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Whitepaper

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Artificial Intelligence – Transforming Regulatory Affairs

Summary

Introduction

Artificial intelligence (AI)/Machine Learning (ML) is emerging on the scene of the ever-evolving landscape of regulatory affairs. As the pharmaceutical industry navigates through a complex web of regulations, the integration of AI presents itself as a useful tool. From expediting approval processes to enhancing monitoring and compliance measures, the partnership between AI and regulatory affairs holds promise in terms of increased efficiency and adaptability.

It is worth noting that EMA and FDA are currently in consultation with stakeholders to determine the most appropriate way(s) of implementing and regulating AI in pharmaceutical industry. Read on for an overview of various ways in which AI could reshape the landscape of regulatory affairs, exploring the promises and challenges that lie ahead.

Overview

Artificial Intelligence (AI) is a field of computer science that focuses on creating machine learning systems that can perform tasks requiring human intelligence with some degree of autonomy. Learning from experience, making decisions, understanding language, recognising patterns, and solving complex problems are some of the examples of tasks requiring human intelligence, where AI can be used. AI aims to develop computers and software that can simulate human-like cognitive processes, with a level of proficiency that approaches or surpasses human capabilities. One of the key areas where AI has proven itself to be as good as, if not better than human capabilities, is the analysis and processing of large datasets to make predictions or decisions.

Machine Learning (ML) is a subset of AI that involves the development of algorithms and models that enable computers (machines) to learn and make predictions or decisions without being explicitly programmed for every specific task.
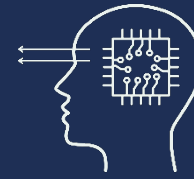
Artificial Intelligence

A field of computer science & technology that aims to create systems, programs, or machines capable of performing tasks that typically require human intelligence.

Machine Learning

A subset of artificial intelligence that focuses on developing algorithms and statistical models that enable computers to learn from and make predictions or decisions based on data without being explicitly programmed.

Deep Learning

A subfield of machine learning that uses artificial neural networks with multiple layers (deep neural networks) to model and solve complex problems.

AI and Modern Medicine

Modern medicine is advancing partly due to the integration of technology. Recently, AI is being used at an increasing capacity for the purposes of patient care, diagnosis, and treatment planning, offering accurate insights, improved efficiency, and better patient outcomes. AI-enabled devices have the capacity to analyse vast amounts of data efficiently, whilst supporting the decision-making process.

AI and AI-enabled devices hold promise when used with wide range of applications such as medical imaging analysis, drug development and more.

Given the capabilities of AI in a wide range of applications, Health Authorities around the world can implement tools to speed up assessment timelines, reduce the need for unnecessary requests for information, and effectively monitor safety of a medicine/device in real world use.

Exploring Potential Uses of AI By The Industry, FDA, and EMA

The European Medicines Agency (EMA) and Food and Drug Administration (FDA) have plans to implement AI and are currently consulting stakeholders for their comments. Some of the ways EMA and FDA could use AI includes, but not limited to:

Data Analysis and Pattern Recognition

AI algorithms can analyse large amounts of data from clinical trials, real-world evidence, and other sources to identify patterns and correlations that might not be immediately apparent to human reviewers. They are helpful in identifying potential safety concerns, efficacy tends, and patient subpopulations that might benefit from the medication.

Predictive Analytics

AI models can predict the likely outcomes of a drug's performance based on historical data, characteristics, and real-world evidence. This can be helpful in identifying potential risks or benefits associated with a new medicine/device.

Safety Monitoring and Risk Assessment

AI can continuously monitor post-marketing safety data to quickly identify and assess any adverse events. Potentially, this can result in a faster response to safety concerns and the ability to make regulatory decisions promptly. AI can assist in evaluating potential benefits and risks of medication based on a wider range of data sources than what human experts can manage.

Natural Language Processing for Review of Applications and Dossier Assessment

Natural Language Processing can be used to review and extract relevant information from clinical and non-clinical study reports, medical literature, and patient records. This can expedite the review process and help EMA/FDA experts to focus on critical areas. AI can also assist in review of application dossiers by highlighting key points, discrepancies, or missing information, allowing experts to focus on critical aspects. This will free up human resources, potentially reducing the overall review time.

Drug Interaction Analysis

AI algorithms can predict potential drug-drug interactions by analysing and comparing chemical properties of medications and applying the analysis to computer models representing human anatomy.

Personalised Medicine

AI can help identify patient subgroups that are more likely to respond positively or negatively to a medication enabling tailored treatment strategies.

In conclusion, AI systems can learn and adapt over time, incorporating new information and insights into the overall decision-making process that the agencies adopt. It will be a useful tool that could potentially help the agencies improve efficiency and focus.

Progress Update from The European Medicines Agency

[EMA has published a draft reflection paper](#), outlining EMA's current thinking on the use of AI. The responsibilities of the stakeholders, and EMA's future intentions are described, while exploring different ways of implementing AI and Machine Learning (ML) to the lifecycle of medicinal products.

The agency recommends a risk-based approach for development, deployment and performance monitoring of AI and ML tools. It is important to pro-actively define the risks to be managed throughout the medicinal product lifecycle.

EMA recommends that the Sponsors and Marketing Authorisation Applicants seek early regulatory interaction or Scientific Advice, if AI/ML system(s) is used in the context of development, evaluation, or monitoring. A through impact assessment of such systems on benefit-risk of a medicinal product should be

conducted, and if there is a potential impact, the agency recommends an early regulatory interaction or scientific advice.

The agency explicitly states that:

> *It is the responsibility of the marketing authorisation applicant or MAH to ensure that all algorithms, models, datasets, and data processing pipelines used are fit for purpose and are in line with ethical, technical, scientific, and regulatory standards as described in GxP standards and current EMA scientific guidelines.*

EMA's Regulatory Vision

From a regulatory perspective, the application of AI in the process of drug discovery is potentially a low-risk setting. The main justification for such risk classification is that a non-optimal performance of AI often mainly affects the sponsor.

The application of AI/ML to non-clinical development may take place in various forms. AI/ML modelling approaches could change the way the animal studies are conducted. The agency recommends consideration of '*Application of GLP Principles to Computerised Systems*' and '*GLP Data Integrity*' during non-clinical development.

ICH (GCP) E6 applies to the use of AI/ML within the context of clinical trials. If a model is generated, the full model architecture, logs from modelling, validation and testing, training data and description of the data processing pipeline should be made available for comprehensive assessment at the time of marketing authorization application or clinical trial application. It is important to reflect the use of AI/ML in the benefit/risk assessment. In the context of early phase clinical trials, where data from early phase trials may have a substantial regulatory impact, it is recommended that the regulatory requirements are discussed with the agency through early regulatory interaction(s). In the context of late-stage pivotal clinical trials, all risks related to overfitting and data leakage must be carefully mitigated. Incremental learning approaches are not accepted, and any modifications of the model during the trial requires a regulatory interaction to amend the statistical analysis plan.
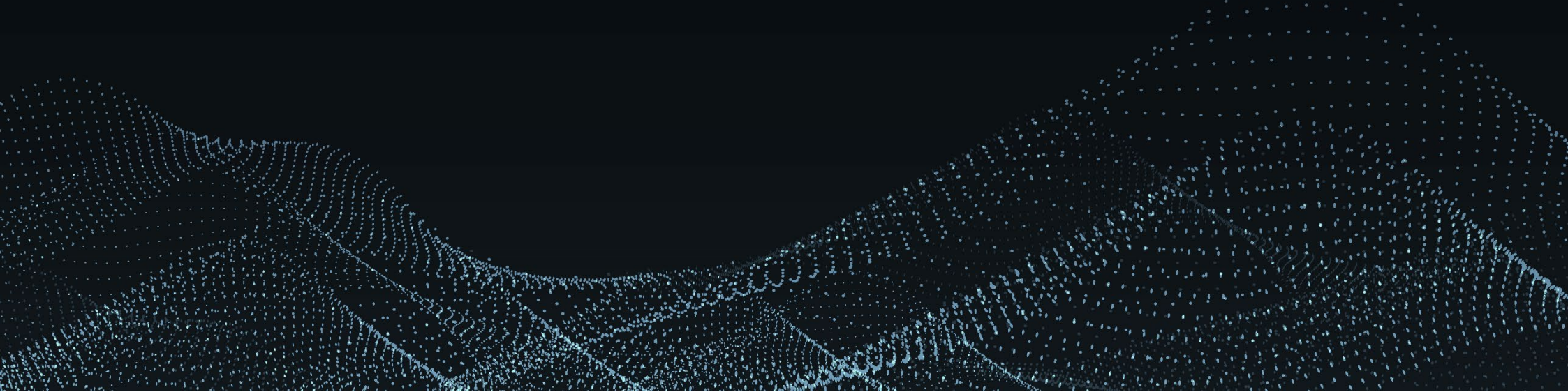
In the context of statistical analysis, AI/ML models should include analysis of the impact on downstream statistical interference.

In the context of precision/personalised medicine, AI/ML shows promise. AI/ML applications can be referenced in the Summary of Product Characteristics (SmPC) to aid decision making. Such use is classed as a high-risk use by the Agency, related to both patient risk and level of regulatory impact.

Post-authorization activities can be effectively supported by AI/ML tools. Incremental learning approaches to enhance models for classification and severity scoring of adverse event reports as well as signal detection is allowed. In the context of a post-authorisation study (PASS and PAES), AI/ML applications should be discussed with the Agency.

AI/ML models are vulnerable to the integration of human bias. It is recommended that necessary precautions are taken to minimise the risk of human bias within AI/ML models.

It is the responsibility of the applicant to ensure that all personal data, including those indirectly held within AI/ML models are stored and processed in accordance with GDPR.

Progress Update from The Food and Drug Administration

FDA has published an AI/ML for Drug Development Discussion Paper. It is worth noting that the information discussed in the FDA publication is should not be taken as guidance or policy. The publication is an initial communication with the stakeholders, intended to promote mutual learning and discussion.

The content of the discussion paper is similar to the content of the draft discussion paper published by the EMA. Hence, a short summary of the unique discussion points from the FDA discussion paper is provided:

- In the context of drug development, AI/ML can analyse significant amounts of information from existing scientific research, publications, and other data sources. The growth of available genomic, transcriptomic, proteomic, and other data sources from healthy persons and those with a specific disease of interest provide a significant opportunity to inform biological target selection. It can also provide information on the potential structure and function of biological targets to predict their role in a disease pathway.
- During compound screening process, AI/ML can predict chemical properties and bioactivity of compounds,

efficacy and potential adverse events based on the specificity and affinity for a target.

- In the context of non-clinical research, there are efforts to explore the use of novel algorithms such as neural network models for PK/PD modelling.
- AI/ML has the potential to be a very powerful tool for clinical research. AI/ML has the potential to inform the design and efficiency of non-traditional designs such as decentralised clinical trials, and trials incorporating the use of Real-World Evidence/Data. In addition:
  - AI/ML is increasingly being developed and used to connect individuals to trials, intended to improve the recruitment process.
  - Enrichment strategies can aid participant selection to reduce risks such as early dropouts, adherence, retention and site selection.
  - Predictive models can be used for participant stratification. For example, AI/ML has the potential to predict the probability of a serious adverse event before an investigational medicinal product is administered.
  - AI/ML can be used to optimise the dose/dosing regimen selection.
- Advanced analytics leveraging AI/ML in the pharmaceutical manufacturing industry offers many possibilities such as, enhancing process control, increasing equipment reliability and throughput, monitoring early warning or signals.
- Digital twins can be used in process design optimisation.
- Trial operational conduct could be optimized by utilising AI/ML to help identify which sites have the greatest potential for a successful trial and to aid sites in identifying process gaps.
- In the context of manufacturing, advanced process control algorithms allow dynamic control of the process to achieve a desired output. Neural networks along with real-time sensor data with smart monitoring of production lines improve the efficiency and output.

FDA established various initiatives to support development of innovative and robust AI/ML systems. CDER AI Steering Committee is responsible for coordinating the efforts around AI/ML uses across therapeutic development. CDRH and DHCoE (Digital Health Center of Excellence) provides consultation for drug submissions that involve AI/ML and are developing a framework for AI/ML based devices. In addition, CDER developed the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program, which is designed to expand drug development tool (DDT).

Conclusion

The synergy between AI/ML and regulatory affairs presents an exciting, innovative, and transformative opportunity. The potential benefits are vast and captivating, from streamlining approval processes to the potential reduction of animal use during non-clinical testing with the use of accurate models.

The challenges of ensuring transparency, interpretability and ethical decision making with AI-driven regulatory processes should not be taken lightly. Privacy concerns and harmonisation of human expertise with AI automation add layers of complexity that demand careful consideration and early discussions with the regulatory agencies.

By embracing the opportunities and addressing the challenges through dialogue, all stakeholders can work together to forge a path towards a new era in regulatory affairs.

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