Trends in the Application of Pharmacometric Modeling and Simulation in the Development of Orphan Drugs in the 21st Century

Janelle Hajjar1,2*, Jeannine Fisher3, Marc Gastonguay1,2,3

1Metrum Institute, Augusta, ME, 2University of Connecticut, Storrs, CT, 3Metrum Research Group LLC, Tariffville, CT

Objectives: This investigation evaluates trends in the application of mathematical modeling and simulation (M&S) to support U.S. regulatory filings of drugs approved for treatment of orphan indications in the last 15 years.

Methods: The FDA orphan drug approvals website [1] was searched for all approved orphan drugs from January 1, 2000 to June 5, 2015. The resulting list of drugs was then searched in the FDA database [2]. From the 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. For drugs that had been approved for other non-orphan indications, only the M&S activities directly related to the orphan indication were considered.

Results: In the studied period of time, 297 drugs were approved for orphan indications. 143 of those approvals were included the analysis subset. Of this subset, 24 approvals (17%) did not include any pharmacometric M&S in the review documents. The remaining filings included the following M&S methods: pop-pkpd, which included any population pharmacokinetic/pharmacodynamic or pharmacokinetic or pharmacodynamic M&S (75%); pbpk, physiologically-based pharmacokinetic M&S (8%); exposure-response M&S (15%); mechanistic M&S (0.7%); and systems pharmacology M&S (0.7%).
Conclusions: This investigation reveals an overall increasing trend in the use of M&S in orphan drug approval over the last 15 years. Although the pop-pkpd methodology is most common, a variety of M&S methods have been applied in more recent years. This analysis only reflects M&S in regulatory filings, and does not necessarily reflect the application of M&S for internal drug development decision-making.

References: