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Artificial Intelligence Regulation

October 2024

Introduction

Every drug sponsor wants to make the best use of Artificial Intelligence, but doing so requires understanding where health authorities are drawing the lines. That's always something of a moving target, especially in a field as new as AI. The Pink Sheet's globe-spanning has produced one rule of thumb, however: The closer Artificial Intelligence is to patient care, the more scrutiny it will get. Regulators seem content to allow firms to make product development decisions based on AI without significant oversight.

But if AI is used to assess a clinical trial outcome or examine manufacturing process, authorities will want to make sure that model has been thoroughly vetted – though it doesn't necessarily need to be completely explainable.

Below is a sample of our coverage from Asia, Europe and the United States of the emerging framework for artificial intelligence regulation.

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EMA's AI Principles Intended To Be 'Flexible & Long Lasting'

Eliza Slawther
04 Oct 2024

Executive Summary

There is "a lot of flexibility" in the European Medicines Agency's reflection paper on the use of artificial intelligence during drug development, which is principles-driven rather than setting rigid recommendations, says the agency's Florian Lasch.

The European Medicines Agency recently finalized a reflection paper on the use of artificial intelligence (AI) during the lifecycle of medicinal products to help manufacturers use AI in a safe and effective way.

The approach taken by the EMA is a flexible one that is "focused on principles, rather than on specific recommendations," Florian Lasch, a biostatistics specialist at the EMA, said on 1 October during the TOPRA (The Organisation for Professionals in Regulatory Affairs) Symposium 2024.

He explained that the AI reflection paper, which was initially drafted in July last year and finalized 14 months later based on a review of 1,342 feedback comments from stakeholders, did not set any specific metrics or technical requirements for companies. (Also see "EMA Finalizes AI In Medicines Paper After Reviewing 1,342 Comments" – Pink Sheet, Oct. 2 2024.).

"There is a lot of flexibility following this risk-based approach," Lasch said, which could help companies to define their metrics and measure the performance of AI systems used in drug development.

"With this approach, we hope that the principles can actually live quite a long while, whereas the specific application of the principles might change," he added, pointing out that translating AI principles into practice could be where the challenge lies.

"We have interaction channels like scientific advice that I would encourage every company to make use of if any AI applications are to be used for real-world evidence generation," Lasch continued.

EMA's AI Principles Intended To Be 'Flexible & Long Lasting'

He said that companies also had the opportunity to engage in informal exchanges with the regulator through innovation task force meetings and portfolio technology meetings.

EMA Working On New Tools

In March, the EMA rolled out Scientific Explorer, an AI-enabled knowledge mining tool that allows regulatory assessors in the EU to more easily find the information they need to help inform their scientific decisions. (Also see "EU Regulatory Assessors Get AI Boost In Reaching Scientific Decisions" – Pink Sheet, Mar. 28 2024.). During a question-and-answer portion of the discussion, Lasch was asked by an audience member whether the EMA planned to develop AI tools for applicants, starting with an AI search tool for its website.

He said that there was an ongoing "use case collection" for the development of both inward and outward-facing AI tools within the EMA, and that while he could not comment on specific plans, a "lot of work" was going into this process.

Lasch said that the EMA would prioritize the development of new AI tools based on which use cases could generate the biggest gains in the shortest development time.

Sanofi's AI-Powered Mission

Karen Philippe, generative AI regulatory lead at Sanofi, spoke on the same panel as Lasch to offer an industry perspective on how her company was using AI for regulatory and commercial purposes.

"At Sanofi, we think of AI as systems that use data to learn and to adapt their actions or their outputs accordingly," she said, noting that AI was "not a replacement for human intelligence" and was "only as powerful as the data it is given."

Philippe said that AI was "revolutionizing the whole value chain" and helping Sanofi to become an "AI-powered biopharma." For example, the company is using AI to speed up research by predicting clinical trial results, as well as in manufacturing to improve processes, resulting in better yields of medicines, she said.

"For [the] supply chain, we're using generative AI to redact the product quality reports," Philippe added, explaining that such reports were made by aggregating, synthesizing and summarizing large amounts of data.

She emphasized the importance of using AI in a responsible way to mitigate its potential risks, and said that Sanofi had implemented an AI framework "based on accountability."

"AI will most likely impact the way we work in the next couple of years. It won't replace us, but we need to foster that culture of innovation and adapt to the new tools," Philippe said, stressing that it was important that AI regulations "are able also to evolve accordingly to [match] the fast pace of the technologies."

EU Regulators Should Use AI Only When 'Safe And Responsible,' Says EMA

Eliza Slawther
06 Sep 2024

Executive Summary

Medicines regulators in the EU have "much to gain" from using AI models in their processes, but this technology must be used in a "safe and responsible" way, says the European Medicines Agency.

The European Medicines Agency and the EU's Heads of Medicines Agencies have published guiding principles for EU drug regulators regarding the use of large language models (LLMs), a type of AI.

According to a 5 September statement by the EMA and HMA, LLMs have "enormous transformative potential" for medicines regulation, and can be used for a variety of tasks – from generating and translating text to summarizing documents.

A spokesperson for the EMA told the Pink Sheet that LLMs are not currently used to review marketing authorization applications, and said the agency could not provide "exact figures" on how widespread the use of AI by national EU regulators was.

"The guiding principles on the use of LLMs are part of a larger set of deliverables under the multi-annual AI workplan. They provide an added layer of safety and security that may boost confidence in and increase the responsible use of these tools," the spokesperson explained. In December, the European medicines regulatory network – the group comprising the EMA, the European Commission, and the member states' national competent authorities – proposed a multi-annual AI workplan that will run until 2028. (Also see "AI Regulation: EU Network Announces Four-Year Action Plan" – Pink Sheet, Dec. 6, 2023.).

EU Regulators Should Use AI Only When 'Safe And Responsible,' Says EMA

In a 10-page guiding principles document, the EMA and HMA set out recommendations for regulatory staff members around using LLMs in a way that is "safe and responsible."

"The output [of LLMs] can infringe on other legal rights, such as copyright, or have ethical implications, for example if it influences people's freedom of choice or moral values," the agencies say in the guiding principles document.

With this in mind, the EMA and HMA urge regulatory agencies to "empower staff to be able to leverage the capabilities of LLMs only where they can be used in a safe and responsible manner."

AI Not Trained On 'Novelty' Of Regulatory Tasks

Regulators should consider whether AI systems have been trained using data that is specific to drug regulation, the EMA and HMA say.

For example, LLMs "may have not been exposed to information that answers a scientific or regulatory question, due to the novelty of many tasks performed by regulators, eg those concerning new active substances" they explain. While the guiding principles do not explicitly state how regulators might use LLMs in a way that could directly impact drug manufacturers, they note that caution should be taken when using AI in regulatory processes because "severely biased or erroneous outputs include generated text that can have a negative impact in decision-making in regulatory science."

The agencies encourage regulatory staff to educate themselves on the LLMs they are using, and say they should "apply critical thinking and cross check the output" of any AI systems.

Protecting Trade Secrets

LLMs can be used to summarize documents, something that the EMA and HMA highlight in their guidance for regulators.

The organizations stress the importance that regulatory staff take steps to protect trade secrets when using LLMs in this way, and say that prompts fed into AI systems should be drafted carefully to avoid revealing sensitive information.

This includes "personal data, trade secrets, data that is protected by intellectual property law, data where existing contracts impose restrictions on sharing and other secrets," such as passwords.

"Furthermore, if not properly secured, LLM outputs might reveal sensitive or private information included in datasets used for training, leading to potential or real data breaches," the EMA and HMA warn.

While the EMA was unable to provide detail on which EU medicines regulators are using AI and in what ways, the UK's drug regulator, the MHRA, revealed in April that it was using AI to improve its own processes.

The MHRA said that it planned to use a type of AI known as "supervised machine learning" internally to review marketing authorization applications and also to enhance its understanding of real-world data. (Also see "UK's MHRA To Use AI In Regulatory Review Process & RWD Analysis" – Pink Sheet, May 1, 2024.).

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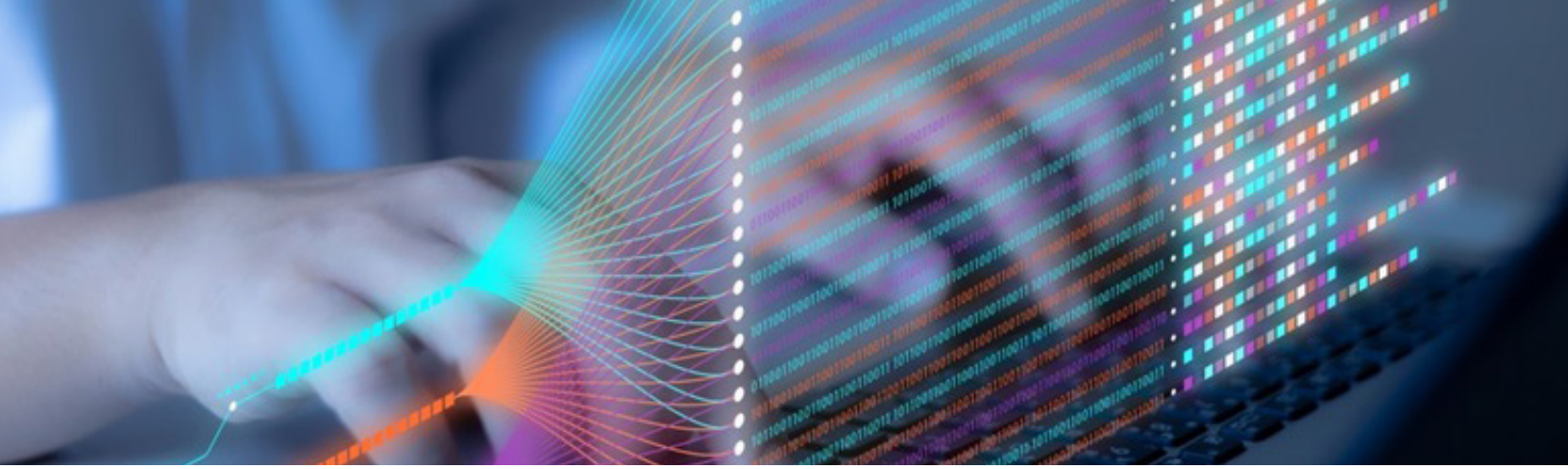

US FDA And AI: Who Is In Charge?

Michael McCaughan
02 Oct 2024

Executive Summary

The FDA is developing several structures and a broad group of experts across disciplines to help craft artificial intelligence policy. But the proliferation of AI-related initiatives raises the question of who, ultimately, will make decisions about when novel applications of AI are acceptable.

When it comes to developing artificial intelligence policy, the US Food and Drug Administration has a broad base of staff expertise to use.

That fact was evident during a recent FDA/ Clinical Trials Transformation Initiative meeting on AI in drug and biological product development. (Also see "AI And The 'Black Box' Problem: US FDA Is More Comfortable Than Some May Think" – Pink Sheet, Sep. 3, 2024.)

The FDA team at the meeting was led by Center for Drug Evaluation and Research Director Patrizia Cavazzoni and CDER Principal Deputy Director Jacqueline Corrigan-Curray. But individual sessions included CDER's AI policy lead Tala Fakhouri, Marsha Samson, a senior analyst in the Office of Medical Policy, and Qi Liu, an associate director from the Office of Clinical Pharmacology.

Key Takeaways

- The FDA has a wide variety of AI expertise to help develop policy.
- Multiple AI-related groups also have been created that will help deal with AI issues.
- However, with so many leaders in the AI space, the agency may add more bureaucracy than consistency to the effort.

US FDA And AI: Who Is In Charge?

The Center for Biologics Evaluation and Research was represented by a postmarketing safety official, Hussein Ezzeldin, Office of Biostatistics and Pharmacovigilance senior digital health expert, and by Senior Advisor for Translational Science Scott Steele. The Center for Devices and Radiological Health also was represented at the biopharma-focused event by Anindita Saha, Digital Health Center of Excellence associate director for strategic initiatives.

And perhaps most surprisingly given the focus of the meeting, the Center for Veterinary Medicine was represented by Senior Epidemiologist Hesha Jani Duggirala. Her background in AI and related work is, in fact, quite extensive. She joined the FDA in 2001 and was a co-founder of the agency's Data Mining Council in 2007, which now is called the Data Science Council. She was lead author of the council's data mining white paper from that era.

Duggirala also best expressed the notion that AI is not necessarily something new for the FDA.

"This is very clearly an evolution in technology and not a new technology," she said.

That isn't always clear, even to people doing the work in the FDA. Duggirala added that "I will speak with people within the FDA" and ask for "a couple of paragraphs on the AI you're working on" and the person will say, "I don't do AI." But they are doing pharmacovigilance work using machine learning tools that have been around for a long time. "And this is AI."

While AI may be more evolution than revolution, the agency's drug center clearly is treating it as something that requires careful management attention. The latest step is the creation of a new AI Council charged with ensuring coordinated and consistent response to those issues in the center. (Also see "Artificial Intelligence: CDER's New Council Takes Charge Of Oversight, Coordination" – Pink Sheet, Aug. 29, 2024.)

Of course, that is only the most recent structural move by CDER to address AI and related activities. In just the past year, the center has created a new Quantitative Medicine Center of Excellence, a new Center for Clinical Trial Innovation, and a new Emerging Drug Safety Technology Program. Each was created in part to address applications of AI to different aspects of the drug development lifecycle.

CBER and CDRH have their own AI experts and structures, including the Digital Health Center of Excellence housed within CDRH. And then, of course, there are the Commissioner's Office-level teams like the Office of Digital Transformation.

Each of those groups has its own governance and leadership, creating a truly extensive list of AI policy leaders.

CDER tapped Office of Clinical Pharmacology Associate Director Rajanikanth Madabushi as the inaugural QM center director. Liu also is one of the initial board members. (Also see "US FDA Developing Model Master File System To Grow Modeling, Simulation Field" – Pink Sheet, May 1, 2024.)

The Center for Clinical Trial Innovation (C3TI) was led by Office of New Drugs Deputy Director for Operations Kevin Bugin, who recently joined Amgen, Inc.. The search for a replacement is ongoing, but the program continues to move forward. (Also see "US FDA's CBER Seeks Associate Director Overseeing Rare Disease Work" – Pink Sheet, Sep. 17, 2024.)

And the new EDSTP program is led by one of the FDA's most senior drug safety experts, Office of Surveillance and Epidemiology Deputy Director Robert Ball. (Also see "AI and Adverse Events: Tech Not Ready For Prime Time For Case Safety

Reports, US FDA Says" – Pink Sheet, Jun. 14, 2024.)

As for the AI Council, that group has three co-directors, including Fakhouri and Liu. In addition, Office of Strategic Programs Director Sridhar Mantha will be part of the leadership triumvirate.

That is a lot of people with input into AI policy at the agency. So many, it begs the question of who exactly is in charge of the issue?

Each new structure was created to ensure consistency and coordination in overseeing AI adoption with an avowed goal to maximize the technology's potential to enhance drug development and patient safety. But it bears watching to see if the proliferation of new structures and councils ends up adding bureaucracy rather than consistency to the agency's policy work.

AI And The 'Black Box' Problem: US FDA Is More Comfortable Than Some May Think

Michael McCaughan
03 Sep 2024

Executive Summary

A recurring question about using artificial intelligence in drug development is whether the US Food and Drug Administration can accept a model that operates as a black box, meaning that developers cannot explain exactly how the model does what it does.

The US Food and Drug Administration is very much prepared to consider artificial intelligence applications that are not explainable, that is, models that operate essentially as a "black box."

That was one key message from a recent FDA/Clinical Trials Transformation Initiative meeting on AI in drug and biological product development. The event more broadly served as an opportunity for the agency to gather input and share initial thoughts about its upcoming guidance on the use of AI in drug development. (Also see "AI In Drug Development: Regulatory Clarity Needed On Inspections, Human Role" – Pink Sheet, Aug. 28, 2024.)

Key Takeaways

- The FDA will consider AI applications even if the model is not fully explainable.
- If the AI model is hard to understand, but there is other evidence supports the findings, a discussion with FDA may be possible.
- Not using AI because we do not understand how it works is not the best path forward, A Parexel official said.

AI And The 'Black Box' Problem: US FDA Is More Comfortable Than Some May Think

FDA officials said that in the absence of guidance, there are some industry misconceptions about the agency's AI stance.

"We have heard FDA does not allow" large language models," said Tala Fakhouri, Center for Drug Evaluation and Research associate director for data science and artificial intelligence policy. "I'm not sure where that came from."

Fakhouri also said she has heard "that the models have to be explainable."

"Again, not all models are explainable," she said. "It will depend on the context of use and model risk, where we might ask more questions."

"Generally, at the FDA, we put more emphasis on transparency," Fakhouri added. "We want to know more about the data that you may have used to train your model. We want to know why you chose a specific modeling technique. We want to understand the methods behind AI, not necessarily explainability."

Fakhouri and a panel of agency colleagues were asked to elaborate on the point during a wrap up session. Fakhouri read the question: "How do we propose to validate an AI model that is not explainable? In other words, how do you validate a black box model? If you don't know how it works, how can you claim you validated it?"

"If you are only asking me to trust this model that I don't understand, and this is the only piece of evidence that you have, I think this is going to be a hard pill to swallow," said Hussein Ezzeldin, senior digital health expert in the Center for Biologics Evaluation and Research's Office of Biostatistics and Pharmacovigilance. "But if you're bringing something that may be hard to understand, but it has other evidence that would support these findings, then maybe it might be a different discussion."

"If you don't understand how the model works, but you see concurrence between the output of the model and the data that you already have, then this is some sort of a validation, even though you don't really understand how the model works," Ezzeldin added.

Another FDA official, speaking from the audience, said that there is often a misperception that models are either fully explainable or a complete black box.

"It is not 0/1," she said. "Typically, you don't work with models that you don't understand" at all.

"You understand some things about those models, and there are certain other things that you don't know completely," the official added.

She then used an analogy similar to one offered by FDA Commissioner Robert Califf about the importance of understanding a drug's mechanism of action. (Also see "The Aspirin Test For AI?" – Pink Sheet, Apr. 24, 2024.)

There are many drugs "where we have some understanding of the mechanism of action, but we don't know in detail how these drugs work," the official said. She specifically cited SSRI antidepressants, where it is well established that the drugs block reuptake of serotonin.

"How does that translate into improvement in depression or anxiety? We have no clue," she said. "That is a principle that not only we are comfortable with as a society and in clinical trials and drug development, we have been using many of these drugs for ages in one of the most demanding tasks and more serious tasks, which is treating people."

Fakhouri gave a different example, indicating that meeting speakers reported that "Generative AI is being used to generate the first draft" of regulatory documents. "Even the

makers of those tools don't understand how they work."

Parexel Executive VP Stephen Pyke, who chairs the Association of Clinical Research Organizations' AI/ML Committee, stressed the importance of becoming "comfortable" with the concept.

"I'm a statistician and I got trained about Occam's Razor: simple is preferable wherever it can do the job," he said. However, "some jobs can't be done with simple. We have to get used to this idea. There are certain tasks that will only be amenable to AI that we can't explain."

"It is just about recognizing that there are going to be those applications, and we have to figure out, what do we do?" Pyke said. One option is "we won't use those solutions, even though we think as best we can tell they work and work well, because we don't understand how they work. That does not seem to me a good place to go."

Korea Lays Out Roadmap For Use Of AI Across Drug Development

Jung Won Shin
24 Sep 2024

Executive Summary

The five-year roadmap aims to expand support for AI research and development in essential health care and new drug development, as well as advance medical data usage systems and enable its safe use.

South Korea has released a five-year roadmap to research and develop artificial intelligence in healthcare as part of a wider vision to harness innovation in the technology to improve national health.

The Ministry of Health and Welfare intends for the plan, which extends to 2028, to strengthen support of AI R&D in essential health care and new drug development, as well as advance medical data usage systems to enable its safe use.

Korea's AI healthcare market is expected to grow 50.8% in the 2023 to 2030 period, higher than the 41.8% growth estimated globally, according to the health ministry. In the past five years, the country's medical AI related national R&D investment totaled KRW2.2tn ($1.7bn), rising an average of 33% per year.

Korea Still Lacks Relevant Laws, Labor Force

However, an average 2.7-year technology gap has emerged with the US, which leads in major AI health care technology development, including AI-based new drug development algorithms.

Despite sharp growth in the AI healthcare market, South Korea still lacks relevant laws and regulations as well as the labor force. Through the roadmap, the government aims to more than double commercialization of healthcare AI technology, reduce the technology gap by more than a year, and increase its R&D investment.

"The ministry plans to continue to seek diverse efforts to improve national medical quality and national health by expanding health medical data and AI-based digital healthcare services," Vice Minister of Health and Welfare Minsoo Park

said during a recent health and medical data policy review meeting.

The government also discussed key medical data policy during the meeting, such as the health information highway and national integrated bio big data, as well as measures to improve opening up and using medical data managed by the Korea Disease Control and Prevention Agency (KDCA), National Health Insurance Service (NHIS), Health Insurance Review and Assessment Service (HIRA), and National Cancer Center.

Details Of Roadmap

Under the roadmap, the government intends to expand AI R&D, focusing on essential health care, such as emergency care, serious diseases and cancer. Generative AI also will help develop technology supporting communications between physicians and patients to increase the convenience of treatment.

The plan also will strengthen support to use AI in every process of new drug development, including drug discovery, and clinical R&D, as well as boost AI-based digital therapeutics and cutting-edge medical devices.

A platform to enable AI researchers and companies to conveniently use health and medical data is proposed, which will seek advancement of data usage systems for AI development and learning, as well as support field studies and foster biohealth AI experts.

The plans for boosting the use of AI across the new drug development process include:

- **Drug discovery:** A project has been proposed to accelerate new drug development through sharing algorithm analysis results without integration of data to develop various AI models to discover drug candidates. Twenty pharma firms, universities and research institutes will team up and learn the models to validate and optimize them.
- **Clinical trial prediction:** Plans will increase the use of AI in various trial stages, from selecting patients to drawing expected success rates by clinical trial phases.
- **Test optimization:** The government expects to use AI to automate processes and seek autonomous and continued test and data analysis.
- **Clinical research:** A platform, which can be used for various clinical research activities by combining AI technology based on the next generation clinical research management system, is proposed.
- Advancing the health and medical data usage system: A data connection platform is proposed to enable AI researchers and companies to use medical data currently scattered at medical institutions and public institutions.

To support use of data, the roadmap includes creating support systems for the entire process, including study application, pseudonymization, pseudonymization adequacy review and data analysis, as well as an ecosystem to reinvigorate health and medical data research to connect data at key medical and public institutions, such as medical data centered hospitals, NHIS and HIRA.

Basic principles of comprehensive and general ethics and detailed guidance are needed to research, develop and use AI in the health and medical sector also are expected to be established.

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