BLA REGULATORY

PHARMAFOCUS

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About Us

BLA Regulatory is located in the State of Maryland, conveniently close to the FDA's headquarters. We offer U.S. agent services for all types of FDA-regulated products, including drugs, cosmetics, medical devices, and more. Our team can guide you through the entire application and registration process to ensure FDA compliance. Please visit our office website for more information or if you need any assistance.

From Animal Models to NAMs-driven AI Tools

FDA's Preclinical Testing Revolution

The U.S. Food and Drug Administration (FDA) is steering the evolution of preclinical testing towards more accurate, human-centric, and technology-driven approaches. Traditional reliance on animal testing is gradually being replaced by **New Approach Methodologies (NAMs)**—cutting-edge innovations such as **organs-on-chips, computational modeling, and artificial intelligence (AI)-powered simulations**.

While various NAMs are being explored, this article focuses specifically on the transformative impact of **AI and Machine Learning (ML)** in preclinical testing. It provides an overview of how the industry and the FDA are advancing towards AI-driven simulations, computational modeling, and other upcoming innovations. The goal is to offer practical insights for non-clinical experts and Contract Research Organizations (CROs) aiming to stay ahead and adopt AI-driven NAMs.

Need for Animal Use Alternatives in Preclinical Testing

- **High Failure Rate:** **Over 90% of drugs** that pass animal testing fail in human trials due to inaccurate pharmacological effects and toxicity predictions.
- **Poor Mimicry:** Animal models mimic human immune responses poorly, leading to false safety assurances (e.g., tragic cases like TGN1412 cytokine storm).
- **Enhanced Accuracy:** NAMs-based tools have the potential to improve predictive accuracy, thereby lowering development costs and addressing ethical concerns.

FDA's Bold Move Towards AI-Driven Drug Safety

The FDA has laid the groundwork for AI-driven drug safety assessments through legislation and regulatory guidance:

- **FDA Modernization Act 2.0 (2022)** removed the requirement for animal studies in investigational new drug (IND) applications, explicitly authorizing computational models and AI-based assessments.
- **FDA Science Board Recommendations (2024)** outlined NAMs-driven alternatives to accelerate the approval process and improve the reliability of drug approvals. Recommends creating a centralized repository for NAMs to facilitate their use in regulatory decision-making.
- **ISTAND Pilot Program** evaluates AI-based predictive models, such as ML algorithms trained on toxicity datasets, to replace conventional animal studies.

"Public sentiment supports the transition — over 85% of surveyed U.S. citizens prefer phasing out animal testing in favor of modern methodologies."

Cutting-Edge AI Tools for Preclinical Drug Safety

🔬 **AI for Drug Toxicity Prediction** - Machine learning algorithms analyze thousands of molecular structures to flag potentially harmful compounds before clinical trials. For example, CATMoS (Collaborative Acute Toxicity Modeling Suite) can predict toxicity levels using AI-driven pattern recognition from historical data.

💻 **Physiologically-Based Pharmacokinetic (PBPK) Modeling** - AI-powered PBPK models simulate how a drug is absorbed, distributed, metabolized, and excreted in virtual human systems. The FDA actively reviews AI-enhanced PBPK models to enable first-in-human dosing decisions without relying on animal data. These models are integral in small-molecule drug development and are increasingly applied to biologics.

🧬 **AI Screening for Immunogenicity Risks** - Recent AI tools, such as AbImmPred, leverage deep learning on antibody sequences to predict immune responses and off-target effects, reducing the need for primate immunogenicity tests.

🔍 **Quantitative Systems Pharmacology (QSP) & AI Simulation** - AI-powered QSP models can simulate complex drug interactions with human biological pathways, providing better predictions of adverse effects than traditional animal testing.

📊 **Bioinformatics-Driven Off-Target Screening** - AI algorithms scan proteomic databases to detect unintended drug interactions with human tissues. This approach outperforms animal receptor-binding studies, ensuring precise targeting with fewer side effects.

🩸 **AI for Cytokine Release Prediction** - After the tragic TGN1412 clinical trial failure, AI-driven cytokine release assays (CRAs) were developed using human blood samples, ensuring mAbs don't trigger dangerous immune reactions

FDA's Strategic Blueprint for AI Integration

The Agency's Three-Year Plan

📁 **Data Integration:** Expanding AI-accessible databases containing international human toxicity data like CAMERA (Collection of Alternative Methods for Regulatory Application).

🧪 **ISTAND Pilot Program:** Encouraging pharmaceutical companies to submit AI-generated results alongside traditional data for comparative analysis and validating AI-driven NAMs.

📉 **Reducing Animal Use:** AI models will replace extended primate testing for monoclonal antibodies, significantly cutting costs and ethical concerns.

🔬 **International Collaboration:** Partnering with NIH, VA, and ICCVAM* to develop standardized AI-based models for toxicity screening.

"Submissions involving AI/ML components have surged from one per year in 2016-2017 to 132 in 2021, indicating growing pharma-tech collaboration. Of the 158 applications submitted to CDER by 2021, 88% were for clinical drug development, with the remainder in drug discovery (3%), pre-clinical development (5%), and post-market stages (4%), demonstrating the growing interest and opportunity."

FDA Looking Ahead

The Agency's Five-Year Vision

According to the FDA, validated AI and ML systems could become the default method for toxicity screening within five years, replacing conventional animal testing.

- **Exception Rather Than Rule:** The FDA aims to make animal studies an exception rather than the rule in drug development. This means that Sponsors need to consult with the FDA on acceptance of their plan to use NAMs (AI) for their IND enabling pre-clinical studies via FDA meetings or other communication channels.

- **Regulatory Adaptation:** As AI technology advances, regulatory frameworks will adapt to ensure data transparency, validation, and accuracy, ultimately benefiting patients, researchers, and pharmaceutical innovation. The FDA Modernization Act 2.0 and the ISTAND Pilot Program are key initiatives that encourage the use of AI-based models in preclinical testing.

Pharma Industry's AI Adoption in Preclinical Testing

The pharmaceutical industry is rapidly embracing AI to revolutionize drug development:

- **Investment Surge:** Since 2015, investors have injected **over $50 billion** into AI-driven R&D companies.

- **Efficiency Gains:** AI is driving innovation and efficiency across R&D, with generative AI alone projected to generate **$60 billion to $110 billion** in economic value.

- **Preclinical Development:** AI is optimizing toxicity screening, pharmacokinetic modeling, and real-time adverse event monitoring, significantly cutting costs and timelines.

Enhanced Collaboration: AI is facilitating real-time data exchange between sponsors and CROs, enhancing collaboration and speeding up decision-making. This integration is crucial for optimizing preclinical workflows and improving experiment design.

Practical Insights for Non-Clinical Experts & CROs

For non-clinical experts and Contract Research Organizations (CROs), integrating AI into preclinical workflows offers several advantages:

- **Enhanced Data Analysis:** AI can process vast datasets quickly, identifying patterns and predicting outcomes with high accuracy. This reduces the time and resources needed for manual data analysis.
- **Improved Experiment Design:** AI-assisted experiment design can optimize protocols, ensuring more reliable and reproducible results.
- **Real-Time Data Exchange:** AI facilitates real-time data exchange between sponsors and CROs, enhancing collaboration and speeding up decision-making.
- **Automated Laboratories:** The future of preclinical research includes fully automated laboratories powered by AI, reducing human error and increasing efficiency.

Noted below are a few challenges for non-clinical experts and CROS to consider:

- **High Initial Costs:** Implementing and training AI requires significant initial financial investment.
- **Need for Skilled Personnel:** AI integration necessitates skilled personnel for operation and maintenance.
- **Privacy & Energy Concerns:** AI use raises ethical concerns about data privacy and bias. Additionally, it requires significant energy to generate and compute large amounts of data.

🚀 Feel free to reach out to us if you have any questions!

Disclaimer: This newsletter is for informational purposes only and does not constitute legal or regulatory advice. Please refer to the official FDA guidance document for detailed recommendations.

*NIH – National Institute of Health
VA - Department of Veterans Affairs
ICCVAM -Coordinating Committee on the Validation of Alternative Methods
CDER – Center for Drug Evaluation and Research, FDA

References & Sources:

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