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Received: 31 October 2022 | Revised: 10 January 2023 | Accepted: 19 January 2023

DOI: 10.1002/psp4.12931

MINI REVIEW

Establishing the suitability of model-integrated evidence to demonstrate bioequivalence for long-acting injectable and implantable drug products: Summary of workshop

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Abstract

On November 30, 2021, the US Food and Drug administration (FDA) and the Center for Research on Complex Generics (CRCG) hosted a virtual public workshop titled "Establishing the Suitability of Model-Integrated Evidence (MIE) to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable (LAI) Drug Products." This workshop brought relevant parties from the industry, academia, and the FDA in the field of modeling and simulation to explore, identify, and recommend best practices on utilizing MIE for bioequivalence (BE) assessment of LAI products. This report summerized presentations and panel discussions for

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topics including challenges and opportunities in development and assessment of generic LAI products, current status of utilizing MIE, recent research progress of utilizing MIE in generic LAI products, alternative designs for BE studies of LAI products, and model validation/verification strategies associated with different types of MIE approaches.

INTRODUCTION

Long-acting injectable and implantable (LAI) drug products are intended for prolonged drug release over a long period of time to reduce frequency of medication and improve patient adherence. Currently, marketed LAI products mainly include those for the treatment of chronic conditions, such as antipsychotic drugs, hormonal contraceptives, cancer drugs, etc.[1–3] LAIs pose unique challenges for conducting bioequivalence (BE) studies and thus for development of generic drugs, mainly due to costly and lengthy in vivo BE studies.[4] Model-integrated evidence (MIE) has been increasingly applied for generic drug development and assessment, especially for complex drug products for which in vivo BE studies are challenging to conduct.[5] MIE has the potential to help overcome the challenges in LAIs (e.g., they can provide more efficient study designs to demonstrate BE). On November 30, 2021, a virtual public workshop titled "Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products" was held,[6] sponsored by the Center for Research on Complex Generics (CRCG; www.complexgenerics.org), a collaboration initiated in 2020 among the Food and Drug Administration (FDA), the University of Maryland Baltimore, and the University of Michigan.[7]

Drs. James Polli and Anna Schwendeman opened the workshop and provided the summary of the findings from the recently completed survey conducted by the CRCG regarding the scientific challenges in the development of complex generics where there were 281 examined responses.[8] Over half of respondents were from the generic drugs industry. The three main areas of polling were directed toward which types of complex products, which methods of analysis to support a demonstration of BE, and which educational topics are the most interested ones to the responders that the CRCG should prioritize. The top selection of the most challenging complex products was complex injectables, formulations, and nanomaterials, which also corresponds to the top educational topics. Use of modeling to help assess BE was also broadly supported by respondents to both the methods of analysis and education areas of polling.

Dr. Robert Lionberger delivered the opening remarks for the workshop. He noted that MIE is a new concept that requires to establish the processes and procedures for its application to generic drug development and regulatory submissions (i.e., best practices), to ensure confidence in the use of MIE. He elaborated the goal of this workshop was to share the current status in using MIE for generic LAI products, progresses in MIE methodologies, and challenges associated in MIE applications, as an interactive discussion from experts in the industry, academia, and the FDA. In addition, Dr. Lionberger encouraged the applicant to interact with the agency to discuss their proposed modeling methods in pre-abbreviated new drug application (ANDA) meetings, such as the product development or pre-submission meetings to help clarify regulatory expectations early.

MEETING SUMMARY

Session 1: Challenges in life cycle management of long-acting injectable and implantable drug products

In the first presentation, Dr. Miyoung Yoon discussed the challenges in conducting BE studies for generic LAI products, which also presents the opportunities of using MIE approaches. She outlined the challenges based on the types of in vivo BE studies recommended. For the LAI products with safety concerns, such as long-acting antipsychotics, studies in patients are recommended with multiple-dose, steady-state study design.[9,10] Challenges are mainly due to the extremely long study duration. Moreover, the potentially high dropout rate and increased variability that are associated with the patients as well as the study duration present additional challenges. For the LAI products without safety concern, such as long-acting contraceptive, single dose studies are recommended in healthy subjects.[11,12] Usually, the parallel design is recommended due to an extremely long washout period needed for the crossover design, which will greatly reduce study power thereby requiring a large sample size. Therefore, a major purpose of incorporating MIE for generic LAI product development would be to reduce in vivo study duration and/or sample size, as MIE may justify the use of alternative study designs and/or alternative BE metrics through the model-based BE analysis framework. From a

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regulatory perspective, the most important consideration in using MIE for BE is to demonstrate its sensitivity to detect the formulation difference with confidence. There should be sufficient model verification and validation for the intended regulatory use, including the demonstration of type-I error control and the proper characterization of uncertainty in the model. In addition, the proposed MIE approach should be prespecified prior to data unblinding. The utility and validity of using an MIE approach are still being explored and this workshop could serve as an initiative to establish the best practices for MIE to be used in generic LAI development.

Next, Dr. Hao Zhu shared the FDA's experience on the use of modeling and simulation approaches to support the development of LAI drug products from a new drug development perspective. Psychiatry diseases, such as schizophrenia and bipolar I disorder, are debilitating mental disorders. Although continuous treatment is essential to manage symptoms, compliance is a common issue in this patient population. Several LAI antipsychotics, such as Risperdal Consta (risperidone intramuscular injection), Invega Sustenna (paliperidone intramuscular injection), and Abilify Maintena Kit (aripiprazole intramuscular injection) are developed to reduce dosing frequency and improve compliance.[13–15] In their development programs, modeling and simulation are broadly used to optimize dosing regimens, to define dosing windows, to select re-initiation plans, and to adjust dosing regimens in patient subgroups. An example for Invega Sustenna was presented where pharmacokinetic (PK) profiles following various alternative dosing regimens were simulated and compared. Dr. Zhu highlighted the final loading dosing regimen that was selected through simulations in combination with clinical safety findings without conducting additional clinical trials. Additional simulation examples were presented on the selection of (1) re-initiation of dosing regimens under various scenarios when patients discontinue the treatment; and (2) dosage adjustment in patients with compromised renal function.[16] In summary, modeling and simulation is an essential tool to support the development of long-acting antipsychotics.

Mr. Ameya Kohojkar and the other industry speaker presented the industry perspectives on the challenges in development of generic LAIs. The major challenges in conducting in vivo BE studies for LAIs are that they need to be conducted in patients.[9,10,17] Considering the difficulty in recruiting and managing patients, multiple clinical centers need to be utilized to ensure sufficient sample size. Planning BE studies for LAIs with rare or orphan indications creates additional burden and recruitment may be extremely challenging. The associated long study duration and higher costs impact the submission timelines and the market entry of affordable generic LAIs. Furthermore, several LAI products have complex dosing procedures,[13,14,18] such as reconstitution and/or use of infusion devices, which presents a risk of protocol violations in BE studies adding additional burdens to conducting in vivo BE studies.

Due to the aforementioned challenges, from the industry perspectives, generic industry would greatly benefit from the development and endorsement from the FDA of a new/alternative approach, such as MIE, to accelerate development and subsequent commercialization of generic LAIs. The industry views that potential benefits of using MIE may include: (1) selection of lead product based on simulated data during product development; (2) selection of optimal study design for potential smaller sample size or shorter study duration; (3) utilizing in vitro in vivo correlation approach; (4) supporting alternative BE standards; and (5) supporting product lifecycle management and post approval changes. However, guidance and mutual understanding between the FDA and the industry are needed on how such an innovative approach could be routinely implemented. The speakers highlighted that it is important for the generic industry to understand the roadmap to potential product approval for the application of MIE to the development of complex generic LAI formulations, which will help increase availability of affordable generics to the public. For example, the FDA may consider publishing a draft guidance listing general expectations on the minimum required data, including MIE validation and verification to be submitted in pre-ANDA meetings, and/ or in the ANDA submissions.

Session 2: Current status of the model-integrated bioequivalence for long-acting injectable and implantable drug products

Professor Andrew Hooker presented the MIE approaches and innovative study designs for generic LAI product to shorten the BE study duration, which were developed under the Generic Drug User Fee Amendment (GDUFA) funded research program (75F40119C10018). An alternative study design, referred to as a switch study design, to the conventional multiple dose crossover steady-state design that needs to be conducted in patients was presented. For the proposed switch study, BE is assessed by comparing the steady-state PK metrics of the reference product with those of the test product at the first dosing interval after the switch from the reference product. Population PK models can be used to perform simulations to determine new BE limits for a switch design or to separate the superposition of the test and reference products in the first period after the switch. Past research has shown that the pharmacometrics approaches usually have higher power

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than traditional statistical approaches.[19,20] Because model-based methods focus on the PK observations for each individual instead of secondary PK summary statistics (area under the curve [AUC], maximum concentration [C_{max}], etc.), relative differences in bioavailability and absorption rates between treatments can be identified with accuracy and precision, even in situations where traditional methods may fail, such as the switch design. Professor Hooker shared a model-integrated BE framework that uses a model averaging technique, which fits multiple candidate models to the available BE study data, estimates model parameters and parameter uncertainty (from sampling importance resampling[21] or case resampling bootstrap). The models, parameters, and their uncertainties are then used to simulate populations of individuals. Subsequently, population mean PK metrics (e.g., geometric mean of AUC and C_{max}) are computed for the simulated populations, weighting different model predictions according to model fit to data, and BE is established based on the uncertainty distribution of those BE metrics.[22–24] The proposed model-integrated approach has shown control of type-I error and high power even with high variation and sparse data.[22,23] In addition, Professor Hooker shared some model qualification criteria and indicated the selected models should be identifiable with the proposed study design and are able to simulate comparable PK metrics to those from the real data.

Dr. Murray Ducharme presented the experience that generic drug industries have had so far with the FDA in using MIE for LAI products. Two main MIE approaches were contrasted. The first one is where the clinical data that is being fitted by a population PK (PopPK) model is sufficient in terms of power (80% or more) to demonstrate BE. Examples of innovative study designs were presented for diverse LAIs, in which the PK characteristics of both test and reference products could be determined robustly in all patients enrolled, which would then allow in silico the "continuation" of dosing to these exact same patients through, for example, a "standard" two- or four-way single dose study design. The second approach is the one where the clinical data are not used to establish BE. Rather, the clinical data are used to create and/or validate an existing PopPK model, which is then used to simulate patients in a virtual BE study.

The advantages of one may be the disadvantages of the other. The first approach has the advantages of having the formal BE assessment based on actual patient data, whereas having a much simpler validation threshold. On the other hand, the second approach has the advantage of a smaller clinical sample size. Regardless of the approach used, the proposed plan must be documented and presented in advance to the FDA during a product development meeting. The innovative model-based study design must be described in detail and demonstrated a priori to be associated with appropriate power and alpha error compared to a standard study design.

Session 3: Examples of model-integrated bioequivalence for long-acting injectable and implantable drug products – focus on best practice development

Session 3 in the workshop highlighted the latest research in the area of MIE application to LAI generics from the best practice development perspectives with case examples. The presented research outcomes showed the potential of MIE to (1) find a more efficient study design that can provide high confidence to shorten the time duration and/or reduce the sample size, (2) find alternative BE limit for PK metrics, and (3) assess type-I error risk and study power to pass a BE product.

The first talk, given by Dr. Joga Gobburu, proposed a "learn-apply paradigm" that can be used to LAI generic drug development. In the proposed paradigm, first, an abbreviated BE study is performed, which is a shorter, single dose BE study with fewer subjects. Second, a model-based analysis is performed to learn from the abbreviated BE. Third, model and parameters derived from the abbreviated BE study are used to simulate a full BE study with more subjects and full sampling scheme. Current progress was shared which showed the model-integrated full BE study generated from the proposed framework can potentially control type-I error and maintain high power. In summary, the lifecycle for a faster and more cost-effective LAI generic development with the proposed "learn-apply paradigm" would include the following steps: (1) product development; (2) model-integrated BE planning, which would include simulations of various abbreviated BE and full BE scenarios; (3) the FDA agreement on the design and analysis of the abbreviated BE study and full BE study simulations; (4) conducting the abbreviated BE trial; (5) applying the model-integrated full BE analysis; and (6) submitting an ANDA.

Dr. Géraldine Cellière proposed a novel two-treatment, two-period, one-sequence, "reduced crossover" design with no or limited washout period, combined with a model-based correction of the data from the second period (test product), as a substitute for the single-dose, parallel BE design for LAI products. Individual model parameters are estimated using the data from the first period (reference product) and used to predict the carryover of the reference product from the first period. The predicted carryover is subtracted from the second period data for BE analysis. The procedure is exemplified with a published model for buprenorphine extended-release injection.[25] For the buprenorphine example, with reduced

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crossover design for dose duration for 4 months per treatment period, the power is above 90% with 30 individuals, with controlled type-I errors. The results showed that this reduced crossover design would be three times shorter than the traditional crossover design and allow higher power than the parallel design. The analysis procedure is implemented as an R script to be used with MonolixSuite. This approach would be applicable to LAIs satisfying the following requirements: single dose design allowed, available PopPK model and linear PK.

Dr. Parmesh Gajjar shared a potential MIE pathway to demonstrate BE for LAI products in a reduced study

TABLE 1 Summary of panel questions and discussion points.

Panel questions	Major discussion points
What are the challenges we are facing to apply MIE for regulatory use?	• How to validate the adequacy of a PopPK model to be used in BE establishment? • How much prior data are needed to propose and evaluate an MIE approach if PopPK model of the reference product is not available by the NDA developer? • Does the amount of data required for method validation negate the benefit of reduced time and cost when using the MIE approach for assessment of BE? • How to translate the scientific findings into regulatory use? • With different MIE approaches available, how to generalize the process and find the best practices for regulatory use?
When PopPK models are used for generating MIE for BE, what would be the appropriate model validation strategy? What are the basic elements for MIE to be considered suitable to demonstrate BE?	• For the purpose of using models in generating pivotal BE evidence, additional model validation strategies may be needed using more quantitative measures beyond the general predictive/diagnostics checks. • Different criteria for validation are required for different objectives of using the MIE approach. • The selected model should be identifiable with the proposed study design, such as using fisher matrix to understand the uncertainty of the model before using the model. • The PK metrics (C_{max} and AUC) calculated from the simulated data using posterior predictive checks should be comparable with the real data. • The model development and validation process and criteria should be prespecified. Using an MIE approach in BE assessment should not be interpreted as post hoc analyses that may lead biased BE results. • The selected MIE approach should be able to detect the formulation difference between reference and test product, estimate type-I and type-II errors with high confidence based on the model simulation.
What are the pros and cons of the two main types of MIE approaches? 1. Virtual BE that model built on a small sample size is used to simulate results for a larger population. 2. Continuation of "in silico" dosing to the exact same group of individuals. Depending on which approach to take, the model validation criteria might be different.	For the virtual BE approach: • The first approach could use data from an underpowered clinical study to simulate virtual subjects to achieve adequate power. • Because the model will be used to simulate a large population from a small population, the simulation outcome may be biased by the PopPK model developed form the small population. Approaches including model reduction, model averaging, and sampling and resampling can be considered to overcome this issue. • Model validation criteria could be stricter. External validation may help assure/refine the model, such as a pilot study before the pivotal study for model development. For the "in silico" continuation approach: • The second approach requires adequately powered clinical study, but the "in silico" dosing may help shorten the study duration. • As the simulated individual PK data will be used for pivotal BE assessment, sufficient model verification/validation should be conducted, especially for individual parameters (e.g., shrinkage), to provide confidence in the predictive performance of the model. For example, the individual shrinkage may lead to over/under prediction of carryover, thus leading to bias in the "in silico" continuation approach. Rich sampling may be helpful to solve the problem.
What are other innovative study designs that can control the type-1 errors and maintain the study power with the most efficient sample size/study duration?	• Crossover design is the preferred design to be used to explore further MIE approach because each individual will have real data for both formulations. Otherwise, the formulation difference will have to be estimated by assigning as a covariate. • MIE may be used to support study without complete washout as washout in LAI product can be problematic and extremely long. • All alternate model proposals may need to address inter-laboratory assay variation if test and reference drug levels are not coming from the same laboratory or not cross-validated.

Abbreviations: AUC, area under the curve; BE, bioequivalence; C_{max}, maximum concentration; MIE, model-integrated evidence; NDA, new drug application; PK, pharmacokinetic; PopPK, population pharmacokinetic.

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duration (i.e., single dose) for those products which are recommended to be assessed at steady-state. The case study used a published model for paliperidone palmitate injection[26] to demonstrate the concept. By making the assumption that certain parts of the model are drug-specific, whereas other parameters are formulation dependent, it is possible to simulate PK profiles under a specific study design for a given population for thousands of different test products by varying formulation parameters. By comparing the simulated profiles to that of the reference product, a parameter space can be identified for the products that are classified as BE after multiple doses, and among which those will also be BE after a single dose.[27] The proposed approach may help reduce study duration for LAIs with multiple dosing studies are recommended for BE determination. A potential usage is to fit a PopPK model to individuals only receiving the test product, and to compare the parameter estimation with the identified parameter space for BE assessment. The proposed approach may be useful for other complex parenteral products other than the presented example drug model. However, the proposal may need to be discussed with the FDA during pre-ANDA review.

PANEL DISCUSSION

The panel includes the moderator, Dr. Lanyan Fang, all speakers, CRCG co-directors, and additional experts from the FDA and generic drug industries: Drs. Bing Li, Liang Zhao, Raja Velagapudi, and Yu Chung Tsang. The panel discussed the current understanding and knowledge gaps of utilizing MIE approaches in generating pivotal BE evidence, as well as the potential path for developing the best practice. The discussion covers not only for the generic LAI products, but also for MIE approaches in general, including challenges, opportunities, model validation/verification strategies, and potential innovative study designs. The panel questions and main discussion points are summarized in Table 1.

CONCLUSION

Dr. Liang Zhao provided closing remarks. The workshop facilitated the discussion on the challenges and opportunities related to the use of MIE approaches for generic LAI product development. As utilizing MIE approaches in generic LAI product development is at an earlier stage, future discussions among the FDA, the industry, and academia are needed to close scientific gaps and to develop the best practices in the use of MIE approaches.

ACKNOWLEDGMENTS

The authors thank Drs. Sameersingh Raney (FDA), Vishalakshi Krishnan (CRCG), Rachel Turow (Teva Pharmaceuticals), and other industry participants for helping organize the workshop. We would also like to thank for all speakers and panelists who participated in the workshop.

FUNDING INFORMATION

This workshop was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of financial assistance award U18FD007054 for $1,000,000 to the Center for Research on Complex Generics (CRCG), $180,000 of which was utilized to support contracts to conduct the research presented by G.C. and J.G. that was 100% funded by the CRCG contracts. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by the FDA/HHS, or the US Government. In addition, A.C.H's work was supported by FDA contracts: HHSF223201710015C and 75F40119C10018. The others' work reported in this paper are not funded/sponsored.

CONFLICT OF INTEREST STATEMENT

The opinions expressed in this paper are those of the authors and do not necessarily represent the views or policies of their affiliated organizations/agencies. J.G. is co-founder of Vivpro Corp. which commercializes R&D Intelligence Assistant tool, and co-founder of Pumas-AI Inc. which commercializes Pumas and Lyv. A.C.H. is a co-founder and an advisor to the pharmaceutical consulting company Pharmetheus AB. G.C. is an employee of Lixoft, which commercializes MonolixSuite. All other authors declared no competing interests for this work.

DISCLAIMER

The opinions expressed in this paper are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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How to cite this article: Gong Y, Zhang P, Yoon M, et al. Establishing the suitability of model-integrated evidence to demonstrate bioequivalence for long-acting injectable and implantable drug products: Summary of workshop. *CPT Pharmacometrics Syst Pharmacol*. 2023;12:624-630. doi:10.1002/psp4.12931

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