Use of Artificial Intelligence to Facilitate the Development and Regulatory Assessment of Complex Generic Drugs

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 1: Cutting Edge Science

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Disclaimer

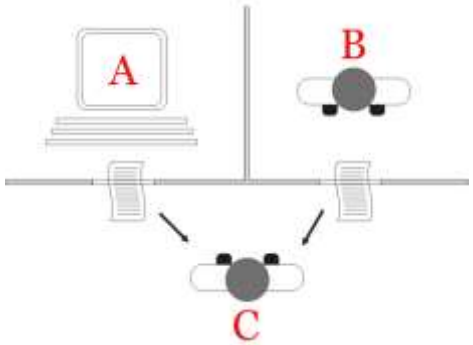
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- Artificial Intelligence (AI) is everywhere
- AI offers opportunities to facilitate generic drug development and regulatory assessment
- DQMM's efforts to answer the opportunity call
- Actions from other stakeholders
- Challenges and lessons learned
- Takeaways

AI is everywhere

- What is AI?
  - *Turing Test* proposed by **Alan Turing** in 1950
  - "*It is the science and engineering of making intelligent machines, especially intelligent computer programs*." by **John McCarthy** in 2004



AI is everywhere – continued

- The thriving AI community should thank the advances in information technologies and powerful chips
  - –Big data
  - –Data analytics tools (e.g., machine learning and natural language processing)
  - –HPC (High-performance computing) / Cloud computing
- AI is transforming many areas of everyday life
  - –Smartphone (e.g., face recognition)
  - –Autopilot
  - –Chatbot
  - –Personalized recommendation
  - –ATM (automated teller machine)

AI offers opportunities to facilitate generic drug development and regulatory assessment

- Automating labor-intensive tasks
  - Enhanced efficiency (e.g., saving time)
  - Improved consistency (e.g., reducing human error)
  - High-quality deliverables

- Exploiting advanced data analytics methods
  - Promoting business intelligence
  - Supporting regulatory assessment

DQMM's efforts to answer the opportunity call

Automating labor-intensive tasks

Development of:

- **BEAM tool (bioequivalence assessment mate)**
- data analytics tool to facilitate product-specific guidance (PSG) development

Adopting advanced data analytics methods

Promoting business intelligence based on machine learning methodologies

- **Prediction of abbreviated new drug application (ANDA) submission**
- Heterogeneous treatment effect analysis
- Modeling the process of ANDA assessment

Supporting regulatory assessment

- Equivalence assessment for complex particle size distribution based on the earth mover's distance
- Multivariate analysis method to facilitate active pharmaceutical ingredient sameness assessment

Example Case

Predictive Analysis of First ANDA Submission for New Chemical Entities (NCEs) Based on Machine Learning Methodology

Project background

- An approved ANDA is required to ensure that generic drugs are available to facilitate drug availability and accessibility to U.S. public

- Under GDUFA II, the ANDA assessment process involves multiple offices in FDA, multiple disciplines, and tight turnaround times

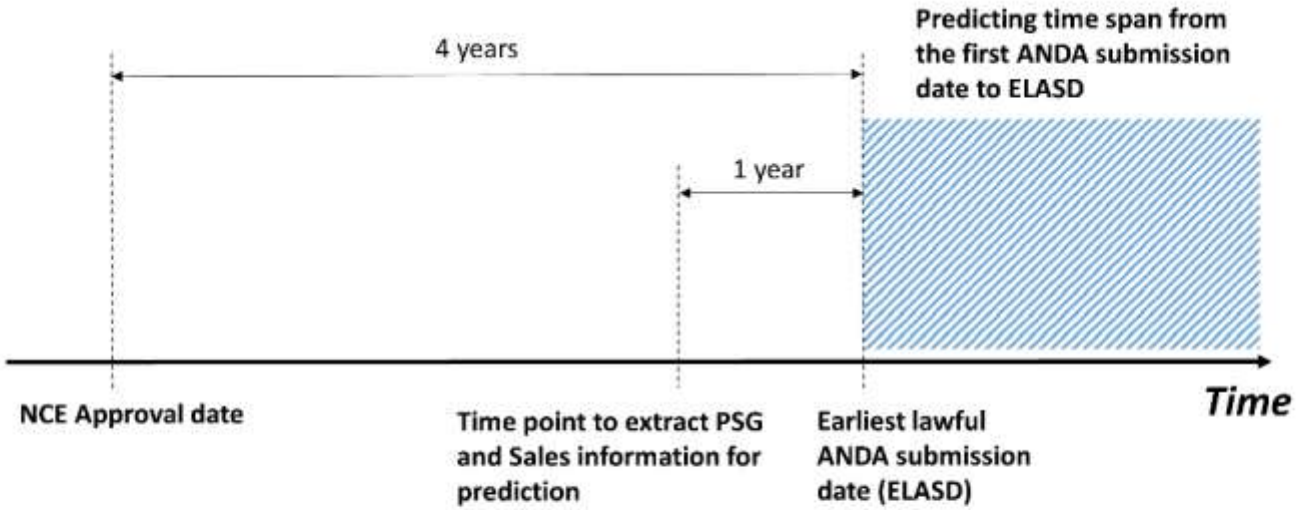
- Predictive analysis of ANDA submission will critically inform resource allocation and workload management
  - Prioritizing product-specific guidance (PSG) development and research efforts
  - Optimizing resource allocation (e.g., pre-ANDA interactions)

- Study scope: Time to first submission for ANDA referencing NCE

Collecting data for prediction

- **Drug product information**
  - Complex API
  - Complex Dosage Form
  - Complex Delivery Route
  - Complex Drug-Device Combination
  - Abuse Deterrent Formulation
  - Oral Modified Release
  - Anatomical Therapeutic Chemical (ATC)
  - Acute/Chronic Disease
- **Regulatory information**
  - NDA Approval Date
  - NCE Exclusivity Expiration Date
  - Patent Expiration Date
  - First ANDA Submission Date
  - First PSG Publication Date
  - Risk Evaluation and Mitigation Strategies (REMS)
- **Pharmacoeconomic information**
  - Drug sales from 2011 to 2017

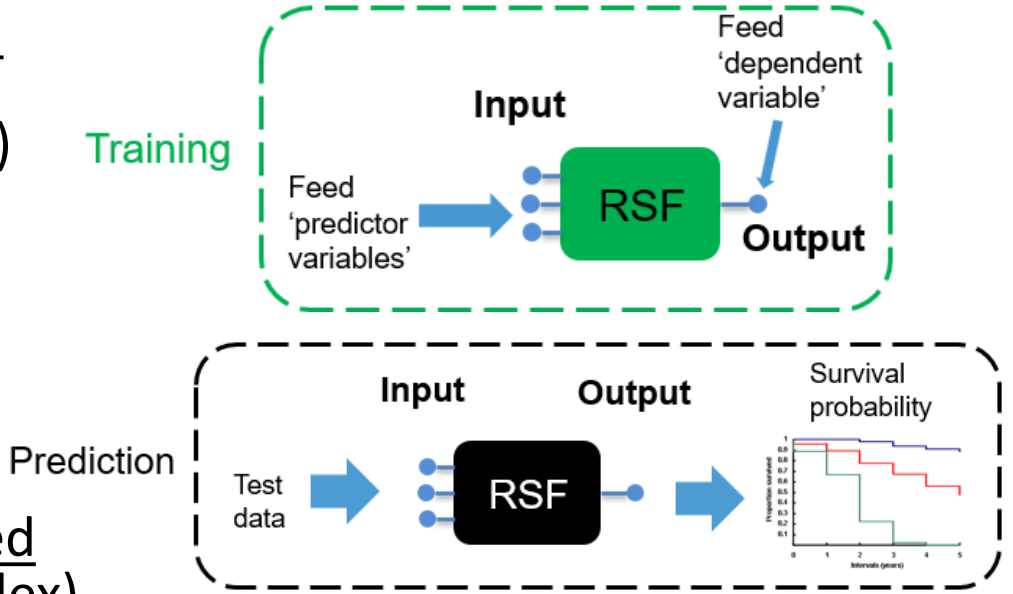
Data model



$$\textit{Time span from the first ANDA submission date to ELASD} \sim f(\text{Drug Information, Regulatory Information, Pharmacoeconomic Information})$$

Method

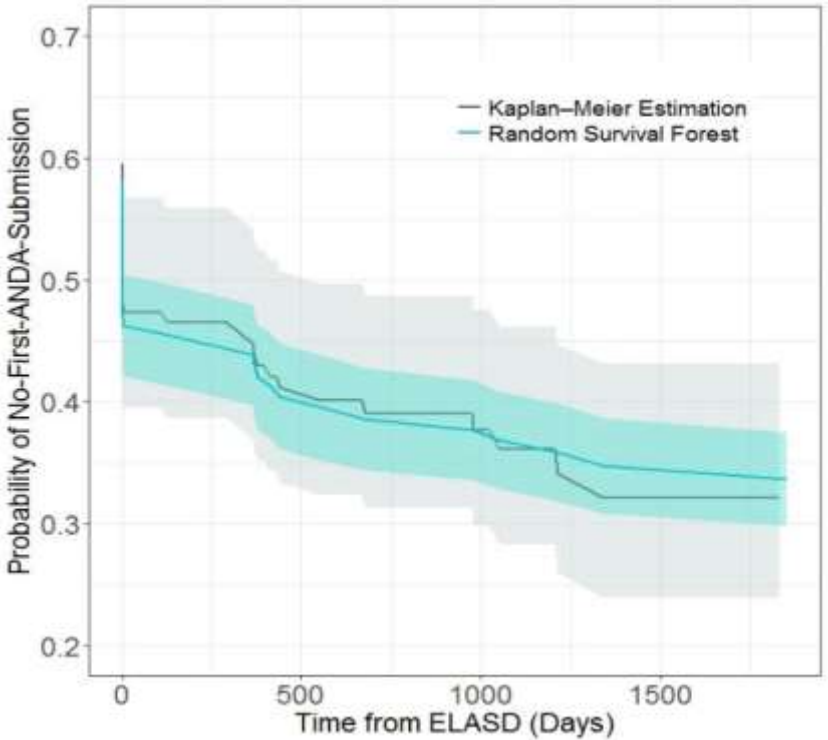
- Machine-learning based survival method
  - Random Survival Forest (RSF)
  - Data adaptive (no model assumptions)
  - Capable for large-feature problem



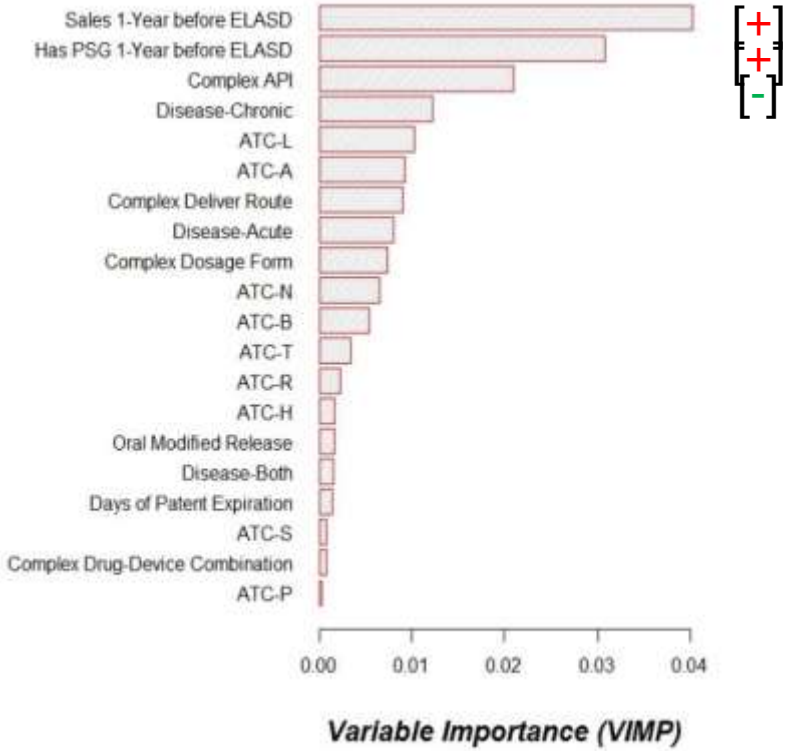
- Predictive Performance Evaluated by the Concordance Index (C-index)
  - C-index = 1 Perfect prediction
  - C-index = 0.5 Random guess

Results

Prediction based on leave-one-out method (C-index = 0.767)



Identification of important variables



Actions from other stakeholders:

A brief summary of the breakout session (1C) on AI in the Generic Drug Science and Research Initiatives Public Workshop (2021)

https://sbiaevents.com/grs-2021/

Session Design

Sub Session 1C: Exploring opportunities and challenges for utilizing artificial intelligence (e.g., machine learning and natural language processing) to support generic drug development and application assessment

3:30 PM – 3:40 PM	***Artificial Intelligence in Pharmaceutics***	
	Defang Ouyang, PhD	Assistant Professor, Univ. of Macau
3:40 PM – 3:50 PM	***Artificial Intelligence in Generic Drug Development – Experience and Opportunities***	
	Jerneja Opara, PhD	Leading Scientist, Sandoz Pharm.
3:50 PM – 4:00 PM	***Improving Generic Drugs and Streamlining Their Approval Through Artificial Intelligence***	
	Charlie DiLiberti, PhD	President, Montclair Bioequivalence Services, LLC
4:00 PM – 4:30 PM	Panel Discussion (Sub-Session 1C)	
Moderator:	**Meng Hu, PhD**	Team Lead, DQMM, ORS, OGD, FDA
Panelists:	**Defang Ouyang, PhD**	Assistant Prof., Univ. of Macau
	Jerneja Opara, PhD	Leading Scientist, Sandoz Pharm.
	Charlie DiLiberti, PhD	President, Montclair Bioequivalence Services, LLC
	Stella Grosser, PhD	Director, DB-VIII, Office of Biostatistics, OTS, FDA
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, FDA
	Robert Lionberger, PhD	Director, ORS, OGD, FDA
	Donald Mager, PhD	Prof. and Vice Chair, Department of Pharmaceutical Sciences, SUNY
	Robert Bies, PhD	Associate Prof., Department of Pharmaceutical Sciences, SUNY

 (Excerpted from the workshop agenda: https://sbiaevents.com/files2/2021-GDSR-Agenda.pdf)

Presentations in the session

- *AI in pharmaceutics*
  - Challenges for formulation development and values provided by AI
  - Case study: predicting physical stability, in vitro dissolution and in vivo performance of solid dispersion

- *AI in generic drug development - experience and opportunities*
  - AI models were used to predict BE outcomes (e.g., Cmax T/R ratio)
  - Discussion on other opportunities of AI models in generic drug development

- *Improving generic drugs and streamlining their approval through AI*
  - Needs to develop regulatory framework for AI
  - Potential applications of AI to the generic drug development

https://sbiaevents.com/grs-2021/

Highlights from the panel discussion

- Priority order of potential applications, the low-hanging fruits (e.g., handling outliers)
- Feasibilities from the technical perspective
  - Combination of AI models and conventional tools (e.g., Physiologically based pharmacokinetic (PBPK) models)
  - Integrating domain knowledge
  - Leveraging AI to utilize data from different resources
- Transparency / interpretability of AI models
- Business model of collaborations (e.g., between industries and the FDA)

Challenges and Lessons Learned

- Availability of reliable data
- Incorporation of domain knowledge
- Enabling complex projection between complex datasets
- Transparency/interpretability - turning the black box into a gray (or even transparent) box
- Extrapolation ability of AI models
- Lack of guidelines for regulatory purpose
- Teamwork and collaboration

Takeaways

- AI technologies:
  - bring opportunities to advance development and regulatory assessment of generic drugs.
  - have been applied to facilitate BE assessment, PSG development, business intelligence and regulatory assessment, etc.
  - will play more important role in providing high-quality generic drugs for U.S. public as more challenges get addressed.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