November 19, 2023

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Attention: Discussion Paper on Artificial Intelligence in Drug Manufacturing

Submitted electronically to: http://www.regulations.gov

Re: Discussion Paper: Artificial Intelligence in Drug Manufacturing; Request for Information and Comments (FDA-2023-N-0487)

Dear Dr. Califf:

Premier Inc. appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) regarding the discussion paper titled *Artificial Intelligence in Drug Manufacturing.* As described, this discussion paper presents the FDA with the opportunity to support innovation, build resiliency in the drug supply chain and elucidate regulatory gaps and procedural pitfalls at a commensurate pace with evolving artificial intelligence (AI) and machine learning (ML) technology.

Premier supports the development of this discussion paper as a positive step towards recognizing the ways in which technology can be leveraged to reduce costs, improve data quality and access, expedite administrative processes and advance health equity. Specifically, Premier applauds the FDA's efforts to incorporate emerging technologies into drug development and provide clarity and use case examples for manufacturers. In our comments, Premier recommends that FDA:

- Harmonize current regulations and guidance with principles of responsible AI in order to minimize confusion and disruptions that impede drug development and manufacturing;
- Identify clear data quality guidelines for the use of AI in drug manufacturing processes;
- Clarify and bolster cybersecurity standards;
- Ensure that any future AI standards adequately mitigate risks of bias and promote transparency and explainability; and
- Enable the development of standardized intended use certifications or reporting requirements for AI technologies, which would prevent new systems from producing harmful outcomes due to use outside of the technology's design.

Our detailed recommendations are included below.

I. BACKGROUND ON PREMIER INC.

Premier is a leading healthcare improvement company, uniting an alliance of more than 4,350 U.S. hospitals and health systems and approximately 300,000 continuum of care providers to transform healthcare. With integrated data and analytics, collaboratives, supply chain solutions, consulting and other services, Premier enables better care and outcomes at a lower cost. Premier plays a critical role in the rapidly evolving healthcare industry, collaborating with members to co-develop long-term innovations that reinvent and

improve the way care is delivered to patients nationwide. Headquartered in Charlotte, N.C., Premier is passionate about transforming American healthcare.

Premier is already leveraging AI to move the needle on cost and quality in healthcare, including:

- Premier's PINC AI™ Applied Sciences (PAS) is a trusted leader in accelerating healthcare improvement through services, data, and scalable solutions, spanning the continuum of care and enabling sustainable innovation and rigorous research. These services and real-world data are valuable resources for the pharmaceutical, device and diagnostic industries, academia, federal and national healthcare agencies, as well as hospitals and health systems. Since 2000, PAS researchers have produced more than 1,000 publications which appear in 264 scholarly, peer-reviewed journals, covering a wide variety of topics such as population-based analyses of drugs, devices, treatments, disease states, epidemiology, resource utilization, healthcare economics and clinical outcomes.

- Stanson Health, a subsidiary of Premier, designs technology to reduce low-value and unnecessary care. Stanson leverages real-time alerts and relevant analytics to guide and influence physician's decisions through clinical decision support technology, providing higher-quality, lower-cost healthcare. Stanson's mission is to measurably improve the quality and safety of patient care while reducing the cost of care by enabling context-specific information integrated into the provider workflow.

- Conductiv, a Premier purchased services subsidiary, harnesses AI to help hospitals and health systems streamline contract negotiations, benchmark service providers and manage spend based on historical supply chain data. Conductiv also works to enable a healthy, competitive services market by creating new opportunities for smaller, diverse suppliers and helping hospitals invest locally across many different categories of their business.

In addition, Premier has been a leader in addressing drug shortages for more than twenty years and is committed to eliminating drug shortages from both a policy perspective via legislative and regulatory action as well as pursuing market-based solutions. Premier's ProvideGx program identifies safe, high-quality supply sources for drugs that are or may be at risk of being added to the national drug shortage list. Guided by health systems with more than 1,600 hospitals across the nation, Premier's ProvideGx program creates long-term committed buying contracts that provide participating manufacturers with the surety needed to increase production. Premier's programs, including ProvideGx, currently provide hospitals access to more than 150 drugs that are or have been recently designated as shortage drugs.

Premier's detailed feedback, based on our depth of experience in using AI in healthcare, is included below.

II. APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN PHARMACEUTICAL MANUFACTURING

Premier sees potential for AI to transform three key segments of the drug manufacturing process: supply chain visibility, advanced process control and quality monitoring.

Supply chain visibility. Premier believes the application of AI can advance national security by helping build a more efficient and resilient healthcare supply chain. Specifically, AI can enable better demand forecasting for products and services, such as drug components, through analysis of historical and emerging clinical and patient data. As the COVID-19 pandemic demonstrated, the ability to understand and react to shortages poses a critical challenge to healthcare providers; AI enables better planning and

response time to national or regional emergencies. AI can drive better inventory management by automating the monitoring and replenishment of inventory levels. Healthcare providers can leverage AI to better manage suppliers through faster more efficient contracting processes and by monitoring of supplier key performance metrics. As Premier works to combat drug shortages, the most effective remedies begin with supply chain visibility and reliable predictions that allow manufacturers to plan for and respond to shortages or disruptions – this crucial element of the drug manufacturing process presents a key value-add opportunity for AI technology.

Advanced process control. Another significant value-add for AI in the drug manufacturing process is in the development and optimization of advanced process control systems (APCs). Process controls typically regulate conditions during the manufacturing process, such as temperature, pressure, feedback and speed. However, a recent report found that industrial process controls are overwhelmingly still manually regulated, and less than 10 percent of automated APCs are active, optimized and achieving the desired objective. These technologies are now ready to transform drug manufacturing on a commercial scale; however, challenges still remain to widespread adoption. Premier strongly believes that the FDA should issue clear guidance that supports the industry-wide transition to AI-powered APCs. Such technologies offer drug manufacturers the opportunity to assess the entire set of input variables and the effect of each on system performance and product quality, automating plant-wide optimization. This application of AI technology can transform the physical manufacturing of drugs and pharmaceuticals, leading to cost-savings and increased resiliency, transparency and safety in the drug supply chain.

Quality monitoring. AI can also provide value-add to drug manufacturing in the field of quality monitoring and reporting. Current good manufacturing processes (cGMPs) provide an immense volume of data from imagers and sensors that, if processed and analyzed more quickly and efficiently, could transform approaches to safety and quality control. AI models trained on this data can be used to predict malfunctions or adverse events. AI can also perform advanced quality control and inspection tasks, using data feeds to quickly identify and correct product defects or catch quality issues with products on the manufacturing line. Taken together, these capabilities can improve both the accuracy and speed of inspections and quality control, helping companies to reliably meet regulatory requirements and avoid costly delays that disrupt the drug supply chain. These proactive measures can also help avoid downstream quality manufacturing issues that result in shortages and impact patient care.

III. LIMITATIONS OF CURRENT REGULATORY FRAMEWORK AND POTENTIAL TOPICS FOR FUTURE GUIDANCE

Premier is a strong proponent of harmonizing current regulations with principles of responsible AI to minimize disruptions. Rather than considering new regulations, Premier urges the FDA to consider the priorities for AI regulation highlighted below and incorporate them into current regulations, providing clarity and supporting innovation. Premier fundamentally believes that principles for responsible AI in the drug manufacturing process, and in healthcare more broadly, are well-aligned with the current priorities of the FDA, including data quality, transparency and unbiased outcomes. Therefore, Premier asks the FDA to incorporate clear guidance on the use of AI into existing regulations and issue comprehensive, harmonized guidance in a timely manner. Aligning and harmonizing timelines for guidance on the use of AI in drug manufacturing and guidance on AI in clinical trials is particularly critical for preventing fragmentation of the drug development and manufacturing pipeline.

Premier strongly believes that AI can play a transformative role in supporting private sector initiatives to alleviate drug shortages, such as Premier's ProvideGx program, and re-imagining a more transparent and

resilient drug supply chain. To effectively harness recent and future advances in AI technology, Premier calls on the FDA to emphasize the following areas in future guidance:

1. Data Quality Guidelines. Premier understands the importance of data standards, responsible data use and data privacy in the development and deployment of AI technology. Data standards should specifically focus on objective assessment of potential sources of bias or inaccuracy introduced through poor dataset construction, cleaning or use. These may include, but are not limited to, appropriately representative datasets, bias in data collection (e.g., subjectivity in clinical reports) or introduced by instrument performance or sensitivity (e.g., pulse oximetry devices producing inaccurate measurements of blood oxygen levels in patients with darker skin), bias introduced during curation (e.g., datasets with systemically introduced nulls and their correlation, such as failure to pursue treatment due to lack of ability to pay), and training and test data that is appropriately applicable to various patient subpopulations (e.g., data that sufficiently represents symptoms or characteristics of a condition for each age/gender/race of patient that the tool will be used to treat). Premier also supports the establishment of guidelines for proper data collection, storage, and use that sufficiently protect patient rights and safety. This is particularly important given the sensitivity of health data.

2. Cybersecurity Standards. The baseline standards currently proposed by the FDA to govern data storage and cybersecurity are inadequate to ensure patient data is protected and secure. The provisions of 21 CFR part 11 are valuable to ensure the integrity and validity of patient records, but do not adequately establish best practices for confidentiality, privacy or cybersecurity. These crucial components of patient protection should not be left up to trial administrators to determine. Premier strongly recommends that the FDA provide guidance on key cybersecurity concerns arising during decentralized clinical trial design and execution.

The FDA should lay out a minimum cybersecurity standard for the transmission and storage of participant health data on or using digital health technology. In addition to the standards for authentication and access control contained in 21 CFR part 11, these standards should include a requirement for end-to-end encryption for data-in-transit and encryption standards for data-at-rest. The FDA could even consider bolstering the access control requirements of 21 CFR part 11 to include a zero-trust architecture mandate. The FDA should also require that all data collected during a decentralized clinical trial should be stored in a secure centralized repository to mitigate cybersecurity and privacy risk. Administrators of a decentralized clinical trial should also be required to develop a cybersecurity plan that covers each of the digital health technologies that will access patient health information during the trial.

By clarifying and bolstering these standards, the FDA can ensure that the privacy and confidentiality of health data that may be used at various stages of drug manufacturing or testing is prioritized. Premier expects a period of innovation in trial design, drug development and drug manufacturing as the permitted uses of AI expand, and the FDA should take care to ensure participant privacy is not an unintended casualty of digitization.

3. Eliminating Bias. Premier believes that AI technology must be developed and deployed with special attention towards algorithmic discrimination for vulnerable, underserved communities. While AI has immense potential to improve healthcare and drug supply chains across the ecosystem, developers and users of AI technologies must be conscious of unique challenges introduced by data limitations, inappropriate or unintended use of AI technologies and potential automation bias among medical professionals.

Premier has unique expertise in harnessing data to improve care for underserved populations. PINC AI Applied Sciences has assembled a HIPAA-compliant database containing over one billion data points representing 25 percent of U.S. hospital inpatient and outpatient discharges drawn from a geographically diverse collection of more than 1,000 U.S. hospitals over the past twenty years. PINC AI Applied Sciences has used this data to identify disparities among patients diagnosed with opioid use disorder, educate on the impacts of trauma and design and test solutions to drive health equity. Premier is able to leverage AI technology to move the needle on health equity because we are committed to ensuring our data sources, collection, curation and use adhere to the highest standards of quality.

It is also critical to ensure that AI tools are used as intended to limit bias, discrimination or other adverse impacts. Premier understands that an AI technology or dataset that is highly accurate for one patient, subgroup, drug or condition may not provide the same insight or accuracy for another. Premier strongly recommends that any standard or certification of AI technology include a requirement that developers provide a detailed description of the intended use cases for the tool or device. Users should then be required to only use that device for certified use cases. In many cases, AI technologies are highly specialized. The dataset that an AI device is trained on may be representative of a particular population, condition, procedure, or specialty; however, there should be no assumption that the same dataset is representative for use cases beyond that design.

4. Promoting Transparency and Explainability. Trust – among all members of the drug supply chain – is critical to the development and deployment of AI tools in healthcare settings. To earn trust, AI tools must have an established standard of transparency. Recent policy proposals, including those proffered by the Office of the National Coordinator for Health Information Technology (ONC), suggest transparency can be achieved through a "nutrition label" or "model card." This approach seeks to demystify the "black box" of an AI algorithm by listing the sources and classes of data used to train the algorithm and/or used as an input. Unfortunately, some versions of the "nutrition label" approach to AI transparency fail to acknowledge that when an AI tool is trained on a large, complex dataset, and is by design intended to evolve and learn, the initial static inputs captured by a label would not provide accurate insights into an ever-changing AI tool. Premier recommends that AI technology in healthcare should be held to a standardized, outcomes-focused set of metrics, such as accuracy, bias, false positives, inference risks, recommended use, and other similarly well-defined values. Outcomes, rather than inputs, are where AI technologies hold potential to drive health or harm. Thus, Premier believes it is essential to focus transparency efforts on the accuracy, reliability and overall appropriateness of AI technology outputs in healthcare to ensure that the evolving tool does not produce harm.

Premier has commented repeatedly about the importance of ongoing testing to determine accuracy and prevent bias in AI applications. Additionally, Premier has advocated for transparency into when information or recommendations are generated by an AI system. However, the concept of transparency cannot be completely disentangled from the concept of explainability. In response to any discussion draft on AI, the FDA will likely receive many comments urging them to incorporate explainability; however, Premier urges individuals designing regulations for the use of AI in drug manufacturing to carefully tailor explainability requirements to the end user of the AI system. While Premier's recommendations for a "nutrition label" or "model label" represent a general vehicle for transparency and explainability, it is important to remember that different uses of AI, such as for drug manufacturing or supply chain management, have different end users who may need a higher degree of visibility into how the AI system reaches a decision and the factors it considers.

5. Appropriate Use. The risks and safety concerns around AI technology are unique to each use case, and Premier supports the requirement of a risk assessment and mitigation plan specific to the level of risk associated with the use case. For example, the use of AI systems to identify potential patients or clinical trial participants involves different concerns, such as privacy and confidentiality, and carries a different level of risk than the use of AI to develop a dosing regimen for a trial. Similarly, AI used to predict drug component shortages has a different level of risk than applications used for quality assurance testing.

Premier also supports the development of standardized intended use certifications or reporting requirements for AI technologies, which would prevent new systems from producing harmful outcomes due to use outside of the technology's design. Whether the intended use of a technology is ongoing safety and quality monitoring, digital endpoint analysis, supply chain visibility, or industrial controls, the training protocol and appropriate data set will have several key differences. Therefore, it is crucial that drug developers know the intended context, such as condition, applicability, and use case, of each AI system.

IV. NECESSARY ELEMENTS FOR MANUFACTURERS TO IMPLEMENT AI-BASED MODELS IN A CURRENT GOOD MANUFACTURING PRACTICE (cGMP) ENVIRONMENT

While Premier has highlighted above the ways that AI can support manufacturing, the FDA must highlight how cGMP regulations translate to AI technology to remove regulatory uncertainty and allow innovators to implement AI throughout the drug manufacturing process. Premier offers solutions and specifically requests guidance or clarification on how the following elements of GCMP translate to AI technologies.

- **21 CFR Part 211.84.** Premier urges the FDA to issue specific guidance and standards permitting the use of AI technology to augment quality control data collection and analysis. These standards should outline basic standards for the use of data to train AI and the required procedure, explainability and disparity/quality testing for AI technology.

- **21 CFR Part 211.105, Part 211.119.** Premier suggests that the FDA offer guidance on these sections to include specific callouts for AI technology, to also include requirements for AI data retention, auditability and reporting.

- **21 CFR Part 211.160.** Premier suggests that the FDA include a specific definition of AI technologies used as instruments. This should include details such as requirements for quality monitoring of AI tools, limits for accuracy/precision and procedures for remediation if standards are not met.

- **21 CFR Part 211 Subpart J.** Premier urges the FDA to issue explicit guidance on Subpart J containing details on data and record retention for AI technologies, the decisions and predictions made by AI technologies and related data and records. Premier also suggests that the FDA issue guidance on the production and contents of auditable AI reports to establish compliance with general cGMP reports and records requirements.

V. VALIDATING AND MAINTAINING SELF-LEARNING AI MODELS

In recent years, the FDA has taken important steps to consider how AI/ML-driven medical devices should be treated during the trial and approval process. The resulting guidance and action plan introduced a new strategy for handling the evolving nature of AI algorithms in Software as a Medical Device (SaMD). One

core component of this model involves outlining SaMD Pre-specifications (SPS), a collection of potential changes that the device manufacturer intends to incorporate into the device over its lifetime. Types of pre-specifications include retraining for performance improvement, new data acquisition systems, and changes related to the intended use. While this discussion draft specifically asks about how SPS can be managed within drug development, the corollary Algorithm Change Protocol (ACP) – which details how changes in the SPS will be performed and validated – provides an equally important guide to navigating evolving algorithms in drug development. Premier believes that this same model can be used to effectively validate and maintain AI models used throughout the drug manufacturing process.

1. Pre-specification: Premier suggests that the FDA can use this model to acknowledge and address the evolving nature of algorithms, but any application of this model to drug manufacturing must first acknowledge that the AI/ML systems used are not SaMD and are not themselves subject to approval. It is necessary to adjust the purpose of Pre-Specification reporting and logging from approval to the appropriate drug development use case. For the use cases highlighted in this discussion draft, Premier suggests that three principles can guide management:

- **Predictability**: Pre-specification activities should be predictable. Changes to intended use or the introduction of new data acquisition systems should be done in a predictable and auditable manner. For example, if an AI system is being used to monitor quality or manage component supply chains, the manufacturers should be able to predict the timeline for an update or new feature to ensure consistency and provide the cGMP-required audit trail. Premier suggests that all developer-driven updates detailed in Pre-Specification should be implemented on a publicly available timeline that allows manufacturers and regulators to build in consistency across the use of the tool, with the goal of ensuring that the use of different AI tools does not introduce variability or inaccuracy into drug manufacturing. For Pre-specification activities driven by a continuously adaptive algorithm, such as the incorporation of new data for retraining or enhancement, the process used should be predictable, consistent and technically explainable to manufacturers and regulators.

- **Reliability**: Pre-specification activities should not affect the reliability of an AI tool. Elsewhere in these comments, Premier has argued the importance of ongoing disparity testing and evaluation. Pre-specification activities should be no exception. Premier supports the implementation of a standardized format for reportable, continuous model evaluation to ensure that the overall accuracy and reliability of the AI system does not change after any update, either developer-driven or as the result of an adaptive algorithm. This could take the form of regular tests or a method to flag irregular results, either of which would provide indicators that a pre-specification activity fundamentally changed the AI system. This is also a crucial step to compliance with cGMP's data retention and audit requirements.

- **Attributability**: Premier believes that the recommendations above should be logged and tracked. Any form of update to the AI/ML system should be recorded in a log available to drug manufacturers currently using the system, should be attributable to either a developer update or continually adaptive algorithm feature, and should be trackable over time.

2. Algorithm Change Protocol: The Algorithm Change Protocol (ACP), as described in this FDA presentation, provides a roadmap to implementing the principles outlined above. Premier urges the FDA to issue guidance on a similar procedure that AI/ML technologies designed for use in drug manufacturing would provide to trial administrators. As the FDA cannot directly regulate the technologies used as a resource by drug developers, Premier suggests that they instead establish

minimum reporting standards for sponsors based on the information above, which must be provided to the FDA as part of pre- and post-trial submissions. These could detail the information that drug manufacturers should require from the AI tools they use, as well as require pre-specification plans and ACPs for the technology used to ensure those standards will be met.

VI. MITIGATING RISKS OF BIAS AND MISUSE

Premier reiterates our comments above on the need for data quality standards, transparency and explainability, and cGMP data retention and reporting requirements for AI used in drug manufacturing. In addition, Premier would like to highlight the following potential ways to ensure quality, accuracy and fairness in AI technology:

1. Ongoing Disparity Testing. Premier has previously supported ongoing disparity testing and quality assurance as a cornerstone of responsible AI. This element should be adapted to the drug manufacturing process by requiring the creation of auditable reports detailing outputs or decisions from AI technologies used in advanced process control or quality evaluation. This requirement would both ensure relevant records are maintained and also provide a quantifiable yet unintrusive metric to evaluate AI performance. Most importantly, this requirement would provide transparency and regulatory clarity without sacrificing intellectual property or publicizing proprietary algorithms.

2. Workforce Training. Premier believes technology can work alongside and learn from healthcare professionals, but current technology cannot and should not replace the healthcare workforce. Premier reiterates the importance of comprehensive risk assessments, recommended use, and trainings that combat automation bias and incorporate human decision-making into the use of AI technology in healthcare. The risks and safety concerns around AI technology are unique to each use case, and Premier supports the requirement of a risk assessment and mitigation plan specific to the level of risk associated with the use case. Premier also supports the development of standardized intended use certifications or reporting requirements for AI technologies, which would prevent new systems from producing harmful outcomes due to use outside of the technology's design. Finally, Premier acknowledges the risks of automation bias and fully automated decision-making processes.

To reduce these risks, promote trust in AI technologies used in healthcare and achieve the goal of supporting the healthcare workforce through AI, Premier recommends that federal workforce training programs provide comprehensive AI literacy training for the healthcare workforce. Healthcare workers deal with high volumes of incredibly nuanced data, research, and instructions – a growing percentage of which may be supplied by AI. This is particularly true for applications of AI in drug development, where manufacturers and quality control specialists may be reviewing high volumes of AI-powered recommendations or insights and making rapid decisions that affect the safety of patients. By ensuring our healthcare workers, including healthcare workers in drug manufacturing facilities, understand how to evaluate the most appropriate AI use cases and appropriate procedures for evaluating the accuracy or validity of AI recommendations, we can maximize the advisory benefit of AI while mitigating the risk to patients. Additionally, clear, risk-based guidance on which uses of AI technology in healthcare require human review and decision-making, similar to the principles discussed in section five of the OSTP's AI Bill of Rights, is essential.

3. Watermarks. Watermarking or provenance data/systems for AI-generated content were a component of the voluntary commitments recently announced by the White House. Premier generally supports the development of similar metrics for scientific research or clinical decision

support recommendations produced by AI technology. It is important that patients, scientists, drug manufacturers and medical professionals understand when decisions or recommendations are made by AI so they can consciously respond and evaluate the new information accordingly.

Specifically, watermarking is one potential strategy to combat automation bias, a risk especially pertinent to the use of AI technology in healthcare. Automation bias refers to human over-reliance on suggestions made by automated technology, such as an AI device. This tendency is often amplified in high-pressure settings that require a rapid decision. The issue of automation bias in a healthcare setting is discussed at length by the FDA in guidance on determining if a clinical decision support tool should be considered a medical device. Premier suggests that future guidance or standards for the use of AI should consider automation bias in risk assessments and implementation practices, such as workforce education and institutional controls, to minimize the potential harm that automation bias could have on patients and vulnerable populations, including to mitigate any potential risk of AI used in unintended settings or built on biased datasets. In the drug manufacturing process, it is important that workers evaluating a supply chain disruption prediction, optimization recommendation or quality control report know that the data or recommendation is AI-generated and evaluate it effectively.

VII. CONCLUSION

In closing, Premier appreciates the opportunity to respond to FDA's comment solicitation on AI in drug manufacturing. If you have any questions regarding our comments, or if Premier can serve as a resource on these issues for policy development, please contact Mason Ingram, Director of Payer Policy, at Mason_Ingram@premierinc.com.

Sincerely,

Soumi Saha, PharmD, JD
Senior Vice President of Government Affairs
Premier Inc.