U.S. FOOD & DRUG ADMINISTRATION

# The Future of AI and the Generic Drug Community

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# Impact of AI on Generic Drugs

- AI will change
  - How generic drug submissions are evaluated
  - How generic drugs are developed

AI: Artificial Intelligence

# Elsa

- FDA has made a leading LLM broadly available to all staff in a secure computing environment with protected access to FDA data
- The huge win is broad accessibility of high-end tools
  - This allows FDA staff to directly use AI in their daily work without gatekeeping
  - Strong encouragement for bottom-up innovation!

LLM: Large Language Model

# Builder Perspective

- Elsa is fantastic for users
- In ORS, for Quantitative Medicine/AI we have a **builder** culture (write code to solve a generic drug problem)
- What did I learn from our initial AI projects?

ORS: Office of Research and Standards

# Focus of Current Effort --- Database

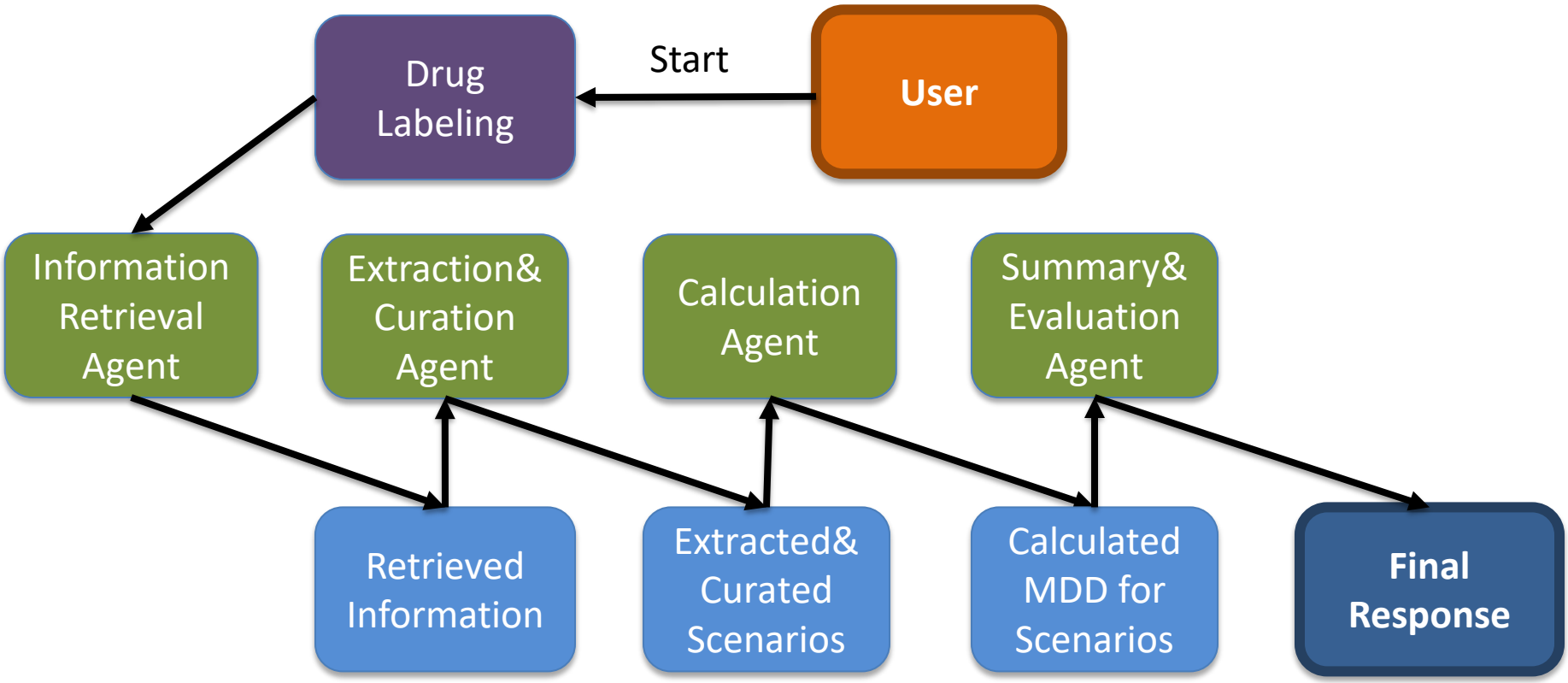
- High-quality datasets: crucial for the success of AI development
  - Accurate & complete
  - Integrated data from different sources (ANDA submissions, review documents, info on APIs, formulation [dosage form & excipients], in vitro and in vivo studies)
- **We aim to establish robust data and knowledge bases for generic drugs** via streamlining data source connections and information retrieval
  - Data standardization, integration from diverse sources
  - AI assistants make this possible
  - Important infrastructure development!!!

API: Active Pharmaceutical Ingredient

# Focus of Current Effort --- Workflow Automation

- Building agentic AI systems to automate workflows (rather than simple prompting)
  - Domain expertise guided workflow establishment for different tasks
    - Generally dynamic workflow
    - logic analysis, based on information from various sources
    - Time consuming and human errors are common
  - AI can automate the execution of developed workflows

# Agentic AI MDD Tool - Workflow




MDD: Maximum Daily Dose

# What is the Role of a Reviewer in an AI Future?

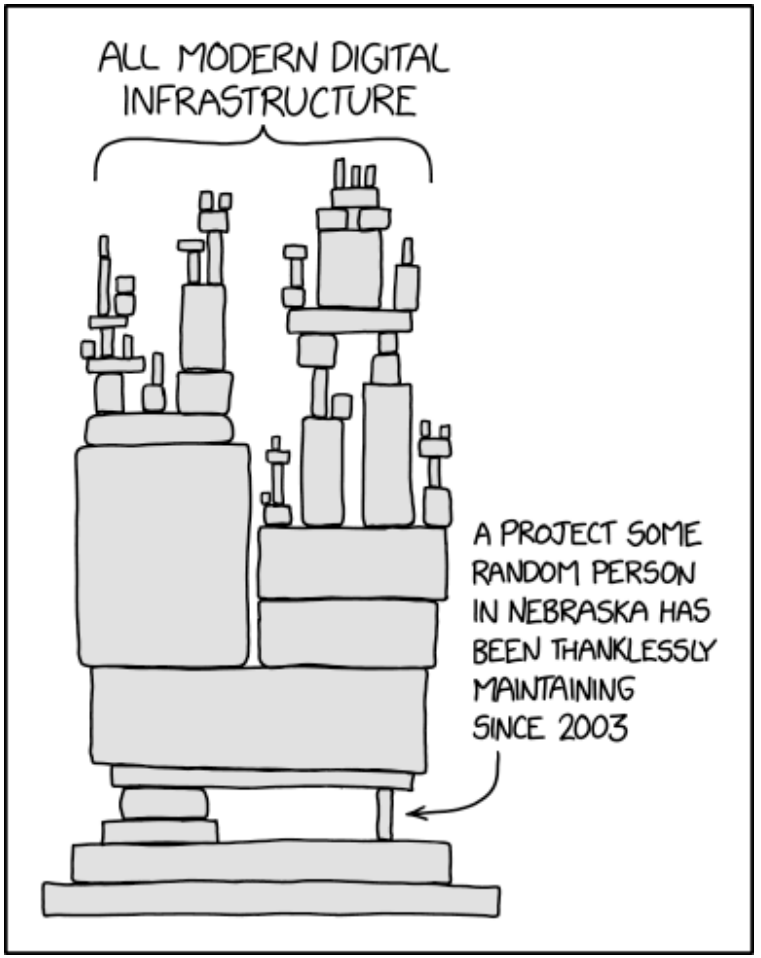
- "To be the responsible person"
  - Application assessments require a final human conclusion
- In an AI future humans can do more
  - Systems will expect more
  - Computers have never reduced the numbers of knowledge workers

# Data Integrity Example

- In the past problems were found by humans noticing things
- In the future AI can notice more things and bring them to human attention

# Number of Reviewers

- 2000 FDA staff support the entire US generic drug supply chain
  - 90% of all prescriptions
  - $100 billion in lost-cost sales
  - $30 billion in Savings per year
- In September big pharma fired 3 times that many people




xkcd: Dependency

# Value of FDA Expertise

- FDA staff are useful to society because they are broadly knowledgeable about cross-application trends in drug development
  - I still learn from each application
  - AI will make this type of impact more sustainable

# When Will AI Accelerate ANDA Approval Times?

- What is the limiting factor?
  - Patent, exclusivity, facilities, 80% of ANDA with first cycle deficiencies, time spent by the FDA reviewer
  - AI will likely first make FDA review more consistent
- Future State
  - Applicants use AI to improve the quality of the submission

# Impact of AI on Generic Drug Development

- Product Development
  - Machine learning directed drug formulation development
    - enabling data-driven predictions of critical performance indicators of complex formulation spaces, such as solubility, viscosity, and stability
  - Enable quantitative medicine approaches via faster model building
- Submission Development
  - Automate tasks like data analysis, report generation, and regulatory submissions
  - Eliminate replication of common deficiencies

# GDUFA Regulatory Science Programs Use AI

- The ORS has been investing in AI and machine learning (ML) research since 2018, to drive innovation and adoption of emerging technologies.

- AI/ML has been used to support the OGD's missions, highlighted by:
  - The first ML-based predictive analysis for ANDA submission [1-2]
  - Development of the BEAM (BE Assessment Mate) to streamline the labor-intensive work in BE assessment [3]
  - Development and release of the PyDarwin – a ML-based tool for automating the population PK model selection [4]
  - The first large language model finetuned based on drug labeling – PharmBERT - to support the PSG development [5]
  - The feasibility analysis of using ChatGPT to facilitate regulatory assessment [6]

[1] Gong, et al. Clin Transl Sci (2018) 11, 305–311; [2] Hu, et al. Clin Pharmacol Ther. 2019;106(1):174-181; [3] OGD 2021 Annual Report [4] Li, et al. Clin Pharmacol Ther. 2024;115(4):758-773; [5] ValizadehAslani, et al. Briefings in Bioinformatics, 2023, 1–10; [6] Shi, et al. Journal of Biomedical Informatics 148 (2023)104533.

# Formulation Science Use of AI

- **Scientific Approach:** Use pharmaceutical science and clinical pharmacology to identify required sameness, avoiding clinical trial repetition for competitive access.
- **Industry Evolution (FY24 vs FY04):**
  - **Oral Dosage Forms:** 56% approvals (down from 70% submissions in FY04)
  - **Solutions (Topical/Injectable):** 31% approvals (up from 20% in FY04)
  - **Complex Generics:** 13% approvals (up from 10% in FY04)

# Research Priorities and AI Applications

| Focus Area | Current Challenge | AI Impact |
|---|---|---|
| **Impurities** | Nitrosamine risk assessment | Computational toxicity, reduced BE studies |
| **Complex APIs** | Peptides (10% competition), oligonucleotides (0%) | Computational immunogenicity |
| **Complex Dosage Forms** | LAIs (4 of 39 have competition) | In vitro BE methods, PLGA predictions |
| **Complex Delivery** | Limited inhalation/topical generics | Predictive deposition models |
| **Drug-Device Combinations** | User interface evaluation | AI-enhanced software assessment |
| **Quantitative Medicine** | Efficient BE evaluations | Accelerated PBPK modeling, MIE |

LAI: Long-Acting Injectable

# What about the Next 10 Years?

- Complex Generics
  - Bigger percentage of OGD work
  - Bigger value for industry
  - More meetings/interactions
  - Implementing novel methods with Center for Complex Generics
  - Drug Device Combinations
- Quantitative Medicine
  - More efficient studies (MIE pilot)
  - Model Master Files
  - PK data warehouse
  - Use Quantitative Medicine to reduce unneeded studies or making in vitro BE limits clinically relevant for complex generics
  - Prediction for pediatric populations not used in BE studies

MIE: Model-Integrated Evidence

# What about the Next 10 Years?

- Non-complex Generics
  - More biowaivers
  - Non Q1-Q2 injectables
  - Global harmonization
  - Confidence in commodity products
  - Robustness to shortages
- Artificial Intelligence
  - Review transformation
  - Faster model building
  - Data foundation and open environments

# Summary

- AI will be transformative in a sector that values efficiency of product development and review
- Predictions
  - FDA assessments become more consistent
  - Quantitative Medicine approaches will be easier to develop and support more efficient bioequivalence methods
  - Complex Generics become even more important and are a key use for AI aided product development
  - Industry use of AI reduces common deficiencies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