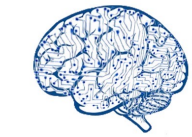

CIfAI

Cognitive Insights for Artificial Intelligence

Call for Comments for the U.S. Food and Drug Administration (FDA) and U.S. Department of Health and Human Services (DHHS) on Using Artificial Intelligence (AI) and Machine Learning (ML) in the Development of Drug and Biological Products, Docket No. FDA-2023-N-0743, Document Number 2023-09985.

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On behalf of Cognitive Insights for Artificial Intelligence (CIfAI), we write in response to the Call for comments for the U.S. Food and Drug Administration (FDA) and U.S. Department of Health and Human Services (DHHS) on Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products. We support FDA-DHHS efforts in seeking stakeholder input on using AI and ML in the Development of Drug and Biological Products.

We at CIfAI provide strategic research-based solutions from a human-centered perspective to ensure the safe and ethical design, development, deployment, and management of AI-enabled autonomous systems across various industries. Our values-based approach is founded on accuracy, consistency, and context-dependency, and supports trusted data across every phase of the AI lifecycle to achieve confident and fair decision making.

CIfAI has reviewed all major topics and subtopics and provides comments and a set of seven recommendations for the six questions outlined under the topic **Section III: Considerations for the Use of AI/ML in Drug Development, Question (1) Human-Led Governance, Accountability and Transparency.**

Preamble

As with other areas, current debate on the use of AI/ML for drug development lies in how to balance innovation and potential risks through regulation and governance. In the pharmaceutical

industry, AI/ML, including semi-supervised learning (SSL),[1] deep learning (DL), and neural networks (NN),[2] has proliferated across a variety of applications and uses. Such techniques are guiding daily healthcare decisions and are specifically influencing a range of therapeutic areas like drugs and biologics. This has created an enormous challenge for the U.S. FDA to ensure the safety and efficacy of such drugs.[3],[4] Since AI/ML is already playing a critical role in drug development, the need to establish risk management frameworks and auditing systems[5] has become paramount to ensure not only further innovation but, in this particular use case, patient safety. It is well documented that AI/ML algorithms introduce risks (e.g., amplification of errors and preexisting biases present in underlying data sources, extrapolation of findings outside of the testing environment). The regulation of drugs and biologics generated via AI/ML and other techniques, however, is very complex and depends on the application and decision-making process. Areas of consideration for risk management auditing include drug discovery where potential drug candidates can be generated; drug screening to find molecules likely to have therapeutic effects; prediction of drug interactions and adverse effects; and drug repurposing to find new applications beyond the original indication. A comprehensive review of drug development studies that uses AI and real-world data and their applications was published in 2020.[6]

Responses to Questions

Section III: Considerations for the Use of AI/ML in Drug Development

(1) Human-led governance, accountability and Transparency. This section states that as a part of governance, a risk management plan that considers the context of use may be applied to identify and mitigate risks.

Question #1. *In what specific use cases or applications of AI/ML in drug development are there the greatest need for additional regulatory clarity?*

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[1] Evangelista, J. E., Clarke, D. J., Xie, Z., Marino, G. B., Utti, V., Jenkins, S. L., Ahooyi, T. M., Bologa, C. G., Yang, J. J., Binder, J. L. and Kumar, P. 2023. Toxicology knowledge graph for structural birth defects. *Communications Medicine*, *3*(1), p. 98. https://doi.org/10.1038/s43856-023-00329-2.

[2] Callaway, E. 2023. Transformative AI designs custom proteins on demand. *Nature*. 619: 236-238.

[3] US Food and Drug Administration. Artificial Intelligence and Machine Learning (AI/ML) for Drug Development. https://www.fda.gov/science-research/science-and-research-special-topics/artificial-intelligence-and-machine-learning-aiml-drug-development.

[4] US Food and Drug Administration. Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products. Discuss Paper and Request for Feedback. https://www.fda.gov/media/167973/download.

[5] Holistic AI. AI Governance, Risk and Compliance. https://www.holisticai.com/.

[6] Chen et al. 2020. Applications of artificial intelligence in drug development using real-world data. Drug Discovery Today. 26 (5):1256-1264.

While there are standards and practices developed for a variety of AI-enabled systems by different organizations,[7],[8] it is possible to apply them for drug development to improve efficiency, safety, and efficacy. In general, AI systems rely heavily on high-quality data for training and validation. Thus, standards should be established for the collection, curation, and sharing of data, including data representativeness, data anonymization and overall protection of patient privacy. For drug design and discovery, standardizing AI-driven methods, like ML and DL, can lead to more accurate and reproducible results. For specific applications like drug repurposing, standardization approaches can enable efficient screening of approved drugs to find potential candidates for new therapeutic indications. For drug safety and adverse event monitoring, standards can be established for integrating AI systems into pharmacovigilance processes to ensure early detection and appropriate responses to safety concerns. Standardization approaches for other applications like predictive toxicology and safety assessment, manufacturing and quality control, adverse event retention and reporting, and others, could be applied to generate more accurate and reproducible results. The challenge lies in ensuring model transparency, algorithmic interpretability and overall reproducibility of AI/ML models and their outputs to gain regulatory approval and acceptance.

Recommendation #1: Regulatory agencies should provide clear guidelines on the evidence required to support the approval of specific applications with AI. Evidence required should at minimum contain detailed technical specifications of the AI system like its data sources, algorithms used, and architecture; this will help both regulators and experts understand how the AI system works, including its potential strengths and limitations as well as validation of representative data. It is important to point out that data sets must be extensive and representative of different groups, highlighting the importance of proper selection and curation to ensure their high quality. This will result in accurate and unbiased trained algorithms while avoiding over-fitting. Furthermore, when testing the AI application on a representative dataset, it should closely resemble real-world scenarios similar to where the AI will be deployed. Finally, a thorough ethical analysis identifying potential risks and negative impacts on individuals, society, and the environment should be required. Regulatory bodies such as the U.S. FDA and the European Medicines Agency (EMA) are beginning to request the auditing of AI algorithms to obtain approvals for new drugs. On the topic of auditing, it is important to point out that there are already available high quality auditing systems for AI[9] based on empirical scientific research that can be improved and updated based upon the specific AI system being audited.

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[7] U.S. National Institute of Standards and Technology (NIST), Information Technology Laboratory. 2023. AI Risk Management Framework. https://www.nist.gov/itl/ai-risk-management-framework.

[8] Institute of Electrical and Electronics Engineers (IEEE). Standards. Piscataway, NJ, USA. https://www.ieee.org/.

[9] Holistic AI. AI Governance, Risk and Compliance. https://www.holisticai.com/.

Question #2. *What does transparency mean in the use of AI/ML in drug development (for example, transparency could be considered as the degree to which appropriate information about the AI/ML model—including its use, development, performance, and, when available, logic —is clearly communicated to regulators and/or other stakeholders)*?

Transparency essentially refers to the openness and clarity with which the processes, algorithms, and data used in developing new drugs or making therapeutic decisions are communicated and understood by all stakeholders (e.g., researchers, regulators, healthcare professionals, patients and the public). Transparency is a critical aspect of AI/ML applications in drug development because it ensures that the decision-making processes and the factors influencing those decisions are comprehensible and can be validated. This is important in drug manufacturing where the development of new drug candidates for a specific indication involves significant safety and ethical considerations.

Recommendation #2: Transparency should be established in AI/ML drug development for any specific drug and its indication. This will require regulatory agencies to ask drug developers to embrace transparency in AI/ML drug development. This should be reflected in the type of data collected, the reasons for the algorithms selected and the model used to explain the prioritization of drug candidates over others. Also, for potential drug candidates, sharing how these candidates were selected for further investigation and clinical trials should be required. Data sharing should include the drug safety profile, mechanism of action, and efficacy in preclinical studies. For the submission of data to regulators, developers should include comprehensive documentation and explanations of the AI/ML processes used in drug development that are prepared in accordance with clear guidance to promote standardization. This will provide regulatory transparency. The purpose of doing this is to promote trust among stakeholders, foster collaboration, and facilitate the development of safe and effective drugs for several diseases.

Question #3. *In your experience, what are the main barriers and facilitators of transparency with AI/ML used during the drug development process (and in what context)*?

Barriers will definitely impact how effectively AI/ML technologies are employed. They may include limited expertise, complexity of the AI/ML algorithms, lack of standardization, data privacy and security, and intellectual property concerns.

Recommendation #3: To deal with barriers it is recommended to follow an approach that includes experts who understand the AI/ML technology and can interpret the algorithms and the results. Expertise should include knowledge of how to interpret the decision-making process of algorithms given their complexity. Otherwise, any lack of transparency will hinder the understanding of how the algorithm arrived at a specific conclusion or decision. This is important because in the absence of standardization it will be difficult to assess the transparency of different drug development processes. It will therefore be required to seek and implement a risk-based regulatory approach to ensure transparency. For data privacy and security, it is

recommended that AI/ML developers balance the need for transparency with strict data protection measures. Regarding intellectual property concerns, it will be necessary for companies to seek a balance between disclosing their AI/ML models and processes and protecting the technology and their competitive advantage. For facilitators of transparency, it will be necessary to use model explainability techniques.[10] For example, LIME (Local Interpretable Model-agnostic Explanations), which provides local ML explainability by approximating "black boxes" with an interpretable model for each prediction, and SHAP (SHapley Additive exPlanations), a method used to break down individual predictions of a complex model, can provide insights into the model's decision-making process. Other insights include open-source initiatives, regulatory guidelines, ethical considerations, collaboration and external validation, and education and training.

Recommendation #4: To support facilitators it is recommended to encourage open-source practices in AI/ML, as is done with other AI systems, to allow collaboration and scrutiny by researchers. This can be done by sharing data, codes, and methodologies to replicate and validate findings. Recent highlights of the vulnerabilities of large language models and their propagation through open-source platforms (e.g., PoisonGPT,[11] WormGPT[12]), for example, raise awareness of the vital need to maintain a secure supply chain of models to guarantee AI safety with model provenance. Regulatory agencies should play a critical role in setting standards and requirements for transparency, and it should be a requirement for developers to submit AI/ML-based drug development data. Additionally, collaboration with relevant stakeholders should be implemented to facilitate external validation of AI/ML models and processes as well as the prioritization of ethical practices to enhance transparency. Education and training for professionals in AI/ML and its applications in drug development is recommended to foster transparent practices.

Question #4. *What are some of the good practices utilized by stakeholders for providing risk-based, meaningful human involvement when AI/ML is being utilized in drug development*?

It is essential to ensure meaningful human involvement to manage risks and maintain ethical standards. Good practices should be therefore incorporated to achieve safer and more effective drug development processes that prioritize patient safety and ethical considerations. Good practices for AI/ML may include a variety of activities that are like activities already in place for drug development. These may include the creation of cross-disciplinary teams, regulatory

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[10] Dhinakaran A. 2021. What are the prevailing explainability methods. https://towardsdatascience.com/what-are-the-prevailing-explainability-methods-3bc1a44f94df.

[11] Huynh, D. and Hardouin, J. (July 9, 2023). PoisonGPT: How we hid a lobotomized LLM on Hugging Face to spread fake news. Mithril Security Blog. https://blog.mithrilsecurity.io/poisongpt-how-we-hid-a-lobotomized-llm-on-hugging-face-to-spread-fake-news/.

[12] Schrader, A. July 15, 2023. WormGPT tool for criminals discovered by cybersecurity firm. UPI. https://www.upi.com/Science_News/2023/07/15/wormgpt-poisongpt-how-generative-ai-becomes-tool-criminals/5881689467029/.

compliance, validation against gold standards, model explainability, transparent documentation, continued monitoring and feedback, ethical review boards, human-in-the-loop approaches, robust data governance, patient involvement, and external auditing and validation.

Recommendation #5: In the order listed above, it is recommended to establish cross-disciplinary teams comprising data scientists, domain experts, healthcare professionals, and ethicists; ensure compliance with relevant regulatory requirements for AI/ML applications in drug development; validate AI/ML predictions against gold standard data or results from clinical trials; utilize AI/ML models that offer explainability or are interpretable; monitor AI/ML models' performance in real-world scenarios and gather feedback from human experts; for transparency, document the entire AI/ML development process, including data collection, preprocessing, model selection, and validation; establish ethical review boards or committees to assess the use of AI/ML in drug development; implement human-in-the-loop approaches where human experts actively participate in decision-making; implement robust data governance practices to safeguard patient privacy and ensure data integrity throughout the AI/ML process; involve patients and patient advocacy groups in the drug development process; and encourage third-party auditing and validation of AI/ML processes. For auditing, existing auditing platforms[13] for risk and compliance evaluation and management can be adapted and utilized for any AI/ML systems used in drug development.

Question #5. *What processes are in place to enhance and enable traceability and auditability*?
Currently there are no systems for traceability and audibility of AI/ML systems that are used in drug development. As a result, there is no accountability, transparency and compliance with regulations. This will require the implementation of processes and practices that allow for the monitoring and tracking of data, actions, and decisions taken by AI/ML systems used in drug development. Implementation of processes and practices will be challenging since it requires considering many activities (e.g., discovery and development;[14] preclinical research; clinical research; FDA drug review; FDA post-market drug safety monitoring). Nevertheless, for companies, adherence to traceability and auditing will help them establish a strong foundation for these activities but also bring confidence in AI/ML systems and in their compliance, particularly with regulatory requirements in drug development.

Recommendation #6: We recommend the implementation of the following activities that will ensure traceability and auditability: Maintain a record of the origin and history of data used in the

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[13] Holistic AI. AI Governance, Risk and Compliance. https://www.holisticai.com/.

[14] Just to highlight the complex, long-term, expensive, and risky nature of processes in the pharmaceutical industry, discovery and development includes at least the following steps, each with their own set of unique steps: looking for a target (compound or biologic); once hitting a target and considering it the lead compound, optimizing the compound (e.g., purity, efficacy, safety, stability, bioactivity, formulation, batch preparation, scale up); and starting clinical studies to test optimized compound. These highly complex procedures make it challenging to adapt everything with AI.

AI/ML system; AI/ML systems should log all relevant data points used during training, validation, and inference; document all aspects of the AI/ML process, including data collection, model development, testing, and deployment; capture metadata on the data used, such as its source, quality, and any data transformations applied; implement version control systems to track changes in the AI/ML models and associated code; design AI/ML systems with robust error handling and feedback mechanisms, and record events related to AI/ML system performance, errors, and user interactions; implement strict access controls to limit system access to authorized personnel only; utilize explainable AI/ML models or techniques to provide insights into how decisions are made; deploy monitoring systems to observe AI/ML systems in real-time; utilize blockchain technology,[15] if appropriate, to create an immutable ledger of data transactions and model updates, enhancing traceability and preventing data tampering; conduct regular internal and external audits to assess the AI/ML system's performance, compliance with regulations, and adherence to established protocols.

Question #6. *How are pre-specification activities managed, and changes captured and monitored, to ensure the safe and effective use of AI/ML in drug development*?

Drug development is a well-established process in the pharmaceutical industry that involves many processes that include drug formulation development, manufacturing process development, scale-up, process validation, and quality control. Each of these processes requires meticulous planning, precision, and adherence to stringent regulatory guidelines to ensure the safety and efficacy of the resultant drug product. For AI/ML systems used in drug development, there are currently no risk management strategies or regulations that ensure their safety. Therefore, in the context of AI/ML in drug development, risk management would refer to the process of defining and documenting the objectives, methodologies, analytical plans and intended use of AI/ML models before applying them to real-world data. Managing these activities and capturing and monitoring changes are critical steps to ensure the safe and effective use of AI/ML in drug development. To achieve this, it will be necessary to implement a series of activities and methods as is already done in standard drug development.

Recommendation #7: Include pre-registration of the study and protocols to ensure transparency; implement version control systems and change documentation to allow for changes in the model, code and/or data; document and make traceable the data and code used to develop and train the AI/ML model; establish and maintain a review process and oversight with domain experts to maintain objectives and adhere to ethical and safety standards; validate the AI/ML model to established bench marks; ensure the independent replication of results to validate the reliability and generality of the AI/ML model; implement a process of continuous monitoring to report unexpected outcomes so that they can be investigated, and ensure compliance with regulatory guidelines (data privacy, reporting requirements, transparency guidelines, etc.) including auditing of the AI/ML system. The purpose of carrying out such activities is to ensure the safety of the drugs, to obtain better outcomes for patients, and to advance healthcare more broadly.

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[15] IBM. Blockchain and Artificial Intelligence (AI). https://www.ibm.com/topics/blockchain-ai.