REVIEW

Regulatory utility of pharmacometrics in the development and evaluation of antimicrobial agents and its recent progress in China

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Abstract

Pharmacometrics is an emerging science that interprets drug, disease, and trial information in a mathematical fashion to inform and facilitate efficient drug development and/or regulatory decisions. Pharmacometrics study is increasingly adopted in the regulatory review of new antimicrobial agents. We summarized the 31 antimicrobial agents approved by the US Food and Drug Administration (FDA) and the 26 antimicrobial agents approved by European Medicines Agency (EMA) from January 2001 to May 2019. We also reviewed recent examples of utilizing pharmacometrics to support antimicrobial agent's registration in China, including modeling and simulation methods, effects of internal/external factors on pharmacokinetic (PK) parameters, safety and efficacy evaluation in terms of exposure-response analysis, refinement of the wording of product labeling and package leaflet, and possible postmarketing clinical trial. Ongoing communication among regulator, academia, and industry regarding pharmacometrics is encouraged to streamline and facilitate the development of new antimicrobial agents. The industry can maximize its benefit in drug development through continued pharmacometrics education/training.

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INTRODUCTION

Pharmacometrics is an emerging science that pursues a model-based study on the data of pharmacokinetics (PKs), pharmacodynamics (PDs), body functions, disease processes, and trial project progression using modeling and simulation (M&S) methods.[1] This emerging discipline usually describes and reflects the relationships among drug dosage, exposure, response, and patient characteristics in terms of concentration-effect, dose-response, and PK/PD correlations. M&S has been utilized in antimicrobial drug development and evaluation for decades. However, we did not find any published articles that systemically review this activity specifically. In this article, we (1) reviewed the impact of M&S in antimicrobial drug development based on the US Food and Drug Administration/European Medicines Agency (FDA/EMA) published reviews from 2001 to 2019; (2) shared a couple of examples of M&S facilitated antimicrobial drug development in China; and (3) described trend and potential opportunities for M&S informed antimicrobial drug development in China.

The goal of antimicrobial treatment is to cure patients by inhibiting or killing the invading pathogens and minimize the emergence of bacterial resistance by an effective, safe, and rational dosing regimen. M&S is critical in developing antimicrobial agents to achieve such a goal, is particularly instrumental in efficacy evaluation, dose selection, regimen optimization, and end point analysis when combining the in vitro susceptibility results with the findings of bacterial resistance surveillance. For example, pharmacometrics methods can be used to define the PK/PD indices and breakpoints indicating antimicrobial activity in clinical patient population by combining PK with the preclinical in vitro susceptibility results; develop the optimal effective and safe dosing regimens for general and special patient populations (e.g., pediatric/geriatric patients, patients with hepatic or renal impairment); and further optimize the dosing regimen in clinical development and postmarketing evaluation.[2,3]

Unlike other drug classes, antimicrobial treatment is based on the key mechanism of action (MOA) of each antimicrobial agent against pathogens, and the outcome of treatment can be measured by clinical cure and microbiological cure rate. PK/PD index/target is a key parameter frequently used in antimicrobial drug development, which combines the results of in vitro/animal studies based on MOA with clinical data to facilitate human dose selection. M&S approach is instrumental in probability of target attainment (PTA) analysis using the PK/PD target. Pharmacometrics research can play a more important role in the PTA research,[4] as appropriate PK/PD targets can be determined by associating the microbiological and clinical efficacy with PK/PD indices based on in vitro and or in vivo studies, such as the percentage of time the free concentration of antibiotic is above the minimum inhibitory concentration (MIC; $fT\%>MIC$), the ratio between the area under the plasma drug concentration-time curve (AUC) and MIC ($fAUC/MIC$), and the maximum plasma concentration (C_{max}) to MIC ratio (fC_{max}/MIC). Monte Carlo simulation based on population PK (PopPK) models developed in healthy volunteer and/or patients clinical studies can provide simulated drug concentration, C_{max}, and AUC, so can be applied to calculate the PTA of different dosing regimens for the selection of optimal dosage and regimen to support registration.[5,6] Furthermore, pharmacometrics researches based on the understanding of tissue penetration can reveal the relationship between the concentration of antimicrobial agent at the site of infection and treatment efficacy, which is more relevant than plasma concentration in predicting the antimicrobial efficacy.[7]

As members of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), China National Medical Products Administration (NMPA), the FDA, and the EMA, all adopt the important ICH guidelines that are relevant to pharmacometrics, including ICH E1, E4, and E5.[8] In addition, regulatory agencies also issued a series of guidelines concerning pharmacometrics according to national or regional reality. These efforts not only reflect the concerns of regulatory authorities but also provide specifications and guidance for the development of antimicrobial agents. The FDA and EMA released a series of pharmacometrics guidelines since 1999.[9–16] However, pharmacometrics was only introduced into drug R&D in China in the late 2000s. In recent years, the NMPA has made strong moves to encourage the development of innovative drugs and facilitate the application of pharmacometrics in new drug development.[17,18] The NMPA has released several guidelines relevant to pharmacometrics, including the Technical Guidance on Population Pharmacokinetics,[19] Model Informed Drug Discovery and Development,[20] the Pharmacokinetic and Pharmacodynamic Study of Antimicrobial Agents,[21] the Breakpoints of Antimicrobial Agents,[22] and Technical Guidance on Clinical Pharmacology of Innovative drugs.[23] These guidelines provide important specifications and guidance to pharmaceutical companies regarding drug development and evaluation in China. Besides guidelines, the NMPA also published several significant papers to encourage industry to incorporate pharmacometrics research in drug development.[18,24–27]

On the academic society side, in 1979, the Society of Pharmacometrics under Chinese Pharmacological Society was founded, led by Sun Ruiyuan and Jin Zhengjun. Sun Ruiyuan published the first textbook

of Pharmacometrics in China in 1987.[28] Haitang et al. compiled an anthology titled *Pharmacometrics and New Drug Evaluation*[29] in October 2011 on the basis of the proceedings of the first International Conference of Pharmacometrics and New Drug Evaluation, which was held in October 2007. This publication summarizes the basic principles of pharmacometrics and its applications in new drug development. Pharmacometrics meetings of Chinese Pharmacological Society and the "International Conference of Pharmacometrics and New Drug Evaluation" have promoted academic communication in the field. The Society of Infectious Diseases under China Medical Education Association published the *Expert Consensus on Clinical Application of Antimicrobial Pharmacokinetic/Pharmacodynamic Theory* in 2018,[30] which emphasizes the importance of PK/PD on guiding antimicrobial therapy in clinical practice and summarizes the antibacterial and antifungal agents in terms of PK/PD profile. This Consensus document also proposes recommendations and common understanding for optimizing the dosing regimen for common infectious diseases in the patients complicated with chronic organ dysfunction, hypoproteinemia, or infected with resistant microorganism. Dongyang et al. published *The value and general consideration of pharmacometrics study in new drug development* in September 2018,[31] which expounds the value, characteristics, application, and technical specifications of pharmacometrics study in new drug development and provides insights for new drug R&D in China.

In this article, we summarized the focus of regulatory concerns in the perspective of pharmacometrics by analyzing the review reports of the antimicrobial agents approved by the FDA and the EMA from January 2001 to May 2019. We compared the role of pharmacometrics content in FDA-approved and EMA-approved drug labeling and package leaflet for our colleagues' consideration and reference to accelerate and standardize the development of new antimicrobial agents for benefits of patients. We also summarized recent utility of pharmacometrics in the approval of antimicrobial agents in China to the best of our knowledge and based on literature research, as drug review reports of the NMPA are not widely open to the public.

THE ANTIMICROBIAL AGENTS APPROVED BY THE FDA AND THE EMA

The Drugs@FDA database and EMA official website were searched to retrieve the review reports of the antimicrobial agents approved during the period from January 2001 to May 2019. PubMed was searched to retrieve the pharmacometrics elements of antimicrobial agents approved in China during the period from January 2001 to May 2019. The FDA approved 31 antimicrobial agents (Table S1), including antibacterial agents (21, 68%), antifungal agents (9, 29%), and antituberculosis drug (1, 3%; Table 1, Figure 1). The antibacterial agents (18 single-component and 3 combination products) are licensed to treat community- or hospital-acquired pneumonia, urinary tract infections, and skin and skin structure infections. All the approved antifungal agents ($n = 9$) and antituberculosis drug ($n = 1$) are single-component products. The EMA approved 26 antimicrobial agents (Table S1), including 18 (69%) antibacterial agents, five (19%) antifungal agents, and three (12%) antituberculosis drugs (Table 1, Figure 1). The antibacterial agents (16 single-component and 2 combination products) are approved to treat pneumonia, urinary tract infections, skin, and other infections. All the approved antifungal agents ($n = 5$) and antituberculosis drugs ($n = 3$) are single-component products. Overall, 13 antimicrobial agents (9 antibacterial, 3 antifungal, and 1 antituberculous drugs) were approved by both the FDA and the EMA. New approved antimicrobial agents are all for resistant pathogens and there was no new target identified during this period of time.

REGULATORY UTILITY OF PHARMACOMETRICS IN THE DEVELOPMENT AND EVALUATION OF ANTIMICROBIAL AGENTS

From the review reports of the antimicrobial agents approved by the FDA and the EMA, we summarized the key common concerns of both regulatory agencies in pharmacometrics review as follows:

TABLE 1 Summary of the antimicrobial agents approved by FDA and EMA from January 2001 to May 2019

Product type	FDA-approved			EMA-approved		
	Total	Combination	Single-component	Total	Combination	Single-component
Antibacterial/antibiotic	21	3	18	18	2	16
Antifungal agent	9	0	9	5	0	5
Anti-tuberculosis drug	1	0	1	3	0	3

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration.

FIGURE 1 Number, percentage, and types of the antimicrobial agents approved by FDA (a) and EMA (b) from January 2001 to May 2019. EMA, European Medicines Agency; FDA, US Food and Drug Administration

(a)

1, 3%

9, 29%

21, 68%

(b)

3, 12%

5, 19%

18, 69%

■ Antibacterial/antibiotic ■ Antifungal ■ Anti-tuberculosis
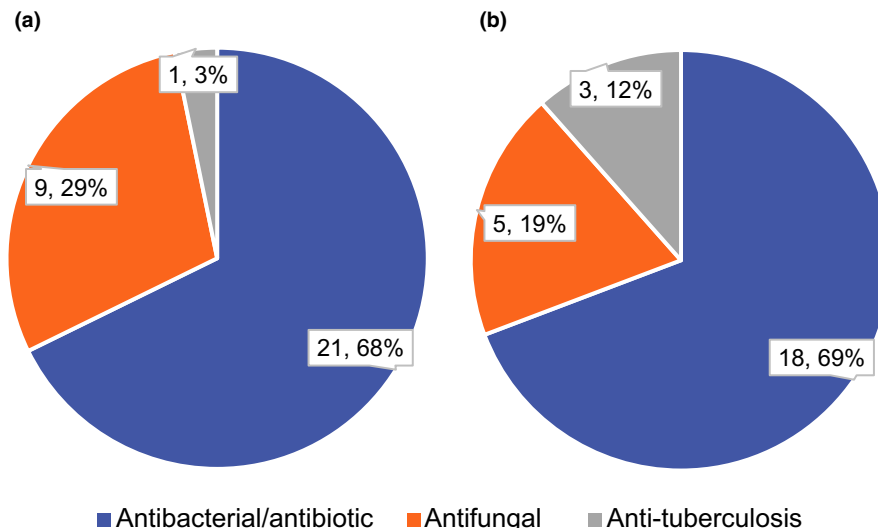
The impact of M&S in antimicrobial drug evaluation

More than half (54.8%) of the 31 FDA-approved antimicrobial agents are supported by PopPK modeling analysis (Figure 2) for the safety and efficacy evaluation in the new drug applications (NDAs) of 12 antibacterial agents, four antifungal agents, and one antituberculosis drug (including 14 single-component and 3 combination products).[32] Most (73.1%) of the 26 EMA-approved antimicrobial agents are supported by PopPK modeling analysis (Figure 2) for the safety and efficacy evaluation in the NDAs of 14 antibacterial agents, three antifungal agents, and two antituberculosis drugs (including 17 single-component and 2 combination products). As time went by, the drugs that have not been studied by pharmacometrics are all at early years (before 2010), in which the modeling technique has not been widely accepted and used.

PopPK modeling analysis is not available for some drugs (e.g., ozenoxacin [Xepi], efinaconazole [Jublia], and finafloxacin [Xtoro]), due to the low-level absorption or lack of systemic exposure after topical administration.[32–34] As for the other drugs without PopPK modeling analysis, PK analysis in special populations (in terms of sex, age, and hepatic/renal impairment) was provided to support the submission and evaluation of NDAs.

PopPK model is developed primarily upon the pooled data from phase I to III clinical trials in healthy subjects and the patients with target indication, which are provided by the applicant. The PK data from animals were also used to develop models in some cases. As for combination products (e.g., ceftolozane-tazobactam), development of the PopPK model is recommended for each drug component on a case-by-case basis.[35] If there are major active metabolites, PopPK analysis is recommended for such metabolites. If there are multiple routes of administration (e.g., delafloxacin), multiple models are developed on a case-by-case basis. In the case of delafloxacin, PopPK modeling analysis was provided not only for intravenous administration but also for oral administration.[36]

PTA analysis is a unique and powerful tool in dose selection/optimization for antimicrobial agents. Furthermore, Monte Carlo simulation and other tools are also used simultaneously in the PK/PD analysis of antibacterial agents. The MICs of an antibacterial agent against various target pathogens are combined with the PK data to calculate the PTA for the proposed PK/PD target value. Based on the calculated PTA, the probability of different dosing regimens to reach the expected maximal in vivo bactericidal or bacteriostatic effect has been evaluated. In this way, the optimal dosing regimen could be recommended with sound rationale. Just take ceftolozane-tazobactam, for example, its PTA of PK/PD target was calculated via PopPK modeling analysis of ceftolozane alone and tazobactam alone, nonclinical PK/PD target values, in vitro susceptibility testing results, and Monte Carlo simulation.[35] Model selection and development may have a substantial impact on the subsequent simulation. There are advantages and disadvantages for different models (e.g., MIC-based model, killing curve model, and other sophisticated methods), and we should select the appropriate models with justification based on the characters of the compound. In the model development, we recommend paying attention to whether it is a concentration-dependent or time-dependent pattern of bactericidal activity observed in time-kill studies, and then the relevant parameters could be selected to predict of efficacy in a PK/PD model. During the whole M&S process, we recommended to always think about the clinical meaning of each step, for example, in covariates screening step, think about whether adding or deleting a covariate is clinically meaningful; in the treatment regimen recommendation
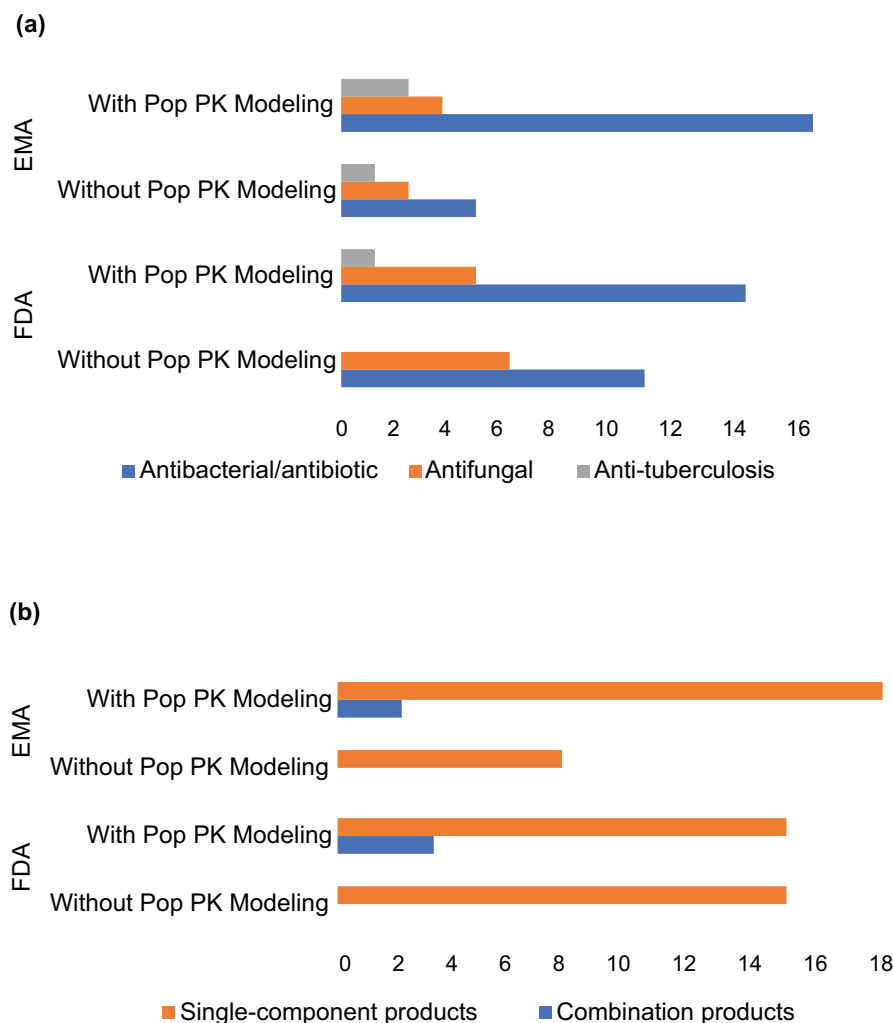
(a)

(b)

FIGURE 2 The antimicrobial agents approved by FDA and EMA from January 2001 to May 2019 in terms of PopPK modeling support. Panel (a), by type (anti-tuberculosis, antifungal, or antibacterial/antibiotic); (b) by component (single-component or combination product). EMA, European Medicines Agency; FDA, US Food and Drug Administration; PopPK, population pharmacokinetic

step, think about whether the recommended regimen is clinically practical or not.

NONMEM and R are the software programs most commonly used for modeling. The applicant can develop models according to specific data characteristics. For example, a three-compartment model featuring zero-order absorption and first-order elimination was used to describe the plasma concentration-time data pooled from phase I, II, and III clinical trials of plazomicin. Model selection can be informed by goodness-of-fit plots, including the accuracy of parameter estimates, scatter plot, correlation, and convergence between parameter estimates, modification, and conditions of the object function. Nonparametric bootstrapping methods are also appropriate for evaluating the final model and estimating the index with SD and 95% confidence interval (CI) of PopPK parameters.[37] The regulators would repeat the PopPK analysis submitted by the applicant to assess its rationality and adequacy in describing the PK data of the drug and the effects of relevant covariates on PK parameters. If any fault is identified, the regulator would correct it by pointing out that the parameters and range of sample selection in the model

of meropenem-vaborbactam were not set up appropriately by the applicant, and proposing to run an independent PopPK analysis of updated dataset to assist evaluation.

The role of M&S in evaluating intrinsic/extrinsic factors

The ICH E5 guideline summarizes the possible intrinsic/extrinsic factors (covariates) affecting PK parameters. This is also the focus of the FDA and the EMA concerns in pharmacometrics review.[38] The common intrinsic factors include race, genetic polymorphisms, sex, age, body weight, body mass index, and hepatic/renal functions. The frequently mentioned extrinsic factors are diet, culture, medical care system, treatment compliance, treatment modality, and infectious pathogen.[8] The pathogen is an antimicrobe agent unique extrinsic factor, as pathogens in different countries/regions may have a different drug resistance profile. Correct selection of covariates is very important, which should be based on the specific characteristics and dosing regimen of a drug.

Ceftazidime-avibactam (Avycaz), for example, is eliminated through the kidneys, so parameters of renal function like augmented renal clearance and end-stage renal disease (ESRD) are among the significant covariates.[39]

The Chinese NMPA requires applicants to adequately analyze the ethnical sensitivity between the Chinese and non-Chinese populations when applicants apply for registration in China, and the use of M&S in this evaluation was encouraged by the agency.[40] For example, race was identified as a significant covariate of isavuconazole because the plasma level of isavuconazole was lower in westerners than in Chinese descents.[41]

The role of M&S in evaluating drug-drug interactions

The interaction between the active ingredients of a combination of products is also a focus of concern.[27] For instance, vabomere is a combination of meropenem and vaborbactam. The applicant assessed the effect of vaborbactam on the PK profile of meropenem where M&S was used.[42] M&S is also a powerful tool to investigate the possibility of drug-drug interactions (DDIs). For example, the data from the in vitro and in vivo studies of the ceftazidime-avibactam combination were used to investigate whether there was any significant interaction among drug ingredients and the substrates, inhibitors, and inducers of cytochrome P450 enzymes. The DDI liability can be confirmed at the covariate screening step during the model development stage. DDI liabilities can also be predicted by physiologically-based pharmacokinetic model (PBPK).[43,44] However, the DDI evaluation results from M&S should be carefully interpreted due to the relatively small number of data points; a comprehensive DDI evaluation requires both M&S and traditional intensive PK studies.

Covariate analysis

Covariate analysis may be affected by trial design and implementation. For example, more than 60% of the administered dose of ceftaroline fosamil is eliminated in urine in unchanged form. However, urinary excretion data of ceftaroline were not available in phase II/III clinical trials. It was impossible to assess the significant covariate (i.e., renal clearance) of ceftaroline simply based on the PopPK model.[45] This is also the case of the antibacterial agent dalbavancin.[46]

When concluding whether the adding of significant covariates will result in a treatment regimen change or not, a thorough analysis of exposure-response relationship

and therapeutic window of the commodity needs to be performed.

The importance of M&S in exposure-response analysis for efficacy

Except the topical agents lacking systemic exposure, all antimicrobial agents are evaluated through exposure-response (E-R) analysis to determine whether the dosage and efficacy outcome data from the completed clinical trials are adequate to support its efficacy for the proposed indications. Vabomere (meropenem-vaborbactam) is an example in this case. PopPK models, nonclinical PK/PD analysis, and Monte Carlo simulation are used to calculate the probability of achieving the PK/PD target. These results are combined with in vitro susceptibility data to support the clinical efficacy of the drug. All the available efficacy end points of oritavancin in the patients with acute skin and soft tissue infection caused by *S. aureus* were used to establish PK/PD correlation for evaluating the efficacy of oritavancin in patients with *S. aureus* infection.[47]

When sufficient data of PK, PD, and microbiology tests are available from clinical trials, optimized regimen can be recommended via PK/PD target and PTA analysis. If the results showed clinical failure in very few cases or low prevalence of target pathogens, it is impossible to establish the quantitative relationship between PK/PD indices and clinical or microbiological efficacy. If clinical PK/PD target value is not available, it is recommended to use the PK/PD target value from animals or in vitro studies and Monte Carlo simulation to evaluate the dosing regimen. It is very important to determine the breakpoints of an antimicrobial agent in exposure-response analysis, which involves multidisciplinary study covering in vitro and in vivo preclinical studies, clinical trials and microbiological testing, and comprehensive analysis. In the example of ceftolozane-tazobactam, clinical efficacy data were not available for the patients at higher MIC. The FDA reviewers, therefore, selected a relatively conservative target value (equivalent to 2-$\log_{10}$ kill effect) according to the clinical efficacy of ceftolozane-tazobactam in the patients with complicated intra-abdominal infections (cIAI). Accordingly, the susceptibility breakpoint of this drug against *Enterobacteriaceae* and *Pseudomonas aeruginosa* is 2 μg/ml and 4 μg/ml, respectively, lower than the breakpoints (8 μg/ml for both *Enterobacteriaceae* and *P. aeruginosa*) proposed by the applicant.[48] The E-R relationship is evaluated more reasonably by this breakpoint modification.[47]

However, the PK/PD guided treatment regimen optimization has its own limitations. First, the reliability of

the results depends heavily on the quality of the prior studies where data were generated. Data generated from studies with poor quality might be misleading. Second, the human immune system contributes significantly to the pathogen clearance, but it cannot be modeled without the use of more mechanistic models, such as PBPK and quantitative systems pharmacology (QSP). Last, a recommended regimen needs to be verified in real life clinical trials or practice.

The role of M&S in E-R analysis for safety

The E-R analysis is also a focus of the FDA and the EMA concerns for safety evaluation. All antimicrobial agents should be evaluated for their safety profile in general and special populations by analyzing the correlation between dose/exposure and the safety end points and adverse reactions defined in clinical trials. In the example of ceftaroline fosamil, QT interval prolongation was considered as a safety end point in the E-R analysis.[49] So, if patients use the inhibitors or inducers of these isozymes, voriconazole should be prescribed cautiously, especially in the patients receiving concomitant treatment which are associated QT prolongation.[50]

The role of M&S in the potential dosing regimen adjustment in specific populations

The FDA and the EMA will determine whether the proposed dosing regimen is reasonable; whether the recommended dosage is acceptable in adult and special populations (e.g., geriatric, pediatric, or patients with impaired renal/hepatic function) by examining the E-R relationship in terms of drug efficacy and safety. If not, the Agency will decide how to adjust the dosage or dosing regimen. The corresponding method and wording of dose adjustments are also required to be reflected in the package leaflet (labeling). For instance, the E-R analysis in terms of efficacy and safety supports Vabomere 4 g (meropenem: vaborbactam = 1:1) by i.v. over 3 h, every 8 h (q8h), up to 14 days in adult patients (≥18 years old) with adequate renal function evidenced by estimated glomerular filtration rate (eGFR) greater than or equal to 50 ml/min/1.73 m^2. However, for patients with impaired renal function (eGFR <50 mL/min/1.73 m^2), the dosing regimen should be adjusted. Specifically, Vabomere 2 g, i.v. q8h if eGFR ranges from 30 to 49 ml/min/1.73 m^2; Vabomere 2 g i.v. q12h if eGFR ranges from 15 to 29 ml/min/1.73 m^2; and Vabomere 1 g i.v. q12h if eGFR is lower than 15 ml/min/1.73 m^2.[51]

Pharmacometrics review also provides important evidence for justifying the adequacy of the completed preclinical and clinical studies in support of NDA. For example, ceftazidime is excreted through the kidneys, dose adjustment is required for ceftazidime-avibactam in the patients with renal impairment. Based on pharmacometrics review, because of lacking data from renal impairment patients, the FDA reviewers advised the applicant to conduct a postmarketing study on ceftazidime-avibactam in patients with cIAI whose creatinine clearance was less than or equal to 50 ml/min to assess the PK, efficacy, and safety after dose adjustment. The PK results from the proposed postmarketing trial are used to analyze whether it is necessary to further adjust the dosing regimen. Another example is the antituberculosis drug delamanid. The relationship between the exposure and antibacterial activity of delamanid was inconsistent. Therefore, the EMA reviewers request the applicant to perform a postmarketing study to further examine the correlation between 2-month sputum conversion and long-term efficacy following different dosing regimens.

From the relevant NMPA guidelines and the prescribing information of some new antimicrobial agents approved in China, we can see that the NMPA has essentially the same focus of concerns as the FDA and the EMA in pharmacometrics review. The NMPA approved the new antibacterial agent nemonoxacin malate capsules in 2016. Various PK parameters of nemonoxacin were evaluated thoroughly in the heathy subjects and the patients with community-acquired pneumonia. PopPK analysis was also provided to examine the effect of multiple covariates (sex, age, the severity of renal impairment, and diet) on PKs. These analyses provide robust justification of the efficacy and safety of the drug in patients and demonstrates whether it is necessary to adjust the dosing regimen.[52]

PHARMACOMETRICS INFORMS LABELING AND PACKAGE LEAFLET OF ANTIMICROBIAL AGENTS

The EMA-approved labeling of antimicrobial agents is concise in content, but the package leaflet provides an easy-to-understand summary of product characteristics for patients and healthcare professionals separately, and detailed information about storage, usage, and precautions. However, the data and information relevant to pharmacometrics are infrequently described in the EMA-approved labeling and package insert. This is consistent with the EMA guideline on the *Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use* published in 2009.[53]

The FDA-approved labeling of antimicrobial agents has relatively profuse content. The pharmacology section includes the data of drug absorption, distribution, metabolism, and excretion in healthy subjects and patients, including those with impaired hepatic/renal function. The effect of covariates on exposure and PopPK analysis (if any) is also described. The results of in vivo and in vitro DDI studies are also summarized in labeling to inform if there is any drug incompatibility or contraindication. The FDA also issued a series of guidelines, such as *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* in 2006 and *Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products – Content, and Format* (2016).[54,55] These guidelines provide clear-cut guidance and specifications for the industry regarding the content and format of the pharmacology section of drug product labeling. At the Precision Dosing Public Workshop held on August 12, 2019, Robert Temple from the Center for Drug Evaluation and Research (CDER) of the FDA also advised the FDA to consider adding the content of PK/PD modeling analysis to drug labeling for guiding individualized dosing.

The NMPA also highly values the importance of the standardization and management of drug package leaflet and labeling and provides a clear guidance to the industry in relevant policies, including *Regulations for Management of Drug Package Leaflet and Labeling*, *Detailed Specifications for Package Leaflet of Chemical Drugs and Biological Products*, and *Technical Guidance for Drafting Package Leaflet of Antimicrobial Agents*. We can see that the NMPA clearly advises applicants to include the information regarding antimicrobial susceptibility testing, results of PK and PD parameters, DDI study, precautions in special populations, and the effect of various covariates on PKs in the package leaflet, for better clinical use of the drug by patients and healthcare professionals.

PHARMACOMETRICS INTEGRATED INTO THE R&D OF ANTIMICROBIAL AGENTS IN CHINA

Pharmacometrics, as an emerging discipline, started relatively later in China. The application of pharmacometrics approaches in new drug development is inadequate in depth and extent. Among the antimicrobial agents receiving regulatory evaluation, only a few drugs, such as nemonoxacin, have a full set of pharmacometrics studies.

Nonetheless, in recent years, China scientists have participated in more and more international multicenter clinical trials. A number of innovation-based pharmaceutical companies are emerging. It is encouraging to note the buy-in of pharmacometrics concepts by the industry due to vigorous promotion by the regulator and academia. China has made great progress in new drug R&D partly thanks to the application of pharmacometrics.

Example 1: Levofloxacin

The first case of pharmacometrics research in antimicrobial agents in China is levofloxacin. In 2009, based on PopPK and PK/PD research, oral levofloxacin regimen was optimized to 500 mg once daily, which has favorable PK parameters and PK/PD features in patients with community acquired lower respiratory tract infections.[56] Based on the result, the former Chinese FDA (CFDA) issued the Notice of Amending Labels of Levofloxacin Oral Preparations and Injections on December 31, 2012, to standardize the dose regimen of levofloxacin.

Example 2: Nemonoxacin

From 2011 to 2016, extensive pharmacometrics research were done in the development of nemonoxacin for treatment regimen optimization and use of the drug in special populations[52,57,58] approved by the former CFDA in 2016. In nemonoxacin, a series of covariates were analyzed via pharmacometrics research and the renal function was found to be the key one in the dosage selection; it is not necessary to consider dose adjustment of nemonoxacin in patients with mild or moderate hepatic impairment.

Example 3: Contezolid (MRX-I)

MRX-I is an oxazolidinone antibiotic against Grampositive pathogens. We performed pharmacometrics research for this drug in each development stage described as follows:

A. Preclinical study

We performed the in vitro susceptibility test and in vitro PD study (static time kill experiment). Results showed that the MRX-I was bacteriostatic against *S. aureus*, and was bactericidal against *S. pneumoniae*.[59] Then we performed the PK/PD study using murine infection model. PK/PD analysis showed that the AUC_{0-24}/MIC was the best index predicting the efficacy ($R^2 = 0.972$). The target of AUC_{0-24}/MIC was 4.3 for the bacterial static effect against the infection by *S. aureus*.[60]

B. Phase I study

The phase I clinical trial was performed in China. We performed the PopPK analysis after the finish of phase I study. Results showed that, the food and dose are the covariates on the bioavailability.[61] After comparison of exposure under fasted, regular diet, or fat-rich diet, the drug administration within 30 min after eating was recommended. After PK/PD analysis, the dosing regimen 600 mg (q12h), 800 mg (q12h) were recommended to the phase II clinical trial.[62]

Because MRX-I was mainly eliminated by metabolism,[63] we performed the PK investigation of MRX-I in subjects with decreased liver function. Compared to healthy controls, the AUC_{0-24} of MRX-I increased by 10% in subjects with liver dysfunction.[64] This indicated that there was no need to adjust the dosing regimen in subjects with liver dysfunction. This was consistent with PopPK and PBPK model prediction results.[65] Neither of the two models showed the high impact of liver function of PKs of MRX-I in humans.

C. Phase II and phase III study

We performed the PopPK/PD analysis based on combination dataset from phase I–II clinical trials after the finish of the phase II study. The results showed that satisfied efficacy could be obtained for both 600 mg (q12h) and 800 mg (q12h) regimen against the pathogens causing complicated skin and soft tissue infections (cSSTIs). The PTAs for the two regimens were greater than 90%.[66] Because the PK/PD cutoff for 800 mg (q12h) regimen was higher than that of 600 mg (q12h; 4 vs. 2 mg/L), and the percentage of drug-related adverse effect (AE) did not increase along with the dose, the regimen 800 mg (q12h) was recommended for the phase III clinical trial.

After the finish of the phase III clinical trial, the phase I–III clinical trial data were combined for the PopPK/PD analysis, where the PK/PD target was from the animal study. The results showed that the 800 mg (q12h) regimen is a satisfied regimen for the treatment of cSSTIs.[67] The phase I–III clinical trial study reports and the pharmacometrics study reports were submitted to the NMPA for approval. Then the NMPA approved this drug for the treatment of cSSTIs via priority review and approval procedure.

D. Thorough QT study

In order to evaluate the impact of MRX-I on cardiac safety, we collected the phase I to perform C-QT analysis. Results showed that the MRX-I do not have impact on the QT interval at the therapeutic dose.[68] Then we carried out the thorough QT (TQT) study. Results showed that the 800 mg of MRX-I do not have impact on QTc interval, which is consistent with C-QT analysis results. At the super-therapeutic dose (1600 mg), although the effect of MRX-I on QTc was shown at 3–4 h following administration, this was much weaker than that of the control drug moxifloxacin.[69,70] Hence, the C-QT study may replace the TQT study, which could reduce the research cost obviously.

E. Clinical development of MRX-I in another country

The applicant performed a phase I clinical trial in Australia. Because the first-in-human clinical trial was performed in China, so the phase I clinical trial in Australia was a bridging study. Compared to the phase I in China, the clinical trial design in Australia was relatively simple. In the single ascending dose (SAD), the dose of MRX-I included 400, 800 and 1200 mg. In the multiple ascending dose (MAD), the regimen was 800 mg (q12h) for 14 days or 28 days. Based on the phase I data from Australia and China, the applicant applied for the phase II clinical trial of MRX-I in the United States. It was approved. Because the applicant developed a pro-drug for MRX-I (MRX-4; reason: the solubility of MRX-4 is higher than that of MRX-I, which allows the development of injection for clinical use), so the phase III clinical trial of MRX-I was not performed in the United States.

F. After the approval

After approval in China, the applicant planned to expand the indication population of MRX-I to children. Hence, we performed the simulation study using the PopPK/PD model developed from phase I–III data. Results showed that the dose for children need decrease because the AUC and C_{max} of MRX-I was obviously higher than the adults if using regimen 800 mg (q12h). Meanwhile, the PBPK study of MRX-I also showed that the AUC, C_{max} of MRX-I in children was much higher than that of adults for the regimen 800 mg (q12h), indicating the need for reducing the dose.[65]

However, the knowledge gap and misunderstanding still exist among drug manufacturers about the advantages, role, and application of pharmacometrics in new drug development. Consistently integrating pharmacometrics methods into new drug development still requires concerted efforts of the regulator, academia, and industry in China.

SHORTENING THE GAP BETWEEN DRUG DEVELOPMENT AND THE DRUG APPROVAL

Despite regulatory agencies emphasizing the use of pharmacometrics in drug R&D a lot, however, the gaps between the drug development and the approval still exist, mainly because the role of pharmacometrics is still not well-understood enough by pharmaceutical companies and some investigators. What is more, is there is also a gap between the communication between pharmacometricians and medical teams. In order to bridge the gap, we propose some solutions to pharmaceutical companies as follows:

- Recruit dedicated pharmacometricians, build specialized a pharmacometrician team, or assign the pharmacometrics responsibility to a clinical pharmacology team. The research-based pharmaceutical companies should make the size of their pharmacometrician team appropriate to their product pipeline.
- Actively encourage the staff members to attend pharmacometrics training programs. Pharmacometrics is developing rapidly as an emerging discipline with ever-changing research hot spots. The concerned pharmaceutical companies are recommended to keep an eye on the latest training information and develop a customized training plan according to the background knowledge and experience of pharmacometrics staff. A lot of resources could be used for the training of pharmacometricians:
  A. Academic meetings: For example, International Symposium of Quantitative Pharmacology (ISQP), American Conference on Pharmacometrics (ACoP), and Population Approach Group Europe (PAGE) are three academic meetings on pharmacometrics. The ISQP is held in China every 2 years, whereas the ACoP and PAGE are held every year in the United States and Europe, respectively. We encourage the people to attend these meetings and communicate with each other. The post-graduates and young scientists are encouraged to make the poster and show them in the meeting.
  B. Workshops:
    1. Workshops before or after the meeting: Often, there are several workshops before or after the academic meeting. For example, for the ISQP, which would be held in November this year, there are four workshops before the meeting: PKPD, model-informed drug development (MIDD) on anticancer drugs and biotechnology drugs, population model building, and gene the cell therapy based on clinical pharmacology and pharmacometrics.

2. Software training workshop held by the company. For example, GastroPlus software (PharmaGo Co., Ltd.), WinNonlin software (Tri-I Biotech Co., Ltd., and Neotrident Co., Ltd.), SimCYP software (Cetera) and R software (Cetera).
3. Academic workshop held by hospitals and universities: For example, the PopPK/PD workshop held by Shanghai Chest Hospital (Main organizer: Prof. Zheng Jiao) the PopPK workshop held by Beijing Children's Hospital and Beijing Friendship Hospital (main organizers: Libo Zhao and Xingang Li).

- Encourage pharmacometricians to learn more medical knowledge to always think about clinical meaning of the results of pharmacometrics; and encourage medical staff to learn more pharmacometrics knowledge to better understand how pharmacometrics can help drug development. Few people knew both the pharmacometrics and clinical medicine well, so our solutions are as follows:
  1. As a clinical research project is about to launch, pharmacometricians should be involved together with the clinical physicians, decision on the development strategy should be made based on careful consideration, and integration of the pharmacometrics analysis result and clinical practice is absolutely essential.
  2. Invite the clinical physicians to attend the internal pharmacometrics training program.
  3. Ensure the pharmacometricians fully understand all the information on related disease and/or new drugs before carrying out the pharmacometrics research or analysis.
- Integrate pharmacometrics strategy and study into Company's Target Product Profile (TPP), Clinical Development Plan (CDP), and Clinical Pharmacology Development Plan (CPDP) to boost product development. Innovative pharmacometrics methods should also be considered in the development of generic drugs to conduct modeling analysis of key parameters for bridging the safety and efficacy of the generic drug with the original brand drug, improving the quality of generic drugs, and shortening the development cycle. For example, at the preclinical stage, in vitro PK/PD and dynamic time kill studies are recommended before the phase I study of antimicrobe agents to obtain PK/PD target; PBPK and PK/PD modeling are recommended to predict target human dose; at clinical stage, in all phase I–III studies, follow regulatory guidelines to collect data to perform PopPK, PK/PD, and E-R modeling to optimize the dose regimen.
- Actively communicate the strategy of pharmacometrics study and development milestones with investigators and regulatory agencies at official meetings. Agree

with investigators and regulatory agencies about the purpose, design, and execution of the pharmacometrics part of the planned clinical studies.

- Include the data of the pharmacometrics study in the clinical trial application and NDA package submitted to Chinese regulatory agency and to standardize the wording of package leaflet.
- Actively attend pharmacometrics meetings held regionally or globally to communicate scientific findings and advance pharmacometrics research.

The pharmaceutical companies should also pay attention to the following issues when applying the pharmacometrics strategy and approaches to new drug development:

- The requirement for pharmacometrics study may vary with the stage of new drug development and evaluation. Pharmaceutical companies should plan scientifically with reference to current guidelines. During the development of innovative antimicrobial agents, PK data should be combined with in vitro bacteriostatic results. PopPK data should be combined with PK/PD analysis to optimize the dosing regimen. The clinical and microbiological efficacy data should be collected in clinical studies for dynamic pharmacometrics analyses.
- At each stage of new drug development, the industry should work with the investigator and regulator to conduct analysis and use the strategy of the pharmacometrics study for an individual drug.
- The results of the pharmacometrics study should be confirmed in subsequent clinical trials or practice.

In conclusion, pharmacometrics is an intricate emerging discipline involving clinical pharmacology, physiology, pharmacology, toxicology, clinical medicine, microbiology, biology, and statistics. Pharmaceutical companies should strengthen pharmacometrics team building via systematic professional education and training to meet the requirements of increasingly complicated new drug development.

CONFLICT OF INTEREST
C.L. and Z.H. were paid employees of CSPC Zhongqi Pharmaceutical Technology (Shijiazhuang) Co., Ltd. when conducting this work. D.Y. is a paid employee of Covance Pharmaceutical Research and Development (Beijing) Co. Ltd. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.