisions concerning medical devices, applications submitted prior to March 30, 2023 were not affected by it.[278] Also, some critics suggested that many of the leading medical device manufacturers and providers already adhered to the suggested security and safety guidelines prior to their formal introduction and therefore the binding protocol did not actually make a difference.[279]

Another closely linked concern to cybersecurity in this under-regulated domain of AI is the matter of privacy. Privacy regulations primarily stem from the Privacy Act of 1974[280] and the Code of Federal Regulations (CFR).[281] Nevertheless, it is worth mentioning that these regulations do not specifically target the application of AI in medical devices.[282] Given the swift proliferation

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[275] *Cybersecurity in Medical Devices: Refuse to Accept Policy for Cyber Devices and Related Systems Under Section 524B Of the FD&C Act; Guidance for Industry and Food and Drug Administration Staff; Availability*, 88 Fed. Reg. 19148 (announced Mar. 30, 2023)

[276] Jennifer Korn, *FDA requires medical devices be secured against cyberattacks*, CNN Bus. (Mar. 29, 2023, 3:36 PM), https://edition.cnn.com/2023/03/29/tech/fda-medical-devices-secured-cyberattacks/index.html.{\\scaps CNN Business}, Mar. 29, 2023, https://edition.cnn.com/2023/03/29/tech/fda-medical-devices-secured-cyberattacks/index.html (last visited Nov 9, 2023

[277] DiMolfetta, *supra* note 265.

[278] Veronica Salib, *Understanding the FDA Medical Device Cybersecurity Protocols*, LifeSciencesIntelligence (Apr. 25, 2023), https://lifesciencesintelligence.com/features/understanding-the-fda-medical-device-cybersecurity-protocols..

[279] *Id.*

[280] Privacy Act of 1974, 5 U.S.C. § 552a.

[281] Protection of Privacy, 21 C.F.R. § 21 (1977).

[282] Holly Fechner & Matthew S. Shapanka, *U.S. Artificial Intelligence Policy: Legislative and Regulatory Developments*, Covington & Burling LLP (Oct. 20, 2023), https://www.cov.com/en/news-and-insights/insights/2023/10/us-artificial-intelligence-policy-legislative-and-regulatory-developments; Daniel J. Felz, Kimberly Kiefer

of AI systems, there is a pressing necessity for the FDA to craft rules that squarely tackle the concerns within this distinct context, and not to defer powers to other regulatory departments.[283]

As the United States worked to advance towards a more comprehensive regulation of AI, in 2022, the White House unveiled the "Blueprint for an AI Bill of Rights," identifying privacy as one of the five core principles in designing such regulatory regime.[284] The Blueprint emphasizes the importance of embedding privacy considerations directly into the formulation of any AI policies.[285] At the core of protecting privacy is the principle of obtaining consent.[286] The Blueprint mandates that AI system designers, developers, and users obtain individuals' permission when handling their personal data.[287] On this front, in August 2032, the FDA released its guidance, titled "*Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors*," which was a notable advancement in setting guidelines for obtaining informed consent in clinical trials.[288]

The FDA's guidance provides that informed consent should not be viewed narrowly as obtaining signatures on the consent form, as this is only one part of the consent process.[289] Instead, an informed consent should be obtained after the prospective subject is provided with adequate information about the clinical investigation prior to enrollment, and should include assisting the subject to comprehend the information.[290] This guideline effectively addresses some of the prevalent ambiguities related to securing informed

Peretti, & Alysa Austin, *AI Regulation in the U.S.: What's Coming, and What Companies Need to Do in 2023*, Alston & Bird LLP (Dec. 9, 2022), https://www.alston.com/en/insights/publications/2022/12/ai-regulation-in-the-us.

[283] David W. Opderbeck, *Artificial Intelligence in Pharmaceuticals, Biologics, and Medical Devices: Present and Future Regulatory Models*, 88 Fordham L. Rev. 553, 577 (2019).

[284] White House Off. of Sci. & Tech. Pol'y, *Blueprint for an AI Bill of Rights*, (Oct. 2022), https://www.whitehouse.gov/wp-content/uploads/2022/10/Blueprint-for-an-AI-Bill-of-Rights.pdf.

[285] *Id.*

[286] *Id.* at 6.

[287] *Id.*

[288] U.S. Food & Drug Admin., *Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors* (Aug. 2023), https://www.fda.gov/media/88915/download.

[289] *Id.*

[290] *Id.*

consent, particularly concerning children and subjects who do not speak English.[291]

However, the guidelines do not encompass other AI-related areas that need regulation, such as the "notice and explanation" principle. This principle, as pointed out in the Blueprint, asserts that individuals should be informed when an automated system is in operation and individuals should be able to comprehend how and why the system influences any outcomes that affect them.[292] Indeed, this poses potential challenges in the workings of the FDA. Theoretically, if the FDA approves a drug, it has implications for a broad swath of the population, especially for those who are prescribed that specific medication. Without clear "notice and explanation" mechanisms in place, individuals might not fully understand or be aware of the automated processes and AI-driven systems that played a role in the approval of that drug. This can lead to questions about transparency, trust, and the overall efficacy of the drug approval process. Nonetheless, determining the depth of information about the AI process to provide to patients, and identifying the appropriate timing for such disclosures, presents its own set of challenges. Moreover, another suggestion in the Blueprint emphasizes the provision of a human alternative, which would allow individuals to opt-out from automated systems.[293] However, for simulated clinical trials, this does not seem like a practical alternative as the product has already undergone testing and received approval with AI involvement by the time it is released to customers.

C. Intellectual property

The creation of novel drugs and AI systems, whether integrated into drug development or embedded in medical devices, demands significant investment. Hence, companies often seek protection through intellectual property laws.[294] These laws provide a competitive edge by restricting rivals from accessing specific

[291] *Id.*

[292] White House Off. of Sci. & Tech. Pol'y, *supra* note 284.

[293] *Id.* at 7.

[294] *See* Opderbeck, *supra* note 283, at 584; Katarina Foss-Solbrekk, *Three Routes to Protecting AI Systems and Their Algorithms Under IP Law: the Good, the Bad and the Ugly*, 16 J. Intellect. Prop. L. & Pract. 247 (2021)..

innovations, ensuring a better return on the company's investment. As the adoption of AI systems in the healthcare sector accelerates, intellectual property will attain a significance comparable to that of drug chemical compositions.[295] Various intellectual property tools can be employed to protect AI applications, including patents, copyrights, design rights, and trade secrets. Yet, with the swift rise of AI innovation, there has been a surge in legal disputes surrounding these protections.[296] In general terms, design rights may not be the most suitable form of protection for AI applications, as they primarily safeguard the design of a graphical user interface rather than the underlying AI invention itself.[297] On the other hand, copyrights may provide stronger protection against direct forms of copying, like verbatim coding; however, they do not shield the underlying concepts, which can be easily bypassed.[298] In contrast to previous methods, patents are generally more favored and have indeed been utilized as a tool to safeguard AI inventions at present.[299]

A nuanced intellectual property concern emerges from the creation of the Virtual Family and Virtual Patient.[300] While the FDA has provided guidelines regarding the reliability of computational models employed in the creation and regulatory submission of medical devices, there remains an absence of clear direction concerning the ownership or origin of the data used in these models.[301] Manufacturers sometimes recruit clinical research organizations to conduct clinical trials due to the expenses and

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[295] Opderbeck, *supra* note 283 at 584.

[296] Christopher J. Valente et al., *Recent Trends in Generative Artificial Intelligence Litigation in the United States*, K&L Gates (Sept. 5, 2023), https://www.klgates.com/Recent-Trends-in-Generative-Artificial-Intelligence-Litigation-in-the-United-States-9–5-2023..

[297] .

[298] *Id.* at 50.opportunities for commercial artificial intelligence (AI

[299] *Id.*; *see also* Andrew Rapacke, *The AI Patent Boom: Why Companies Are Racing to Protect Their Artificial Intelligence IP*, Rapacke L. Grp. (Jan. 20, 2023), https://arapackelaw.com/patents/the-ai-patent-boom/ .{\\scaps The Rapacke Law Group} (2023 (The Annual AI patent applications has increased by more than 100% from 2002 to 2018. The largest increased of AI fillings took place in 2021, reaching the highest average annual growth rate of 28%).

[300] Credibility of Computational Models Program, *supra* note 50.

[301] *Id.*

complexity of running a well-designed clinical trial.[302] However, data related to human subjects is primarily overseen by ethical guidelines and the aforementioned FDA guidance on informed consent, while other intellectual property-related issues are beyond the FDA's regulatory authority.[303] For example, the issue of database ownership introduces a myriad of complexities in this legal realm, particularly considering that there are no financial impediments or restrictions to accessing data from human participants in clinical trials.[304] This is further complicated by the fact that neither pharmaceutical entities nor clinical research institutions lay exclusive claim to these databases.[305]

Owing to the unique characteristics of human data, especially genetic information, the question of who owns virtual human patient models has been a hotbed of discussion.[306] Some proponents believe that these models should be viewed as communal assets, not proprietary to any one entity.[307] This question was addressed by the Supreme Court in *Ass'n of Molecular Pathology v. Myriad Genetics, Inc.*, where the court held that naturally occurring DNA sequences cannot be patented because they are products of nature and not

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[302] Opderbeck, *supra* note 283 at 579.

[303] *Id.*

[304] *Websites with Information About Clinical Trials*, US Food & Drug Admin. , https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/websites-information-about-clinical-trials (last visited Feb. 16, 2024); Kathy L. Hudson & Francis S. Collins, *Sharing and Reporting the Results of Clinical Trials*, 313 JAMA 355 (2015).]

[305] Opderbeck, *supra* note 283 at 579.

[306] Julian Segert, *Understanding Ownership and Privacy of Genetic Data*, Sci. News (Nov. 28, 2018), https://sitn.hms.harvard.edu/flash/2018/understanding-ownership-privacy-genetic-data/; William S. Konicki et al., *Virtual Surgical Planning and Data Ownership: Navigating the Provider-Patient-Vendor Relationship*, 36 Bioethics 494 (2022); Gabrielle Campbell, Angela Miller & Chara Balasubramaniam, *The Role of Intellectual Property in Creating, Sharing and Repurposing Virtual Patients*, 31 Med. Teach. 709 (2009); Béatrice Godard et al., *Data Storage and DNA Banking for Biomedical Research: Informed Consent, Confidentiality, Quality Issues, Ownership, Return of Benefits. A Professional Perspective*, 11 Eur. J. Hum. Genet. S88 (2003); Henri-Corto Stoeklé & Christian Hervé, *Ownership of Genetic Data: Between Universalism and Contextualism?*, 21 Am. J. Bioethics 75 (2021).{\\scaps Science in the News} (Nov. 28, 2018

[307] Opderbeck, *supra* note 283 at 580.

human-made inventions.[308] However, the Supreme Court noted that synthetic DNA, which does not include non-coding regions present in natural DNA, could be patented because it is not naturally-occurring.[309] Consequently, under prevailing legislation, human virtual patient models might qualify for both patent and copyright protections.

While, currently, the FDA's virtual patient models are available on public domains and are thus not subject to the protection of intellectual property for exclusive access,[310] the FDA has also historically contracted with private entities in the development of the virtual "living heart" model.[311] The latter scenario prompts concerns about the exploitation of public resources by private entities. [312] A potential remedy to this concern, inspired by the NIH's Public Access Policy, is that the FDA might mandate that virtual patient models, utilized for simulated clinical trials during the approval phase, be released on public platforms once the submission receives approval.[313] This approach would not hamper corporations' motivation to create these models, given the time gap between their application in clinical trials and the subsequent approval.[314] Additionally, placing the model in an open-access repository would not nullify its copyright protection.[315] On the contrary, a policy like this promotes transparency and the ability of users to scrutinize and modify existing models, which may stimulate derivative creations .[316]

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[308] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013).
[309] *Id.*
[310] Séverine Dusollie, Scoping Study On Copyright and Related Rights and the Public Domain, (2011) https://www.wipo.int/meetings/en/doc_details.jsp?doc_id=182617 (last visited Feb. 16, 2024).
[311] Opderbeck, *supra* note 283 at 580.
[312] *Id.*
[313] *Id.* at 581.
[314] *Id.* at 580–81.
[315] *Id.*
[316] For a discussion around how open-source software boosts innovation, see *id.* at 581; Walter Bender, *How the Open-Source Movement Will Build a Better Future*, Built In (Apr. 19, 2022), https://builtin.com/founders-entrepreneurship/open-source-future; Tan Tran & Evens Salies, *How Important Is Open-Source Science for Invention Speed*, Sciences Working Paper (2023); Michael Heron, Vicki L. Hanson & Ian Ricketts, *Open Source and Accessibility: Advantages and Limitations*, 1 J. Interaction Sci. 2 (2013).

A limitation of this solution is that simple access does not inherently grant third parties the right to replicate or disseminate the work. As a result, individuals may still require licensing permissions from the creator of the model to utilize the stored resources for additional developments. Additionally, there are situations where referencing or replicating databases and data, particularly relating to data mining and data analytics, might be exempted from intellectual property rights violations by third parties.[317] For instance, regarding copyright protection, while the software utilized to gather and analyze the datasets can be protected, the functional nature of nonrelational databases can impose difficulties in securing copyright protection due to their non-creative nature.[318] This uncertainty, arising from the intricate relationship between aspects of software that can and cannot be protected has sparked numerous legal battles among interested parties, including data scientists and data proprietors.[319] Additionally, there is a need for continued debate on whether creations generated by AI without direct human intervention should be eligible for copyright protection, even though the current legal stance leans towards a negative response.[320] Although the foundational inputs from humans might suggest that an AI system's original work can be patented as the creator's invention, the inherent unpredictability and obscurity of ongoing AI processes, particularly in deep learning methods, often produces outcomes that are both unforeseen and difficult to interpret.[321] Based on this unpredictability, the question remains: How

[317] Sara Gerke, Timo Minssen & I. Glenn Cohen, *Ethical and Legal Challenges of Artificial Intelligence-Driven Healthcare, in* Artificial Intelligence in Healthcare 295 (Adam Bohr & Kaveh Memarzadeh eds., Elsevier 2020).

[318] *Id.*

[319] Gerke, Minssen, and Cohen, *supra* note 317 .

[320] Opderbeck, *supra* note 283 at 585.

[321] For example, the case of Device for the Autonomous Bootstrapping of Unified Sentience (DABUS) illustrates that AI-generated contents may face legal challenges when filing patent applications as some jurisdictions require a human inventor within the current framework. DABUS has failed patent applications in multiple jurisdictions, including the United Kingdom, the European Union, and the United States. *See* Kim O'Connell et al., *DABUS Dismissed Again! United States Supreme Court Declines to Consider Whether AI Can Be an Inventor*, Lexology (Apr. 27, 2023), https://www.lexology.com/library/detail.aspx?g=0ed00ef9–6d2c-4b5d-ae06-da3b8a079049 (last visited Feb. 16, 2024); Sorry, DABUS. AI cannot be an

can one copyright a result when the creator could not anticipate that result from the outset?

Additionally, when AI systems are utilized by pharmaceutical firms and incorporated into the FDA's approval process, they warrant more rigorous oversight compared to other domains. The increased level of rigor is due to the AI system's critical role in public health, which can have profound implications for society.[322] Granting long-lasting copyrights—which could provide protection for over a century—to these systems owned by private entities is a concerning prospect.[323]

Another area of intellectual property that might be relevant to the use of AI in healthcare is patent law. According to a 2019 report by the World Intellectual Patent Organization (WIPO), there has been a swift surge in AI-related innovations.[324] Over half of these AI innovations have been disclosed since 2013, and, from 2012 to 2017, AI-related patent submissions saw an average annual growth of 28 percent.[325] In general, for an AI invention to be eligible for patent protection, it must satisfy both the novelty and technicality patent criteria.[326] Specifically, the system's technical features should demonstrate inventiveness.[327] The Supreme Court case of *Alice Corporation Pty. Ltd. v. CLS Bank Int'l* was pivotal for its significant influence on patent eligibility considerations for software-related innovations.[328] In this ruling, the Supreme Court established a dual-phase analysis: firstly, it examines if the patent claims pertain to

inventor on a U.S. Patent, Reed Smith LLP (2022), https://www.reedsmith.com/en/perspectives/2022/08/sorry-dabus-ai-cannot-be-an-inventor-on-a-us-patent (last visited Feb. 16, 2024).

[322] *See* Trishan Panch, Peter Szolovits & Rifat Atun, *Artificial Intelligence, Machine Learning and Health Systems*, 8 J. Glob. Health 020303; Rajpurkar et al., *supra* note 58; Keo Shaw & Christine Lentz, *FDA Is Embracing AI for Its Own Purposes. Are You Keeping Pace?*, DLA Piper, https://www.dlapiper.com/en/insights/publications/ai-outlook/2023/fda-is-embracing-ai-for-its-own-purposes-are-you-keeping-pace (last visited Feb. 16, 2024).

[323] Opderbeck, *supra* note 283 at 585.

[324] *See* World Intellectual Property Organization, WIPO Technology Trends 2019: Artificial Intelligence (2019) https://www.wipo.int/edocs/pubdocs/en/wipo_pub_1055.pdf (last visited Mar. 19, 2024).

[325] *Id.* at 13–14.

[326] de Bruin, Breimer & Veenhuis, *supra* note 297, at 554.

[327] *Id.*opportunities for commercial artificial intelligence (AI

[328] Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208 (2014).

a conceptual notion; and secondly, if they do, it assesses whether the "innovative element" makes certain that the patent embodies more than merely the conceptual idea at its core.[329] This technicality requirement shifted towards the more stringent European laws, which typically require a demonstration of technical contribution or an inventive step that goes beyond a mere abstract concept for patent eligibility.[330]. Concerning the inventiveness criterion, the invention should not be apparent to an expert in the field who is familiar with existing literature and advancements.[331] A distinction is that the U.S. judiciary has recognized the patent eligibility of medical procedures, which is generally excluded from patent eligibility in the European law, implying that a novel technical AI invention could be patented, even if it pertains to a medical methodology.[332]

The patenting of AI systems utilized in drug development presents complexities. While pharmaceutical companies may leverage AI to strengthen their drug patent portfolios , the same AI tools could be exploited by competitors or patent inspectors to pinpoint situations where an invention may not merit patent protection due to its lack of originality.[333] For example, competitors might employ AI to identify gaps that could show that what companies claim as a new invention might actually be foreseeable based on prior knowledge.[334] Additionally, similar to how drug patents are vital for public health—leading to modifications in the Hatch-Waxman Act that permit generic manufacturers to challenge drug patents without the risk of incurring damages—AI patents might encounter analogous regulatory environments.[335] This could be particularly relevant for AI-powered medical devices that receive

[329] *Id.*

[330] de Bruin, Breimer, & Veenhuis, *supra* note 297 at 554–55.

[331] *Id.* at 555.opportunities for commercial artificial intelligence (AI

[332] *Id.* at 557.opportunities for commercial artificial intelligence (AI

[333] Gerke, Minssen, & Cohen, *supra* note 317 at 326.

[334] *See* Dan Maloney, *AI Patent Trolls Now On The Job For Drug Companies*, Hackaday (Jan. 30, 2019), https://hackaday.com/2019/01/30/ai-patent-trolls-now-on-the-job-for-drug-companies/.

[335] Allen M. Sokal & Bart A. Gerstenblith, *The Hatch-Waxman Act: Encouraging Innovation and Generic Drug Competition*, 10 Curr. Top. Med. Chem. 1950 (2010); Colleen Kelly, *The Balance between Innovation and Competition: The Hatch-Waxman Act, the 2003 Amendments, and Beyond*, 66 Food Drug L. J. 417 (2011).

FDA approval.[336] Encouraging competition through this method could drive growth in the field, but it may also inadvertently increase the number of costly and lengthy legal battles.[337] This proposed regulatory adjudgment might also impede innovation, as patent holders' resources could be better spent on further innovations instead. Hence, these concerns warrant further dialogue.

Lastly, pharmaceutical companies might lean on trade secret laws to safeguard their innovations. Revealing information through the patenting process might risk the protection of trade secrets, but copyrights generally do not require such disclosure.[338] Therefore, combining trade secret protection with copyrights can effectively safeguard complex algorithms, along with the datasets, findings, and correlations generated by AI systems.[339] However, this could exacerbate the "black box" issues previously addressed, further undermining the credibility of decisions derived from AI systems. While the FDA has provided guidelines on the necessity of explainable outcomes coming from the AI systems, legal amendments might be proposed in the future, potentially exempting trade secret claims for systems that are paramount to public health.[340]

In conclusion, while the presence of intellectual property rights could potentially enhance investments in the healthcare domain, bringing benefits to the public, it may also inadvertently stifle innovation due to restrictions imposed by such protections. Additionally, striking a balance between safeguarding intellectual property and advocating for transparency in the FDA's decision-making is essential to bolster trust and credibility in the agency. In particular, this concern is prominent in the realm of public-private collaborations focused on AI development initiatives.[341]

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[336] Opderbeck, *supra* note 283 at 584.

[337] *See* IP Litigation Costs, 1 WIPO Magazine, 2010, https://www.cambridge.org/core/product/identifier/S0020782900056321/type/journal_article (last visited Feb. 16, 2024); Abby Dorland, *A Guide to Intellectual Property Litigation*, Thomson Reuters (Dec. 23, 2022), https://legal.thomsonreuters.com/blog/guide-to-intellectual-property-litigation/ (last visited Feb. 16, 2024) .

[338] Opderbeck, *supra* note 283 at 585–86.

[339] Gerke, Minssen, & Cohen, *supra* note 317 at 326.

[340] Opderbeck, *supra* note 283 at 585–86.

[341] Gerke, Minssen, & Cohen, *supra* note 317 at 327.

D. Delegation of Power

Some have drawn parallels between the concerns surrounding AI utilization by administrative agencies and the incorporation of algorithms into military weapon systems, both involving decision-making processes with direct and profound consequences on human lives.[342] The incorporation of AI in drug approval processes by pharmaceutical companies and the FDA can also be mirrored in the administrative agencies' and military weapons situations, raising similar questions.[343] This prompts debates regarding whether delegating such pivotal decisions to AI systems can be legitimized under current legal frameworks.

The U.S. Constitution states in Article I, Section 1 that "[a] ll legislative Powers herein granted shall be vested in a Congress of the United States, which shall consist of a Senate and House of Representatives."[344] For a considerable time, courts have recognized that Congress can assign authority to administrative bodies, but this delegation is subject to specific constraints, such as the requirement of the intelligible principle.[345] While the doctrine of nondelegation has been applied consistently to human beings, the emergence of novel AI systems poses questions as to whether the same legal principle can be extended to computer software. Theoretically, if administrative decisions are to be made by humans, delegation to AI may sit outside of the legally permitted delegation power granted by the Constitution.[346] Two possible scenarios could arise, one being Congress expressly allowing agencies to use machine-learning algorithms to make administrative decisions, and the other being Congress delegating some degree of administrative power to an agency, which then exercises that power with the assistance of AI systems.[347]

In the context of "cyberdelegation,"[348] if Congress provides a clear and intelligible guideline in the authorizing legislation, then

[342] Coglianese & Lehr, *supra* note 222 at 1177.
[343] *Id.* at 1177.
[344] U.S. Const., art I, § 1.
[345] Coglianese & Lehr, *supra* note 222 at 1178.
[346] *Id.*
[347] *Id.*
[348] Mariano-Florentino Cuéllar, *Cyberdelegation and the Administrative State, in* Administrative Law from the Inside Out: Essays on Themes in the Work of

delegating that power should be in line with the Constitution.[349] Courts have historically established that the criteria for intelligible guidelines is not rigorous, so agencies can be granted power under "broad general directives" that enhance the effectiveness of governance.[350] Cary Coglianese and David Lehr posit that having a clear objective function is crucial for the application of machine learning.[351] They believe that since these system's goals are set in exact, quantifiable, and assessable terms, they undoubtedly meet the standard of the intelligibility test.[352] Moreover, because human officials still maintain overarching and final oversight of the system and its regulatory decisions, in this context, AI merely acts as a legally accepted tool to aid officials in their decision-making processes.[353] Additionally, delegation of power to algorithmic systems is distinguished from that to private entities, which the court held to be "the most obnoxious form".[354] Indeed, even though AI systems operate without self-interest and act based on human-defined values and objectives, the increasing collaboration between private entities and public sectors in AI development raises concerns.[355] Specifically, the legal clarity surrounding delegation in partnership between the FDA and private institutions, including the construction of the molecular model, might be murky and open to interpretation.[356] This concern aside, the delegation of administrative power to AI systems could be constitutionally sound.

The "statutory subdelegation" scenario may be more likely to occur in practice, since many laws are not explicitly crafted with the idea of algorithmic governance in mind.[357] Here, the underlying question is whether the transfer of decision-making authority from sanctioned agencies to machine-learning platforms goes beyond

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Jerry L. Mashaw, (Nicholas R. Parrilo, ed. Cambridge Univ. Press, 2017).

[349] Coglianese & Lehr, *supra* note 222 at 1179.

[350] *Id.*

[351] *Id.*

[352] *Id.*

[353] *Id.* at 1181–82.

[354] *Id.* at 1180.

[355] Marks, *supra* note 11 at 1262.

[356] *Id.*the Food and Drug Administration ("FDA"

[357] Coglianese & Lehr, *supra* note 222 at 1178.

the permissions granted by existing laws.[358] In such a setting, Coglianese and Lehr perceive of no problems.[359] They liken it to the act of delegating authority to private bodies, where agencies merely utilize AI systems as instruments for quantifiable assessments, while maintaining the final say in decision-making.[360] It is important to acknowledge that the legality of this kind of delegation hinges on how courts interpret the statutes, although courts have shown considerable deference to agencies when it comes to interpreting vague or ambiguous laws.[361]

IV. Further Guidance and Policy Concerns

As of now, there are no established guidelines for automating agency decision-making as a whole, nor are there specific standards for employing AI to direct decisions in the medical and public health regulatory sectors.[362] However, the FDA has introduced a few non-binding guidelines to facilitate a seamless shift into the digital age. In 2021, the FDA published the draft guidance, *Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions,* which laid out a foundational structure for evaluating the credibility of computer modeling and simulation in medical device regulatory submissions.[363] This framework takes into account both conventional Verification & Validation (V&V) evidence set out by the American Society of Mechanical Engineers (ASME) as well as other forms of supplementary data.[364] Verification is the process of ensuring that the equations used by a model are solved correctly in a mathematical sense, while validation is about confirming that the model is using the appropriate equations to answer the specific questions it is designed to address.[365]

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[358] *Id.*
[359] *Id.* at 1179.
[360] *Id.* at 1182–83.
[361] *Id.* at 1183–84.
[362] Marks, *supra* note 11 at 1262.
[363] U.S. Food & Drug Admin., *Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions* (2021) https://www.fda.gov/media/154985/download (last visited Sept. 14, 2023).
[364] *Id.*
[365] Marks, *supra* note 11 at 1264.

The V&V framework operates on the premise that the amount of evidence needed to establish the credibility of a model should be proportionate to the risks involved when using that model to inform clinical or regulatory decisions.[366] The model is comprised of four steps: identification of the issue, defining the context that the model would be used and its specific role in addressing the question of interest, assessment of the model risk, and identification of credibility factors and goals.[367] While the framework offers a structured approach, it is not without limitations, particularly in its scope of generalization. Although it can be employed in the evaluation of regulatory decisions, it might not be as effective when analyzing models that steer these decisions, given that such models introduce distinct types of risks and credibility considerations.[368] Acknowledging these shortcomings, the draft guidance released in 2021 presents a more holistic and encompassing model. Yet, even this draft guidance overlooks certain crucial recommendations, notably the supervision of training data, as well as concerns about its quality and lineage.[369] Additionally, while the FDA positions the draft guidance as a risk-based approach to assessing credibility, its definition of risk is rather limited.[370] The risk it primarily focuses on is potential harm to individual patients, those participating in trials, or healthcare professionals, while neglecting to consider the wider ramifications on society and overall public health.[371]

To better improve relevant guidance, Mason Marks suggested that research organizations, product manufacturers, and public health entities should establish independent committees to evaluate the risk and credibility of models.[372] Furthermore, the FDA should reevaluate its perspective on risk, as it currently appears to be narrowly defined and antiquated.[373] There is also an imperative to enhance the transparency of AI systems by emphasizing the

[366] *Id.*the Food and Drug Administration ("FDA"
[367] *Id.*the Food and Drug Administration ("FDA"
[368] *Id.* at 1267.the Food and Drug Administration ("FDA"
[369] *Id.* at 1271.the Food and Drug Administration ("FDA"
[370] U.S. Food and Drug Admin., *supra* note 363.
[371] Marks, *supra* note 11 at 1271.
[372] *Id.* at 1276.the Food and Drug Administration ("FDA"
[373] *Id.* at 1277.the Food and Drug Administration ("FDA"

in-house creation of models.[374] As alluded to in previous discussions, building models internally not only tackles the credibility concern, but also supports adherence to the nondelegation doctrine. Lastly, both the FDA and industry participants should evaluate the lineage of training data, delving into the variety and dependability of data sources, the likelihood of biases, and the degree to which the suitability and precision of the datasets can be confirmed.[375]

When integrating AI systems, agencies should prioritize both the credibility of models and the broader societal implications involved. These considerations encompass various issues such as quantification, the absence of empathy, and potential job displacements. For instance, agencies must address the challenge of transforming value judgments into codified quantities. Furthermore, citizens expect their government to not only operate competently and efficiently but also to demonstrate understanding and empathy, expectations that may be undermined by an excessive reliance on algorithms in government operations. Additionally, it is crucial to recognize that automation often leads to job losses, thus necessitating caution when restructuring the workforce.[376] To help with this problem, the government should consider providing training opportunities to aid workers in transitioning to alternative roles. By acknowledging and addressing these societal implications, agencies can ensure responsible and ethical integration of AI systems into their operations.

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[374] *Id.* at 1278.the Food and Drug Administration ("FDA"

[375] *Id.* at 1278–79.the Food and Drug Administration ("FDA"

[376] *Which Workers Are the Most Affected by Automation and What Could Help Them Get New Jobs?*, U. S. Gov't Accountability Off. (Aug. 23, 2022) https://www.gao.gov/blog/which-workers-are-most-affected-automation-and-what-could-help-them-get-new-jobs (last visited Feb. 16, 2024); Harry J. Holzer, *Understanding the Impact of Automation on Workers, Jobs, and Wages*, Brookings (2022), https://www.brookings.edu/articles/understanding-the-impact-of-automation-on-workers-jobs-and-wages/ (last visited Feb. 16, 2024); Alana Semuels, *Millions of Americans Have Lost Jobs in the Pandemic—And Robots and AI Are Replacing Them Faster Than Ever*, TIME (2020), https://time.com/5876604/machines-jobs-coronavirus/ (last visited Feb. 16, 2024).

Conclusion

Our exploration has encompassed the FDA's evolution from its inception as a singular department to its current paramount position as a national agency. Demonstrating an unwavering commitment to innovation, the FDA has embraced AI technologies, exemplified by noteworthy initiatives such as FAERS, PHASE, virtual patients, and simulated clinical trials. These endeavors underscore the agency's recognition of the advantages offered by AI in the field. Of particular significance is the introduction of virtual patients and the promotion of simulated clinical trials, yielding benefits for both pharmaceutical firms and patients alike. Such approaches not only streamline the cost and time associated with research trials, but also expedite the availability of new drugs in the market.

Nevertheless, the rapid progression towards an increasingly automated administrative framework raises genuine concerns regarding the sufficiency of existing regulations to effectively govern AI applications. This serves as a pressing reminder for regulatory bodies to diligently revamp and update their protocols, ensuring they are appropriately tailored to the intricacies of artificial intelligence. The integration of AI into regulatory frameworks gives rise to substantial legal challenges, encompassing multifaceted issues such as transparency, privacy, cybersecurity, intellectual property rights, and the ramifications of the nondelegation doctrine. By addressing these concerns, we foster not only the seamless integration of AI, but also an assessment of attendant societal costs, which should be outweighed by the extensive benefits AI offers. Hence, a timorous and well-considered legal response is indispensable, enabling the harnessing of AI's potential while safeguarding against its inherent pitfalls. Failure to implement proactive and comprehensive solutions may inadvertently usher in unintended consequences that undermine trust and compromise the overarching objectives of regulatory bodies. To effectively navigate the future landscape shaped by the continued influence of AI on administration and governance, the establishment of a robust legal framework assumes paramount importance. Such measures ensure that technological advancements proceed hand in hand with societal well-being, without undue compromise.

Beyond the formulation of a legislative framework, forging active collaboration between the FDA and diverse stakeholders is of utmost significance. The incorporation of computational models in drug submissions presents a novel frontier in the realm of pharmaceutical regulation. While these models offer notable enhancements in terms of efficiency and precision, they also introduce novel complexities. Through close engagement with industry experts, research institutions, and other pertinent entities, the FDA can develop comprehensive and proactive guidance that guarantees the efficacy and safety of drug submissions. This collaborative approach effectively harnesses collective expertise, fostering an environment of trust and clarity. In an era where technology reshapes the healthcare landscape at a remarkable pace, a united front proves indispensable in responsibly and effectively harnessing AI's potential.