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Artificial intelligence and machine learning in veterinary medicine: a regulatory perspective on current initiatives and future prospects

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Abstract

The US FDA's Center for Veterinary Medicine (CVM) is advancing its leadership in veterinary science by integrating AI and machine learning (ML) into its regulatory framework and scientific initiatives. This paper explores the CVM's strategic approach to harnessing these technologies to enhance human and animal health by supporting innovative products and methods. Key areas of focus include regulatory adaptation, genomic research, and information technology modernization. The Animal and Veterinary Innovation Agenda outlines the Center's commitment to fostering innovation in veterinary medicine while addressing emerging challenges. This includes developing AI/ML-driven tools for antimicrobial resistance research, genome editing safety, and postmarketing safety surveillance. The paper discusses the CVM's participation in the FDA's role in shaping guidance documents for AI in regulatory decision making. In genomic research, the CVM is utilizing AI/ML to study antimicrobial resistance and improve genomic editing techniques. These technologies enhance the understanding of resistance mechanisms and facilitate the precise identification of genetic alterations. Artificial intelligence is also pivotal in information technology modernization efforts, aimed at streamlining data management and enhancing operational efficiency. The paper highlights the efforts to integrate AI/ML in safety surveillance, including signal detection and case processing. It emphasizes the importance of human-led governance, data quality, and model validation in ensuring the ethical deployment of AI technologies. The CVM's initiatives represent a transformative shift toward more efficient and innovative regulatory approaches. The paper concludes with a call for continued collaboration among researchers, industry, and regulatory bodies to advance AI integration and achieve mutual goals in animal health.

Keywords: artificial intelligence, epidemiology, machine learning, government regulation, antimicrobial resistance

The Center for Veterinary Medicine (CVM) is enhancing its role in scientific leadership within the use of advanced technologies and AI in veterinary medicine through proactive measures and innovative approaches. Currently, the CVM's focuses in the area of AI/machine learning (ML) include the CVM Innovation Agenda; advancing regulatory processes involved in AI; genomic research, specifically antimicrobial resistance and genome editing; IT modernization efforts; and safety surveillance.

The CVM Innovation Agenda

We are in an exciting moment where new technologies and a new understanding of biological and chemical processes hold great promise for advancing human and animal health—while global market changes, strife, and increased disease and climate threats mean our food system and animal industries need to become more resilient.

The CVM is more than just a regulator. We take action to advance human and animal health by supporting innovative products and approaches to real-world problems and preparing the Center for the future. The CVM has published the Animal and Veterinary Innovation Agenda,[1] a vision for how the CVM can support and spur innovation to better protect human and animal health and implement methods to monitor emerging technologies. Today's Animal and Veterinary Innovation Agenda is an initial catalog of the CVM's current and intended actions toward these goals.

For example, the CVM is establishing 4 Animal and Veterinary Innovation Centers to advance

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regulatory science and encourage the development of innovative products to better support animal health and veterinary interventions. The Animal and Veterinary Innovation Centers are a step forward on the CVM's Science Vision, which includes forming multiyear partnerships with external research institutions where coordination between government and academic networks will best advance science.

In addition, the CVM is collaborating with the Reagan-Udall Foundation via a grant to support an in-depth analysis of the CVM's regulated industries and propose new ideas to spur innovations that can promote animal and human health. An independent panel has been seated and has started conducting the analysis.[2]

Advancing Regulatory Processes

The CVM is committed to adapting and refining its animal and veterinary product review programs to align with its Innovation Agenda. Embracing cutting-edge technologies, such as AI/ML, is integral to this evolution. These technologies offer promising avenues to address challenges spanning human, animal, and environmental health sectors, enhancing the efficiency and efficacy of regulatory processes.

The CVM is a member of the FDA's dedicated crosscenter team of experts in AI-enabled drug development. The agency is engaging internal and external experts with a deep understanding of ML algorithms, data preprocessing, predictive modeling, and model validation, who will help inform the evaluation of the reliability and trustworthiness of AI models trained on complex datasets.

The CVM has participated in the development of the FDA guidance document *Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drugs and Biological Products*.[3] When finalized, this guidance will be the first of its kind written by the FDA to offer recommendations around the use of AI in premarket drug applications.

Future considerations for drug development would include discussions around human-led governance, data quality, and improvement and model validation.

The CVM expects human-led governance in AI/ML deployment, which prioritizes human oversight and accountability throughout the AI/ML lifecycle. This governance model, critical for fostering trustworthy AI, ensures that legal and ethical values are upheld by incorporating human judgment in all stages of AI/ML application, including planning, development, use, modification, and discontinuation within drug development.

A key component of this approach is the development of a context-specific risk management plan, which is vital for identifying and mitigating potential risks associated with AI/ML applications. Furthermore, maintaining comprehensive documentation, ensuring transparency in processes and decision making, and providing clear explanations for AI/ML outputs are essential for building trust and understanding. Finally, implementing processes for traceability and auditability, including mechanisms to track, record, and audit key steps and decisions as well as to document justifications for deviations, is crucial for sustaining oversight and accountability.[4]

Artificial intelligence/ML for data improvement focuses on leveraging AI and ML techniques to identify and address data quality issues, thereby enhancing the reliability of datasets used for model development and decision making. Although AI/ML cannot inherently rectify poor-quality data, it plays a critical role in managing data-related challenges.

One significant issue is bias, where AI/ML models may amplify existing biases in the input data. Mitigating this requires careful evaluation of data sources, data collection processes, and biases arising from human or systemic factors. Another challenge is missing data, which can be addressed using AI/ML-driven data cleaning and curation techniques, such as imputation, to estimate and fill in missing values based on patterns in the available data.[5] Additionally, monitoring for data drift is essential to maintain the relevance and accuracy of AI/ML models over time. Data drift occurs when the real-world data encountered by the model diverges from the data used during training, necessitating ongoing assessment and adaptation. The CVM welcomes that stakeholders include us in discussions of how AI/ML tools may be incorporated into industry regulatory processes to improve data quality.

Comprehensive documentation represents a cornerstone of regulatory compliance in AI/ML model development. Maintaining transparent and detailed records of model development, performance monitoring, and validation processes enables thorough regulatory assessment and ensures traceability. This approach supports accountability and provides clear insights into the model's development and operational characteristics.

Our goal is to work collaboratively to incorporate AI into the regulatory process effectively. We welcome input from stakeholders on what would help them feel more comfortable with this transition and to further discuss considerations for utilizing AI throughout the animal product development life cycle. Stakeholders are welcome to reach out to the CVM for discussions.

Artificial Intelligence and Genomic Research in Antimicrobial Resistance

Advances in next-generation sequencing (NGS) technologies and computational methods are facilitating rapid antimicrobial resistance gene detection, identification, and characterization in genomes and metagenomes. These approaches not only complement traditional culture-based antimicrobial resistance surveillance programs, like the National Antimicrobial Resistance Monitoring System (NARMS), but also provide opportunities for characterizing resistomes beyond what can be determined by culture-based methods alone. The NARMS was established in 1996 as a collaborative program of the FDA, the CDC, the USDA, state and local public health departments, and universities. The NARMS monitors trends in antimicrobial resistance among enteric bacteria, including *Salmonella*,

Campylobacter, *Escherichia*, and *Enterococcus*, and disseminates timely information on antimicrobial resistance to stakeholders and outbreak investigations and assists the FDA's decision of approving safe and effective antimicrobial drugs for animals. Traditionally, NARMS uses the antimicrobial susceptibility test (AST) to determine the lowest antibiotic concentration, the MIC, that inhibits the growth of the bacteria. In recent years, NARMS incorporated whole-genome sequencing to characterize resistance genotypes and predict resistance phenotypes of bacteria with great sensitivity and specificity.[6–9]

Studies have shown the potential of ML algorithms for predicting resistance phenotype directly from whole-genome sequences.[10–15] The NARMS has over 30,000 curated foodborne pathogens' sequence data along with extensive metadata, including antimicrobial sensitivity profile, to build an effective and robust ML-based classifier for antimicrobial resistance phenotype. Scientists in NARMS at the CVM have implemented the Boost Machine Learning Model (XGBoost) to improve upon categorical resistance versus susceptible classifications by predicting antimicrobial MICs from whole-genome sequencing data. XGBoost is a scalable ML algorithm that generates a regression model based on ensemble decision trees to maximize the accuracy of the model.[10] A collection of 16,129 *Salmonella* genomes, 2,891 *E coli* genomes, 11,837 *Campylobacter* genomes, and 1,302 *Enterococcus* genomes with AST data, collected from retail meats, humans, and food-producing animals over 20 years in the US,[16] was used to create the XGBoost ML models for predicting MICs to 25 antimicrobials across 4 genera. Because of sequence diversity among different species, different models were built for different species. To build a model, the sequence for each genome was divided into a set of nonredundant, overlapping nucleotide 10-mers using the k-mer counting program KMC,[17] and a matrix was created containing the k-mers, MICs, and antibiotics as features for each genome. The MIC prediction model was built using an XGBoost regression model[18] and following the methods previously described by Nguyen et al.[10]

To evaluate the performance of the built models, 10-fold crossvalidations were performed to determine the sensitivity and accuracy of the models.[19] The accuracy of a model is determined based on the ability to predict the correct MIC within ± 1 2-fold dilution step of the true MIC that was determined using the AST method. The MIC prediction models created in this study had no a priori information about the underlying gene content of the strains and had an overall average accuracy of 96.9% (CI, 96.7% to 97.1%), 94.5% (CI, 94.3% to 94.7%), 96.2% (CI, 96.1% to 96.3%), and 94.2% (CI, 93.8% to 94.6%) within ± 1 2-fold dilution step for the *Salmonella*, *E coli*, *Campylobacter*, and *Enterococcus* genomes, respectively **(Figure 1)**. Furthermore, to determine if the predicted MICs can really demonstrate the antimicrobial resistance/susceptibility of a strain, clinical breakpoints based on Clinical & Laboratory Standards Institute and FDA guidelines[20] were used to evaluate if the predicted MICs can demonstrate the same antimicrobial resistance/susceptibility as the laboratory-derived MICs from the AST method for various drugs. We had an overall average accuracy of 98.1% (CI, 98.0% to 98.2%), 97.1% (CI, 97.0% to 97.3%), 98.4% (CI, 98.4% to 98.5%), and 96.3% (CI, 96.0% to 96.6%) to determine the antimicrobial resistance/susceptibility of a strain for the *Salmonella*, *E coli*, *Campylobacter*, and *Enterococcus* genomes, respectively. These efforts demonstrated the potential of AI/ML for rapid monitoring of emerging

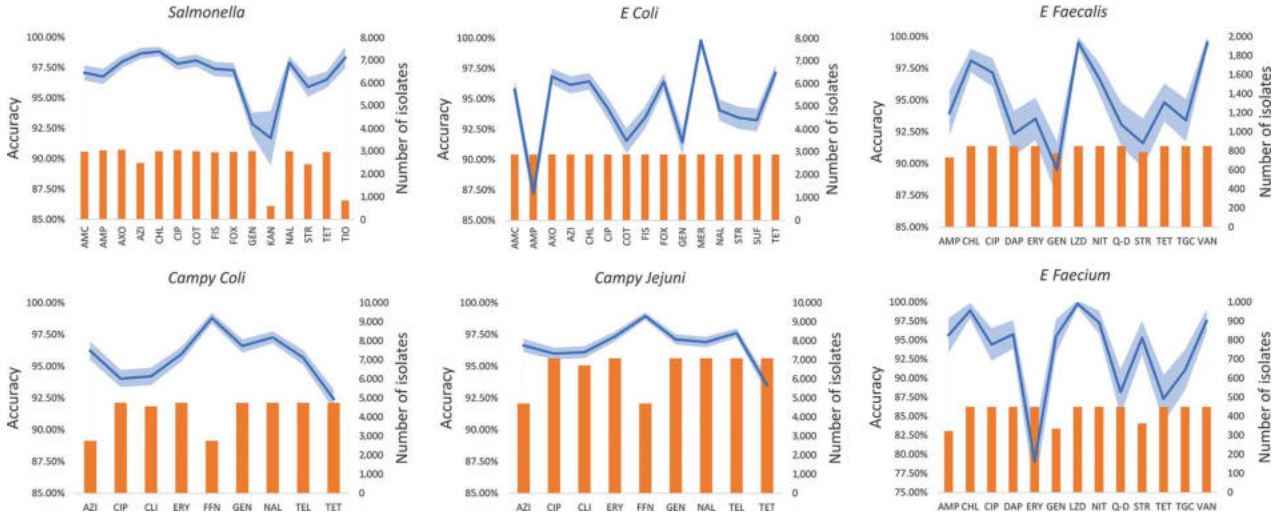

Figure 1—Minimal inhibitory concentration prediction model for *Salmonella*, *Escherichia coli*, *Enterococcus*, and *Campylobacter*. Genomes with antimicrobial susceptibility test data were selected to train and validate the model. A 10-fold crossvalidation was used to assess the overall sensitivity and accuracy of the model. The accuracy within ± 1 2-fold dilution factor of the actual MIC was measured. AMC = Amoxicillin-clavulanic acid. AMP = Ampicillin. AXO = Ceftriaxone. AZI = Azithromycin. CHL = Chloramphenicol. CIP = Ciprofloxacin. CLI = Clindamycin. COT = Trimethoprim-sulfamethoxazole. DAP = Daptomycin. ERY = Erythromycin. FIS = Sulfisoxazole. FFN = Florfenicol. FOX = Cefoxitin. GEN = Gentamicin. KAN = Kanamycin. LZD = Linezolid. MER = Meropenem. NAL = Nalidixic acid. NIT = Nitrofurantoin. Q-D = Quinupristin-dalfopristin. STR = Streptomycin. TEL = Telithromycin. TET = Tetracycline. TGC = Tigecycline. TIO = Ceftiofur. VAN = Vancomycin.[19]

resistance genes, enhancing the accuracy of antimicrobial resistance prediction, and understanding antimicrobial resistance at a deeper level.

Genome Editing and Intentional Genomic Alterations

Clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein (Cas) genome editing can be used to introduce heritable intentional genomic alterations (IGAs) in animals, such as via the editing of embryos or cloning of edited cell lines, for a variety of applications, including industrial, agricultural, medical, and ornamental uses. While CRISPR-Cas enables precise, intended alterations to an animal's genome, unintended alterations are known to occur both at both the target site[21] and off-target sites.[22]

The reliable identification of CRISPR-Cas–related alterations, both intentional and unintentional, is foundational to ensuring the effectiveness and safety of IGAs in animals. Both developers and the CVM are now leveraging AI/ML-based bioinformatics tools for the characterization of IGAs in animals.

First, AI/ML-based tools have been developed to improve the precision of CRISPR-Cas–related editing and to predict sites in the genome where unintended alterations (off-target editing) may occur. Predicting off-target sites is critical for identifying alterations arising from CRISPR-Cas editing and discerning them from alterations introduced through naturally occurring processes. Off-target prediction methods include alignment-based in silico methods (eg, Cas-OFFinder[23]) and experimental (eg, biochemical-based selective enrichment and identification of tagged genomic DNA ends by sequencing [SITE-Seq[24]] and cell-based genome-wide unbiased identification of double stranded breaks enabled by sequencing [GUIDE-Seq[25]]). In silico methods are homology driven and thus produce an often prohibitory number of sites to screen compared to experimentally determined sites. By employing AI/ML models, in silico off-target prediction methods enable accounting for simulated molecular interactions (eg, CRISOT) and experimental data (eg, DeepCRISPR).[26,27]

Second, AI/ML-based tools have been developed to distinguish true genomic alterations from technical artifacts in NGS data.[28–31] Determining if a variant is a true alteration or technical artifact can be a laborious manual task when interrogating the NGS data. Artificial intelligence/ML-based bioinformatics tools aim to improve the programmatic removal of sequencing artifacts as well as improve the identification of variants in poorly mapped regions. The results of "PrecisionFDA Truth Challenge V2"[32] demonstrated the promise of AI/ML-based variant calling tools, particularly for long-read NGS data.

Information Technology Modernization and AI Integration

As part of its ongoing IT modernization project, the CVM is exploring the application of AI/ML, including large language models, to streamline responses to industry regarding animal drugs, food, and devices. This initiative aims to enhance operational efficiency and responsiveness within regulatory frameworks. The CVM's aging infrastructure, systems, and equipment are not positioned to handle the integration of AI/ML. Therefore, we are accelerating our IT modernization transformation journey to better support our business needs and develop capabilities for structured data submissions and data visualization through analytics.

The CVM's data strategy and future governance plan set(s) the foundation for the goal of providing real-time, comprehensive, situational awareness to predict, protect, and promote global human and animal health. The CVM is presently working to improve how we collect source (industry) data to include confirmation of accuracy at the time of collection and creating a design around how the data will be used and analyzed in a transactional data setting.

The CVM is taking a data- and analytics-first approach, meaning the data will be collected with the intent to access, use, share, and maximize efficiencies and outputs. The CVM strives to consolidate disparate data sources to answer questions such as, "What Geospatial impacts are there to supply chain and manufacturing?" Artificial intelligence/ML will assist by providing advanced responsiveness through generative AI and natural language processing. Privacy considerations and ethical and responsible use of AI is the foundation of the CVM's modernization approach, and data sharing is only in the context of ensuring review staff and analysts have the right access to the right data at the right time to assist with their regulatory duties. Modernizing data access better enables staff to protect human and animal health.

Safety Surveillance

Postmarketing safety surveillance activities at the CVM include monitoring adverse drug event reports that are associated with the use of animal drug products as well as monitoring reported product quality issues. The CVM receives over 100,000 reports each year, and our database contains cumulative data from over 1,000,000 individually reported events. Clinical information in adverse event reports can include information reported for a variety of species and breeds (companion animals and food-producing animals), suspect and concomitant product information, temporal information related to the use of the product and the adverse event, medical history, clinical course, and outcome. Much of the clinical information is in unstructured narrative form; however, clinical signs are coded using standardized Veterinary Dictionary for Drug Regulatory Activities terminology.[33]

Machine learning has long been used in the field of pharmacovigilance at the FDA[34,35] to detect safety signal in excess to what would be expected. The CVM uses several statistical methods to identify safety signals within our adverse drug event database, including the use of Bayesian methodology; Bayesian methods involve probabilistic reasoning and statistical inference to detect unexpected associations or

patterns in data. They may be considered an early form of AI in the domain of statistical ML and demonstrate AI-like analytics. In addition to continuing and refining the work on safety signal detection, the CVM is actively exploring opportunities to utilize AI/ML to assist with the automation of tasks, including signal management, such as adverse event case processing. Examples include exploring the use of AI/ML to determine if a case is a "valid" case, which contains the minimum requirements for reporting, and the use of AI/ML to assist with the automation of coding cases using Veterinary Dictionary for Drug Regulatory Activities terminology. We are exploring opportunities to use AI/ML to improve case prioritization using our signal detection and management processes.

The CVM is also interested in learning more about the utility of AI/ML for other postmarket surveillance applications, including the screening of literature, social media, clinical trials, and electronic animal health records. The CVM pharmacovigilance reviewers currently utilize PV Wizard to more efficiently screen literature in EMBASE for adverse event reports. PV Wizard uses a structured query to assist with developing comprehensive text searches. Artificial intelligence could potentially be used to further improve and automate the scanning and summarization of scientific literature or clinical trial data.

The full use of AI/ML in veterinary pharmacovigilance and drug safety surveillance is currently limited by several factors, including but not limited to: lack of funding for postapproval activities, limited standardization of electronic health record data, data quality and availability, integration challenges, and limited interoperability between medical data systems.

Although the application of AI and ML in veterinary pharmacovigilance is still emerging, notable work includes a study[36] that evaluated 5 statistical distance measures applied to the FDA's open-source adverse event dataset for animal drugs.

Another promising proof-of-concept study[37] explored the application of an ML model to an animal health company's pharmacovigilance dataset to test hypotheses related to potential drug-drug interactions and data quality and completeness.

Summary

Future endeavors will focus on expanding AI/ML applications in veterinary medicine; fostering collaborations between academia, industry, and regulatory bodies; and ensuring the ethical and responsible deployment of AI technologies for the benefit of animal and human health. The integration of AI and ML into veterinary medicine offers transformative potential, not only in advancing veterinary care but also in shaping the future of human medicine. As AI/ML technologies continue to evolve, they could lead to groundbreaking synergies between these fields, driving innovations in diagnosis, treatment, and overall health outcomes.

The CVM is interested in understanding how the animal health industry's use of AI/ML establishes the credibility and trustworthiness of AI/ML models, including the following areas of consideration:

- Human-led governance, accountability, transparency, and explainability
- Data quality, reliability, representativeness, and bias mitigation
- Model development, performance, monitoring, and validation

This article provides a snapshot of the CVM's current initiatives and future prospects in integrating AI and ML within veterinary medicine, highlighting its transformative potential in advancing scientific leadership and regulatory excellence. We believe that further conversation and collaboration is needed to meet mutual goals of animal health. We encourage veterinary researchers, industry, and regulators to reach out to us to discuss best practices and knowledge gaps.

The integration of AI and ML into veterinary medicine represents a pivotal advancement toward achieving the CVM's goals of innovation, efficiency, and product safety. By leveraging these technologies across various domains—from regulatory processes to genomic research and surveillance—the CVM is poised to lead veterinary medicine into a new era of scientific excellence and public health protection.

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