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EXPERT REVIEW

Review: Role of Model-Informed Drug Development Approaches in the Lifecycle of Drug Development and Regulatory Decision-Making

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Abstract

Model-informed drug development (MIDD) is a powerful approach to support drug development and regulatory review. There is a rich history of MIDD applications at the U.S. Food and Drug Administration (FDA). MIDD applications span across the life cycle of the development of new drugs, generics, and biologic products. In new drug development, MIDD approaches are often applied to inform clinical trial design including dose selection/optimization, aid in the evaluation of critical regulatory review questions such as evidence of effectiveness, and development of policy. In the biopharmaceutics space, we see a trend for increasing role of computational modeling to inform formulation development and help strategize future *in vivo* studies or lifecycle plans in the post approval setting. As more information and knowledge becomes available pre-approval, quantitative mathematical models are becoming indispensable in supporting generic drug development and approval including complex generic drug products and are expected to help reduce overall time and cost. While the application of MIDD to inform the development of cell and gene therapy products is at an early stage, the potential for future application of MIDD include understanding and quantitative evaluation of information related to biological activity/pharmacodynamics, cell expansion/persistence, transgene expression, immune response, safety, and efficacy. With exciting innovations on the horizon, broader adoption of MIDD is poised to revolutionize drug development for greater patient and societal benefit.

KEY WORDS biopharmaceutics · generic drugs · gene therapy · model-informed drug development · new drugs

Introduction

Bringing a new therapeutic agent into the market is expensive and time consuming. A recent report estimates the median capitalized research and development investment to bring a new drug to market was $985.3 million (1). The median clinical development time for FDA-approved drugs from 2010 – 2020 was reported to be 8.3 years (2). Given the rising costs and time, newer approaches and technologies are being incorporated into drug development to bring in much needed efficiencies. One such approach that has been recognized as critical to streamline and accelerate the development of new medical products and enable more informed decision-making, and reduce uncertainty is model-informed drug development (MIDD).

Model-informed drug development (MIDD) is an approach that involves developing and applying exposure-based, biological and statistical models derived from preclinical and clinical data sources to inform drug development and decision-making (3). Fundamentally, MIDD is based on three key elements:

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1. Leveraging a thorough understanding of a drug, a disease, and how a drug affects the human body, as well as how the body responds to the drug
2. Integrating the information by developing mathematical models based on full use of all available data. The data can come from diverse sources such as *in vitro*, preclinical, and clinical studies
3. Applying this knowledge to address issues pertaining to the development of drugs, biological, and generic products, inform regulatory decisions, and clinical use

A Brief History of MIDD at FDA

You Have to Know the Past to Understand the Present – Carl Sagan

The earliest application of MIDD approaches to inform regulatory decisions at the FDA can be traced to the 1990s and since then the applications of MIDD have notably evolved and at times have been transformative (Fig. 1). During the early days, the application of MIDD approaches were primarily focused on drug and product characterization. This included application of methods such as *in vitro – in vivo* correlation aimed at informing relevant dissolution specification and support biowaivers. This period also marked the advent of population pharmacokinetics (popPK) and pharmacokinetic / pharmacodynamic (PK/PD) modeling applications in regulatory submissions. The Pharmacometrics Group was formed in the Center for Drug Evaluation and Research's (CDER) Office of Clinical Pharmacology (OCP) in 1991 to advance the application of these approaches in drug development and review. The importance of the MIDD approaches as part of the drug development was first highlighted in the regulatory guidance document "Dose-Response Information to Support Drug Registration" and the regulatory perspective on the application of population pharmacokinetics (4,5).

The first decade of the 21st century saw a rapid growth in the application of MIDD approaches in drug development and regulatory review. The first of these developments was the publication of the seminal regulatory guidance for industry on exposure-response relationships in 2003 that provided considerations for MIDD approaches in regulatory decision making (6). The scope of MIDD applications expanded to include informing dose selection and trial design, characterizing safety, and supporting evaluation of effectiveness. The Pharmacometrics Group was charged with the application of MIDD approaches across all therapeutic areas. The Agency proactively communicated experiences with the application of MIDD approaches in regulatory reviews through a series of "impact publications" (7–9). In addition, regulatory science research informed regulatory policy in areas of high

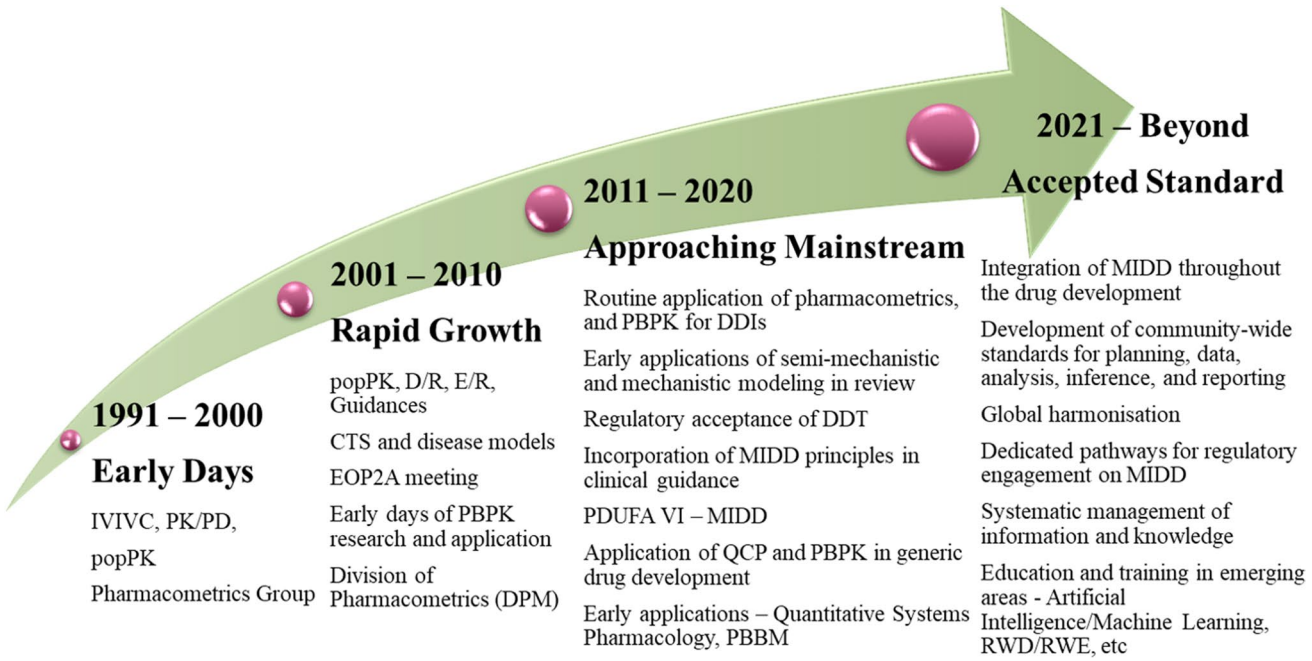

Fig. 1 Evolution of MIDD at the FDA. A brief summary of key highlights for every decade with future aspirations are provided. Abbreviations: ICIVC – *in vitro-in vivo* correlation; PK/PD – pharmacokinetics/pharmacodynamics; popPK – population pharmacokinetics; D/R – dose-response; E/R – exposure-response; CTS – clinical trial simulations; EOP2A – end of phase 2A; PBPK – physiologically based pharmacokinetics; DDI – drug-drug interactions; DDT – drug development tools; MIDD – model-informed drug development; QCP – quantitative clinical pharmacology; PBBM – physiologically based biopharmaceutics models; RWD/RWE – real world data/real world evidence; RTRT – real time release test; MIE – model-integrated evidence; PDUFA - Prescription Drug User Fee Act.

need such as pro-arrhythmia evaluation of new drugs and pediatric drug development. The Agency also advocated for the use of clinical trial simulations and disease models to inform clinical trial designs and created the end-of-phase 2A (EOP2A) meetings, a novel regulatory avenue to facilitate interaction between the FDA and the sponsors of investigational new drug applications (INDs) (10). Institutional review practices were developed to integrate MIDD approaches into regulatory reviews (11). All these activities resulted in expanded scientific capacity and eventually resulted in the formation of the Division of Pharmacometrics in the OCP.

Building upon the progress of the early 21st century, the next decade focused on mainstreaming MIDD with an emphasis towards consistent review and decision making. In addition to conventional pharmacometrics applications, physiologically based pharmacokinetic (PBPK) modeling and simulations for evaluating drug-drug interaction potential became routine. This period also marked the emergence of novel approaches based on mechanistic principles such as quantitative systems pharmacology (QSP) informing efficacy and safety evaluation as part of regulatory submissions. This triggered the need to standardize regulatory submission expectations and review considerations (12). The Agency engaged in a series of outreach activities in the areas of PBPK, precision dosing, and quantitative systems pharmacology to develop best practices. The Agency's efforts for advancing MIDD received a big boost with the recognition of MIDD as one of the regulatory decision tools to support drug development and review under the sixth iteration of the reauthorization of the prescription drug user fee act (PDUFA VI) (3).

With this as the backdrop, the following sections will describe in further detail the role of MIDD across the development and lifecycle of new medical products. The next three sections will focus on MIDD efforts in the Center for Drug Evaluation and Research which will be followed by a summary of the MIDD efforts in advancing cell and gene therapy products in the Center for Biologics Evaluation and Research at the FDA.

Role of MIDD in New Drug Development

The Applications of MIDD Approaches to Support New Drug Development

MIDD approaches have been broadly used to support various aspects of new drug development, such as clinical trial design, regulatory decision-making and policy development. As a quantitative platform, MIDD approaches allow an integration of information obtained from non-clinical studies and clinical trials in a drug development program. General understandings of the underlying biology, pathophysiology, and pharmacology can also be incorporated into the model. Commonly used modeling approaches include popPK modeling, PBPK modeling, and exposure-response modeling. In recent years, some emerging modeling techniques including QSP modeling, and artificial intelligence/machine learning modeling have also been applied at various stages in new drug development. Depending on the needs, a single modeling approach or a combination of various modeling approaches can be used to drive decision-making and to streamline clinical trial design. Some applications of MIDD approaches in new drug development are summarized in this section based on the FDA's experience.

MIDD Approaches to Assist Clinical Trial Design

High late phase attrition represents a big challenge in new drug development today. MIDD approaches can leverage findings in a specific drug development program, data collected through different programs in the same disease population, and learnings from other compounds with a similar mechanism of action. Simulation allows a direct comparison of the effect from multiple design factors, including sample size, sampling schedule, and trial duration. Optimizing clinical trial design through modeling and simulation may increase the success rate and improve efficiency of a clinical development program. Table I summarizes several examples where MIDD approaches are used to assist the design of clinical trials in different clinical development programs (13–20).

MIDD Approaches to Support Regulatory Decision-Making

Findings based on MIDD approaches are routinely reported in regulatory submissions under INDs, New Drug Applications (NDAs), or Biological License Applications (BLAs). These approaches are also widely used by review teams at FDA to address review questions critical for regulatory decisions. For instance, MIDD approaches can provide substantial or confirmative evidence to support efficacy extrapolation in a new patient population, the use of an alternative dosing regimen, a different route of administration, or a new dosage form, and dose optimization in patient subgroups. MIDD approaches have also proved valuable for filling in knowledge gaps, leveraging information from alternative sources and facilitating decision-making, making MIDD an useful approach in emergent public health challenges. Table II shows the examples on how MIDD approaches have been applied to support various regulatory actions (21–27).

Table I Examples of MIDD Approaches to Optimize Clinical Trial Design in New Drug Development

Disease Area	Modeling Approach	Application
Schizophrenia (13)	Item Response Theory Method and Concordance Analysis	Support the use of a modified alternative endpoint and shorter clinical trials for demonstration of efficacy
Non-Small Cell Lung Cancer (14)	Disease Progression Model	Use early biomarker changes to predict long-term clinical benefit (overall survival)
Duchenne Muscular Dystrophy (15)	Disease Progression Model	Support the use of genetic mutation for patient enrichment, stratified randomization, and patient matching strategy for clinical efficacy and safety trials
Pediatrics (16)	Exposure-matching with popPK or PBPK modeling	Identify dose(s) to be tested in pediatric clinical efficacy and safety trials
Various Disease Areas (17)	Exposure-Response Modeling	Dose selection for clinical trials
Pediatrics (18)	Pharmacokinetic Modeling	Sample size determination
Various Disease Areas (19)	Machine Learning Modeling	Patient enrichment
Various Disease Areas (20)	QSP Modeling	Predict safety risks

Table II Examples of MIDD Approaches to Support Regulatory Decision-making

Drug Name (Brand Name)	Modeling Approach	Regulatory Action
Aripiprazole Lauroxil (21) (Aristada ®)	Exposure-response and popPK modeling and simulation	Support the approval of a new strength and a new dosing regimen without additional clinical trial
Adalimumab (22) (Humira ®)	popPK modeling and simulation	Support the pediatric extrapolation and dose determination in patients with Hidradenitis Suppurativa.
Hydroxychloroquine (23)	PBPK modeling in combination with pharmacodynamics evaluation	Assess the potential effectiveness of a compound.
Paliperidone Palmitate (24) (Invega Sustena®)	popPK modeling and simulation	Support approval of a loading dose, dosing window, re-initiation strategy and dosage adjustment in patient subgroups without clinical trials.
Pembrolizumab (25) (Keytruda®)	popPK modeling and simulation	Support the approval of patient-friendly dosing (less frequent dosing) regimen.
Sotalol injection (26)	popPK and exposure-response modeling and simulation	Support the approval of loading doses for treatment initiation and up-titration.
Remdesivir (Veklury®) Baricitinib (Olumiant ®) Bamlanivimab and etesevimab (27)	popPK modeling and simulation	Support the use of the drugs in pediatric patients.

MIDD Approaches to Support Policy Development

Experiences accumulated through decades of application of MIDD approaches have been translated into policies to facilitate new drug development. In recent years, there has been an increased trend in the development and incorporation of MIDD approaches into new policy and regulatory guidance (28). For example, prior to 2000, MIDD approaches were discussed only in three guidance documents including FDA's population pharmacokinetics guidance, ICH E4 guidance, and SUPAC guidance. In the next 10 years, the number increased to five. Between 2015 to 2018, there were 13 guidance documents published which contain MIDD components. In early years, MIDD approaches were mainly discussed in pharmacometrics or clinical pharmacology related guidance, such as exposure-response guidance or renal/hepatic impairment guidance. Recently, several clinical guidance documents in areas such as hypertension, human immunodeficiency virus /hepatitis C virus, ulcerative colitis, and attention deficit and hyperactivity disorder, have highlighted the value of MIDD approaches. Table III summarizes some recent examples on FDA's new policies which are supported by MIDD approaches (29 – 32).

Regulatory Interactions to Enhance MIDD Approaches for New Drug Development

MIDD generally employs novel concepts and modeling approaches and as such, regulatory acceptance of these novel approaches is critical. Early interaction and engagement

Table III Examples of New Policies Supported by MIDD Approaches

Areas	Role of MIDD Approaches
Partial onset seizures (29)	To support full extrapolation of efficacy from adults to pediatric patients
Attention deficiency and hyperactive disorder (30)	To support back extrapolation of efficacy from children to adolescents and adults for CNS stimulant products
Schizophrenia and bipolar I disorder (31)	To support full extrapolation of efficacy from adults to pediatric patients
Oncology (32)	To support the use of the modeling and simulation-based pharmacokinetic criteria for the approval of an alternative dosing regimen of programmed death 1 (PD-1) and programmed death ligand 1 (PD L-1) antibodies

between regulators and drug developers is critical to overcome any potential barriers and promotes appropriate application of MIDD. Therefore, FDA has established multiple avenues for regulatory interaction besides routine channels under INDs, NDAs and BLAs to enhance communication for MIDD approaches. The most relevant programs are the MIDD paired meeting pilot program and the fit-for-purpose (FFP) initiative.

The MIDD paired meeting pilot program was initiated as part of the commitments under the reauthorization of the sixth iteration of PDUFA (3). This program is designed to promote early interactions between drug developers and FDA on the use of modeling approaches to support a specific drug development program (33). FDA announced the availability of the pilot program in April 2018. This program is jointly administered by the CDER and the Center of Biologics Evaluation and Research (CBER). Any drug developer for small molecule compounds or biologics with products registered under the INDs, NDAs or BLAs may qualify for the program. FDA accepts meeting requests on a continuous basis and is expected to grant 2-4 submissions per quarter. Once the submission is accepted under the pilot program, FDA grants two sponsor meetings within 120 days. The meeting program is anticipated to engage a broad discussion with review teams, usually including pharmacometricians, clinical pharmacologists, medical officers, and statisticians.

Under this pilot program, FDA has granted 42 meeting requests as of December 2021. These meeting requests span almost all major therapeutic areas including oncology, autoimmune diseases, hematology, cardiovascular diseases, neurology, psychiatry, infectious diseases, and diabetes. Submissions to the meeting program include a broad range of issues amenable to application of MIDD approaches. The most common issue is related to dose selection. Other design components such as alternative endpoints, patient risk management, and safety monitoring also featured as part of these pilot program meetings (34). With the success of the pilot program, FDA will continue the MIDD meeting program into PDUFA VII (35).

The FFP initiative provides a unique regulatory pathway for FDA to accept quantitative tools for use in drug development (36). These tools can be applied to support various drug development programs. The drug development tool is deemed fit for purpose after a thorough evaluation of the model performance with the intended use by the review team. In general, pharmacometricians, clinical pharmacologists, statisticians and medical officers work together to assess the potential use of the modeling tool for various development decisions, which is usually risk based. So far, two modeling tools have been considered fit for purpose. The first one is the Alzheimer's disease model tool developed by Coalition Against Major Diseases (CAMD). The tool is considered suitable to inform the design of certain Alzheimer's Disease clinical trials with the information on patient baseline demographics and dropouts (36). The second drug development tool, MCP-Mod, is developed by Janssen Pharmaceuticals and Norvatis Pharmaceuticals. The tool is granted FFP designation to explore and identify adequate doses for drug development (36).

Role of MIDD Approaches in Addressing Biopharmaceutics Issues

As the biopharmaceutics scientific discipline has continued to evolve, a trend has been observed for a larger role of computational modeling to help in decision making during the drug development process. Largely, during NDA or ANDA drug product development phases, pre-formulation scientists utilize biopharmaceutics modelling approaches to help inform potential iterations of formulations to meet patient needs (e.g., quality target patient profiles or pharmacokinetic dispositions). This often includes strategies to determine optimal drug product dosage forms or routes of delivery, such as solid oral dosage forms, oral solutions, oral suspensions, and non-oral routes (e.g., parenteral, transdermal or medical device products).

In vitro tests are an important tool in the drug development process as they are often used as an indirect surrogate for the pivotal clinical safety and efficacy studies and can inform drug manufacturers of potential *in vivo* outcomes of investigational drug product variants. The relationship between the clinical trial and relevant in-vitro testing (i.e., dissolution) are illustrated in Fig. 2.

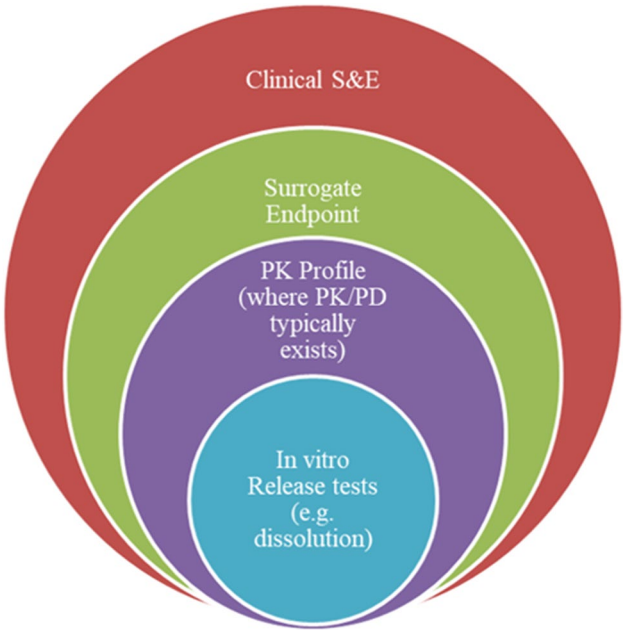

Fig. 2 Relationship between clinical trials and relevant *in vitro* tests illustrating the concept of nested surrogacy. Abbreviations: S&E – safety and efficacy; PK – pharmacokinetics; PK/PD – pharmacokinetics/pharmacodynamics.

From its inception, *in vitro* dissolution testing of drug products was expected to exhibit a relationship between the *in vitro* dissolution data and the pharmacokinetic profile (i.e. *in vivo* bioavailability) of the drug. However, since its original debut in the 1970's, *in vitro* dissolution testing evolved into more of a quality control test. Most recently, efforts have been made to utilize the dissolution test as a more predictive tool to provide insight into drug disposition based on specific drug product formulations. As such, these *in vitro* tools have started to appear in MIDD approaches, particularly with the advent of physiologically based pharmacokinetic (PBPK) modeling. Since PBPK models employ a mechanistic approach, biopharmaceutics tools naturally can be input as variables into the model. PBPK models with biopharmaceutic inputs are more generally referred to as Physiologically Based Biopharmaceutics Models (PBBM). Biopharmaceutics inputs often include a wide variety of *in vitro* tests such as the *in vitro* dissolution test, the biopharmaceutics classification system framework, solubility profile data, and related physicochemical active pharmaceutical ingredient (API) parameters that may impact the pharmacokinetic disposition or profile. PBBM in silico approaches in the regulatory landscape are being leveraged to provide information into the relative bioavailability of product variants for bridging purposes as well as lifecycle management.

Moreover, additional MIDD approaches in the biopharmaceutics setting include *in vitro in vivo* correlation (IVIVC) models. Briefly, IVIVC modeling is a mathematical model that predicts the relationship between an *in vitro* property of a dosage form (i.e. dissolution) and a relevant *in vivo* response. As with the PBBM approach, IVIVC modeling has found usages in both early drug development and lifecycle management. A primary intention of IVIVC modelling when the FDA IVIVC guidance was finalized in 1997, was to reduce regulatory burden, as IVIVCs could be used in lieu of some *in vivo* studies, providing a time or cost savings during product development and reducing testing in human subjects. Similar to PBBM, IVIVC modeling can inform formulators as to potential challenges or benefits with particular drug product recipes and help strategize future *in vivo* studies or lifecycle plans in the post approval setting.

An additional MIDD approach also includes the real time release test (RTRT). With advances in analytical detection methods and continuous manufacturing, relevant real time in-line variables can be measured during drug product manufacturing. Since dissolution phenomena are well characterized and understood (Noyes-Whitney introduced their mathematical model in 1897), these live measurements can then be input into multivariate models to predict the dissolution and therefore provide insight into the *in vivo* response (if the primary dissolution model was shown to be clinically relevant). Although the dissolution test is a highly valuable tool during drug development, it has its limitations as it can be time consuming and costly. With the RTRT tool, drug manufacturers using a continuous manufacturing approach can make small tweaks to a formulation or manufacturing process and can quickly ascertain relevant information on potential *in vivo* dispositions of the API.

Currently, in silico models are quickly gaining traction in both innovator and generic drug regulatory dossiers and are utilized during MIDD. From a biopharmaceutics perspective, PBBM provides the most flexibility and utility, while traditional IVIVC approaches yields similar uses but typically need more resources to validate and implement. RTRTs are a promising MIDD approach but are still not conventional as the approach is currently limited to continuous manufacturing processes, which are not yet commonplace. During IND phases of drug development, most biopharmaceutics MIDD approaches relate to PBBM. PBBM discussions between industry and FDA have focused largely on the types of mechanistic inputs needed, verification and validation steps for the model, and data submission needs. With regards to the various in silico models thus far discussed, there are a variety of commercial and proprietary software that can handle the data entry and modeling capabilities needed for regulatory assessment. Each software provides distinct advantages, such as ease of use, data handling speeds, transparency of certain model assumptions, flexibility in input selection and calculations, and even input optimization. The same software could also have various disadvantages, such as the need for the user to know how to manually code in the native computational language of the platform,

black box approaches to some software defined equations, limitations in biopharmaceutics variable selection, or even availability of the software itself. With the implementation of the FDA MIDD program and the novel approaches mentioned above, it is anticipated biopharmaceutics modeling uses will continue to expand in regulatory applications and ultimately reduce regulatory burdens.

Role of MIDD on Informing Developing Generics

Model Integrated Evidence in Generic Drug Assessment

There are four main areas in regulatory science to support generic drug development and approval: *in vitro* bioequivalence (BE) methods, *in vivo* BE methods, drug device combinations, and post market surveillance of generic drugs (Fig. 3). Quantitative Methods and Modeling (QMM) are an indispensable part of all of them. With more information and knowledge available post NDA approval and as a continuum of MIDD, a new concept, the model integrated evidence (MIE), has emerged in the realm of generic drug development. MIE refers to use of model generated information such as virtual bioequivalence (VBE) study simulations, not just to plan a pivotal study but to serve as confirmatory evidence. In combination with relevant *in vitro* BE testing, MIE can support alternatives to conventional *in vivo* BE studies, including but not limited to PK, PD, or comparative clinical endpoint BE studies as confirmatory information.

Quantitative clinical pharmacology (QCP) and PBPK programs have been shown as promising tools to support the assessment and/or approval of multiple Abbreviated New Drug Applications (ANDAs) for generic drug products and product-specific guidance recommendations (37 – 39). Modeling and simulations have also served as the basis for the BE assessment of narrow therapeutic index products or highly variable drugs (40,41). QCP represents one of the most frequently applied scientific disciplines in generic drug development. It has been widely used for BE study design and data analysis to support science-based BE recommendations. Depending on the type of product, BE can be evaluated using PK endpoint, PD endpoint, and/or comparative clinical endpoint. When using PK endpoints, sparse PK sampling, endogenous baseline corrections, and long study durations for long acting injectables can pose challenges in practice and assessment. MIDD and MIE focused modeling tools serve as a critical toolset to optimize study design with reduced study duration and sample size, to identify the

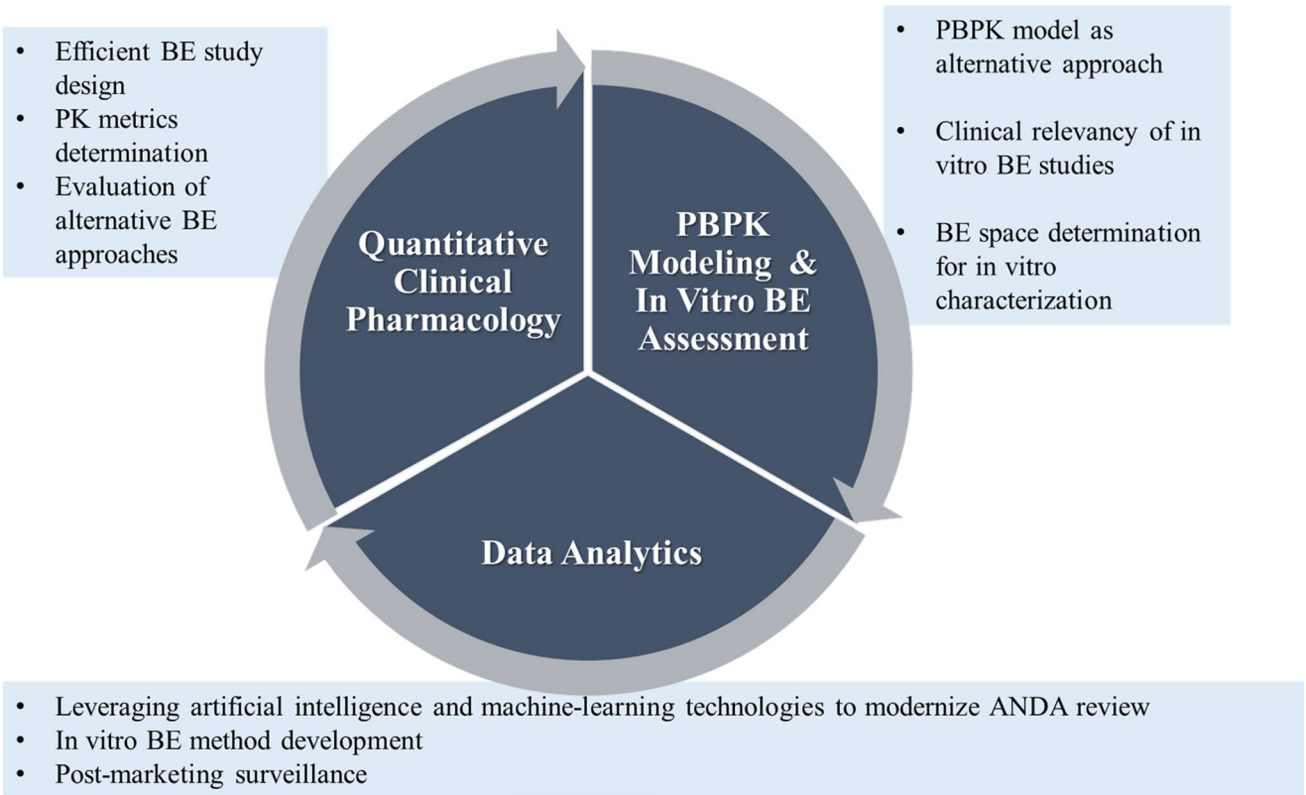

Fig. 3 Commonly used MIDD toolsets in generic drug development. Abbreviations: BE – bioequivalence; PK – pharmacokinetics; PBPK – physiologically based pharmacokinetics; ANDA – abbreviated new drug application.

most sensitive BE metrics, and/or establish science driven BE acceptance criteria with appropriate error controls. For instance, partial area under curve (pAUC) for PK can be used to assess the opioid products with abuse deterrence properties (42). For BE study design, one prominent case goes to the publication of Product-Specific Guidance for the levonorgestrel Intrauterine System (IUS) in January 2020. The progestin containing IUS was approved in United States for intrauterine contraception for up to 5 years. However, a 5-year clinical study has been considered not realistic for generic drug developers. Modeling and simulation work was conducted and translated the BE assessment criteria at year 5 to its equivalent at year 1 (43). When using PD points for BE assessment, PK-PD/exposure-response models can be used to guide data analysis, conduct endpoint identification and sensitivity evaluation, and inform the most efficient study design. For instance, when using PD or comparative clinical endpoints for BE assessment, a platform for virtual clinical trials can critically help us evaluate the study design efficiency and conduct sample size estimation. Exposure-response analyses can critically guide the assessment of the Narrow Therapeutic Index potential for a drug product. For PD endpoint data analysis, population-based method has been used for data imputation. For instance, it played an important role in the BE assessment of Albuterol Sulfate Inhalation Aerosol, a beta2-adrenergic agonist indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older. The PD BE bronchoprovocation study conducted by the applicant included considerable amounts of censored values in the PC20 data in 26% of the subjects FDA's internal analysis adopted a modern likelihood-based modeling approach (M3 model) to perform data imputation for censored values. This modeling approach supported the final ANDA approval as one of the first generics in 2020.

The other most frequently used quantitative method in the generic drug development realm is PBPK modeling and simulation. It has been widely used for both locally acting and systemically acting products. The impact of PBPK modeling ranges from serving as an alternative approach to the comparative clinical endpoint or PD endpoint BE studies, to assessment of the clinical relevancy of *in vitro* characterizations, and determination of BE specifications for *in vitro* testing parameters (e.g., relationship between formulation physical attributes and *in vitro* permeation test and drug skin bioavailability outcomes).

For topical dermatological products, PBPK modeling has been successfully applied as an alternative approach to comparative clinical endpoint or PD endpoint BE studies. This practice has been highlighted in the FDA approval of the first generic drug product for Diclofenac topical gel, where a virtual BE simulation leveraging a verified and validated dermal PBPK model was performed instead of conducting a comparative clinical endpoint study as recommended in the current draft product-specific guidance (39). The modeling approach was utilized to characterize the relationship between systemic (plasma) and local (skin tissue and synovial fluid) diclofenac drug exposures. On May 16th, 2019, the first generic drug product (Voltaren® topical gel, 1%) was approved based on the totality of evidence where the virtual modeling results provided critical information, in combination with the product Q1/Q2/Q3 similarity and systemic PK BE. Of note, given the nature of the problem, sensitivity analysis was conducted based on the PBPK model with and without a perfect match to the observed systemic PK data, to rule out the chance of approving a bioinequivalent generic product.

For orally inhaled drug products, PBPK model coupled with computational fluid dynamics (CFD) has been viewed as a promising alternative approach to the currently recommended FEV1 based PD BE studies. For such products, an equivalent systemic PK exposure may not reflect an equivalent drug regional lung deposition, and thus will not render enough evidence for equivalent therapeutic performance. Therefore, PD and/or comparative clinical endpoint BE studies are generally recommended as part of weight of evidence. However, the FEV1 based PD responses can be insensitive to dose changes and it usually involves >1000 patients per arm to achieve enough study power to conduct the recommended PD BE studies. An alternative regulatory approach by applying PBPK-CFD modeling to reduce the burden of *in vivo* PD BE studies will lead to tremendous development cost reduction. Similar approach can be adopted for the BE establishment for intranasal products.

PBPK models have been used in the identification of critical quality attribute and bio-predictive dissolution method for both complex and noncomplex generic products. PBPK modeling is a key toolset in advancing *in vitro* or, sometimes, *in vitro* only BE approaches, especially for locally acting products. It has been pursued to determine appropriate BE metrics on systemic PK to ensure local equivalence (44). When a PBPK model based IVIVC is established, it can potentially be used to conduct virtual BE simulations on local drug exposure based directly on formulation inputs. PBPK models present critical tools to assess the food effect for BE extrapolation from fasting BE studies to Fed BE studies and potential space expansion for BCS waivers, especially on the BE risk assessment for excipient effect on drug absorption permeability and drug transporter. All of these topics will critically support ICH harmonization efforts on BE establishments in terms of necessity of fed BE studies and guidelines for BCS III biowaivers.

In summary, QMM in combination with MIE have made great impact on a broad spectrum of regulatory and research activities. Earlier and enhanced communication between FDA and industry under Generics Drug User Fee Act (GDUFA) II supports the development of generic drugs,

including complex generic drug products, and should continue to help reduce overall time to approval for generic drug submissions. The pre-ANDA program features product development, pre-submission and mid-review cycle meetings with the generic drug industry for complex drug products to help clarify regulatory expectations and provide scientific advice early in product development and during application assessment.

GDUFA Sponsored Research for Modeling and Simulation

To promote innovation and wide application of QCP and PBPK approaches in generic drug development, the GDUFA established a GDUFA Science and Research Program. This program is implemented through extensive intramural and extramural collaborations. Quantitative methods and modeling approaches are one of the focuses of this program to support the development of additional innovative methodologies and more efficient tools to help establish drug equivalence standards and support the development of, and access to, safe, effective, and high-quality generic drug products for the American public. To date, FDA awarded a total of 39 research contracts and 50 grants for model-related research projects relevant to establish bioequivalence. FDA also utilized its laboratories and computer systems to conduct more than 50 intramural GDUFA Science and Research projects focused on best using our resources to improve generic drug development and regulatory assessment. All the established research will serve as a powerhouse for generating cutting-edge modeling methods in the coming decades. Modelers in both new and generic drug development should join the effort to make modern tools available to drug developers in general.

Role of MIDD in Advancing Cell and Gene Therapy Products

In the United States, the number of cell and gene therapy (CGT) products entering early development continue to grow at a fast rate and several of these products are advancing in clinical development (45,46).

CGT products have distinctive features that require special consideration for design of clinical trials including dose selection. For instance, dose selection for CGT products often considers features such as total number of cells, specific cell type delivered, cells viability, *in vivo* expansion/persistence of cells, viral vector, transgene expression, biological activity, and immunogenicity. These product related characteristics are among one of the major factors that make it challenging to apply conventional drug dosing principle such as PK/exposure analyses, dose extrapolation from preclinical species, and dose-response analysis. For CGT products these unique product related attributes coupled with patient related intrinsic and extrinsic factors are leveraged in the quantitative framework of MIDD which can help address knowledge gaps at the interface of biology and pharmacology.

Chimeric antigen receptor T cell (CAR T cell) therapies are an example of CGT products that benefited from MIDD approach during regulatory evaluation by the U.S. FDA. CAR T cell therapies are genetically modified T cells that are engineered to recognize specific cell surface antigens (e.g., CD19 expressed on B cells or B cell maturation antigen, BCMA). Since August 2017, the U.S. Food and Drug Administration has approved five CAR T cell products. Four of these products target CD19 (47–50) and one product target BCMA (51). It is interesting to note that MIDD approaches such as popPK and exposure-response analysis have been evaluated in development and regulatory assessments in the first of its kind approval of the CAR T cell product, tisagenlecleucel (52). Traditional compartmental PK modeling is not directly applicable to CAR T cell products due to unique *in vivo* disposition behaviors such as exponential expansion rate, bi-exponential decline rate and longer persistence and higher variability in exposure following single dose administration. In this respect, an empirical model for describing murine immune responses to Listeria monocytogenes or lymphocytic choriomeningitis virus was employed for characterizing the expansion and persistence of tisagenlecleucel (52,53). Once the structural model parameters were established, a traditional nonlinear mixed effect modeling approach (i.e., popPK analysis) was employed to evaluate the impact of intrinsic and extrinsic factors (e.g., impact of tocilizumab therapy for management of cytokine release syndrome, CRS) on the *in vivo* expansion of tisagenlecleucel. Furthermore, the FDA review team linked the output of this popPK modeling with exposure-response analyses to understand the relationship between CAR T cell kinetics parameters (e.g., expansion rate and Cmax) and safety outcomes (e.g., CRS). Subsequently, during regulatory evaluation of the submission for axicabtagene ciloleucel, the FDA applied similar popPK structural model and exposure-response analysis (54). So far, popPK model-based analysis have been applied for three out of the five approved CAR T cell products (47–50) and exposure-response modeling has been employed for all five cases (47–51) as part of clinical pharmacology/pharmacometric assessments at US FDA.

Scientific studies exploring emerging mechanistic modeling such as QSP models are also being evaluated for CAR T cell therapies. For example, a QSP model was developed and evaluated by integrating published knowledge on physiology, immunology, and adoptive cell therapy together with CAR T cell phenotype, cytokines, and metabolic tumor assessment

(55). Although this QSP model needs to be validated in a larger patient population, the initial model characterized the post-infusion concentrations of four CAR T cell phenotypes and CD19+ metabolic tumor volume and the model derived expansion rate was employed to predict early survival benefit in patients following CAR T cell administration.

Another class of gene therapies that is receiving significant attention is adeno-associated virus (AAV) vector-based gene therapy products. Although quantitative characterization of the *in vivo* fate of AAV vector-based gene therapies was proposed more than two decades ago (56), the MIDD approach has not yet translated to inform dosing, efficacy or safety. The challenges and possible future MIDD topics for AAV vector-based gene therapies including quantitative evaluation of the fate of transduced cells, transgene production, off-target tissue effects and immune response was highlighted in a recent mini-review (57). Dose selection in clinical trials and toxicity risk related to AAV vector-based gene therapy products remain important regulatory issues as recently discussed at the September 2021 Cellular, Tissue and Gene Therapies Advisory Committee Meeting (58). Currently, preclinical and clinical data are accumulating on AAV vector clearance, biodistribution, transgene expression, pharmacodynamics, and immunogenicity, and we expect that innovative translational approaches including MIDD will evolve in the near future to enable appropriate dose selection.

The application of MIDD for CGT products is at an early stage, and future clinical studies that are collecting quantitative information related to biological activity/pharmacodynamics, cell expansion/persistence, transgene expression, immune response, safety and efficacy data will help in the development and evaluation of MIDD tools. In this regard, the MIDD pilot program can be used as a potential resource to facilitate the development and application of exposure-based, biological, and statistical models for CGT products.

Future Perspectives

Built upon decades of exploration, MIDD has evolved into an efficient approach to assist the development of drugs and benefit patients. Through dissemination of successful case studies, MIDD is becoming more broadly accepted in the community. With the commitment of continuous investment from all stakeholders, including industry, academia, and regulatory agencies, MIDD is expected to play an increasingly prominent role in future drug development and regulatory decision-making (Fig. 1). To ensure integration of MIDD throughout the lifecycle of drug development, it will be critical to realize the full potential of the regulatory engagement avenues established under PDUFA and GDUFA not only for conventional drug products but also for newer therapeutic modalities such as cell and gene therapy and complex drug products. Development of community wide standards for planning, data analysis, inference and reporting will be key to ensure clarity of regulatory expectations and promote consistency. The endorsement of a new topic proposal and associated concept paper outline on general considerations for MIDD for establishment of a M15 informal working group by the Internal Council for Harmonisation is a big step towards achieving global convergence (59). Incorporating emerging techniques such as machine learning and artificial intelligence, leveraging newer sources of information such as RWD, applying approaches such as PBBM and RTRT more routinely, and informing regulatory decisions where applicable through alternative sources of evidence such as MIE can be seen as areas with potential to reshape drug development. To realize this potential, investing in comprehensive education and training, community-wide engagement, and collaboration will be crucial. With all the joint efforts, MIDD is expected to become an accepted standard and drive drug development to the next level.

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Declarations

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