Regulatory initiatives for artificial intelligence applications: Regulatory writing implications

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Abstract

Applications of artificial intelligence (AI)/machine learning (ML) components in drug development are growing exponentially. The trend is expected to continue. The growth has resulted in increased engagements on the part of regulatory agencies to ensure safe and effective use. This article explores the utilisation and opportunities in three areas: medical devices (built-in software applications); post-marketing surveillance (processing of large volumes of reported adverse reactions); and clinical development (pharmacokinetic profile, dose selection, clinical trial design, and regulatory writing). AI/ML-based applications are not perfect. Potential risks are enormous. Continued public/private engagement, vigilance, and oversight for all parties is essential for successful utilisation of these tools.

Introduction

Technological innovations have revolutionised computing architecture, opening new horizons in drug development. The processing power, the ability to scan through a variety of data sources and synthesise information using established rules have enabled researchers to explore areas that were previously beyond reach.

As per International Medical Device Regulatory Forum,[1] "Artificial Intelligence" (AI) is a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviours such as learning, making decisions, and making predictions. The subset of AI known as machine learning (ML) allows ML models to be developed by ML training algorithms through analysis of data, without models being explicitly programmed."

The number of regulatory submissions with AI/ML components is growing, with ~10-fold increase in 2021 compared to 2020.[2] This trend is expected to continue. Common types of analysis included outcome prediction, covariate selection, image analyses, modelling, dose selection/adjustment, endpoint/biomarker assessment, and post-marketing surveillance.

The diverse applications of AI/ML in drug development have led to increased focus on part of regulatory agencies in developing guidelines and discussion papers to ensure the safe and effective development of new treatments, including devices. In a broader effort to communicate with various stakeholders, the FDA issued a discussion paper in May 2023, requesting feedback on the use of AI and ML in the development of drugs and biologics.[3] This discussion paper focuses on the landscape of current and potential uses of AI/ML and considerations for the use of AI/ML along with next steps for stakeholder engagement.

This paper reviews recent AI/ML-based applications in drug development, associated challenges, relevant regulatory guidelines, and implications for regulatory writing.

AI/ML applications in medical devices

AI-based systems are typically implemented as software in medical devices or as Software as a Medical Device (SaMD). The first AI-based medical device approved by the FDA in April 2018[4] (IDx-DR) is a software program that used an AI algorithm to analyse images of the eye taken with a retinal camera to detect diabetic retinopathy in adults with diabetes.

Since then, the use of AI/ML-based devices in healthcare settings and daily life has grown exponentially. AI/ML-based technologies are being used by medical device manufacturers for product innovation, patient care, and improving quality of life. The built-in algorithms in the devices are programmed to learn from real-world experiences and adapt accordingly, e.g., sensors, stimulators, glucose monitors, enhanced imaging systems, wearable devices, etc. The number of approvals is steadily increasing, with 41 approvals in 2022 and 15 approvals as of April 30, 2023.[5] Examples of recent approvals include the Prospera™ spinal cord stimulation system, an implanted spinal cord stimulation system intended to treat long-term (chronic) pain, and the MiniMed™ 780G system intended to continuously measure glucose levels to manage type 1 diabetes mellitus in adults and children.[5]

In recent years, there has been increased collaboration between the FDA and other regulatory agencies. The goal is to mitigate potential adverse consequences of algorithm changes on patients' safety and wellbeing and support favourable benefit/risk balance. The complexities involved are enormous, given the continuous auto modifications of rules as part of ML.

The FDA, Health Canada, and MHRA jointly identified 10 guiding principles for medical device development to promote safe, effective, and high-quality medical devices that use AI and ML.[6] Although these principles were developed for medical device development, many of these (e.g., multidisciplinary collaboration; data quality assurance, software engineering and good security practices; representativeness of study participants, and data sets) are also applicable to drug development.

In April 2023, the FDA issued a new draft guidance ''Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device

Software Functions".[7] In this guidance, the FDA recognises that the development of ML-enabled device software functions (ML-DSFs) is an iterative process. The guidance describes an approach that would "support the ability to modify an ML-DSF while continuing to provide a reasonable assurance of safety and effectiveness across relevant patient populations". The guidance also provides helpful tools for medical writers in preparing quality documents for submission. It elaborates on the goals and contents of the device modification protocols. It also describes the required documentation regarding the assessment of the benefits and risks of implementing a Predetermined Change Control Plan for an ML-DSF, as well as the mitigations of those risks. The plan can be submitted as part of the marketing submission to ensure the continued safety and effectiveness of the device.

AI/ML applications in post-marketing safety surveillance

Another AI/ML-based application is in post-marketing surveillance. In the US, FDA's MedWatch, a medical product safety reporting program, is used for reporting adverse drug reactions (ADRs) by healthcare professionals and consumers. The FDA Adverse Events Reporting System is a database containing ADRs, medication error reports, and product quality complaints that have been submitted to the FDA.

The volume of data is large, and the sources consist of a mixture of structured and unstructured data, and substantial processing is required to make these data usable. AI/ML-based systems are used by sponsors, independent pharmacovigilance providers, and regulatory bodies for case processing, case evaluations (assessing the likelihood of a causal relationship between the drug and the adverse event (AE)), and case submissions (aggregate reports in a time-sensitive manner).

The FDA uses the Sentinel system for the safety surveillance of medicinal products.[8] It was initially launched in May 2008. Its capabilities have expanded significantly and continue to grow since the initial launch. It uses natural language processing and other ML approaches to extract and process relevant information from submitted AE reports. The future of the system is outlined in Sentinel System Five-Year Strategy: 2019-2023.[9] The goal is to incorporate emerging data sciences and electronic health records data for safety surveillance.

In the EU, EMA's Pharmacovigilance Risk Assessment Committee is responsible for assessing and monitoring the safety of human medicines. The reported ADRs are collected in the Eudra Vigilance database, which is used to detect emerging safety signals.[10]

Additionally, AI/ML-based applications are useful for data tabulation and summary reports for authoring periodic safety reports and other documents based on post-marketing surveillance data.

AI/ML applications in clinical development

AI/ML-based applications in healthcare have gained considerable momentum in recent years and are continuously growing.[11] The most common applications are in oncology and neurology and are used in the design and conduct of clinical trials, the selection of stratification variables for randomisation, the implementation of enrichment strategies, site selection, clinical outcome measures, and the assessment of endpoints. These tools are also used in modelling and simulation to predict pharmacokinetic profiles, exposure-response relationship to help dose selection, and optimisation.

Additionally, the COVID-19 pandemic led to an uptake in the use of digital health technologies

(DHTs), including telehealth, remote monitoring, and patient portals. The FDA issued a new guidance in Dec 2021 regarding the use of DHTs for remote data acquisition.[12] The guidance provided directions and recommendations for selection of DHTs suitable for clinical investigation, validation of DHTs, and use of DHTs in collecting data. It also elaborated on the identification and management of risks associated with the use of DHTs in clinical trials.

Familiarity with new guidance documents regarding decentralised trials and DHTs is essential for medical writers involved with protocol preparation. It helps to adequately describe the study endpoints, efficacy, and safety measures assessed using a DHT, and the assessment schedule.

The ML based tools are also frequently being used in authoring regulatory documents, particularly for the "reuse" of information from previously approved documents (e.g., trial protocols, statistical analysis plans, data tables, and/or sections of final clinical study reports) in new study reports or summary documents. There is considerable efficiency when these tools are used appropriately.

However, it requires vigilance on the part of the medical writer and others in the development team to ensure the accuracy and validity of all source materials utilised, including data collection tools, curation, and review. It is encouraged to list the details involved in every step and include them in the electronic Common Technical Document to enable verification during the review process. Overall, the AI/ML tools when used judiciously are helpful and can expedite the submission process.

AI/ML applications have opened pathways for disease areas where conventional placebo-controlled randomised trials are not feasible. In these cases, AI/ML-based applications have enabled the use of real-world data (RWD) and real-world evidence (RWE), which refer to data collected outside of trials in routine healthcare settings (such as claims data, electronic health records, registries, etc.). New guidance documents from the FDA and EMA in recent years have provided much needed guidance on the use of these alternative resources and have encouraged discussions with Sponsors to address concerns throughout the development cycle.

One particular application is data curation for data collected from numerous diverse sources outside the clinical trial, each with a different purpose for data collection leading to missing data, incomplete data dictionaries, uncoded data, etc. ML-based tools have helped to make the data fit for use in clinical trials and in sophisticated algorithms for accurate diagnostic assessments.[13]

Other AI/ML-based applications include the ability to interact with patients remotely, reducing the need for in-person visits and enabling access to a diverse population. This has the potential for improved retention and compliance. The opportunities and challenges are further elaborated in the FDA guidance on decentralised trials, that is, trials where the activities occur outside of clinical sites (patient's home or other healthcare settings).[14] The guidance provided is helpful for medical writers to address issues related to protocol deviations, baseline comparability, and remote assessments.

Other regulatory initiatives

Ethics guidelines for trustworthy AI were issued in April 2019 by the EMA High-Level Expert Group on AI.[15] This included seven key requirements: human oversight; technical robustness and safety; privacy and data governance; transparency; diversity, non-discrimination and fairness; societal and environmental wellbeing; and accountability. The goal was to minimise unintentional harm, foster diversity, and ensure adequate data governance mechanisms. Following a piloting process, the prototype was revised and the final list was published in 2020.[16]

The International Coalition of Medicine Regulatory Authorities Informal Network for Innovation working group led by EMA provided the following recommendations to regulators to address challenges posed by AI.[17] The report called for regulatory guidelines related to AI for "data provenance, reliability, transparency and understandability, pharmacovigilance, and real-world monitoring of patient functioning", and recommended that regulators "may need to apply a risk-based approach" when assessing and regulating AI. Additional recommendation for sponsors and developers includes setting up "strong governance structures to oversee algorithms and AI deployments that are closely linked to the benefit/risk of a medicinal product".

These new directives enforce ethical use, reliability, and transparency of the sources and applications, which are vital in authoring high-quality documents.

Discussion and conclusions

The AI/ML applications are wide ranging. The ability to scan through myriad unstructured data sources, synthesise using established rules, and predict new targets and potential solutions have changed the landscape and offer new hope. It has the potential to identify the "bad factor" and further replacements to create a new treatment paradigm.

AI/ML-based applications, like any other tool, are not perfect. The potential risks are not transparent, ML outcomes are not foreseeable, and the consequences could be serious. To be used effectively, all AI-based applications (software and devices) must undergo a stringent validation process before being implemented in clinical practice.

The growing awareness of the potential safety risks has prompted discussions in both public and private settings to seek solutions. The effective use of documents authored using AI/ML applications require parallel review by specialists; one is not a replacement for the other. "AI and human intelligence offer synergy for responsible innovation and veritable prospects for improving healthcare from prevention to diagnosis to therapeutics while unintended consequences of automation emergent from AI and algorithms should be borne in mind on scientific cultures, work force, and society at large".[18]

One other major concern is data privacy. The search and decision-making algorithms built in ML-based applications may lead to unanticipated inferences and predictions. "As artificial intelligence evolves, it magnifies the ability to use personal information in ways that can intrude on privacy interests by raising analysis of personal information to new levels of power and speed".[19] There is also a potential for leaking and misusing patients' data. Adequate steps must be taken to safeguard privacy.[20]

In summary, AI/ML-based applications, when used effectively, hold a lot of promise. These tools have potential applications in all stages of drug development, including designing new molecules, identifying disease targets, increasing the efficiency of clinical trials, and post-marketing safety surveillance.

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