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EDITORIAL

Best Practices for Utilizing Modeling Approaches to Support Generic Product Development: A Series of Workshop Summary Reports

Application of Advanced Modeling Approaches Supporting Generic Product Development Under GDUFA for Fiscal Year 2023

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To ensure timely access to safe, high-quality, effective, and affordable generic drugs, Generic Drug User Fee Amendments (GDUFA) was signed into law on July 9, 2012 and is currently authorized through September 30, 2027 (GDUFA III) (1). The primary objective of the GDUFA is to address challenges associated with complex and non-complex generics and ensure timeliness and consistency of regulatory assessments.

Under the GDUFA regulatory science and research program, the U.S. Food and Drug Administration (FDA) has been openly encouraging the use of quantitative methods and modeling (QMM) approaches with model-integrated evidence (MIE) to support the development and approval of generic drug products (2–6). MIE approaches utilize virtual bioequivalence (VBE) trial outcomes to inform the design of pivotal *in vivo* studies and lead to drug product approval by supporting alternative BE approaches that consider *in vitro* testing and limit the otherwise recommended conventional *in vivo* studies that include but are not limited to PK, PD, or comparative clinical end-point studies (3). Regarding complex generics and oral dosage forms, the application of QMM approaches can be, and is being, used to support alternative BE approaches and regulatory assessments (2, 3, 7–14). These quantitative approaches include mechanistic modeling such as physiologically based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFD) modeling, quantitative clinical pharmacology tool sets such as population pharmacokinetics (PPK) approaches, and advanced data analytics methodologies.

In addition to funding internal and external research on QMM approaches and their integration in MIE supporting drug product development and approval, the FDA has made efforts toward improving the framework for interactions between the pharmaceutical industry and the FDA. Within the scope of these interactions, the FDA has introduced the concept of a Model Master File (MMF) to promote model sharing and model acceptance and ultimately advance generic drug development as well as streamline regulatory submission and assessment (15, 16).

The emerging role of MIE for non-complex and complex generics in characterizing and predicting *in vivo* performance by accounting for drug product quality attributes, in informing study designs that limit human testing and in supporting alternative BE approaches that tackle challenges associated with certain drug products is spotlighted in this themed issue of the AAPS Journal.

On October 27–28, 2022, the FDA and the Center for Research on Complex Generics (CRCG), along with significant input from the pharmaceutical industry, collaborated on the development of a two-day workshop to discuss the best

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practices for utilizing QMM approaches integrated within the MIE in support of generic drug product development. The workshop was titled "*Utilizing Modeling Approaches to Support Generic Product Development*" (15).

The workshop showcased an increase in the regulatory acceptability of MIE approaches across all generics presented by Tsakalozou *et al*. and more specifically for oral dosage forms summarized by Wu *et al*. and for locally acting drug products discussed by Walenga *et al*. (17–19) These workshop reports discussed how the regulatory framework and the development of in silico tools and methodologies may facilitate the development of complex generics. The application of advanced data analytic tools [e.g., multivariate analysis, artificial intelligence/machining learning (AI/ML)] and how these tools can be used to support the development of complex generics and to improve the efficiency and consistency of scientific assessments during regulatory reviews have been summarized by Gong *et al*. (20) Representatives from the FDA, academia and pharmaceutical industry discussed in depth potential types of MMF and MMF case studies underlined the advantages of model reusability, of streamlining regulatory submissions and of enhancing consistency in regulatory assessments with the MMF framework as summarized by Fang *et al*. (21).

This workshop substantially enhanced the communication and alignment between industry, academia, and the FDA. Although the workshop participants identified challenges in the implementation of QMM for regulatory decision making, they laid the foundation for developing best practices on validating them for their intended purpose and applying them to support alternative BE assessments for non-complex and complex generics. The outcomes of the workshop will be utilized to promote applications of QMM approaches and to develop best practices for incorporating such approaches into generic drug development programs and regulatory submissions.

A summary of a post-workshop survey on the study participants, the workshop content and its impact on the acceptability of MIE by pharmaceutical industry and regulatory authorities is provided as Supplementary Material.

The Generic Drug Science and Research Initiative Public Workshop that was held on May 11 and 12, 2023 is also being spotlighted in this themed issue, which laid out the planned efforts on applying advanced modeling approaches in support of generic product development under GDUFA III. The public workshop is a commitment under the Generic Drug User Fee Amendments of 2022 (GDUFA III). It aims to update the public on the current science and research initiatives and, more importantly, to solicit public input on the research priorities related to generic product development and approval that will shape the next 5 years of the GDUFA science and research program. The report by Pal *et al*. highlights the discussions on future research on the development and application of sophisticated quantitative methods and modeling, as well as AI/ML that address challenges and support alternative BE assessments for complex and non-complex generics (22).

As an evolving approach in generic drug development and regulatory application, modeling and simulation approaches have the potential to overcome the current challenges for the development of complex generics or generics with complex issues and minimize the burden for human testing. With the utilization of MIE approaches and the MMF framework, the acceptability of modeling and simulation in regulatory submissions is expected to increase. Experts from regulatory agencies, the generic drug industry, consultants, academia, and others in the field of modeling and simulation are committed to constantly improve MIE practice and regulations.

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Declarations

Conflict of Interest The opinions expressed in the article are those of the authors and should not be interpreted as the position of their organizations/employers. The opinions expressed in the article are those of the authors and should not be interpreted as the position of the U.S. Food and Drug Administration. The authors declared no competing interests for this work.

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