SafetAI Initiative
AI Based Prediction Initiative to Assist Reviewers with Predicting Toxicity End Point

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Introduction

Drug safety is of great concern to public health. In addition, during the Investigational New Drug (IND) application submission process, the FDA specifically reviews the safety of the submitted drug candidate before the sponsor can initiate any clinical trials. SafetAI is a collaborative initiative led by CDER (e.g., funded by a FY2022 CDER Safety Research Interest Group grant), where we are developing a suite of deep learning based QSAR models for various safety endpoints critical to regulatory science and the IND review. Currently, the initiative has focused on five key safety endpoints: hepatotoxicity, carcinogenicity, mutagenicity, nephrotoxicity, and cardiotoxicity.

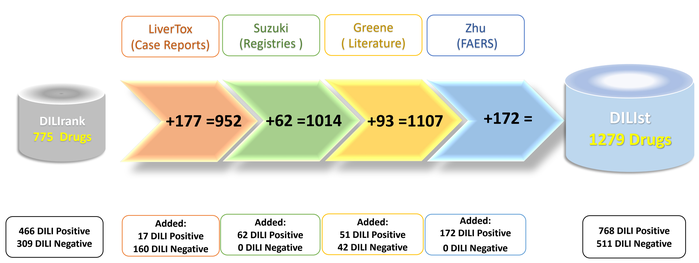
Features

Approaches: We are developing a deep learning framework which is designed to optimize toxicity prediction for individual chemicals based on their chemical characteristics. The method was compared to several conventional machine learning and state-of-art deep learning methods for predicting drug-induced liver injury (i.e., DeepDILI), carcinogenicity (i.e., DeepCarc). The preliminary results from this method yielded significant improvement in these toxicity endpoints in comparison to other deep learning and QSAR methods.

Potential Impact: SafetAI facilitates drug safety research with a novel deep learning architecture that improves the "precision" in toxicity assessment by tailoring prediction to chemical characteristics. It could play a role in providing critical safety information during the IND review process.

DeepDILI for Liver Toxicity

Drug-Induced Liver Injury Severity and Toxicity (DILIst)



Thakkar et al. Drug Discovery Today, 2019

Resources

1.Drug-induced liver injury severity and toxicity (DILIst): binary classification of 1279 drugs by human hepatotoxicity
Drug Discovery Today. 2020 Jan;25(1):201-208.
2.DeepDILI: Deep Learning-Powered Drug-Induced Liver Injury Prediction Using Model-Level Representation.
Chemical Research in Toxicology. 2021, 34:550-565.
3.Deep Learning on High-Throughput Transcriptomics to Predict Drug-Induced Liver Injury.
Frontiers in Bioengineering and Biotechnology. 2020, 8.
4.DeepCarc: Deep Learning-Powered Carcinogenicity Prediction Using Model-Level Representation.
Frontiers in Artificial Intelligence. 2021, 4.

Model Development

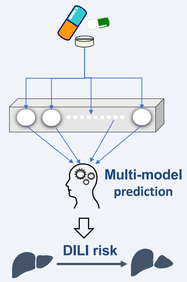
Model #1: Predict Drug-Induced Liver Injury (DILI)

Why? Close to 50% of drugs that fail in late-stage clinical trials or are withdrawn from the market due to liver toxicity are not predicted by the existing pre-clinical models! Kaplowitz, Neil. *Nature reviews Drug discovery* 4.6 (2005): 489-499.

How? Can AI predict human DILI risks better than animal studies based on chemical structure of drugs alone?

Findings: A novel deep learning model (DeepDILI) was developed with ~70% accuracy based on drugs approved before 1997 to predict drugs approved after 1997.

Impact: DeepDILI could be used to support IND review and to screen drug candidates before human testing in drug discovery and development.



Li et al. DeepDILI, *Chemical Research in Toxicology*, 2020, 34, 2, 550–565.

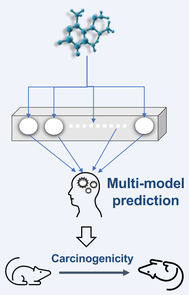
Model #2: Predict Carcinogenicity

Why? Carcinogenicity is a critical component for safety assessment of drugs and environmental chemicals. However, its testing often involves 2-year rodent animal studies.

How? To develop DeepCarc by using the DeepDILI architecture for carcinogenicity prediction.

Findings: The DeepCarc model was developed based on the NCTRIcdb (692 compounds) and evaluated with 171 different compounds, yielding an accuracy of 75.4%. Compared to four advanced deep learning (DL)-based QSAR models, DeepCarc achieved an average improvement rate of 37%.

Impact: DeepCarc is an important addition to the SafetAI initiative.



Li T et al.. *Front Artif Intell.* 2021;4:757780-757780.

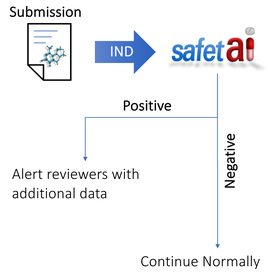
Applicability

SafetAI: Context-of-Use

Objective: Assist IND review of new drug candidates

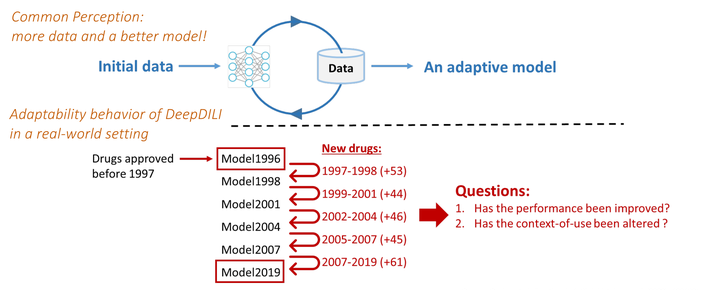
Key considerations: (1) prediction accuracy, (2) applicability domain, and (3) prediction confidence

Additional consideration – Adaptability: Should a model be treated as a static or evolving model over the new data ?



Adaptability

AI model improved over additional data (e.g., DeepDILI)?



Connor, Skylar, et al. *Frontiers in Artificial Intelligence* 5 (2022): 1034631.

Conclusion

Set of AI models for toxicity endpoints that are critical to drug safety research and review with a new deep learning method can be leveraged to aid non-clinical review through an early detection and prediction. This suite of models helps to improve the efficiency and thoroughness of non-clinical review at the FDA.

Acknowledgements

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Disclaimer: The information in this poster does not necessarily represent FDA's position or policy.