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Model-Informed Drug Development: Current U.S. Regulatory Practice and Future Considerations

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Abstract

Model-Informed Drug Development (MIDD) refers to the application of a wide range of quantitative models in drug development to facilitate the decision-making process. MIDD was formally recognized in PDUFA VI. There have been many regulatory applications of MIDD to address a variety of drug development and regulatory questions. These applications can be broadly classified into four categories: dose optimization, supportive evidence for efficacy, clinical trial design, and informing policy. Case studies, literature papers and published regulatory documents are reviewed in this article to highlight some common features of these applications in each category. In addition to the further development and investment in these established domains of application, new technology and areas, such as more mechanistic models, neural network models and real-world data/evidence, are gaining attention and more submissions and experiences are being accumulated to expand the application of model-based analysis to a wider scope.

INTRODUCTION

Quantitative models that leverage our understanding of physiology, disease processes, and pharmacology are routinely applied to inform drug development. Different terms, such as model-aided drug development and model-based drug development, have been used to refer to such approaches.[1] "Model-Informed Drug Development", or MIDD, is the most recent term commonly used to describe the application of a wide range of quantitative models in drug development to facilitate the decision-making process. The evolution of this field and the various stages where MIDD can be applied to streamline the overall drug discovery, development, and regulatory evaluation processes have been well documented[2,3,4,5,6,7]. Of recent significance to the field, MIDD was formally recognized as an important enabler of efficient and effective drug development and included in the

Prescription Drug User Fee Act (PDUFA) reauthorization performance goals and procedures for fiscal years 2018 through 2022 (PDUFA VI)[8]. This article describes the current regulatory applications of MIDD and outlines some future considerations for this ever-evolving scientific area.

CURRENT APPLICATIONS

The regulatory application of MIDD can be broadly classified into four categories: dose optimization, supportive evidence for efficacy, clinical trial design, and informing policy (Figure 1).

Dose Optimization

Dose optimization for patients who receive a therapy once it is approved is a key aspect of clinical pharmacology evaluations at the U.S. Food and Drug Administration (FDA). In fact, whether the tested regimen is optimal for the overall patient population or subpopulations (e.g., based on patient-specific factors) is explicitly evaluated for every new molecular entity reviewed by the Agency[9]. Given there is a finite number of dosing regimens that can be formally evaluated in clinical efficacy trials, dosing regimen optimization can often be informed by modeling and simulation strategies (e.g., through non-linear mixed effect population pharmacokinetic (PK) and exposure-response (ER) analyses). The following section highlights some of the aspects associated with the use of MIDD approaches to dose optimization.

Dose Optimization for the General Patient Population Prior to Drug Approval:

In the MIDD context, dose optimization for the general patient population for which the indication is being sought is accomplished when the approved dosing in labeling is informed by model-based analyses and is different from the regimens studied in the pivotal efficacy trial(s). Typically, there

should be robust evidence of efficacy from these trials, and the motivations to derive a new dosing regimen include 1) reduction in incidence or severity of treatment-emergent adverse events, 2) enhancement of efficacy, and/or 3) improved adherence/reduced complexity in the approved regimen. The literature and FDA reviews are replete with examples of each of these scenarios. There are some common features. First, dose optimization in the general population requires sufficient PK sampling and a meaningful pharmacodynamic (PD) or clinical outcome endpoint across phase 2 and phase 3 to pass regulatory scrutiny. Secondly, because dose optimization after phase 3 trials is typically a post hoc exercise, the degree of comfort in dose optimization can be driven by whether the exercise involves interpolation or extrapolation. Thirdly, the derived dosing regimen based on pharmacokinetic/pharmacodynamic (PK/PD) analyses can be translated into labeling without the need for a confirmatory clinical trial of the derived regimen (i.e., an in-silico trial based on the PK/PD simulation, supplemented by the totality of evidence from the non-clinical and clinical development programs, can serve as the primary evidence for approval of the labeled dosing regimen for the general patient population). Of note, confidence in the in-silico trial evidence is fundamentally rooted in the thorough understanding of the mechanism of action of the investigational new drug, solid clinical trial data to substantiate the PK/PD models, and past regulatory experience in a similar or related therapeutic area. This strategy was applied to support the final dosing regimens for multiple drugs, such as clevidipine butyrate to treat high blood pressure when oral therapy is not feasible or not desirable[10], paricalcitrol to treat secondary hyperparathyroidism associated with chronic renal failure stage 5[11], a once monthly extended release injection formulation of paliperidone palmitate to treat adult schizophrenia[12], and mirabegron to treat over-reactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency[13].

Model-informed dose optimization also figures prominently for products that are developed under the Animal Rule and in rare disease drug development[14]. Dose optimization is notoriously difficult in these contexts for several reasons. First, by definition, products developed under the animal rule are done so because human efficacy trials are not feasible or ethical. As such, there is very limited opportunity to study investigational agents clinically. This reliance requires a reasonable understanding of the pathophysiology and pharmacology, demonstration of the effect in animal with a response/endpoint that is predictive for the desired benefit in humans, and relevant drug related information such as pharmacokinetics and pharmacodynamics that allows selection of a safe and effective dose in humans. Given the very limited opportunity to study investigational agents clinically, model informed approaches play a critical role in bridging information from animal studies, the limited clinical data, and any available relevant clinical data in a related human disease or condition to inform the dosing as shown in Table 1 [15, 16, 17, 18, 19, 20, 21]

Dose optimization in the rare disease area is fraught with its own challenges including limited numbers of patients to be included in clinical trials, heterogeneity in disease pathogenesis and natural history, paucity of accessible pharmacodynamic endpoints. These challenges limit the development of reliable quantitative models to inform drug development and decision-making. However, well planned drug development programs are often able to leverage the MIDD approaches to maximizing the information generated in such settings. An internal survey of orphan drug new drug application (NDA) and biological license application (BLA) submissions reviewed by FDA between January 2008 and January 2014 showed that the pharmacometric analyses in 26% and 84% submissions informed approval and labeling decisions, respectively[22]. MIDD approaches are often useful in providing supporting information as part of regulatory submissions. A recent survey of orphan drug submissions from 2000 to 2015 indicates an increasing trend in the use of MIDD approaches[23]. Two examples of the use of exposure-response analysis to inform dosing are infliximab for the treatment of ulcerative colitis in pediatric patients[24], and the approval of a lower starting dose of pasireotide for Cushing's disease[25].

Dose Optimization for Subgroups:

Once a drug is deemed to have an acceptable risk/benefit profile to warrant approval, considerations around therapeutic individualization must be made. These include determinations as to whether a different dosing regimen for a patient subgroup (e.g., based on body weight or organ dysfunction) is warranted. Evaluation of the need for alternative dosing strategies based on intrinsic patient factors or extrinsic factors (e.g., drug-drug interactions) is routinely performed by regulatory assessors. The ultimate goal is to achieve individualized treatment.

Typically, efficacy and safety data are generated from a reference patient group, minimizing potential PK and/or treatment response variability associated with such factors as organ impairment, concomitant medications, pregnancy, or extremes of body weight or age. Even when certain patients, such as pediatric patients, are the target patient population, it may not be ethical or feasible to conduct a randomized efficacy trial. Under these conditions, model-based analyses, such as physiologically-based pharmacokinetic models (PBPK) and population PK models, are commonly used to derive dosing regimens for these specific subgroups with the goal of matching the safe and effective exposure achieved in the reference patient group under the proposed dosing regimen that was studied in the efficacy and safety trials. Such a strategy relies on the assumption that the exposure-response (ER) relationships for both efficacy and safety are similar between the reference group and the specific subgroups. There are numerous such examples in the literature or in the FDA's public reviews[26,27,28,29,30,31]. Here we highlight a few cases where doses untested in the clinical efficacy and safety trials were approved. Modeling and simulation were applied to leverage efficacy and safety findings from different treatment arms to inform dose optimization.

In the case of paliperidone extended-release tablets to treat adolescent schizophrenia, an unstudied starting dose (3 mg) followed by titration was approved for patients weighing more than 51 kg when 1.5, 6 and 12 mg were studied as the fixed doses (three parallel groups against placebo) in the efficacy trial[32]. The motivation for this change was to approve a common starting dose of 3 mg for all adolescent patients because 3 mg was studied for patients weighing less than 51 kg in the efficacy trial and was found to be efficacious. The new dose was derived based on dose-response analysis and the efficacy for this new dose relative to placebo was predicted.

In the case of canakinumab to treat cryopyrin-associated periodic syndromes, a higher dose (3 mg/kg) for pediatric patients with weights between 15 to 40 kg was approved when the efficacy trial studied 2 mg/kg and showed insufficient efficacy within this subgroup[33]. The rationale for 3 mg/kg was to match the higher and efficacious exposure of 150 mg in the patients with weights more than 40 kg.

In addition to dose levels, in some instances, dose duration for certain subgroups was optimized based on model-informed approaches. For example, when boceprevir was approved to treat hepatitis C virus (HCV) infection, a longer duration regimen was approved for the treatment-naïve subjects who were late responders when the actual regimen studied in the efficacy trial for this subgroup was shorter with suboptimal efficacy[34]. In the case of telaprevir to treat HCV, the approved regimen for experienced patients (relapsers) is a response-guided therapy (24 to 48 weeks treatment duration depending on the response) while the studied regimen in the clinical trial was a regimen with a fixed duration of 48 weeks treatment[35].

One special case led to the exclusion of a subgroup in the final approval. When the phase 3 trial for edoxaban was conducted, prospective dose reduction (50% of the regular dose) was implemented for patients with moderate renal impairment (creatine clearance (CrCL) 30 to 50 mL/min), concomitant use of specific P-gp inhibitors, and low body weight (≤ 60 kg) [36]. The goal was to achieve comparable edoxaban exposure across all patients with different renal functions and other factors that may affect edoxaban exposure. Two doses (30 mg QD and 60 mg QD) of edoxaban were studied to show non-inferiority against warfarin as a comparator. Even though both doses achieved the goal of non-inferiority for the overall patient population, the subgroup with normal renal function (CrCL >= 80 mL/min) receiving edoxaban showed inferior efficacy (prevention of stroke and systemic embolic event) compared with the corresponding subgroup receiving warfarin[37]. This subgroup finding was not considered a chance finding by the FDA's clinical pharmacology and clinical review teams because the exposure-efficacy/safety analyses across the two dose levels demonstrated convincing evidence to support the conclusion that this finding was due to the lower edoxaban exposure in this subgroup[38]. Despite the regular doses (30 mg QD and 60 mg QD), the subgroup with normal renal function achieved the lowest exposure compared with the subgroups with mild renal impairment (regular doses) and moderate renal impairment (half of the regular doses). Efforts were made to derive a higher dose, such as 75-90 mg QD, for patients with normal renal function. The concern of local bleeding risk under the proposed higher dose did not allow the approval of the proposed dose for this subgroup. Instead, the final approved product label includes "SAVAYSA (edoxaban) should not be used in patients with creatinine clearance (CrCL) > 95 mL/min because of increased risk of ischemic stroke compared to warfarin" [39]. The cutoff of 95 mL/min was derived based on a more thorough analysis of the optimal cutoff value of CrCL to minimize the excluded subgroup.

Dose optimization post-approval:

When there are still uncertainties in the optimal dosing regimen at the time of approval, post-marketing clinical trials may be necessary to collect further information to answer this question. Exposure-efficacy/safety analyses have typically served as the basis for requesting such trials and providing rationale for new dosing regimens to be studied. There are several instances of dose optimization after approval across multiple therapeutic areas[40,41]. Either higher or lower doses could be explored in these trials, depending on the risk/benefit profiles of the approved doses. Some of these trials led to a change of dosing regimen in the product labels[42,43,44] or confirmed the expected dose-response relationship[45] while others did not[46]. Optimizing the dosing regimen after approval could be challenging when the drug development pace in that therapeutic area is fast and there is competition for patient enrollment to study new drugs and better drugs could be approved while the post-marking dose optimization trial is still ongoing.

Supportive Evidence of Efficacy

It has been a common practice for clinical pharmacologists at FDA to identify supportive evidence of efficacy based on findings from clinical trials in an NDA or a BLA review. The established exposure (dose)-response relationship generally provides critical evidence to support an efficacy claim of a product. Our experience with everolimus and canagliflozin/metformin fixed dose combination (FDC) are two cases that demonstrate the ability of model-based analysis to address complex questions regarding efficacy.

When everolimus was developed to prevent graft loss after liver transplantation, a unique non-inferiority (NI) trial was designed for ethical reasons[47]. Such a unique design, however, made the calculation of NI margin practically impossible based on the classic method recommended in the

FDA's guidance[48]. Upon completion of the clinical trial, the efficacy results could not be interpreted with a reasonably defined NI margin. A novel ER-based method was applied to derive the NI margin based on the exposure and efficacy data from the control arm in the NI trial[49]. Extensive sensitivity analyses were conducted to address various concerns related to the method. Eventually, the derived NI margin served as the foundation to interpret the efficacy of the NI trial and became the essential part of the totality of evidence that led to the approval of everolimus for the new indication. It is noted that this model-based approach to derive NI is challenging and is assessed case by case.

When canagliflozin and metformin were combined into one pill as a fixed-dose combination (FDC), the challenge was that there were no trials to directly compare the FDC formulation and the two drugs used together as separate entities. A cross-trial comparison showed a numerically worse efficacy for the FDC formulation, raising the concern that there might be a loss of efficacy for the new formulation. Instead of requiring another independent clinical trial to directly compare the two regimens, a PK/PD analysis was conducted to analyze the existing data and an in-silico trial was simulated to compare the two regimens in two patient groups with balanced baseline characteristics[50]. The in-silico trial demonstrated similar efficacy between the two regimens and led to the approval of the FDC formulation. In these two cases, the new regimens would not have been approved without the efficacy evidence provided by the model-based analyses.

There are also cases where the efficacy of excluded subgroups was established based on model-based analyses. When boceprevir was approved to treat HCV patients based on the observed results of the clinical trials, a regimen was also approved for the treatment-experienced subgroup (prior null responders), which was excluded in the phase 3 trial, based on the predicted efficacy from treatment-naïve patients via a novel bridging analysis. The predicted response rate for this subgroup

was later confirmed after approval by a clinical trial that was already ongoing during the regulatory review of this product. Similar strategy was implemented to support the approval of the highly effective anti-HCV drug sofosbuvir for a subgroup that was excluded in the clinical trial. The motivation was to expand the access of such highly effective treatments to as many HCV patients as possible[51].

Informing Clinical Trial Design

Another area for improving drug development efficiency is the application of modeling and simulation during the early phases of clinical development to inform design of late phase clinical trials. A pilot end-of-phase (EOP) 2A meeting program by FDA was initiated in 2004 to support this goal and approximately a dozen cases were reviewed across several years[52]. Areas covered by these applications included dosing regimen selection, patient selection, trial duration and trial design (such as response-based titration or stratification based on genotypes versus the typical parallel fixed dosing groups). Extensive experience was gained in clinical trial simulation that incorporated disease/placebo models, PK/PD or drug models, and clinical trial models (e.g., models that can account for compliance and drop-out). These models were built on the available data from the early phases of the drug development and sometimes literature data from other compounds to inform design of the pivotal clinical trials. A guidance was developed to support this pilot[53].

The value and the positive experience with these early interactions between FDA's scientists and industry scientists were highlighted in the literature[54,55]. However, one key rate-limiting factor impacting the EOP2A program appeared to be resources[56]. EOP2A packages with complicated model-based analyses or methodology should be reviewed in a short timeline. There were insufficient regulatory scientists to support the program with extensive submissions. Years later,

these experiences and lessons were applied in shaping new programs. Fit-for-Purpose (FFP) initiative provides a pathway for the FDA to accept modeling and simulation tools that can be applied to assist clinical trial design (Table 2)[57]. In recent years, an innovative new program was initiated under PDUFA VI. Specifically, the new MIDD pilot meeting program was implemented as a new mechanism for drug developers and regulatory scientists to discuss MIDD in the context of specific drug development programs with unanimous buy-in from key stakeholders. In this regard, a wider range of application of quantitative methods in drug development is expected, along with more consistent acceptance of these approaches by regulatory scientists across therapeutic areas.

Policy Development

Several MIDD applications presented so far could be viewed as special cases under unique conditions. However, accumulated experience with cases like these over the years has led to the development and refinement of policies that leverage quantitative pharmacology for the purposes of both drug development and regulatory review. Perhaps the most recently visible and illustrative example involves the evolution of modeling and simulation for assessing proarrhythmic risk potential of new drugs.

When the policy for assessing the proarrhythmic potential of new molecular entities started more than a decade ago, global regulatory guidance listed the statistical method of intersection-union test as the primary analysis method and required a thorough QT (TQT) trial design that could support such an analysis[58]. The TQT study is a prospectively designed, active controlled, stand-alone study with the primary aim of ruling out a QTc prolongation duration above a specific regulatory threshold of concern. The regulatory, scientific, and drug development communities spent several years deliberating whether another paradigm, perhaps a more efficient alternative to TQT studies,

that leveraged concentration-QT (CQT) analyses could be used.[59,60,61,62,63,64] The robustness and sensitivity of the CQT method was tested and confirmed based on large amounts of data accumulated from drug development studies. The methodology was further refined[65] and substantiated by an independent clinical trial with both positive and negative QT-prolonging drugs[66], leading to endorsement of CQT as an alternative primary analysis in the updated E14 guidance[67]. A detailed technical whitepaper[68], jointly authored by both pharmacometric and statistical scientists, supported its application in new drug development.

The other instance of informing the policy is related to pediatric efficacy extrapolation for anti-epilepsy drugs. The challenge of conducting clinical trials in pediatric patients has been recognized across multiple therapeutic areas for years. Every effort was made to establish similar exposure-efficacy relationships between the adult and pediatric patients to waive efficacy trials for pediatric patients as outlined in the FDA guidance. Historically, efficacy trials were required for both adult and pediatric patients to establish the effectiveness of the same compound to treat epilepsy as an adjunct therapy. When the exposure-efficacy data were analyzed across multiple compounds to compare the exposure-efficacy relationships between the adult and pediatric populations, it was found that, despite the different mechanisms of action of these compounds, similar exposure-efficacy relationships[69] or non-inferior efficacy under similar exposure levels existed between the two populations in general. This finding resulted in the policy change of waiving future efficacy trials in pediatric patients (four years or older) if the drug has been demonstrated to be safe and effective in adult patients. The only required information for pediatric patients is pharmacokinetic data that can be used to derive an appropriate dosing regimen to achieve similar exposure as in the adult patients and the safety under such an exposure level[70]. These policy changes are based on solid data from multiple compounds and extensive model-based analyses to demonstrate the consistency of

the findings across these compounds. This type of MIDD application to inform policy creates consistency and makes the drug development more efficient.

Table 3 provides examples of guidances that endorse MIDD strategies in drug development and regulatory evaluation. Beyond the guidances developed in the U.S., FDA is working closely with global health agencies to further promote the concept of MIDD and enhance new drug development.

FUTURE TRENDS AND CONSIDERATIONS

There have been several important scientific, regulatory, and organizational developments that suggest quantitative and innovative models are expected to play an increasingly prominent role in drug development and regulatory evaluation. For example, the inclusion of several MIDD-related provisions in PDUFA VI will allow for 1) increased resources and new mechanisms at the FDA to engage in MIDD activities in product development and review; 2) more opportunity for public stakeholder interaction on key MIDD-related science policy topics; and 3) updated FDA policies and procedures related to MIDD application and regulatory acceptance. Additionally, other quantitative approaches, such as mechanistic modeling based on a thorough understanding of the pharmacology, physiology, and disease biology, artificial intelligence/machine learning, and modeling of real-world data are several potential new tools that can expand the horizon of MIDD.

MIDD Under PDUFA VI:

Several aims of MIDD include reducing uncertainty and attrition in drug development, providing a regulatory pathway forward for practically challenging drug development contexts, and informing appropriate use of a drug once approved. The potential utility of MIDD was recently recognized by

multiple stakeholders (e.g., regulatory, pharmaceutical industry, and Congress) with the reauthorization of PDUFA to include MIDD provisions. Specifically, PDUFA VI expressly commits to "advancing model-informed drug development" by supporting several FDA activities. Under PDUFA VI, FDA will:

a. develop its regulatory science and review expertise and capacity to support evaluation of model-based strategies and development efforts;
b. convene a series of workshops to identify best practices for MIDD;
c. conduct a pilot meeting program for MIDD approaches;
d. publish draft guidances, or revise relevant existing guidance, on MIDD; and
e. develop or revise relevant manuals of policy/procedures, standard operating procedures, and/or review templates and training, as needed.

Specifically, FDA has identified several potentially critical areas for public workshops, including physiologically based pharmacokinetic modeling, exposure-response analysis, disease progression modeling, and immunogenicity. The emerging techniques and limitations of each method are expected to be discussed. To further transfer the state-of-art techniques into policy, FDA has agreed to publish either new guidance or revise existing guidance to better inform the MIDD effort.

One potentially transformative MIDD-related activity is an update to the FDA's new drug review program. In April 2018, the Agency launched a pilot program to enable drug developers and FDA review staff to directly engage in discussions where modeling and/or simulation approaches are used in drug development[71]. Under the MIDD Meetings Pilot Program, FDA has committed to accepting 2-4 MIDD-based submissions on a quarterly basis. Once a submission is accepted into the MIDD pilot review program, the sponsor is afforded several opportunities to interact with a multidisciplinary review team of clinicians, statisticians, clinical pharmacologists,

pharmacometricians, and senior leadership led by Office of Clinical Pharmacology. The established review process provides a unique opportunity to streamline and accelerate drug development through granular discussion of MIDD strategies. Initial priority areas include dose optimization, clinical trial simulation, and predictive/mechanistic safety evaluation, though the program is not limited to these areas. Early indicators suggest program success, with FDA thus far on track for meeting its commitment.

Overall, MIDD-related programmatic activities are expected to promote early interactions between drug developers and regulatory scientists on key issues during product development. Additionally, public workshops will provide useful opportunities for shared learning, establishment of scientific and best practice processes, and exploring new drug development areas suitable for MIDD.

Mechanistic Models:

Mechanistic models have the potential to support drug target identification, justify certain drug combinations, and make predictions outside the observed data range (extrapolation). There are, however, challenges in quantifying all the relevant interactions of chemical entities with cellular components, cells, tissues, and organs in a biological system. Decades of efforts led to some successful applications of PBPK to predict drug levels under certain conditions[26]. Notwithstanding, most applications of PBPK in regulatory decision making are limited to drug-drug interactions[27]. Active researches are conducted to further explore the utility of PBPK modeling in other areas to potentially expand the scope of PBPK applications.

More research is needed to determine the utility and constraints of quantitative, mechanistic modeling (e.g., PBPK/PD, quantitative systems pharmacology [QSP]) in more complex situations involving complicated drug disposition or special physiological conditions (e.g., in organ dysfunction, pregnancy). We are starting to gain experience with mechanistic models in regulatory evaluation or through collaboration. For example, systems pharmacology has been used to inform benefit/risk balance for new drugs through modeling efficacy or safety[72,73]. These case examples have not been without limitations, and clinical data were needed to confirm model-predicted results, raising questions about whether the ultimate utility of systems modeling resides in drug development (e.g., clinical trial planning) vis-à-vis regulatory review for the purposes of approvability and labeling. Nonetheless, despite the challenges of applying complex mechanistic models to support regulatory decisions, more cases including highly complex mechanistic models are submitted in various drug applications to support a wide range of decisions. We anticipate that through accumulated experience and scientific debate, a clear framework will emerge that delineates when and how systems approaches can be best utilized in both drug development and regulatory evaluation.

Models to analyze medical images

Traditionally, modeling has been used to better understand disease progression and inform endpoint selection[74, 75, 76, 77, 78] .These examples have used model-based meta-analytical techniques to analyze data of relatively low dimensionality. We have become increasingly interested in the use of agnostic approaches to large-scale data analysis as a potential opportunity for MIDD. Specifically, we think that medical images can be invaluable sources for disease diagnosis, patient subgroup identification, and treatment response prediction. We think that applying models to extract useful patient characteristics can be potentially critical to improve clinical trial design and enhance MIDD.

Recent technical advances in modeling, including radiomics, machine learning, and deep learning, provide the potential to obtain useful information directly from medical images. Radiomics aims to extract essential quantitative information from medical images through various algorithms. In general, the acquired medical images may be reduced into essential parts of interest. The features of segmented portions of images can then be quantified and extracted for additional analyses[79]. The various machine learning and deep learning methods provide powerful alternative approaches for medical image analysis compared with the traditional methods.

Recent publications have demonstrated the values of using models to understand medical images and assist trial design. It has been demonstrated that model-based tools can be applied to improve diagnosis. It is possible that these tools can be applied as part of inclusion and exclusion criteria in future clinical trials. Rajpurkar et al. established an algorithm using 121-layer convolutional neural network trained by frontal view of chest X-ray images. The performance of the algorithm was compared with 4 practicing academic radiologists. It was demonstrated that the algorithm performed better than the average performance of the four radiologists in pneumonia detection[80]. The model-based image-processing tools may be applied to identify patient subgroups with different responses to a selected treatment. Therefore, these tools may be applied to enrich patient subgroups in future drug development. For example, Roger et al. combined the contrast-enhance CT images and RNA-seq genomic data from tumor biopsies to assess CD8 infiltration. They have demonstrated that the selected image features may identify the inflamed tumors, which can be applied to predict patient response and overall survival following the treatment of anti-PD-1 or anti-PD-L-1 agents[81].

Overall, we expect that models for medical image analysis can be essential not only to improve medical practice but also to enhance clinical drug development and clinical trial design. Table 4 summarizes a sample of model-based medical image analysis tools approved by the Center for Devices and Radiological Health (CDRH) in 2018. These approved tools and tools under development may add new ways to improve MIDD.

Real-world data/real-world evidence:

There has been significant interest in the use of "real world" data to make inferences about drug safety, efficacy, and dosing[82,83]. The scope of MIDD can be largely expanded with analysis of real-world data to generate real-world evidence to address questions not completely answered by data/evidence obtained in the pre-marketing phase.

Real-world data/real-world evidence refers to medical information on drug selection, dose optimization, and clinical effectiveness or safety outcome obtained from daily medical practice. Patient electronic health records (EHR), product and disease registries, patients' claim and billing activities, and even patient-generated data (including in home-use settings) and patients' discussion on social media are alternative and valuable sources to understand the clinical pharmacology of a drug in a patient population with heterogenous characteristics[84]. Real-world evidence based on real-world data expands the scope of life cycle management creating new opportunities for drug developers, regulatory agencies, and most importantly, patients. This also provides new avenues for quantitative scientists to apply model-based analyses to extract valid evidence from non-randomized data. In a standard drug development program, effectiveness and safety profiles are characterized in randomized, well-controlled clinical trials with carefully selected patients (through well-defined inclusion and exclusion criteria). In contrast, real-world data/real-world evidence can provide

potentially complementary knowledge on drug use in the general patient population receiving routine medical care. For approved products, real-world data have been used to track safety information and to identify new safety signals. It can also provide evidence of effectiveness to develop a new indication based on off-label use, and thus, can expand the use of a marketed drug. In addition, after a drug has been approved, its dose and dosing regimen may become optimized in clinical practice (thus differing from the original recommendations). Assessing dosing information using real-world data may provide information on practical dosing that is different from doses and regimens generated from clinical development programs, thus providing real world evidence for therapeutic optimization. Furthermore, during new drug development, dosage adjustment strategies in patient subgroups (e.g., patients with renal or hepatic impairment) are typically determined through exposure matching based on limited subjects enrolled in dedicated pharmacokinetic trials. Efficacy and safety information in these patient subgroups are often lacking because these patients are generally excluded from clinical efficacy and safety trials. Real-world data and consequently, real-world evidence offer the potential to optimize dose adjustment strategies for subgroups of patients based on clinical outcomes (both safety and effectiveness) in addition to exposure data. Because real-world data are collected in less controlled settings, extensive model-based analysis is critical to extract useful information and ensure proper interpretation of the findings.

The emerging new techniques, such as portable devices, wearables, and applications (apps), may improve the dosing accuracy for patients and the quality of the collected medical information in real-world medical practice. For example, Apple watch may monitor electrocardiogram (ECG) and heart rate change for patients on a routine basis [85]. Multiple apps are developed to assist proper dosing for each patient and keep an accurate dosing record (Table 5). These tools may improve the quality of EHR, making real world data a reliable source for drug development and dose optimization or individualization. Furthermore, the new tools may allow clinical trials to be conducted in real-world

setting. All these tools will make real-world data/real-world evidence a more appealing source for MIDD.

CONCLUSION

Many scientists in academia, the pharmaceutical industry, and regulatory settings have long advocated for the use of quantitative clinical pharmacology. Shared experience through dissemination of case studies and publications have demonstrated how the field could help improve the efficiency of drug development and impact regulatory decisions. Stakeholders are increasingly seeing value in MIDD as demonstrated by organizational commitments to advancing the use of modeling and simulation in medical product development. The umbrella of MIDD is quite large and, while some model-based analyses have become routine and well accepted, others are still evolving and being evaluated. There are both opportunities and challenges to further incorporating MIDD into rational drug development. With increasing investment in this area comes the need for the development of standards, best practices, and knowledge sharing. Furthermore, as the impact of MIDD is likely to reach into more areas, it becomes critical to responsibly and transparently lay out both the strengths and the limitations of these approaches. MIDD has recently and will undoubtedly continue to become more visible to policy makers, decision makers, and the general public. The field has matured to a point where we may reap the rewards of generations of scientific investment in quantitative clinical pharmacology for the benefit of patients and society.

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Figure Legend

Figure 1: Regulatory Application of Model Information Drug Development (MIDD)

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Drug	Indication	MIDD Application	MIDD Approach
Pyridostigmine bromide	For prophylaxis against the lethal effects of soman nerve agent poisoning.	Dosing for the general population	Bridging the pharmacokinetics, dose-survival relationship in rhesus monkeys and human pharmacokinetics to predict human equivalent exposure
Levofloxacin	For treatment of plague, including pneumonic and septicemic plague, due to Yersinia pestis (Y. pestis) and prophylaxis for plague in adults and pediatric patients, 6 months of age and older.	Dose selection for the pivotal animal study; Dosing for adult and pediatric patients	PK simulations to determine a humanized dosing regimen to mimic human plasma profile of levofloxacin in African Green Monkeys. This humanized regimen was used in the pivotal animal efficacy study. Population PK modeling and simulations provided the dosing in pediatric patients.
Raxibacumab	For the treatment of adult and pediatric patients with inhalational anthrax due to Bacillus anthracis in combination with appropriate antibacterial drugs; also indicated for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.	Dosing for adult and pediatric patients	Population PK modeling and simulations provided the dosing in adult and pediatric patients based on body weight categories
Moxifloxacin	For adult patients for the treatment of plague, including pneumonic and septicemic plague, due to susceptible isolates of Yersinia pestis and prophylaxis of plague in adult patients.	Dose selection for the pivotal animal study.	PK simulations to determine a humanized dosing regimen to mimic human plasma profile of moxifloxacin in African Green Monkeys. This humanized regimen was used in the pivotal animal efficacy study.
Pegfilgrastim	To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).	Dosing in adult and pediatric patients	Population PK/PD modeling and simulation to determine effective human dosing regimen and body weight-tiered dosing in pediatric patients.

Obiltoxaximab	Indicated in adult and pediatric patients for treatment of inhalational anthrax due to B. anthracis in combination with appropriate antibacterial drugs and, for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.	Dosing in adult and pediatric patients	Dose-survival analyses of the infected rabbit and monkey monotherapy data to derive fully effective dose in animals. PK simulations to derive effective adult dosing and body weight tiered dosing in pediatric patients.
Tecovirimat	For the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg.	Dosing in adult and pediatric patients	Dose/exposure-survival relationship in animals translated to effective human dose. Human PK simulations to translate dosing from healthy humans to infected humans under fed and fasted conditions. PK simulations to derive dosing for pediatric patients and high body weight patients.

Table 1: A partial listing of MIDD application for products developed under the Animal Rule

Disease Area	Tool	Trial Component
Alzheimer's Disease	Placebo and Disease Progression Model	Patient demographics, Dropout pattern
Multiple	Multiple Comparison Procedure – Modelling (MCP-Mod)	Dose selection

Table 2: Fit-for Purpose Drug Development Tools to Assist Clinical Trial Design

Guidance Name
Guidance for Industry: Population Pharmacokinetics
Guidance for Industry: Exposure-response Relationships-Study Design, Data Analysis, and Regulatory Applications
Physiologically Based Pharmacokinetic Analyses – Format and Content Guidance for Industry
Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older Guidance for Industry
ICH E4 Dose-Response Information to Support Drug Registration
Guidance for Industry: End-of-Phase 2A Meetings
Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations
ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs —Questions and Answers (R3)
Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment
Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases
Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment
Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis
Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment
Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment
Pulmonary Tuberculosis: Developing Drugs for Treatment
Pediatric Rare Diseases — A Collaborative Approach for Drug Development Using Gaucher Disease as a Model
General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products
Product Development Under the Animal Rule

Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies
In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies
Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications
Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
Hypertension: Developing Fixed Dose Combination Drugs for Treatment
Ulcerative Colitis: Clinical Trial Endpoints
Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling
E17 General Principles for Planning and Design of Multiregional Clinical Trials

Table 3: Guidances Endorsing MIDD Strategies in Drug Development and Regulatory Evaluation

Product	Summary	Approval Date
Artyrys Oncology DL	Arterys Oncology DL is a medical diagnostic application for viewing, manipulation, 3D- visualization and comparison of medical images from multiple imaging modalities and/or multiple time-points. The application supports anatomical datasets, such as CT or MR. It is designed to support the oncological workflow by helping the user confirm the absence or presence of lesions, including evaluation, quantification, follow-up and documentation of any such lesions.	January 25, 2018
ContacCT	ContaCT is a notification-only, parallel workflow tool for use by hospital networks and trained clinicians to identify and communicate images of specific patients to a specialist, independent of standard of care workflow. It is an artificial intelligence algorithm for alerting providers of a potential stroke in patients.	February 13, 2018
IDx-DR	IDx-DR is indicated for use by health care providers to automatically detect more than mild diabetic retinopathy (mtmDR) in adults diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy. IDx-DR is indicated for use with the Topcon NW400 (a retinal camera). It is the first medical device to use artificial intelligence to detect greater than a mild level of the eye disease diabetic retinopathy in adults who have diabetes.	April 11, 2018
OsteoDetect	OsteoDetect analyzes wrist radiographs using machine learning techniques to identify and highlight distal radius fractures during the review of posterior-anterior (PA) and lateral (LAT) radiographs of adult wrists. It is an artificial intelligence algorithm for aiding providers in detecting wrist fractures.	May 24, 2018

HealthCCS	The HealthCCS Device is intended for use as a non-invasive post-processing software that can be used to evaluate calcified plaques in the coronary arteries, which may be a risk factor for coronary artery disease. The software can be used to generate reports of the total risk category of coronary calcium. It analyses pre-existing heart or chest ECG-Gated/Triggered CT scans. This information can then be used by a physician for further analysis and treatment.	June 13, 2018
EchoMD Automated Ejection Fraction Software	EchoMD Automated Ejection Fraction software is used to process previously acquired transthoracic cardiac ultrasound images, to store images, and to manipulate and make measurements on images using a personal computer or a compatible DICOM-compliant PACS system in order to provide automated estimation of left ventricular ejection fraction. It applies machine learning algorithms to process echocardiography images in order to calculate left ventricular ejection fraction.	June 14, 2018
AccipioIx	AccipioIx is a software workflow tool designed to aid in prioritizing the clinical assessment of adult non-contrast head CT cases with features suggestive of acute intracranial hemorrhage in the acute care environment. It analyzes cases using an artificial intelligence algorithm to identify suspected findings.	October 26, 2018

Table 4: Examples of Medical Image Analysis Tools Approved by CDRH, FDA in 2018

Product	Summary	Approval Date
Navigator Applications Suite	Navigator Applications Suite (Navigator) is a software package that includes Navigator Therapy, Navigator Protocol and Navigator Device. Navigator software is loaded into a medical grade PC physically mounted to the Anesthesia Delivery System and receives data from supported Anesthesia Delivery Systems, Anesthesia Patient Monitors and Intravenous Drug Infusion Pumps. Navigator Therapy displays pharmacokinetic, pharmacodynamic (PK/PD) and synergistic PD modeling information. Navigator Therapy provides the heath care provider with information about the modeled effect of supported anesthesia pharmaceuticals delivered to the patient.	October 10, 2007
ACCU-CHEK Bolus Advisor	The ACCU-CHEK Bolus Advisor, as a component of the ACCU-CHEK Connect Diabetes Management App, is indicated for the management of diabetes by calculating an insulin dose or carbohydrate intake based on user-entered data. Before its use, a physician or healthcare professional must activate the bolus calculator and provide the patient-specific target blood glucose, insulin-to-carbohydrate ratio, and insulin sensitivity parameters to be programmed into the software.	March 16, 2015
Go Dose System	The Go Dose System, comprised of the Go Dose and Go Dose Pro applications, is for use in home and clinical settings to aid in the review, analysis, and evaluation of historical blood glucose test values to support type 2 diabetes mellitus management. Go Dose System is a mobile application for use with iPad or iPhone mobile devices. The Go Dose System provides recommendations for titrating prandial humalog dosing one meal at a time using blood glucose values entered by the patient.	December 22, 2016
My Dose Coach	My Dose Coach is indicated for single patient use outside the clinic setting by a previously diagnosed Type 2 Diabetic who has been prescribed a once-daily long-acting basal insulin. My Dose Coach is intended as an aid to the patient to provide dose suggestions based upon the healthcare provider (HCP)'s independent professional judgment.	March 22, 2017

Glooko Mobile Insulin Dosing System	An app-driven tool that recommends insulin dose adjustments using data collected directly from a patient's blood glucose meter management of type 2 diabetes by calculating appropriate long-acting basal insulin doses for titrating insulin levels based on configuration by a physician or healthcare provider knowledgeable in the care and management of diabetes.	February 2, 2018
DreaMed Advisor Pro	DreaMed Advisor Pro is indicated for use by healthcare professionals when analyzing continuous glucose monitoring (CGM), self-monitoring blood glucose (SMBG) and pump data to generate recommendations for optimizing a patient's insulin pump settings for basal rate, carbohydrate ratio (CR), and correction factor (CF); without considering the full clinical status of a particular patient. DreaMed Advisor Pro does not replace clinical judgment.	June 12, 2018

Table 5: Examples of Dosing Related Tools Approved by CDRH, FDA