AI for Regulatory Science at FDA

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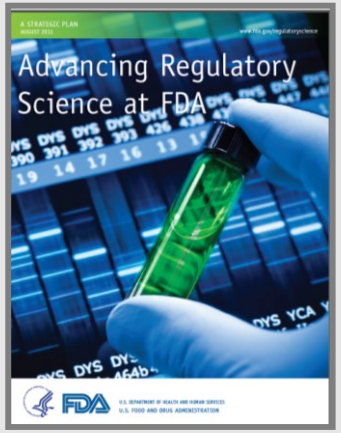
FDA's National Center for Toxicological Research (NCTR)

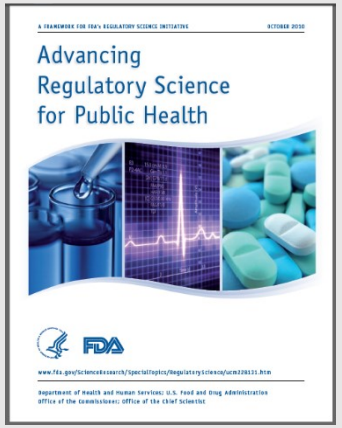
FDA's National Center for Toxicological Research

1. Center for Drug Evaluation and Research (CDER)
2. Center for Biologics Evaluation and Research (CBER)
3. Center for Food Safety and Nutrition (CFSAN)
4. Center for Device and Radiological Health (CDRH)
5. Center for Veterinary Medicine (CVM)
6. Center for Tobacco Products (CTP)
7. Office of Regulatory Affairs (ORA)
8. **National Center for Toxicological Research (NCTR)**

Regulatory Science:

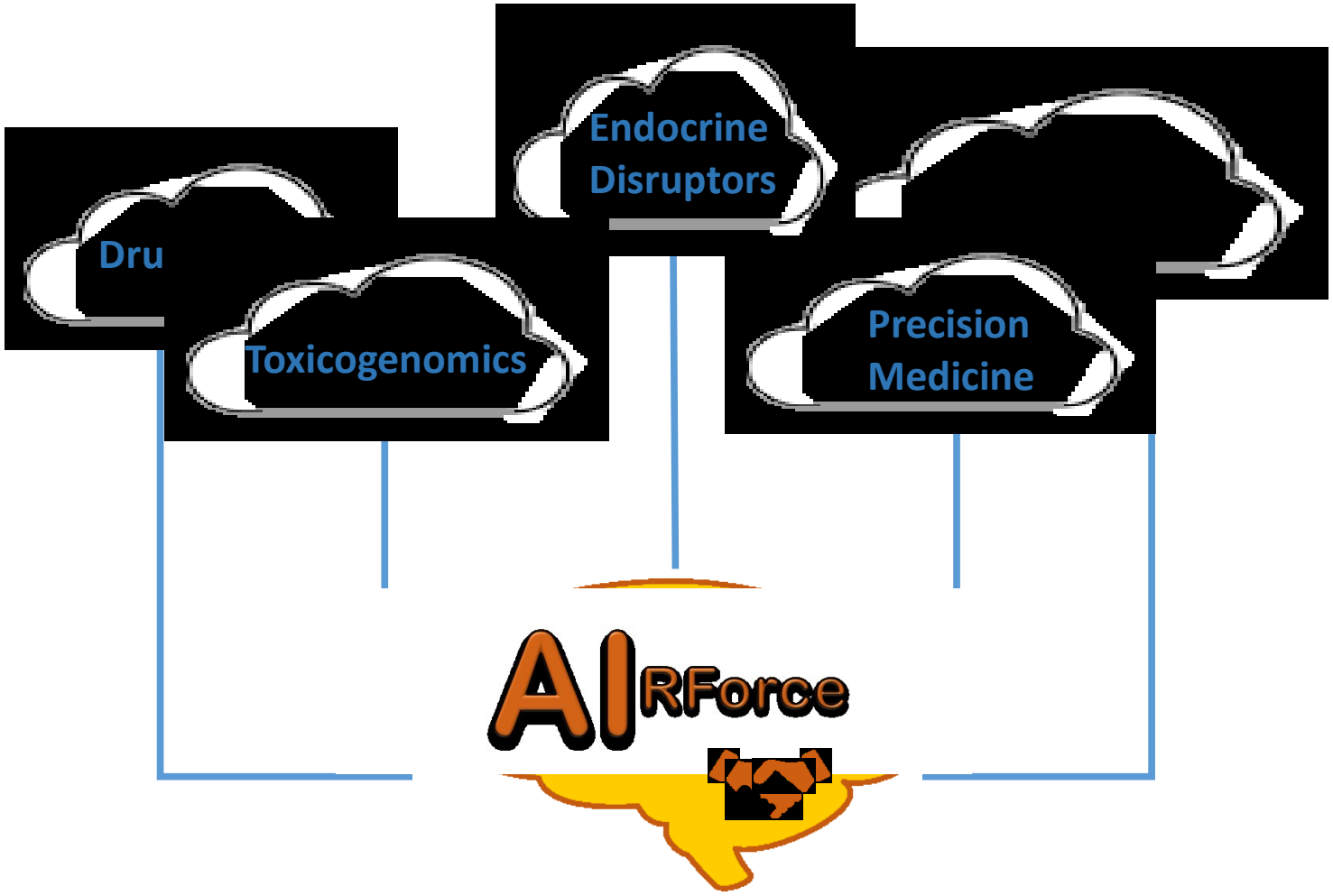
- *Regulatory science* is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.





Division of Bioinformatics and Biostatistics (DBB)

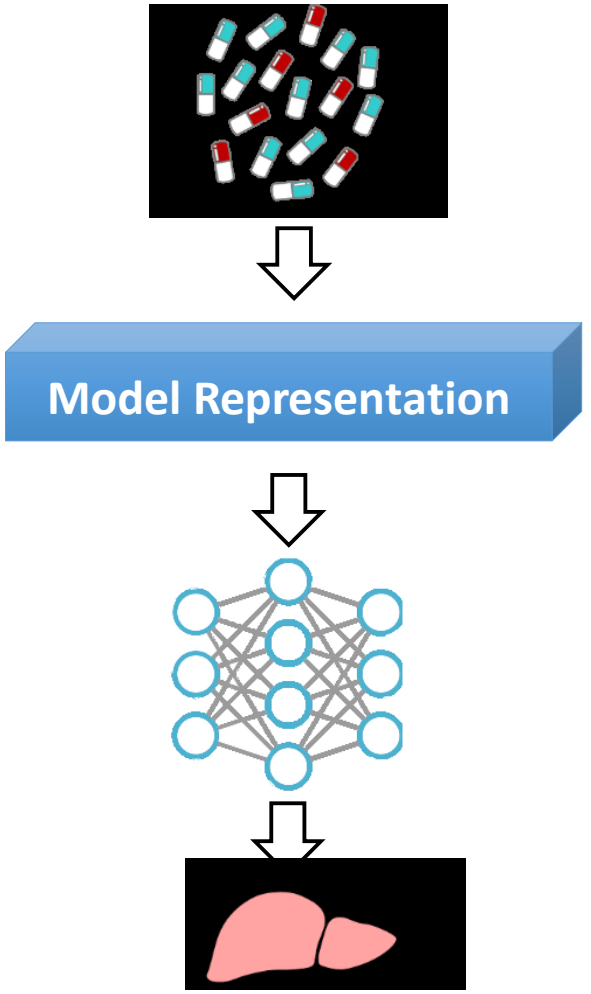
- One of six research divisions at NCTR
- FTEs: ~50 FTEs
- Objective: to conduct Regulatory Science research using computational approaches, including bioinformatics, biostatistics, molecular modeling and simulation, cheminformatics, knowledgebase, and AI/ML



AI Research Force (AIRForce)

DeepDILI: AI for Drug-Induced Liver Injury (DILI)

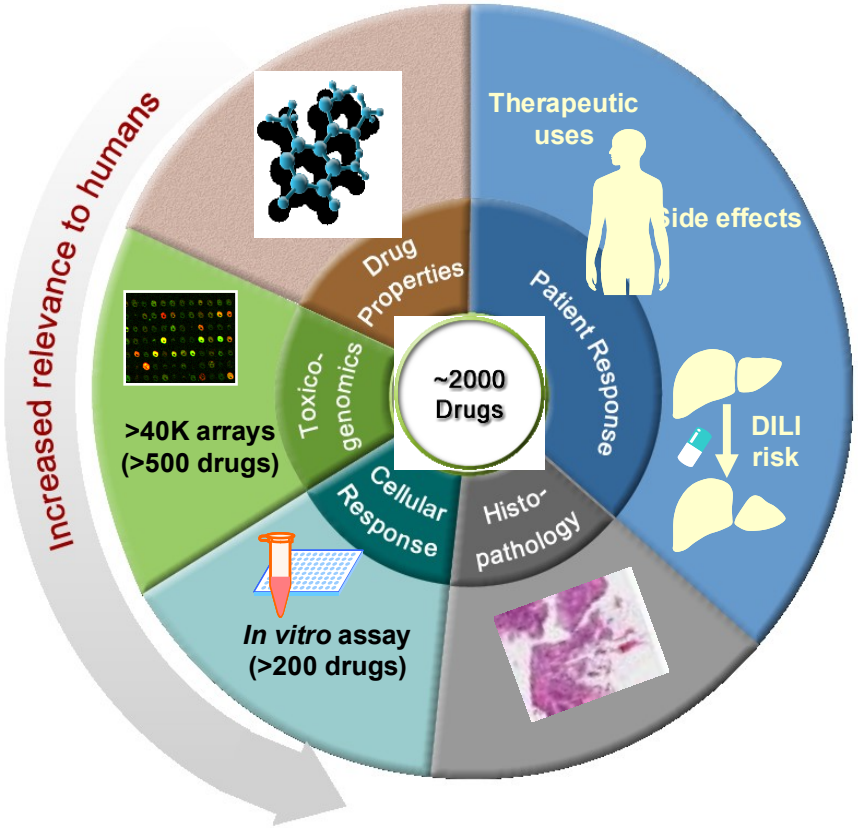
- **Why?** Close to 50% of drugs that are failed in clinical trials or withdrawn from the market due to liver toxicity are not predicted by the existing pre-clinical models!
- **How?** AI approaches for human DILI prediction based on chemical structure alone.
- **Findings:** A novel deep learning model (DeepDILI) was developed with ~70% accuracy based on drugs approved before 1997 to predict drugs approved after 1997.
- **Meaning:** DeepDILI could be used to support IND review at FDA; Investigational New Drug (IND) review clears a drug candidate to proceed clinical trial, which has a 30-day clock.



Li et al, CRT, 2021

Liver Toxicity Knowledge Base (LTKB)

- Classified drugs for DILI risk with drug labeling
- Curating diverse datasets for the market drugs
- Developing DILI predictive models



nature medicine

Published: 05 May 2016

Foretelling toxicity: FDA researchers work to predict risk of liver injury from drugs

Mechanistic-driven models:

- "Rule-of-two" or RO2 model (Chen, et al., Hepatology, 2013)
- DILIscore model (Chen, et al., Hepatology, 2016)

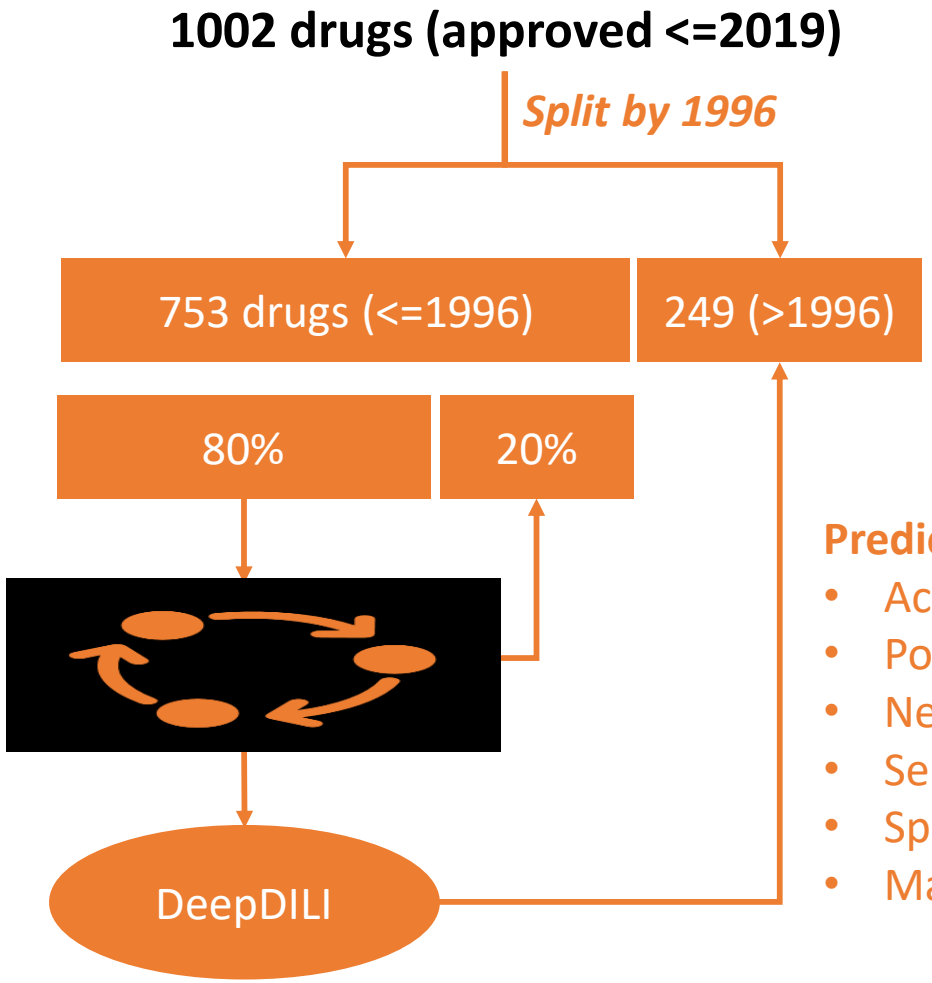
QSAR models:

- DILIps model (Liu, et al., PLoS Comput Biol, 2011)
- QSAR models (Chen. et al. Tox Sci, 2013)
- Multi-class QSAR model (Hong, et al, Sci Rep, 2017)

In vitro and genomics models:

- High content screen assay (Chen et al., Arch Tox, 2015)
- DILI models with Tox21 and QSARs (Wu et al., JCIM, 2017)
- Genomics model (Liu et al., CRT, 2020)

DeepDILI: an AI Model for DILI Assessment



- DeepDILI was developed with a novel AI approach that integrates multiple ML models in a deep learning architecture
  - A binary classification: DILI positive or negative
  - ~70% accuracy based on drugs approved before 1997 to predict drugs approved after 1997

Predictive performance:

- Accuracy (ACC): 0.687
- Positive predictive value (PPV): 0.710
- Negative predictive value (NPV): 0.638
- Sensitivity (SE): 0.805
- Specificity (SP): 0.510
- Matthew's Correlation Coefficient (MCC): 0.331

Li et al, CRT, 2021

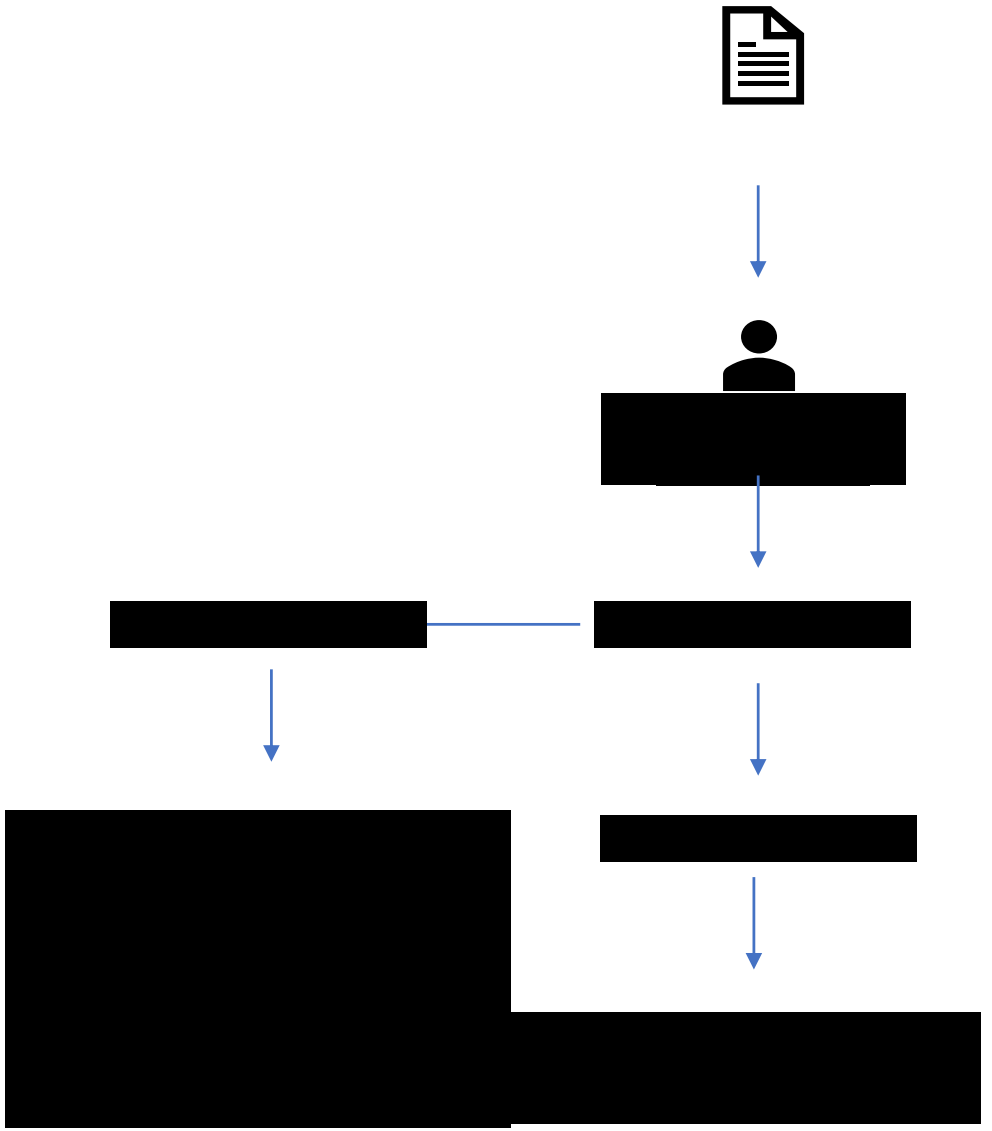
FDA ISTAND (Innovative Science and Technology Approaches for New Drugs)

- To qualify Drug Development Tools (DDTs) that don't fit the definition of a biomarker and clinical outcome assessment, e.g.,
  - Computational approaches: (1) Use of artificial intelligence (AI)-based algorithms to evaluate patients, develop novel endpoints, or inform study design and (2) Use of novel digital health technologies (e.g., wearables) for patient assessment
  - Scientific tools and technologies that use human biology to predict human outcomes to help reduce and replace animal testing as part of drug development.
- Qualification is intended to provide a pathway for new nonanimal approaches to be integrated into drug development and regulatory decision-making.
- Once qualified, DDTs will be available to use in any drug development program for the qualified context of use. Additionally, the qualified DDT can generally be included in IND, NDA, or BLA applications without needing FDA to reconsider and reconfirm its suitability.

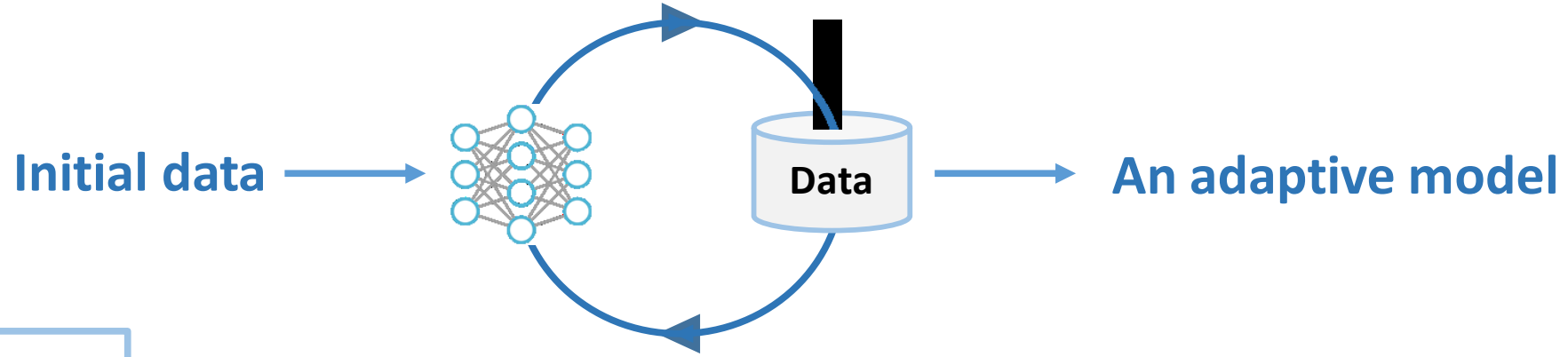
DeepDILI for ISTAND

- The qualification process includes three submissions:
  - The Letter of Intent (LOI)
  - The Qualification Plan (QP)
  - The Full Qualification Package (FQP)

- Context of Use
  - Where it will be applied: support IND review
  - How it will be applied:
    - Applicability domain
    - Prediction confidence
    - **“Locked” or “adaptive”?**



AI is a Living Model and Improved Over Additional Data



Process

Drugs approved before 1997

Model1996
Model1998
Model2001
Model2004
Model2007
Model2019

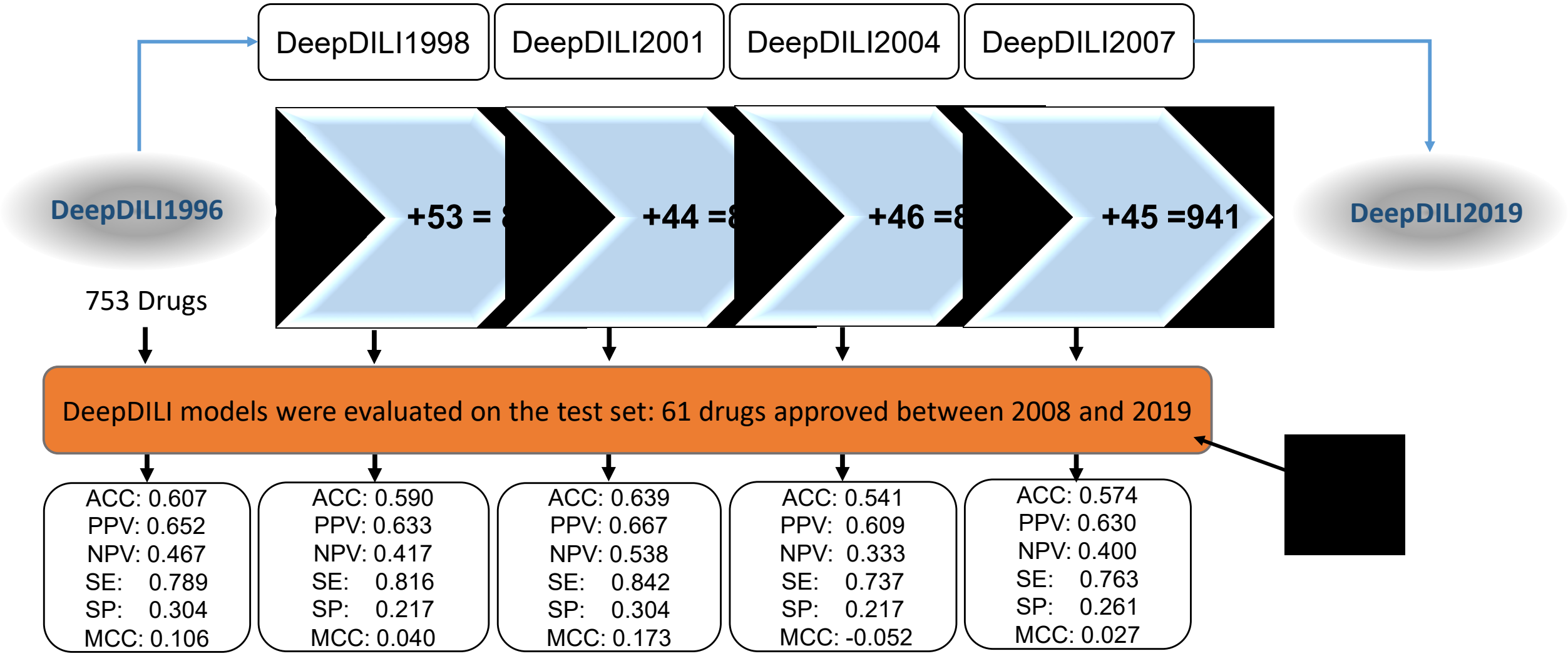
New drugs:

1997-1998 (+53)
1999-2001 (+44)
2002-2004 (+46)
2005-2007 (+45)
2007-2019 (+61)

Questions:

1. Has the performance been improved?
2. Has the context-of-use been altered ?

DeepDILI Adaptative Behavior



safetAI · FDA/CDER Initiative

- Objective: To develop a set of AI models for a broad range of toxicity endpoints critical to drug safety, particularly IND review

- SafetAI pilot:
  1. DeepDILI – Published (CRT in 2021) and for ISTAND qualification (LOI)
  2. DeepCarc – Published (Frontiers AI, 2022)
  3. DeepAMES – Developing
  4. DeepCardio – Data collection
  5. DeepKidney – Data collection

Summary

- DeepDILI is the first AI model under SafetAI initiative to support IND review
  - A novel deep learning approach, which outperformed other AI/ML methods for DILI prediction
  - The same approach is being used to develop AI models for other endpoints such as DeepCarc and DeepAMEs

- DeepDILI is undergoing the ISTAND qualification process as a “static” model to provide additional data for the IND review
  - To assess the likelihood of a molecule with potential hepatotoxicity concern in humans, which could lead to a severe warning from FDA or even withdrawn from the market for such a concern.
  - To be applicable for single small molecules with MW<1000.
  - To have higher confidence to identify DILI positives than negatives.
  - To be more effective in use for the Alimentary Tract and Metabolism drugs defined by ATC.

AI for Regulatory Science

1. Context-of-use: an adaptive advantage needs to be established
2. AI is NOT all about prediction; AI can generate animal data without conducting animal studies
3. Deep learning is not necessary always the best choice – A systematic evaluation could be beneficial
4. AI can be trustworthy, towards causality assessment
5. Understanding the model is more important than developing one

Acknowledgement

- AI Research Force (AIRForce) team
  - Zhichao Liu – Technical lead
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