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COMMENTARY

Editorial to the themed issue on application of pharmacometrics to the development of drugs for rare diseases

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Rare diseases are defined by their numbers. In the United States, a rare disease is defined as one that occurs in less than 200,000 people [1]. In Europe that number is when fewer than 5 in 10,000 have the disease [2]. Those few numbers would suggest that rare diseases are in fact rare, but consider that it is estimated there may be as many as 7000 rare diseases and that 25 to 30 million Americans may be living with a rare disease [1]. It is been shown that an inverse relationship exists between the number of patients with the disease and the cost per year of therapy. With over 451 billion spent on pharmaceuticals in 2017 in the United States, 10% of this was spent on orphan drugs for orphan indications at a median cost of $46,800 per patient [3].

Genzyme showed that a business model targeting rare diseases, despite the challenges of conducting studies in these populations, could be highly profitable. Despite being frequently criticized for the high cost of their medications [4], which could be higher than $300,000 per year for a single drug, Genzyme succeeded as a company and was acquired by Sanofi in 2011 for $20 billion. Other companies soon realized that pursuing rare diseases as a therapeutic area could be a successful business strategy [5]. Today, more than 100 companies are pursuing treatments for rare diseases and in the EU, over 1900 drugs have been designated with orphan status.

Although profitable, the problems of conducting clinical trials in patients with rare diseases can be formidable. One problem is the identification and diagnosis of patients. Many rare diseases are underdiagnosed around the globe. Even once patients can be identified, this often requires conducting global clinical trials, which can be a strain on small companies. Compared to some therapeutic areas where pivotal trials require thousands of patients, the number of patients used to gain regulatory approval can be astonishingly small. For example, Genzyme's Myozyme® (alglucosidase alfa) was approved based on a pivotal study in 18 patients [6]. Because of the small numbers of patients, limited dose ranging studies can be conducted, so finding an optimal dose can be challenging. Further, placebo controls may be unethical and treatment blinding may not be available. Hence, many clinical trials of drugs used to treat rare diseases are not randomized, placebo-controlled, or blinded. If a compound fails, was it due to lack of effect or maybe because the study was underpowered? [7].

Pharmacometrics may be a useful tool to support development of drugs for the treatment of rare diseases. Because of the paucity of data, extracting all available information from that data is imperative. Population-type methods allow for sparse sampling and can improve patient recruitment with reduced sample burden. Disease-state modeling can be used to look at the natural history of diseases and determine whether an experimental therapy improves outcomes. Exposure–response modeling can be used to support, or even select, therapeutic doses. And translational modeling from preclinical to clinical can be used to support initial dose selection for first-in-man studies.

This issue of the Journal is part of our yearly series on the application of pharmacometrics to particular disease areas. Past issues have included neuroscience (2013), immune-response modeling (2014), infectious disease (2017), and cardiovascular (2018) as therapeutic areas. In 2019, we focus on rare diseases. These articles are a mix of review articles and original research articles with leading scientists from around the globe contributing to this issue. Their work shows the broad utility of pharmacometrics as a tool to improve decision-making in this difficult and challenging area. Many areas of pharmacometrics are represented in this issue: population pharmacokinetics, exposure–response modeling, survival analysis, and

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quantitative systems pharmacology. In addition, two great review articles are presented. The first is from Patel and Miller-Needleman from the Food and Drug Administration who they introduce the Office of Orphan Products Drugs Development. The second is from Ahmed et al. who present a review of clinical pharmacology's role in the development of drugs for the treatment of rare diseases. The editors would like to thank all the authors for their contribution in making this issue a success.

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