A Quantitative Modeling Approach to Predict Availability of Generic Orphan Drug Products

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Background

- Orphan drugs refer to those intended for the treatment, diagnosis or prevention of rare diseases that affect fewer than 200,000 people in the U.S..
- The high price of orphan drugs is often a barrier for patients to access care.
- Generic competition can help reduce drug price and enhance drug accessibility; thus mitigate the accessibility issue.

Objective

This study aims to examine the status of generic availability of orphan drugs and identify impactful factors on generic drug availability using quantitative modeling approaches.

Methods

- The data were collected for analysis and model building (Table 1), including
  - drug product information (e.g., whether the drug is a complex product* (drug complexity), dosage form, administration route, approval dates)
  - regulatory factors (e.g., product-specific guidance (PSG) recommendation dates, orphan drug exclusivity expiration dates)
  - pharmacoeconomic factors (anural sales revenue data between 2011 and 2022)
- Our dataset included 29 potentially relevant variables for 209 orphan reference listed drugs (RLDs) and their related generic products (if available).
- Summary statistics were used to examine the status of generic availability for orphan drugs.
- The oblique random survival forests (ORSF) method was used to identify the highly impactful factors and predict the probability of the first generic product availability at any given time point(s) of a given orphan RLD. The out-of-bag Harrell's C-statistic was used to evaluate the model performance.

- The annual drug sales revenue, whether the drug is a complex product* (drug complexity), and product-specific guidance (PSG) availability were identified as the three most impactful variables to predict the availability of generic orphan drug products through the modeling approach.

Table 1. Data collected in this study for analysis and model building.

Variable	Type	Class
PSG availability 3 years after RLD approval date	Input	Categorical
Exclusivity expiration date availability	Input	Categorical
Drug complexity	Input	Categorical
Dosage form	Input	Categorical
Administration route	Input	Categorical
Annual drug sales revenue 3 years after RLD approval date	Input	Continuous
Time duration between RLD approval and its first generic approval	Output	Continuous
Generic availability for each RLD	Output	Categorical

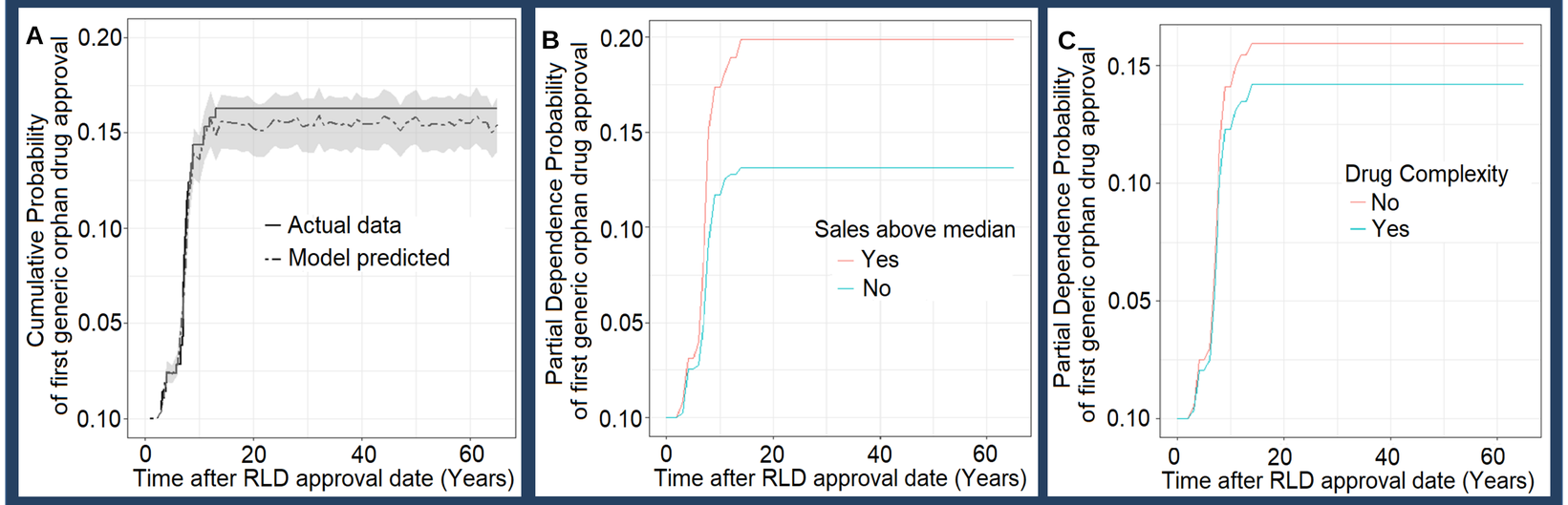

Figure 1. Preliminary results of ORSF model predictions. (A) comparisons of model predictions to the actual data for the cumulative probability of first generic orphan drug approval (shaded area is 95% confidence interval). (B) and (C) are partial dependence plots for annual sales data and drug complexity, respectively. X axis in each plot shows the time after RLD approval date in the unit of year and Y axis in each plot shows the probability of first generic orphan drug approval

*** Complex products, which are a key component of the FDA's Drug Competition Action Plan, are medical products where complexity or uncertainty concerning the approval pathway or possible alternative approaches would benefit from early scientific engagement, such as products with complex active ingredients and drug-device combination products.**

Results

- Among the 209 orphan RLDs (approval dates ranging from 2008 to 2019), 16% of them have at least one generic product available.
- The annual drug sales revenue (e.g., at 3 years after the RLD approval), drug product complexity, and PSG availability were identified as the most impactful variables.
- The results of Harrell's C-statistic show that the constructed machine learning model is a promising tool for predicting availability of generic orphan drugs.
- Figure 1 shows that the preliminary test results of the model performance
  - Model predicted cumulative probability of first generic orphan drug availability generally align with the actual data (Figure 1A).
  - RLDs that have above-median sales generally show a higher probability of having available generic orphan drugs (Figure 1B)
  - RLDs with no indication of drug complexity generally show a higher probability of having available generic orphan drugs (Figure 1C).

Conclusions

- In this study, three most impactful factors (drug sales, drug complexity, and PSG availability) associated with generic orphan product availability were identified and the model performance of predicting availability of generic orphan drugs was assessed.
- The model-informed results may be utilized in future intervention strategy development to promote the availability of generic orphan drug products.

Disclaimer

The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.