AI in Drug Development

CDER Office of Medical Policy

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Artificial Intelligence (AI): a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions and making predictions.
Definitions are important: What is ML?

**Machine Learning (ML):** A subset of AI that allows ML models to be developed by ML training algorithms through analysis of data, without models being explicitly programmed.

*Artificial Intelligence (AI)*
Programming computers to perform tasks to mimic human capabilities—such as understanding language, recognizing objects and sounds, learning, and problem solving—by using logic, decision trees, machine learning, or deep learning.

*Machine Learning (ML)*
Subset of AI that gives “Computers the ability to learn without being explicitly programmed”—based on work by Arthur Samuel.

- **Supervised Learning** (labeled data)
- **Semi-Supervised Learning**
- **Unsupervised Learning**
- **Deep Learning**
  Subset of ML utilizing deeply stacked neural layers that enables streamlined and advanced algorithm development
- **Reinforcement Learning**

※ The descriptions within the diagram are not definitions, and are included to convey a general sense of the technology.
Drivers behind the growth in AI health applications

- Large datasets (e.g., administrative data, EHRs, registries, etc.)
- Diverse and multimodal datasets (e.g., DHTs, genomic, laboratory, imaging, etc.)
- Improvements in data standards (e.g., ICD-10, LOINC, NDCs, UMLS, FHIR/HL7, OHDSI, etc.)
- Improved data interoperability and healthcare data exchange
- Increased computing power
- Advancements in data privacy persevering approaches
- Breakthroughs in methods (e.g., deep neural networks, reinforcement learning, Generative adversarial networks, Variational autoencoders, etc.) and causal inference approaches (e.g., structural causal models and causal Bayesian networks)
Number of medical AI studies by year from 2010 to 2020; and by medical specialties

https://www.nature.com/articles/s41746-020-00333-z/figures/1
FDA’s CDRH has authorized over 500 AI/ML enabled devices
AI use across the drug development landscape

Discovery and Development

- Drug Target Identification, Selection, and Prioritization
- Compound Screening and Design

Preclinical Research

Drug Target Identification, Selection, and Prioritization
Pharmacokinetic (PK), pharmacodynamic (PD), and toxicologic studies

Clinical Research

- Dose optimization
- Recruitment and selection
- Adherence
- Retention
- Site selection
- Data collection, management, and analysis
- Clinical endpoint assessment

Manufacturing and Post-Market Safety Monitoring

- Advanced pharmaceutical manufacturing
- Post-market safety surveillance or pharmacovigilance (PV)
FDA’s **CDER** has seen a rapid increase in drug regulatory submissions with AI/ML components

Count of regulatory submissions for drug development with key terms “machine learning” or “artificial intelligence” from 2016 to 2021

<table>
<thead>
<tr>
<th>Submission Type (n)</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
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<tbody>
<tr>
<td>IND</td>
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<td>1</td>
<td>2</td>
<td>5</td>
<td>11</td>
<td>128</td>
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<tr>
<td>NDA, ANDA, BLA</td>
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<td>2</td>
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<tr>
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<td>Discovery and Development</td>
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<tr>
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<td>5</td>
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<tr>
<td>Post-Market Safety Monitoring</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** Investigational New Drug (IND); New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Biologics License Application (BLA); Drug Development Tool (DDT) Qualification Programs, Critical Path Innovation Meeting (CPIM)

**SOURCE:** Internal databases maintained by the FDA Center for Drug Evaluation and Research (CDER)
FDA’s CDER has seen a rapid increase in drug regulatory submissions with AI/ML components

Regulatory submissions with key terms ML or AI by Therapeutic Area

- Oncology: 42
- Psychiatry: 24
- Gastroenterology: 19
- Neurology: 17
- Medical Imaging: 9
- Pain management and Alcohol Abuse: 9
- Infectious Diseases: 8
- Other*: 30

AI in drug development – challenges

• AI or ML approach can only ever be as good as the underlying data:
  o Scarcity of high-quality, large-scale, and fit-for-purpose datasets for development and testing
  o Identification and mitigation of bias in datasets
  o Poor generalization due to dataset shift, to overfitting to confounders

• Black box algorithms
• Ensuring transparency to users
• Providing oversight/governance for adaptive algorithm
• Need for regulatory clarity in certain areas
Advancing regulatory science in this space can help us promote innovation and public health.
CDER AI

FDA’s efforts in this area?
Center for Devices and Radiological Health (CDRH)

Published AI/ML-SaMD Discussion Paper
First joined Collaborative Community related to AI/ML
Evolving Role of AI in Radiological Imaging
Public Workshop on AI/ML in Radiological Imaging
PEAC Mtg on Patient Trust in AI/ML Devices
Published AI/ML Medical Device Software Action Plan
Posted List of Currently Marketed AI/ML Devices
Public Workshop on Transparency of AI/ML Devices
Published GMLP Guiding Principles

2019  2020  2021

Slide from Dr. Matthew Diamond, Chief Medical Officer for Digital Health, CDRH
<table>
<thead>
<tr>
<th></th>
<th>CDRH’s Good Machine Learning Practice for Medical Device Development: Guiding Principles</th>
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<tbody>
<tr>
<td>1</td>
<td>Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle</td>
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<tr>
<td>2</td>
<td>Good Software Engineering and Security Practices Are Implemented</td>
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<tr>
<td>3</td>
<td>Clinical Study Participants and Data Sets Are Representative of the Intended Patient Population</td>
</tr>
<tr>
<td>4</td>
<td>Training Data Sets Are Independent of Test Sets</td>
</tr>
<tr>
<td>5</td>
<td>Selected Reference Datasets Are Based Upon Best Available Methods</td>
</tr>
<tr>
<td>6</td>
<td>Model Design Is Tailored to the Available Data and Reflects the Intended Use of the Device</td>
</tr>
<tr>
<td>7</td>
<td>Focus Is Placed on the Performance of the Human-AI Team</td>
</tr>
<tr>
<td>8</td>
<td>Testing Demonstrates Device Performance During Clinically Relevant Conditions</td>
</tr>
<tr>
<td>9</td>
<td>Users Are Provided Clear, Essential Information</td>
</tr>
<tr>
<td>10</td>
<td>Deployed Models Are Monitored for Performance and Re-training Risks Are Managed</td>
</tr>
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FDA’s efforts in this area? Center for Drug Evaluation and Research (CDER)

- CDER actively collaborates with CDRH, CBER, and other centers on issues related to AI/ML in medical product development to ensure consistency whenever possible.

- CDER established an AI Steering Committee in 2020 to facilitate effective use and sustainment of AI in CDER’s decision-making and operations.

- Next steps: workshops, white papers, discussion paper, harmonizing and tailoring GMLP to drug development, support development of regulatory science methods.

- Our goal: to develop and adopt a flexible risk-based regulatory framework that promotes innovation and protects patient safety.
Thank you