- What processes are in place to enhance and enable traceability and auditability?

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

(2) <u>Quality, reliability, and representativeness of data</u>

AI/ML is particularly sensitive to the attributes or characteristics of the data used for training, testing, and validation. Although not unique to AI/ML, missing data, bias, and data drift are typically important considerations. Ensuring data quality, reliability, and that the data are fit for use (i.e., relevant for the specific intended use and population) can be critical. Potential data-related issues to consider include:

Bias: AI/ML can potentially amplify preexisting biases that exist in the underlying input data. NIST published a document characterizing three categories of bias (human, systemic, and statistical/computational) and "how they may occur in the commission, design, development, and deployment of AI technologies that can be used to generate predictions, recommendations, or decisions (e.g., algorithmic decision systems), and how AI systems may create societal harms."[37]

Integrity: The completeness, consistency, and ***accuracy*** of data.[38]

Privacy and security: The protection and privacy of data, linked to data classifications and the technical features of the system.

Provenance: Record trail that accounts for the origin of a piece of data (in a database, document, or repository) together with an explanation of how and why it got to the present place.[39] Provenance describes "the metadata, or extra information about data, that can help answer questions such as who created the data and when."[40]

Relevance: Adequate data are available and are appropriate for the intended use.

Replicability: Obtaining consistent results across studies aimed at answering the same question, each of which has obtained its own data.[41] It is important to clarify data access early in the process.

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[37] NIST Special Publication 1270, March 2022. https://doi.org/10.6028/NIST.SP.1270
[38] For additional considerations related to data integrity see the guidance for industry *Data Integrity and Compliance with Drug CGMP* (December 2018). https://www.fda.gov/media/119267/download
[39] Encyclopedia of Database Systems, definition of data provenance. https://link.springer.com/referenceworkentry/10.1007%2F978-0-387-39940-9_1305
[40] 21st Century Cures Act: Interoperability, Information Blocking, and the ONC Health IT Certification Program (March 2019). https://www.federalregister.gov/documents/2019/03/04/2019-02224/21st-century-cures-act-interoperability-information-blocking-and-the-onc-health-it-certification
[41] *Ibid.*

Reproducibility: Obtaining consistent results using the same input data, computational steps, methods and code, and conditions of analysis[42] (while not confirming validity, the transparency required to demonstrate reproducibility permits evaluation of the validity of design and operational decisions (S. V. Wang et al., 2017)).

Representativeness: Confidence that a sample from which evidence is generated is sufficiently similar to the intended population. In the context of patient experience data, representativeness includes the extent to which the elicited experiences, perspectives, needs, and priorities of the sample are sufficiently similar to those of the intended patient population.[43]

Questions:

- What additional data considerations exist for AI/ML in the drug development process?
- What practices are developers, manufacturers, and other stakeholders currently utilizing to help assure the integrity of AI/ML or to address issues, such as bias, missing data, and other data quality considerations, for the use of AI/ML in drug development?
- What are some of the key practices utilized by stakeholders to help ensure data privacy and security?
- What are some of the key practices utilized by stakeholders to help address issues of reproducibility and replicability?
- What processes are developers using for bias identification and management?

(3) Model development, performance, monitoring, and validation

The use of the model may be important to consider in evaluating AI/ML model development and performance, including through practices of pre-specification steps and clear documentation of criteria for developing and assessing models. It may also be important to consider the model risk and credibility; model risk drives the selection of credibility goals and activities.[44] Model risk is determined by two factors, which are

[42] National Academies of Sciences, Engineering, and Medicine, 2019, Reproducibility and Replicability in Science. https://doi.org/10.17226/25303

[43] See discussion document for Patient-focused Drug Development Public Workshop *Collecting Comprehensive and Representative Input*, December 2017. https://www.fda.gov/media/109179/download

[44] Credibility refers to trust in the predictive capability of a computational model for a particular context of use (Kuemmel et al., 2020). This includes steps to document performance and approaches to measure uncertainty at the component level (e.g., model and non-level components, including metrics and

shaped by the ***context of use***: model influence (the weight of the model in the totality of evidence for a specific decision) and decision consequence (the potential consequences of a wrong decision).

In balancing performance and explainability, it may be important to consider the complexity of the AI/ML model. In situations where complex models (e.g., artificial neural network models) are determined to have similar performance, there may be overall advantages to selecting the more traditional and parsimonious (i.e., fewer parameters) model.

It may also be important to monitor and document monitoring efforts of the AI/ML model to ensure it is reliable, relevant, and consistent over time. This includes documentation of the results of monitoring and any corrective action taken to ensure that the AI/ML produces intended results. Subsequent assessments (e.g., postmarket safety monitoring, surveillance) can provide valuable feedback on processes and real-world model performance. Real-world model performance includes applications that may be supported by collection and monitoring of RWD (e.g., electronic health records, product and disease registries). Potential re-training based on real-world performance could provide important insights to model performance, and following such re-training, it may be important to monitor and document the AI/ML model to appropriately manage risks.

Data considerations also include providing the details of the training dataset utilized to develop the AI/ML model, along with the performance, when employing independent, external testing data to support verification and validation ("external validity"). It is generally important for data of sufficient quality for the particular context of use to be representative of the population where the AI/ML method will be utilized. It is important to help ensure AI/ML models are validated to produce results that are credible for the model's use. Credibility activities include verification of the software code and calculations, validation of the model, and evaluation of the applicability of validation assessments to the context of use. These activities include considerations of measuring the level of uncertainty of the model predictions. Upon completion of credibility activities, an assessment can be made to determine whether the model is sufficiently credible for its use and whether the model may be acceptable for a given regulatory purpose.

Questions:

- What are some examples of current tools, processes, approaches, and best practices being used by stakeholders for:

assessing performance and outcome of each component) and system level (e.g., methods for assessment, performance metrics, and outcomes), where feasible. Demonstration of credibility often includes a risk-based approach, where uses presenting the highest risk generally require the greatest standard of evidence, with a gradient of evidence needed based on the associated risk (i.e., informing early-stage drug development for non-serious medical condition versus evaluating drug safety and effectiveness for critical medical condition).

- Documenting the development and performance of AI/ML models that can be applied in the context of drug development (e.g., CONSORT-AI (Liu et al., 2020) and SPIRIT-AI (Cruz Rivera et al., 2020))?

- Selecting model types and algorithms for a given context of use?

- Determining when to use specific approaches for validating models and measuring performance in a given context of use (e.g., selecting relevant success criteria and performance measures)?

- Evaluating transparency and explainability and increasing model transparency?

- Addressing issues of accuracy and explainability (e.g., scenarios where models may provide increased accuracy, while having limitations in explainability)?

- Selecting open-source AI software for AI/ML model development? What are considerations when using open-source AI software?

- The use of RWD performance in monitoring AI/ML?

- What practices and documentation are being used to inform and record data source selection and inclusion or exclusion criteria?

- In what context of use are stakeholders addressing explainability, and how have you balanced considerations of performance and explainability?

- What approaches are being used to document the assessment of uncertainty in model predictions, and how is uncertainty being communicated? What methods and standards should be developed to help support the assessment of uncertainty?

As outlined above, many of the overarching principles and standards related to the characteristics of trustworthy AI can help inform considerations or key practice areas for the application of AI/ML in the context of drug development. In addition to meeting current requirements to support regulatory decision-making regarding a drug's safety and effectiveness, the use of AI/ML in drug development raises challenges related to human-led AI/ML governance, accountability, and transparency; data considerations; and model development, performance, monitoring, and validation. Transparency and documentation across the entire product life cycle can help build trust in the use of AI/ML. In this regard, it may be important to consider pre-specification and documentation of the purpose or question of interest, context of use, risk, and development of AI/ML. While not unique to the use of AI/ML in drug development, there are also a broad range of data quality, relevance, and reliability-related considerations.

Related to the area of model development, performance, monitoring, and validation, the V&V 40 risk-informed credibility assessment framework may be a helpful guide when considering the specific use for AI/ML. In general, use of a risk-based approach may guide the level of evidence and record keeping needed for the verification and validation of AI/ML models for a specific context of use. Engagement with the FDA early in the process can also help inform and address these considerations.

IV. Next Steps: Engagement and Collaboration

The release of this initial discussion paper is part of a broader effort to communicate with a range of stakeholders and to explore the relevant considerations for the use of AI/ML in the development of human drugs and biological products. Coupled with this document, FDA has included a series of questions for feedback, and a workshop with stakeholders is planned to provide an opportunity for further engagement. The FDA will also provide several other mechanisms to engage with stakeholders, sponsors, and developers on this topic, and these can be utilized to address questions before conducting a study that utilizes AI/ML. In addition to formal meetings where these methods can be discussed, the Critical Path Innovation Meetings (CPIM),[45] ISTAND Pilot Program,[46] Emerging Technology Program,[47] and Real-World Evidence Program[48] meetings are examples of additional avenues for communicating and discussing a relevant AI/ML methodology or technology and improving efficiency and quality in drug development. Additionally, communication and engagement with patients and the public regarding considerations for AI/ML in drug development is critical to ensure patient-centered approaches and policies.

Building on this discussion paper, FDA will continue to solicit feedback and engage a broad group of stakeholders to further discuss considerations for utilizing AI/ML throughout the drug development life cycle. These discussions and future collaborations with stakeholders may provide a foundation for a future framework or guidance.

[45] See CPIM, November 11, 2022. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/critical-path-innovation-meetings-cpim

[46] See the ISTAND Pilot Program, February 10, 2021. https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

[47] See Emerging Technology Program, February 22, 2022. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program

[48] See Framework for FDA's Real World Evidence Program, April 14, 2020. https:/fda.gov/media/120060/download

Glossary

Accuracy: The level of agreement between the measured value and the true value of the clinical event or characteristic.

Artificial Intelligence (**AI**): A branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions, and making predictions.[49]

Biomarker: A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics. A biomarker is not a measure of how an individual feels, functions, or survives.[50]

Clinical Outcome Assessment (COA): A measure that describes or reflects how a patient feels, functions, or survives. There are four types of COAs: patient-reported outcome, observer-reported outcome, clinician-reported outcome, and performance outcome.[51]

Context of Use: A statement that fully and clearly describes the way AI/ML is to be used and the drug development-related purpose of the use.[52]

Controlled Terminology: A finite set of values (e.g., codes, text, numeric) that represent the only allowed values for a data item. Generally, controlled terminology standards specify the key concepts that are represented as definitions, preferred terms, synonyms, and code systems.[53]

Decentralized Clinical Trial: A clinical investigation where some or all of the trial-related activities occur at a location separate from the investigator's location.[54]

Digital Health Technology (**DHT**): A system that uses computing platforms, connectivity, software, and/or sensors for health care and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a

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[49] See IMDRF/AIMD WG/N67 Machine Learning-enabled Medical Devices: Key Terms and Definitions, final document, May 6, 2022. https://www.imdrf.org/documents/machine-learning-enabled-medical-devices-key-terms-and-definitions

[50] See BEST (Biomarkers, EndpointS, and other Tools) Resource Glossary, 2016. https://www.ncbi.nlm.nih.gov/books/NBK338448

[51] See Clinical Outcome Assessment (COA), December 2020. https://www.fda.gov/about-fda/clinical-outcome-assessment-coa-frequently-asked-questions

[52] CDISC Glossary, 2022. https://evs.nci.nih.gov/ftp1/CDISC/Glossary/CDISC%20Glossary.html

[53] *Ibid.*

[54] See the draft guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2021). When final, this guidance will represent FDA's current thinking on this topic. https://www.fda.gov/media/155022/download

medical product, in a medical product, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products. Data captured by DHTs can often be transmitted directly to investigators, sponsors, and/or other authorized parties, with the capability to maintain blinding or masking when appropriate. The ability to transmit data remotely increases opportunities for patients to participate in clinical investigations at locations remote from the investigator's site.[55].

Digital Twins: An integrated multi-physics, multiscale, probabilistic simulation of a complex system that uses the best available data, sensors, and models to mirror the behavior of its corresponding twin. A fully developed digital twin consists of a physical component (e.g., unit operations), a virtual component, and automated data communications between the two. The development and application of digital twins are now being extended to manufacturing and complex products to assess sensitivities of material attributes and process parameters, reliability of control strategies, and effectiveness of mitigation plans for potential disturbances.[56]

Drug Development Tool (**DDT**): A biomarker, COA, or any other method, material, or measure determined to aid drug development and regulatory review. Animal models developed to be used for product development under the Animal Rule[57] have been determined by FDA to be DDTs under section 507 of the FD&C Act.[58]

Endpoint: A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.[59]

Machine Learning (**ML**): A subset of AI that allows ML models to be developed by ML training algorithms through analysis of data, without being explicitly programmed.[60]

Natural Language Processing (**NLP**): The branch of computer science, specifically the branch of AI, concerned with giving computers the ability to understand text and spoken words in much the same way human beings can.[61]

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[55] *Ibid.*
[56] See Modeling & Simulation at FDA, November 16, 2022. https://www.fda.gov/science-research/about-science-research-fda/modeling-simulation-fda
[57] See Animal Rule Approvals, June 2022. https://www.fda.gov/drugs/nda-and-bla-approvals/animal-rule-approvals
[58] See the guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (November 2020). https://www.fda.gov/media/133511/download
[59] See BEST (Biomarkers, EndpointS, and other Tools) Resource Glossary, 2016. https://www.ncbi.nlm.nih.gov/books/NBK338448
[60] See IMDRF/AIMD WG/N67 Machine Learning-enabled Medical Devices: Key Terms and Definitions, final document, May 6, 2022. https://www.imdrf.org/documents/machine-learning-enabled-medical-devices-key-terms-and-definitions
[61] "What is natural language processing?" Accessed September 8, 2022. https://www.ibm.com/cloud/learn/natural-language-processing#toc-what-is-na-jLju4DjE

Neural Network: A commonly used form of AI/ML that is used for categorization applications and has been loosely likened to the way that neurons in the brain process signals. Neural networks typically consist of at least three layers of neurons: input layer (which receives information), hidden layer (responsible for extracting patterns and conducting the internal processing), and output layer (produces and presents the final network output).[62]

Real-World Data (**RWD**): The data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices.[63]

Real-World Evidence (**RWE**): The clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWD sources (e.g., registries, collections of EHRs, administrative and medical claims databases) can be used for data collection and, in certain cases, to develop analysis infrastructure to support many types of study designs to develop RWE, including, but not limited to, randomized trials (e.g., large simple trials, pragmatic clinical trials) and observational studies (prospective or retrospective).[64]

Recurrent Neural Network: A type of artificial neural network that uses sequential data or time series data to exhibit temporal dynamic behavior. These algorithms are commonly used for ordinal or temporal problems, such as language translation, NLP, speech recognition, and image captioning.[65]

62 See the Executive Summary for the Patient Engagement Advisory Committee Meeting: Artificial Intelligence and Machine Learning in Medical Devices, October 22, 2020. https://www.fda.gov/media/142998/download

63 See the draft guidance for industry, investigators, and other stakeholders Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (September 2021). https://www.fda.gov/media/152503/download

64 Ibid.

65 Adapted from https://www.ibm.com/cloud/learn/recurrent-neural-networks

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