Trends in the application of pharmacometric modeling and simulation in the development of orphan drugs in the 21st century.

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Objectives

1. Investigate the trend of pharmacometric modeling and simulation (M&S) used in orphan drug development in the 21st century. This trend analysis will expose how M&S has been effectively used in FDA orphan drug filings.

2. Investigate the trend of pharmacometric M&S in filings with dose ranging studies. Link prospective dose ranging studies reported directly in the filings with reported models.

Background

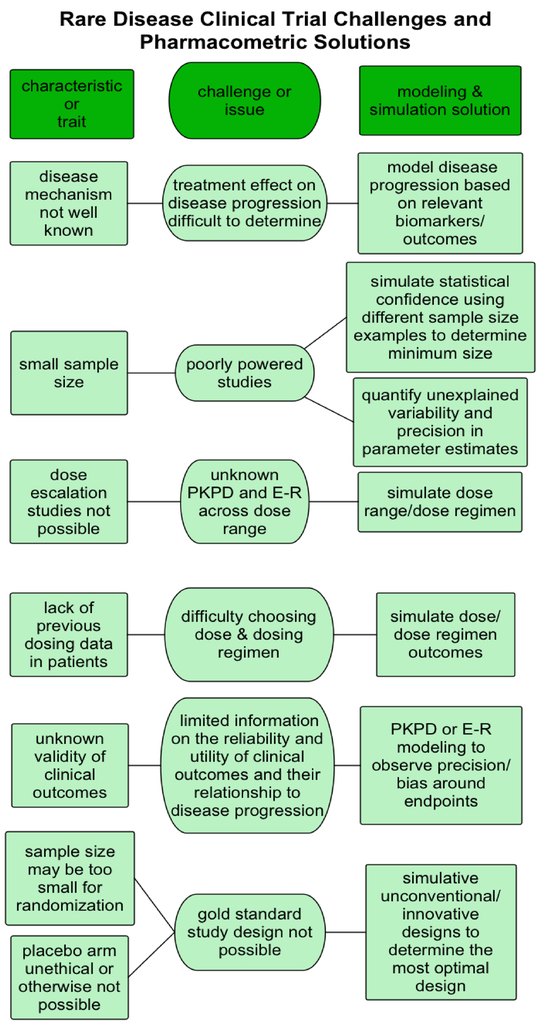

Figure 1: Rare Disease Clinical Trial Challenges and Pharmacometric Solutions

References

[1] FDA. Drugs@fda. fda approved drug products.

[2] FDA. Search orphan drug designations and approvals.

Methods

The FDA orphan drug approvals website [2] was searched for all orphan drug approvals from January 1, 2000 to June 5, 2015. The resulting list of drugs was then searched in the FDA database [1] to obtain filing documents. From the list of Review documents for each drug, the Clinical Pharmacology and Biopharmaceutics Review document was examined. If this document was not available, the Summary Review, Medical Review and/or Statistical Review were examined instead. Only the M&S activities and documents directly related to the orphan indication of a drug approval were considered. The models were captured and grouped into the following categories:

- **PopPK & PK**
  - pharmacokinetic (PK)
  - population pharmacokinetic (pop PK)
- **ER & PD**
  - pharmacodynamic (PD)
  - pharmacokinetic-pharmacodynamic (PKPD)
  - exposure-response (ER)
  - population PKPD (pop PKPD)
- **PBPK**
  - physiologically-based pharmacokinetic
- **Systems Pharm**
  - systems pharmacology
  - mechanistic

Information about prospective dose ranging clinical trials reported in the filings was also captured. Clinical trials reported directly in the filings and explicitly stated the implementation of prospective multiple dosing arms, dose escalating, dose ascending, dose finding, or dose ranging were recorded. It was determined whether the trails were conducted for the purpose of studying efficacy, safety, or both. The dose ranging trials were categorized as follows:

- **SAFETY:** for the purpose of investigating tolerability, adverse events, maximum tolerated dose, pharmacokinetics
- **EFFICACY:** for the purpose of investigating change in endpoints, biomarkers, disease progression or another marker of efficacy due to different dosing regimens
- **BOTH:** for the purpose of investigating one or more aspects of both safety and efficacy as described above

The "full dataset" included all approvals generated from the search. The "analysis subset" included all filings which contained available documentation to be analyzed.

Results

There were 296 filings included in the full dataset, and 192 with documentation included in the analysis subset.

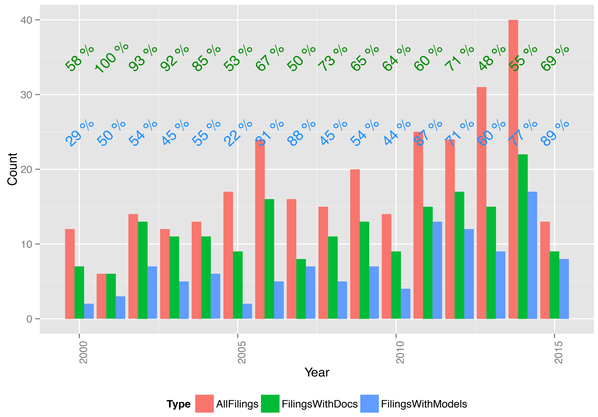

Figure 2: Number of filings. Green text shows fraction of the full dataset included in analysis subset (filings containing documentation). Blue text shows fraction of analysis subset which contained models.

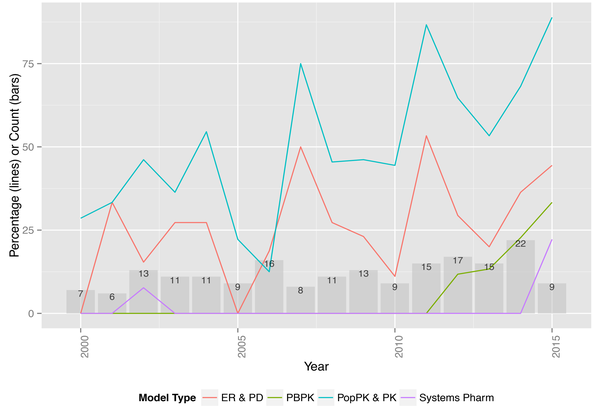

Figure 3: Trend of model types and number of filings over the years. Bars show number of filings in the analysis subset.

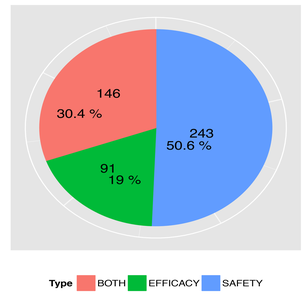

Figure 4: Fraction of prospective dose ranging trials reported in the filings with the intention of analysis of safety, efficacy or both

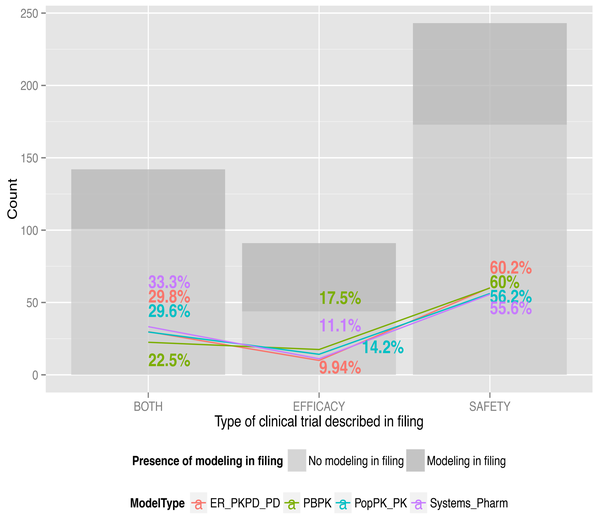

Figure 5: Trend of modeling and prospective dose ranging clinical trials. Percentage shows the fraction of the model type applicable to the type of clinical trial. The sum of the percentage for each model type (colored lines) across trials equals 100.

Discussion & Conclusion

In general, pharmacometric models gained presence as the years progressed (Figure 2). Though only half of the year 2015 was included in the analysis, it had the highest percentage of modeling (Figure 2). Within the filings, PopPK/PK models were most frequently used overall. ER/PD models were the second most used, while PBPK and Systems Pharm models showed no clear trend, In general, the rising and falling pattern was similar for PopPK/PK and ER/PD models (Figure 3).

Of the prospective dose ranging clinical trials reported directly in the filings, half were conducted for the purpose of safety analyses (Figure 4). Only 19% were for the purpose of efficacy studies and almost a third were for both safety and efficacy (Figure 4). **Modeling was most present in filings containing efficacy dose ranging studies (dark gray shading, Figure 4.)** Figure 5 shows the breakdown of model presence across dose ranging trials. The trend is the same across model type (Figure 5). **Within each model category, the majority of the models were linked to safety studies, and least to efficacy studies.** This is likely due to the high amount of safety studies and lower amount of efficacy studies, in general. Also, many filings contained more than one model type, rather than just one single type, so that may have influenced the trend to move in the same way. Nonetheless, it is interesting to note that modeling was found most in filings which reported prospective dose ranging trials for efficacy analyses (Figure 5).

This analysis represents the rigorous endeavor taken to extract pharmacometric modeling and dose ranging trial information from FDA documentation. The analysis was limited to orphan drugs filings for which documentation was available, excluding any other published or unpublished documentation, and is susceptible to human error. However, the trend analysis is useful in analyzing the history of orphan drug development and identifying where pharmacometric M&S could be used in the future to enhance the process. The authors encourage M&S where appropriate and with the proper statistical methodology, especially for the use of dose finding. Initializing clinical trials at an effective dose will save resources and expedite orphan drug development to enhance the treatment of patients around the world with thousands of rare diseases.