9 August 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Via online submission to regulations.gov.

RE: "Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products; Availability. Request for Information and Comments," FDA-2023-N-0743, Fed. Reg. Vol 88, No 91 (11 MAY 2023).

Dear Sir or Ma'am,

Attached are my comments on FDA's AI/ML discussion paper. I applaud FDA's engagement approach and promotion of discussion between stakeholders within the broader trend of digital transformation in healthcare. Thank you for the opportunity to provide input.

As summary of my comments and recommendations:

1) AI Regulatory Jurisdiction. The US Government needs a lead agency on AI regulation and the FDA would be a supporting agency over drug / biologic agent domain.
2) Data sharing. FDA must be able to identify faults in bad data and liability.
3) Data standards. FDA should position itself to promote international harmonization.
4) Patient-AI interaction. FDA should guard patient safety when AI diagnoses and plans treatment.
5) Cybersecurity. Like #1 above, FDA should be a supporting agency on cybersecurity.
6) Regulatory uncertainty. FDA should publish regulatory roadmaps which allow to help stakeholders understand the shape of future markets.
7) Software Change. Like #1, FDA must oversee AI performance by periodically inspecting or certifying like a calibrated scale. This may resolve the change issue with AI-guided drugs.
8) Proliferation of Production. FDA must oversee large numbers of medical clinics and hospitals that can engage in advanced manufacturing. This will enable precision medicine.

There are many promising concepts that will accelerate drug and biologics development. Generally, I believe AI has applicability for every stage of the process and with every function. As passing evidence, I used OpenAI's ChatGPT in preparing this response.

Regards,
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AREA 1: HUMAN-LED GOVERNANCE, ACCOUNTABILITY, AND TRANSPARENCY
AREA 1, Q1: In what specific use cases or applications of AI/ML in drug development are there the greatest need for additional regulatory clarity?

1. Patient safety, data integrity, and the issue of automatic software change are the primary areas for greater clarity. Insider Intelligence stated that AI has the potential to cut drug discovery costs by 70%[1]. McKinsey's research forecasts a reduction of drug development timelines by 25-30%. Anecdotal customer comments about Veeva Systems indicates simple data sharing can shave up to 2 years off time to market. These drivers will accelerate adoption and will require greater regulatory attention to these areas:

A. Clinical Trial Design: The use of AI to optimize clinical trial design, patient recruitment, and endpoint selection requires regulatory guidance to ensure that AI-generated insights are reliable, transparent, and aligned with regulatory standards.

B. Patient Stratification and Biomarker Discovery: AI is used to identify patient subpopulations that respond differently to treatments and to discover potential biomarkers. Regulatory clarity is needed to assess the validity of AI-generated patient stratification and biomarker predictions.

C. Pharmacovigilance and Safety Monitoring: AI can analyze real-world data to detect adverse events and safety signals. Regulatory guidance is necessary to validate the accuracy of AI-generated safety alerts and to determine how they should be integrated into pharmacovigilance processes.

D. Predictive Modeling for Drug Efficacy: AI models predicting drug efficacy based on preclinical and clinical data require validation and clear guidelines on their use in decision-making during drug development.

E. Drug Repurposing and Combination: The use of AI to identify potential new uses for existing drugs or optimize drug combinations necessitates regulatory clarity on how such AI-generated recommendations can be used in regulatory submissions.

F. Biologics and Biosimilars Development: Regulatory agencies need to provide guidance on how AI/ML-generated data can be used in the development of biologics and biosimilars, especially in complex areas like protein folding and modeling.

G. Data Integrity and Validation of AI Models: There is a need for guidelines on ensuring data integrity and validation of AI models used in drug development to maintain their accuracy and reliability.

H. Ethical Considerations: As AI becomes more integrated into drug development, ethical considerations such as bias mitigation, transparency, and fairness need to be addressed in regulatory frameworks.

I. Toxicity Prediction: Clear regulations are needed for AI models predicting drug toxicity to ensure their accuracy and how their results should be interpreted in decision-making.

J. Rare Diseases and Orphan Drugs: Specific guidance is required on how AI can be used effectively in drug development for rare diseases and orphan drugs where data availability is limited.

K. Regulatory Submissions: Regulatory agencies should provide guidance on the use of AI-generated data and models in regulatory submissions and how they will be evaluated during the approval process. An immediately useful AI application for drug dossier update and maintenance using large language models and current CMC data from competitors, academia, nonclinical studies, adjacent pharmacovigilance, and regulatory agencies.

L. Validation of AI-Generated Clinical Endpoints: AI/ML-generated clinical endpoints need to be validated and aligned with regulatory requirements to ensure they accurately represent clinical outcomes.

2. As AI proliferates and accelerates trends in advanced manufacturing and precision medicine, mainstream production will be affected. Mainstream production of approved drugs is currently focused on consistent quality and efficiency as the development in 'done'; however, AI offers a future where production is informed by patient conditions, adverse information, and new CMC information. AI applications in manufacturing likely require greater FDA attention in the future. These are some forecast notes of on timing of AI application adoption in drug production.

A. Short term, immediate value application can be made by embedding proprietary data, knowledge, and procedural references with a ChatBot to deliver a co-pilot tool for nearly any employee as a training and job aid. Of concern, any AI that interacts with patients.

B. Medium term applications involve AI addition to improve processes, automate production, and track and detect objects. There is great potential for AI in the plant because the highly controlled environment lends itself to data capture and controls.

C. More speculative, long-term applications are driven primarily by promising targets to lead screening and design, personalized medicine, health monitoring, and disease diagnostic trends. The large chemical space of $>10^{60}$ molecules illustrate the scope of opportunity; however, there is plenty of improvement to be made with technology. The trends may result in increased demand for modular manufacturing and custom batch production informed by field data. Modular manufacturing may proliferate manufacturing sites as production tasks move closer to patients at clinics or hospitals. Cell and gene therapies will likely contribute to the shift. Another promising long term AI application is the use of patient 'digital twin' through records and monitoring to leverage centralized knowledge and provide behavioral and treatment recommendations. Resultant, customized AI recommendations and subsequent effectiveness monitoring is the basis for a digital connection from patient to the manufacturer. This is speculative but interesting and potentially disruptive.

4. Economic and competitive pressure to automate manufacturing will drive AI into GMP facilities. Below are notes on applications by plant functions of Operations Management, Warehousing, Quality Control, Quality Assurance, Regulatory Compliance, Production, Packaging, Engineering, R&D, and Regulatory/Quality Assurance.

A. Operations Management. Operations officers will be drawn to AI applications that gather plant data and make predictions involving internal people, processes, cGMP reports, and external materials. Key performance indicators, and associated AI predictions, will be in demand by operations personnel.

1) Continuous Manufacturing: AI will be used to make real-time adjustments to manufacturing and material processes. The FDA should consider the implications of dynamic manufacturing processes on product quality and consistency. Maintaining a continuous flow of production is highly attractive as manufacturers seek to optimize plant utilization.

2) Production Technical Support: An immediate application is knowledge embedding, ChatGPT with all relevant SOPs and manuals, for instance. This application will be useful to all functions in the plant.

B. Warehousing, both inbound and outbound: Logistics are a well-known area for digitalization as a part of the larger supply chain. I expect predictive AI to have the great application due to the availability of structured logistics data and standardization in the supply chain. AI can optimize logistics, predict demand, improve inventory management, reduce wastage, and aid in document management. This will streamline the flow of raw materials and finished products, leading to cost savings and improved efficiency. This will have a great effect when implemented by larger firms and a much larger effect across the industry as a value chain.

C. Quality Control: AI-powered systems can monitor and analyze manufacturing processes in real time, ensuring the quality and consistency of pharmaceutical products. The systems can detect deviations from the norm and proactively address potential issues.

1) Automated Inspection: AI-powered computer vision systems can automatically inspect products, components, or packaging for defects, ensuring consistent quality and reducing the need for manual inspection.

2) Anomaly Detection: AI algorithms can analyze production data in real time and detect anomalies or deviations from established quality parameters, enabling immediate intervention to prevent defective products from reaching consumers.

3) Predictive Maintenance: AI-based predictive maintenance models can monitor warehousing, distribution equipment, and production machinery for performance to predict potential failures before they occur. Preventive maintenance can reduce downtime and minimize the risk of product quality issues and is key to continuous manufacturing.

4) Statistical Process Control (SPC): AI-driven SPC models can analyze process data to identify trends and patterns that may indicate variations or potential quality issues, allowing for timely adjustments and process improvements.

5) Root Cause Analysis: AI-based analytics can help identify the root causes of quality issues by analyzing vast datasets, enabling manufacturers to address underlying problems and prevent recurring defects.

D. Regulatory: AI systems can assist pharmaceutical companies in staying compliant with evolving regulations by analyzing vast amounts of data and ensuring adherence to various guidelines and safety standards. For instance, knowledge embedding can assist compliance personnel to ask questions about extensive FDA regulations, guidance, instructions, and manufacturer guidance.

E. Quality Assurance: AI-powered systems can monitor and analyze training, document control, and environmental conditions surrounding the main operational workflow. The system can detect deviations from the norm and proactively address potential issues. For instance, knowledge embedding can assist production technicians to ask questions about extensive documentation, SOPs, procedure references, instructions, and manufacturer guidance.

1) Document Control and Compliance: AI can assist in managing and organizing documents related to quality management systems, ensuring compliance with regulatory standards, and facilitating audits.

2) Supplier Quality Management: AI can assess supplier data, performance metrics, and historical quality data to evaluate and predict supplier quality, aiding in supplier selection and risk management.

3) Process Optimization: AI-driven process optimization can help identify inefficiencies and areas of improvement in manufacturing processes, leading to more consistent product quality and increased efficiency.

4) Risk Assessment and Mitigation: AI can perform risk assessments on various aspects of the manufacturing process, identifying potential risks and suggesting risk mitigation strategies.

5) Audit Automation: AI can streamline the audit process by analyzing documents and records, identifying potential compliance issues, and suggesting corrective actions.

6) Validation and Qualification: AI-based validation models can assist in validating manufacturing processes, ensuring they meet the required quality standards and regulatory requirements.

7) Continuous Monitoring and Reporting: AI can continuously monitor process data and provide real-time reporting, enabling timely identification of quality issues and proactive decision-making. AI monitoring of the post-marketing information environment offers a valuable data stream to inform production quality. This tie of pharmacovigilance to manufacturing offers a strong advantage and indicates a change to the manufacturing process and a more comprehensive root cause analysis.

8) Smart Batch Release: AI can analyze production data to determine whether a batch meets predetermined quality criteria, streamlining the batch release process.

F. Engineering:

1) Predictive AI can assist manufacturing engineers to improve production chemistry, manufacturing, and controls (CMC). I expect generative AI to be an aid to engineers as they seek to develop and improve proprietary processes.

2) Predictive AI will be used to predict equipment failures, schedule maintenance tasks, and calibration, and reduce downtime in pharmaceutical manufacturing facilities. This proactive approach helps prevent costly breakdowns and ensures continuous production.

3) Robotics and autonomous systems for drug manufacturing continue to expand onto the plant floor. FDA may need to expend guidance on cGMP, SOPs, and inspections where AI makes for recommends changes.

4) Facility and equipment management will benefit from autonomous control. Advances in environmental control and monitoring are already proven.

G. Production and Packaging: Traditional production quality and process controls may be impacted by AI.

1) Process Monitoring and Fault Detection: More sensors measuring production will produce the data required for AI. AI can then recommend maintenance activities thereby reducing process downtime. AI can recommend product and packaging, quality improvements.

2) Image and Pattern Recognition: AI-powered computer vision systems can be used for automated inspection of pharmaceutical products, ensuring accurate labeling, identifying defects, and verifying batch codes.

3) Smart Manufacturing: AI-driven smart manufacturing platforms can optimize the entire production process, integrating data from various sources to make data-driven decisions and adapt to changing conditions.

4) Packaging: Stability/shelf-life modeling will improve packaging and distribution planning.

5) Batch Release decisions can be made by AI. The FDA should consider how AI models make these critical decisions and ensure they meet regulatory requirements.

H. Research & Development: This entire response is about AI in drug discovery; these bullets summarize general applicability of R&D to plant operations.

1) Process Improvement: The use of AI to control and optimize manufacturing processes in real time is feasible and highly attractive to optimize production. The FDA should evaluate how AI decisions align with established process control limits and safety parameters. Modeling of the production process, coupled with sufficient data volume, should allow AI applications to quickly identify optimal process parameters to reduce production time and waste.

2) Advanced Process Control (APC): Enhanced control of the process will allow the plant to scale up, scale down, and continuously operate.

3) Tailoring, Repurposing, and New Product Development: With control over production and integration with patient data, adverse information, and safety data, the potential for faster patient feedback to precision manufacturing exists, but this will change the structure of current pharmaceutical production.

AREA 1, Q2: What are the main barriers and facilitators of transparency with AI/ML used during the drug development process (and in what context)?

1. AI transparency will ensure accountability, reproducibility, and regulatory compliance. Balancing barriers and facilitators is essential to ensure that transparency with AI is effectively integrated into the drug development process, ultimately benefiting patient safety, scientific integrity, and regulatory compliance. Here main barriers and facilitators of transparency:

A. Barriers:

1) Model Complexity: AI models used in drug development can be highly complex and difficult to interpret. This complexity can make it challenging to provide clear explanations for model decisions and predictions.

2) Intellectual Property Concerns: Pharmaceutical companies may be reluctant to disclose proprietary AI algorithms and models due to intellectual property concerns, which can limit the transparency of the technology used.

3) Lack of Standardization: The lack of standardized guidelines and frameworks for transparent reporting of AI/ML methods in drug development can lead to inconsistency and hinder transparency efforts.

4) Data Privacy and Security: Concerns about patient privacy and data security may limit the sharing of sensitive clinical and genetic data used to train AI models, reducing transparency.

5) Black-Box Nature of Models: Some AI models operate as "black boxes," meaning their decision-making processes are not easily interpretable. This lack of interpretability can hinder efforts to explain model predictions.

6) Regulatory Uncertainty: Ambiguity around regulatory expectations for transparency in AI applications within drug development can lead to cautious or inconsistent disclosure practices.

7) Concern about Modular Manufacturing. Innovation may be hampered without good guidance for manufacturers exploring advanced manufacturing due to hesitancy. For instance, how will FDA monitor the potential proliferation of drug and biologics production sites? FDA's Emerging Technology Program (ETP) must help resolve with good guidelines.

B. Facilitators:

1) Regulatory Guidance: Clear regulatory guidelines that emphasize the importance of

transparency and explainability in AI applications can encourage pharmaceutical companies to adopt transparent practices.

2) Collaboration and Open Science: Collaborative efforts and partnerships between academia, industry, and regulatory agencies can promote transparency by facilitating data and knowledge sharing.

3) Standardized Reporting: The development and adoption of standardized reporting formats for AI methods can ensure consistent and transparent communication of model inputs, processes, and outputs.

4) Interpretable Models: The use of interpretable AI models, such as decision trees or rule-based systems, can facilitate transparency by allowing for easier explanation of model decisions. Advances in AI may produce causal models that aid in explainability and interpretability.

5) Model Validation and Testing: Rigorous model validation and testing procedures that assess model performance and robustness can enhance transparency by providing evidence of the model's reliability.

6) Data Sharing Agreements: Establishing clear data sharing agreements that address privacy concerns and data security can enable the responsible sharing of data for transparency purposes. The role of social benefit corporations or non-government organization is data quality is an interest way of providing wide access and data sharing.

7) Ethical Considerations: Integrating ethical considerations, including transparency and fairness, into the design and use of AI models can promote responsible and transparent practices.

8) Stakeholder Engagement: Engaging with stakeholders, including patients, healthcare professionals, and the public, can promote transparency by soliciting input and addressing concerns related to AI in drug development.

C. These are a few of the areas for the FDA should monitor where technology may evolve quickly:

1) Validation and Verification: AI systems used in critical production should undergo rigorous validation and verification processes to demonstrate their reliability, accuracy, and consistency. The FDA should establish guidelines for validating AI algorithms and ensuring they meet specific performance metrics before being used in critical processes.

2) Data Quality and Integrity: AI systems heavily rely on data for training and decision-making. The FDA should ensure that the data used to develop and train AI models are of high quality, relevant, and properly curated. Data integrity and security should be maintained to prevent potential bias or manipulation.

3) Explainability, Traceability, and Transparency: Many AI algorithms, especially deep learning models, can be complex and difficult to interpret. The FDA may require pharmaceutical

companies to provide explanations and justifications for the decisions made by AI systems, especially in critical areas like drug discovery and personalized medicine. Errors must be traceable back to faults.

4) Regulatory Pathways for AI-Driven Products: The FDA should establish clear and appropriate regulatory pathways for products such as AI diagnostics, precision formulations, and AI-driven pharmaceutical products. Traditional approval processes may need to be adapted to accommodate the unique challenges posed by AI applications that modify drug manufacturing procedures.

5) Real-World Data and Evidence: The FDA will need to consider the use of real-world data and evidence to assess the safety and efficacy of AI-driven pharmaceutical products. AI systems might adapt and improve over time, necessitating ongoing monitoring, evaluation, and certification.

6) Adverse Event Reporting: Reporting adverse events related to AI-driven pharmaceutical manufacturing processes should be clearly defined, and pharmaceutical companies should have mechanisms in place to identify and address potential issues promptly.

7) Cybersecurity and Privacy: AI that affects production introduces new cybersecurity and privacy challenges. The FDA should address data protection, secure communication, and potential vulnerabilities in AI systems to safeguard patient information and prevent unauthorized access.

2. Where AI has the potential to interact with patients or provide precision medicine assessments, then FDA should consider the implications for tailored manufacturing. The obvious thing that needs to be avoided with precision medicine is that the greater patient population becomes de facto test subjects for dosage and administration changes. An effective policy will be key because real-world evidence, volume data, and a better feedback loop from patient to manufacturer have the potential to be effective.

AREA 1, Q3: How are pre-specification activities managed, and changes captured and monitored, to ensure the safe and effective use of AI in drug development?

1. Pre-specification activities, along with the monitoring and management of software changes, will play a crucial role in ensuring the safe and effective use of AI in drug development. These activities involve defining the scope, objectives, and methods of AI applications and ensuring that any changes to these specifications are properly documented, evaluated, and monitored. Here's how pre-specification activities and change management can be managed:

A. Pre-specification Activities:

1) Define Objectives and Scope: Clearly define the objectives of the AI application in drug development and specify the scope of its use. This includes identifying the specific tasks, processes, and decisions that the AI model will be involved in.

2) Select Data Sources: Determine the data sources that will be used to train and validate the AI model. Ensure that these data sources are relevant, representative, and of high quality.

3) Feature Selection and Model Architecture: Pre-specify the features and variables that will be used as inputs to the AI model. Define the model architecture, algorithms, and parameters that will be employed.

4) Validation Plan: Develop a validation plan that outlines the testing, evaluation, and validation procedures for the AI model. Define the success criteria and performance metrics that the model must meet.

5) Ethical and Regulatory Considerations: Address ethical considerations, potential biases, and regulatory requirements that may impact the use of AI in drug development.

B. Software Change Management: This is especially important given the fundamental nature of AI is the self-writing nature of the software. It is not immediately clear how that change should be monitoring, validated, or certified in light of continuous learning. I imagine FDA could monitor with annual performance certification and adverse incident reporting. These are some of the obvious change management activities:

1) Change Request Documentation: Any proposed changes to the pre-specified objectives, scope, data sources, features, model architecture, or validation plan should be documented in a formal change request. This makes sense for planned major change but concerns of incremental change linger.

2) Impact Assessment: Evaluate the potential impact of the proposed change on the AI model's performance, reliability, safety, and regulatory compliance.

3) Risk Assessment: Conduct a risk assessment to identify potential risks associated with the proposed change. Assess how the change may affect patient safety, data integrity, and overall drug development processes.

4) Validation and Testing of Changes: If the change is approved, perform thorough validation and testing of the AI model with the updated specifications. This may involve retraining the model, testing it on new data, and assessing its performance against the revised objectives.

5) Documentation and Traceability: Document all changes made to the pre-specification activities, including the rationale for the change, the impact assessment, risk analysis, validation results, and any adjustments to the validation plan.

6) Review and Approval: Changes should be reviewed and approved by relevant stakeholders, including regulatory experts, quality assurance, and project leads.

7) Ongoing Monitoring: Continuously monitor the AI model's performance after implementing the change. Regularly assess its performance against the revised objectives and monitor for any unintended consequences.

8) Reporting and Communication: Communicate changes and their impact to all

relevant stakeholders, including regulatory authorities, as required. Maintain transparent communication throughout the change management process.

2. By rigorously managing pre-specification activities and changes, pharmaceutical companies can ensure that the use of AI in drug development remains safe, effective, and compliant with regulatory standards. FDA should set expectations with regard to regular software change involved in optimization. This approach helps maintain the integrity of the AI models, the quality of drug development processes, and ultimately, the well-being of patients.

AREA 2: QUALITY, RELIABILITY, AND REPRESENTATIVENESS OF DATA
AREA 2, Q4: What additional data considerations exist for AI/ML in the drug development process?

1. FDA rightly identifies data as a crux issue. Incorporating AI into the drug development process introduces several additional data considerations that are crucial for ensuring the accuracy, reliability, and regulatory compliance of AI-driven applications. These considerations go beyond traditional data management practices and address the unique challenges posed by AI/ML. Here are some key additional data considerations:

A. Data Quality and Integrity: Ensuring the quality and integrity of data used to train and validate AI models is paramount. Rigorous data curation, cleaning, and validation processes are essential to prevent biases, errors, and inaccuracies that could impact model performance.

B. Data Bias and Fairness: AI models can inherit biases present in the training data, leading to unfair or discriminatory outcomes. Careful assessment and mitigation of biases are required to ensure that AI-driven decisions are fair and equitable across diverse patient populations.

C. Data Representativeness: AI models must be trained on data that accurately represents the target population and clinical scenarios. Adequate representation is crucial to ensure that the model's predictions generalize effectively to real-world situations.

D. Data Privacy and Security: Protecting patient privacy and sensitive clinical information is essential. Data anonymization, de-identification, encryption, and compliance with data protection regulations are critical to maintain patient confidentiality. HIPAA compliance is essential for digital twin and patient data.

E. Data Sharing and Collaboration: Collaboration among stakeholders, including pharmaceutical companies, research institutions, and regulatory agencies, may involve sharing data. Clear data sharing agreements, ethical considerations, and mechanisms for secure data exchange are necessary.

F. Real-World Data Integration: Incorporating real-world data from electronic health records, wearables, and other sources into AI models can enhance their predictive capabilities. However, challenges related to data quality, interoperability, and standardization must be addressed.

G. Data Traceability and Auditing: Maintaining traceability of data sources, transformations, and manipulations is essential for regulatory compliance and auditing purposes. Documentation

of data provenance enhances transparency and accountability.

H. Longitudinal and Temporal Data: Drug development often involves longitudinal data collected over time. AI models must handle temporal relationships and changing patient conditions appropriately, considering the dynamic nature of drug effects.

I. Feature Engineering and Selection: AI models require well-defined features as inputs. Expert domain knowledge is crucial for selecting relevant features and ensuring they capture the right information for accurate predictions.

J. Data Imbalance and Scarcity: In drug development, certain conditions or rare diseases may result in imbalanced or scarce data. Specialized techniques, such as data augmentation or transfer learning, may be needed to address these challenges.

K. Data Transparency and Documentation: Transparent reporting of data preprocessing, transformations, and feature engineering is essential for reproducibility. Detailed documentation ensures that others can understand and replicate the data processing steps.

L. External Data Sources: Integrating external data sources, such as literature, genomic data, or biomarkers, requires validation and consideration of their impact on the AI model's performance.

M. Data Validation and Verification: Additional validation and verification steps are needed to ensure that AI/ML-generated insights align with existing scientific knowledge and clinical expertise.

2. Navigating these data considerations requires close collaboration between data scientists, domain experts, regulatory specialists, and ethicists. By addressing these considerations, pharmaceutical companies can harness the power of AI to enhance drug development while maintaining the highest standards of data quality, integrity, and patient safety.

AREA 2, Q5: What are some of the key practices utilized by stakeholders to help ensure data privacy and security?

1. Data is a crux issue. Ensuring data privacy and security is of utmost importance, especially when implementing AI in drug development. Various stakeholders, including pharmaceutical companies, researchers, and regulatory bodies, employ several key practices to safeguard patient data and maintain data privacy and security. Here are some essential practices:

A. Data Anonymization and De-identification: Before using patient data for AI/ML, personally identifiable information (PII) is removed or transformed to ensure individuals cannot be directly identified. This helps protect patient privacy while enabling data analysis.

B. Encryption: Data is encrypted both during storage and transmission to prevent unauthorized access. Strong encryption methods, such as AES (Advanced Encryption Standard), are utilized to ensure data remains secure.

C. Access Control: Data access is strictly controlled, with only authorized personnel granted

permission to access and manipulate sensitive data. Role-based access control limits who can view, modify, or interact with the data.

D. Secure Data Storage: Data is stored in secure environments, such as protected servers or cloud platforms with robust security features. These environments are regularly monitored and updated to address emerging threats.

E. Data Sharing Agreements: When sharing data with external parties, detailed agreements are established to outline how the data will be used, who can access it, and how privacy and security will be maintained.

F. Privacy Impact Assessments (PIAs): Stakeholders conduct PIAs to assess potential privacy risks associated with AI projects. These assessments help identify and mitigate privacy concerns before implementation.

G. Consent and Ethical Considerations: Clear and informed consent is obtained from patients before their data is used for AI/ML. Ethical review boards ensure that data usage aligns with ethical standards and legal requirements.

H. Secure Data Pipelines: Data pipelines are designed with security in mind, implementing measures such as data encryption, authentication, and regular security audits to prevent unauthorized access.

I. Regular Auditing and Monitoring: Ongoing monitoring and auditing of data systems and processes help detect and respond to any security breaches or anomalies promptly.

J. Vendor and Partner Security: When collaborating with third-party vendors or partners, stakeholders ensure that data privacy and security measures align with their own stringent standards.

K. Data Retention Policies: Data retention policies define how long data is stored and when it should be securely disposed of, reducing the risk of unnecessary data exposure.

L. Training and Awareness: Stakeholders educate their personnel about data privacy best practices and security protocols to ensure that everyone involved is vigilant about protecting sensitive data.

M. Compliance with Regulations: Stakeholders adhere to relevant data protection regulations, such as GDPR (General Data Protection Regulation) or HIPAA (Health Insurance Portability and Accountability Act), to ensure legal compliance and data protection.

N. Incident Response Plans: Preparedness for data breaches includes having robust incident response plans in place to contain and mitigate the impact of any security incidents.

O. Transparency with Patients: Open communication with patients regarding data usage, protection measures, and how AI will benefit drug development builds trust and demonstrates a commitment to privacy.

By implementing these practices, stakeholders in drug development can demonstrate their commitment to data privacy and security, protect patient rights, and build a strong foundation for responsible and ethical AI implementation.

AREA 2, Q6: What processes are developers using for bias identification and management?

1. Bias identification and management are critical processes in drug development data. Detecting and mitigating biases helps ensure that AI-driven insights and decisions are fair, accurate, and unbiased. Some key processes developers are using for bias identification and management in drug development data are:

A. Data Auditing and Profiling: Developers thoroughly audit and profile their data to identify potential sources of bias. This involves analyzing demographic, geographic, and other variables to understand the representation of different groups in the dataset.

B. Bias Detection Algorithms: Developers employ bias detection algorithms to automatically identify biases in the data. These algorithms can analyze patterns and distributions within the dataset to highlight areas of potential bias.

C. Data Preprocessing: Preprocessing techniques, such as re-sampling, over-sampling, and under-sampling, are used to balance the dataset and address imbalances that may lead to biased model outcomes.

D. Fairness Metrics: Developers define and calculate fairness metrics to quantitatively measure bias in AI models. Metrics like demographic parity, equal opportunity, and disparate impact are commonly used to assess fairness.

E. Bias Mitigation Techniques: Various techniques are applied to mitigate bias, such as re-weighting training examples, modifying loss functions, and using adversarial training. These methods aim to reduce the impact of bias on model predictions.

F. Feature Engineering: Developers carefully select and engineer features to minimize the potential for bias. They may exclude sensitive attributes or use techniques like group fairness-aware feature engineering.

G. Algorithmic Auditing: Algorithmic auditing involves investigating how AI models arrive at their decisions. Techniques like interpretable machine learning and model-agnostic methods help developers understand and explain model behavior.

H. External Data Validation: Developers validate AI models using external, unbiased data sources to ensure that model performance is consistent across different populations.

I. Stakeholder Collaboration: Collaboration with domain experts, ethicists, and diverse stakeholders helps identify potential sources of bias and ensures a comprehensive assessment.

J. Continuous Monitoring: AI models are continuously monitored in real-world settings to detect any biases that may emerge during deployment. Regular assessment helps maintain

fairness over time.

K. Model Evaluation on Diverse Groups: Developers evaluate AI models on diverse subgroups within the population to identify disparities in performance and address potential bias.

L. Bias Reporting: Developers provide transparency by reporting on the steps taken to identify and mitigate bias, along with the outcomes of these efforts, in documentation and regulatory submissions.

M. Ethical and Regulatory Review: Ethical review boards and regulatory authorities assess bias identification and management processes during the evaluation of AI applications in drug development.

2. By systematically addressing these issues, developers can minimize biases in AI-driven drug development data and ensure that the insights gained from AI models are accurate, reliable, and equitable across different patient groups.

AREA 3: MODEL DEVELOPMENT, PERFORMANCE, MONITORING, AND VALIDATION
AREA 3, Q7: What practices and documentation are being used to inform and record data source selection and inclusion or exclusion criteria?

1. Data source selection and inclusion/exclusion criteria are critical decisions that impact the quality and reliability of the research. Proper practices and documentation are essential to ensure transparency, reproducibility, and regulatory compliance. Who owns the data is a primary question. Some common practices and documentation methods used for informing and recording data source selection and criteria are:

A. Protocol Development: Develop a clear and comprehensive study protocol that outlines the objectives, research questions, and methodology of the drug discovery or development project. Specify the criteria for selecting data sources, including the types of data (e.g., clinical trials, real-world data), patient populations, and time frames.

B. Data Source Description: Provide detailed descriptions of each data source considered for inclusion, including its origin, purpose, data collection methods, patient demographics, and any potential biases.

C. Inclusion Criteria: Clearly define the criteria that data sources must meet to be included in the study. Inclusion criteria could relate to patient characteristics, disease stages, treatment protocols, or data quality.

D. Exclusion Criteria: Specify the criteria that would lead to the exclusion of data sources from the study. Exclusion criteria could involve issues like data incompleteness, low data quality, or lack of relevance to the research question.

E. Bias Considerations: Document the steps taken to assess and address potential biases in data source selection. Describe any strategies used to mitigate biases or balance the representation of different patient groups.

F. Data Validation and Quality Assurance: Outline the processes used to validate and ensure the quality of selected data sources. This could involve data cleaning, consistency checks, and validation against external sources.

G. Data Source Ranking: Rank or prioritize data sources based on their suitability, relevance, and quality for the research. Provide justifications for the selection and ranking of each data source.

H. Expert Input: Involve domain experts, statisticians, and other relevant stakeholders in the decision-making process for data source selection and criteria definition.

I. Data Governance and Compliance: Ensure that selected data sources adhere to data governance policies, legal requirements, and regulatory standards.

J. Transparent Reporting: Transparently document the rationale behind data source selection, inclusion/exclusion criteria, and any modifications made during the course of the research.

K. Version Control: Maintain version-controlled documentation that captures changes and updates related to data source selection and criteria over the course of the project.

L. Regulatory Documentation: If the research involves regulatory submissions, ensure that data source selection and criteria documentation align with regulatory guidelines and requirements.

M. Audit Trail: Create an audit trail that tracks decisions related to data source selection and criteria. This helps ensure accountability and facilitates future reviews or audits.

N. Post-Analysis Documentation: Document the outcomes of data source selection and criteria application after analysis. Discuss any deviations from the original plan and their justifications.

2. By addressing these issues and maintaining thorough documentation, researchers and drug developers can enhance the transparency, reproducibility, and scientific rigor of their work in drug discovery and development. This documentation not only supports the integrity of the research but also aids in communication with regulatory agencies, peers, and other stakeholders.

AREA 3, Q8: In what context of use are stakeholders addressing explainability, and how have you balanced considerations of performance and explainability?

1. A common ontology or framework contributes greatly to explainability in the context of model interpretation and decision-making. The problem is knowledge representations vary and are debated. Yet explainability is entirely dependent on the ability to understand, interpret, and communicate how AI models arrive at their predictions, recommendations, or decisions. While high-performance AI models can provide valuable insights, their lack of transparency can hinder their acceptance, regulatory approval, and ethical considerations. Balancing performance and explainability is crucial to ensure that AI-driven discoveries are not only accurate but also

understandable and trustworthy. Here's how stakeholders are addressing these considerations:

A. Model Interpretability Techniques: Stakeholders employ interpretability techniques to shed light on model decision-making. Methods like feature importance analysis, partial dependence plots, and SHAP (SHapley Additive exPlanations) values help identify which features influence predictions.

B. Rule-Based Models: Rule-based models, such as decision trees or rule-based systems, are preferred due to their inherent transparency. These models generate interpretable rules that directly explain how input features lead to specific outcomes.

C. Visualization Tools: Stakeholders develop visualization tools that illustrate how AI models process data and make predictions. Visualizations enhance understanding and facilitate communication of complex AI processes.

D. LIME and Local Explanations: Techniques like LIME (Local Interpretable Model-agnostic Explanations) provide local explanations for individual predictions. These methods generate simpler, locally accurate models to explain complex model behavior.

E. Model-Agnostic Approaches: Stakeholders use model-agnostic techniques that can be applied to various types of models. This allows them to balance performance and explainability without compromising the choice of AI algorithms.

F. Transparent Feature Engineering: Stakeholders prioritize feature engineering that is transparent and aligned with domain knowledge. This ensures that AI models rely on meaningful and understandable features.

G. Domain Expert Involvement: Collaboration with domain experts helps ensure that AI models' predictions align with clinical insights and are more easily interpretable by medical professionals.

H. Regulatory Compliance: Stakeholders follow regulatory guidelines that emphasize model interpretability for certain applications, such as drug safety assessment or clinical trial optimization.

I. Ethical and Societal Considerations: Stakeholders consider the ethical implications of using complex AI models without clear explanations. Transparent models are more accountable and trustworthy for patients, healthcare professionals, and regulatory agencies.

K. Trade-off Analysis: Stakeholders conduct trade-off analyses to assess the impact of explainability on model performance. They balance the need for accurate predictions with the requirement for understandable decision-making.

L. Hybrid Approaches: Stakeholders explore hybrid models that combine the strengths of complex AI algorithms with interpretable components, maintaining a balance between performance and explainability.

M. Continuous Improvement: Stakeholders iterate on model development to enhance both performance and explainability. Regularly assessing and refining the model's interpretability contributes to a better understanding of its behavior.

2. These strategies help stakeholders strike a balance between the performance and explainability of AI models in drug discovery and development.

AREA 3, Q9: What are some examples of current tools, processes, approaches, and best practices being used by stakeholders for: selecting model types and algorithms for a given use, determining when to use specific approaches for validating models and measuring performance in a given context, evaluating transparency and explainability, and increasing model transparency, etc.?

1. Stakeholders in utilize a variety of tools, processes, approaches, and best practices to address various aspects of model selection, validation, transparency, and explainability. Below are some examples for each of the specified areas:

A. Selecting Model Types and Algorithms:

1) Domain Expertise: Stakeholders consult domain experts to choose model types (e.g., convolutional neural networks for image analysis) that align with the specific problem and data characteristics.

2) Benchmarking: Comparative analysis of different algorithms on benchmark datasets helps stakeholders identify the most suitable model for their use case.

3) Ensemble Methods: Combining multiple models (ensemble methods) can enhance predictive performance and robustness.

B. Validating Models and Measuring Performance:

1) Cross-Validation: Techniques like k-fold cross-validation assess model performance on different subsets of data to ensure generalization.

2) Hold-Out Validation: Splitting data into training and validation sets allows stakeholders to evaluate model performance on unseen data.

3) Area Under the Curve (AUC): A common metric for evaluating the performance of binary classification models, providing insights into model discriminative power.

4) Precision, Recall, F1-Score: These metrics help evaluate the balance between model accuracy, sensitivity, and specificity.

C. Transparency and Explainability:

1) SHAP (SHapley Additive exPlanations): SHAP values provide a unified approach to explain the output of any machine learning model.

2) LIME (Local Interpretable Model-agnostic Explanations): LIME generates locally faithful explanations for individual predictions.

3) Decision Trees: Rule-based decision trees are inherently interpretable and provide insights into the decision-making process.

4) Partial Dependence Plots: These plots illustrate how the model's predictions change as specific features vary.

D. Increasing Model Transparency:

1) Feature Importance Analysis: Techniques like permutation importance or feature contribution analysis highlight which features drive model predictions.

2) Regularization Techniques: Applying regularization methods (e.g., L1, L2 regularization) can simplify models and promote feature importance.

3) Sensitivity Analysis: Evaluating the impact of perturbations in input features on model outputs enhances understanding of feature importance.

4) Data Visualization: Visualizations help stakeholders explore data relationships and understand how model predictions change with different inputs.

E. Ethical Considerations and Best Practices:

1) Responsible AI Frameworks: Implementing principles from responsible AI frameworks, such as fairness, accountability, transparency, and ethics.

2) Interdisciplinary Collaboration: Engaging with ethicists, clinicians, and regulatory experts to ensure a holistic approach to AI implementation.

3) Clear Documentation: Comprehensive documentation of model development, validation, and transparency efforts enhances reproducibility and regulatory compliance.

4) Stakeholder Communication: Transparently communicate model limitations, uncertainties, and potential biases to stakeholders and end-users.

These examples illustrate some of the tools, processes, approaches, and best practices that stakeholders are employing to address key aspects of AI use in drug discovery and development. It's important to note that these practices may evolve over time as AI technology advances and regulatory requirements become more defined.

REFERENCES

Some Bibliographic Refs
"Adopting AI in Drug Discovery", 29 March 2022, (https://www.bcg.com/publications/2022/adopting-ai-in-pharmaceutical-discovery)

"AI is dreaming up drugs that no one has ever seen. Now we've got to see if they work", 15 FEB 2023 (https://www.technologyreview.com/2023/02/15/1067904/ai-automation-drug-development/)

"AI in the Pharma Industry: Current Uses, Best Cases, Digital Future", 30 APR 2021, (https://pharmanewsintel.com/news/ai-in-the-pharma-industry-current-uses-best-cases-digital-future)

"Artificial Intelligence in Drug Discovery and Development", Jan 2021, Drug Discovery Today, v 26, no 1.

"Tapping into the drug discovery potential of AI", June 2021, Nature Biopharma Dealmakers.

Endnotes

[1] "Big pharma is using AI and machine learning in drug discovery and development to save lives", 15 APR 2022, (AI & Machine Learning in Drug Discovery & Development (2022) (insiderintelligence.com)

Stage/Phase	Stage Time	Stage Input	Illustrative Processes supported by AI/ML	Stage Output
Basic Science			• Disease model hypotheses • Exploratory research • Biomarker identification	Knowledge
Target ID, validation, selection	1-3y	10,000 candidates	• Benchmark compounds set design. • Predict target association to the disease model. • Prediction of compound activity • Prediction support target validation • Characterize genes & proteins in Dz • Validate/invalidate agents. • Molecule design • Structure prediction • -Omics targeting • New pathway targeting • Target drugability predication • Novel binding sites • Biomarker identification	Targets
Target to lead	1y		• Design of ad hoc compound libraries • Identify new targets. • Support chemical improvements. • Predict useful properties for further phases. • Prediction of activity, toxicity, properties • Identification and classification of target cells • Forecast properties such as absorption, elimination rates, potential liabilities. • Patient stratification & Biomarker identification • Lead optimization • Drug Dossier writing and maintenance	Validated Targets
Lead to candidates	1-3y	500 candidates	• Support backup selection • Identify non-expected liabilities. • Detection of undesired interactions beyond toxicity • Drug Dossier writing and maintenance	Lead Molecules (Effective in Target)
Preclinical development	1-2y		• Support backup selection • Identify non-expected liabilities. • Drug Dossier writing and maintenance	Candidate Molecules (Effective in Animals, Drug non-toxic in animals)
Phase 1 (FIH)	X months	10 candidates	• Predict adverse drug effects. • Trial design • Drug Dossier writing and maintenance	Drug (Non-toxic to Humans)
Phase 2 (PoC)	X months – 1y		• Drug repurposing • Selection of patient population to improve success rates. • Drug Dossier writing and maintenance	Drug (Effective in X00 humans)
Phase 3 (Multicenter)	1-4y		• Drug Dossier writing and maintenance	Drug (Effective in X000 humans)
Phase 4 (Post marketing surveillance)	Ongoing	1	• Support pharmacovigilance • RWE, adverse events, and safety signals • Drug Dossier writing and maintenance	Medicine
Common to All			• Training and job aids via augmentation / copilot each worker	Efficiency with regulated or complex tasks