Optimizing antifungal treatment through pharmacometrics: dosing considerations to enhance outcome

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Chapter 6

Summary, lessons learned, perspectives, and overall conclusions

6.1 Summary

Invasive fungal diseases (IFDs) are hidden killers, particularly for immunocompromised patients. Despite recent advances in the diagnosis and treatment of IFDs, the mortality from these diseases remains high. Developing a new antifungal drug is often lengthy and costly, suggesting that maximizing the efficacy of currently available medications is key.

In Chapter 1, we provided an overview of the current treatment options for the IFDs [1]. An exposure-response relationship has been demonstrated for all triazoles. Even so, clinicians still encounter various issues regarding safety and/or (lack of) efficacy in practice, which – among others - result from the highly variable drug exposure levels. To better address them, it is essential to understand the pharmacokinetics (PK) of these triazole agents. This thesis investigated the population PK profiles of two commonly used triazole antifungals, i.e., posaconazole and fluconazole, with a special focus on oral absorption and oral bioavailability (F), to provide scientific evidence on optimal dosing.

Chapter 2 summarized the existing knowledge on posaconazole PK, pharmacodynamics (PD), toxicity, resistance, clinical experience in special populations, and new therapeutic strategies. Posaconazole shows high variability in exposure within patients, but also between the three available formulations, between healthy volunteers and patients, and between different patient populations. Despite administration of a lower daily dose, the two newest formulations, i.e., delayed-released tablet (DR-tablet) and intravenous (IV) formulation, yield higher and more stable exposure than the oral suspension. For this reason, the DR-tablet is often preferred over suspension in practice. However, an integrated analysis comparing posaconazole PK differences among various formulations and populations is still lacking.

To bridge the knowledge gaps identified in Chapter 2, we first characterized the population PK, including the absolute F, of all posaconazole formulations with a focus on healthy volunteers, to circumvent the potentially confounding influence of pathological and clinical factors, in **Chapter 3**. For the oral suspension, the impact of food on both F and absorption rate, as well as a dose-nonlinearity in F, were quantified, resulting in lower F under fasted conditions or when given in a higher dose. Food intake also significantly boosts the F of DR-tablet. The tested concomitant medications, including antacid, ranitidine, esomeprazole, and metoclopramide, had no statistically significant impact on the absorption of the DR-tablet. With a higher and more stable F, the PK superiority of the posaconazole DR-tablet, compared with the oral suspension, was demonstrated. Administering the DR-tablet under fasted conditions however results in a lower-than-expected F, suggesting that administering the DR-tablet with food should be considered, to enhance absorption and ensure sufficient exposure. Model-based simulations in healthy volunteers illustrate that when administered under fasted conditions, more than 35% of individuals receiving

the licensed prophylactic dose of the oral suspension or DR-tablet are at risk of suboptimal exposure.

As considerable differences between healthy volunteers and patients are known, we expanded the integrated PK analysis from the healthy population to (mainly) hematological patients in **Chapter 4**. In patients, the F of the DR-tablet is overall higher than the dose-dependent nonlinear F of the oral suspension and is unaffected by the tested covariates. Five clinical characteristics were found to significantly reduce the F of the oral suspension, including mucositis, diarrhea, administration through a nasogastric tube, and concomitant use of proton pump inhibitors or metoclopramide. Additionally, patients showed a larger peripheral volume of distribution and lower inter-compartmental clearance compared to healthy volunteers, resulting in decreased trough concentrations for all formulations. Patients with hypoalbuminemia showed lower clearance (CL). No racial differences in PK could be found between Chinese and Caucasian patients, suggesting that Chinese patients do not require a different dose compared to Caucasian patients. Though superior to the oral suspension, the F of the DR-tablet is lower than previously reported, meaning that exposure upon administration of the same dose is not equivalent to IV. Switching to IV or increasing the dose of the DR-tablet coupled with therapeutic drug monitoring, should therefore be considered to ensure optimal exposure.

Posaconazole is most widely used for mould-active prophylaxis. Yet fluconazole remains the most widely used antifungal agent in patients suspected or diagnosed with yeast infections such as candidiasis. It is used in a wide variety of individuals, including in patients with obesity. As a special population, subjects who are obese are often left out of pre- or post-marketing clinical trials. To close the knowledge gap of fluconazole prescription in the obese, in **Chapter 5**, we performed a prospective PK study in obese subjects and non-obese healthy controls who received a semi-simultaneous fluconazole oral capsule and IV dose. Based on the population PK, obesity had no impact on the F of the fluconazole oral capsule. Nevertheless, participants with higher total bodyweight were found to have both higher CL and volume of distribution. In addition to total bodyweight, we found sex also statistically significantly impacted the volume of distribution, resulting in a larger volume of distribution in males compared with female subjects of the same weight. As a result, male subjects with high total bodyweight may need increased loading doses to compensate for the slower accumulation of the drug in reaching steady state. The commonly used fluconazole oral dosing regimens illustrate high variability in exposure, likely putting large proportions of obese individuals at higher risk of underexposure. To facilitate the clinical implementation of our findings, we proposed dosing tables for female and male subjects of various total bodyweight.

6.2 Lessons learned

In this section, we summarize and discuss the lessons learned during the development and refinement of the population PK models from Chapters 3-5. Our objective is to contribute to the advancement of modeling practices by sharing our experiences and insights, thereby improving the efficiency and effectiveness of future modeling efforts.

6.2.1 Integrated population PK analysis

Integrated population PK analyses combining data on different formulations and populations should be advocated when feasible. Analyzing all data together, will maximize the benefit of shared information in the data and thereby allow identification of PK differences attributable to the formulations or/and populations. Such integrated population PK analysis can provide several benefits during drug development and for post-marketing studies. First, it can improve our understanding of drug behavior by providing a comprehensive understanding of how a drug behaves in different conditions, such as different dosing regimens or patients with different characteristics and it can avoid wrong conclusions being drawn based on partial data. Second, it can increase the efficiency of drug development, as an integrated analysis of healthy volunteer data in the early stages can help identify areas where further research is needed and allow for more efficient development of formulations or dosing regimens. This can save time and resources by avoiding unnecessary research efforts. Third, it may have a greater regulatory acceptance, as regulatory agencies often require integrated analyses when evaluating new drugs or applications [2]. Going beyond PK, it is expected that integrated analyses can also enhance safety and efficacy evaluations, by pooling data from multiple studies and thereby providing a more robust evaluation of safety and efficacy, particularly for rare adverse events or subpopulations that may not be adequately represented in individual studies. Unfortunately, such integrated analysis is not always implemented during drug development, while performing such analysis after marketing requires the industry to share its data which is typically a time-consuming effort. Facilitating post-marketing open data sharing might be a potential solution.

6.2.2 Using prior knowledge to inform population PK models

When quantifying PK features with limited data, one can either constrain the model based on existing data or broaden its applicability by incorporating prior knowledge from the literature. Literature data could also be used for the model evaluation. For example, in Chapter 3, dosing scenarios for the oral posaconazole suspension were limited to 100 mg under fed and fasted conditions and 400 mg under fed conditions only. During model development for the oral suspension, the available data could therefore only support a linear F with a binary food effect. However, the model obtained with this purely data-driven approach, overpredicted exposure for a dose

of 400 mg under fasted conditions by more than 100% compared with the exposure levels reported in the literature. Moreover, the impact of food was reported to increase with the increasing dose in the healthy volunteers, which cannot be captured by a binary food effect. To expand the applicability of our model to commonly used dosing scenarios, we used a decreasing sigmoidal function to characterize a continuous dose-nonlinear function for F with different parameter values for the sigmoidal function under fasted and fed conditions, to describe the dose-nonlinear impact of food. To deal with the limited available data in the dataset, literature information was included to inform the complex nonlinear functions for F, allowing parameter estimation. In addition to the regular internal model evaluation, we subsequently also compared the simulated area under the concentration-time curve (AUC) values and the ratio of AUC values to the reported literature values under different scenarios of doses and food intake. Using this approach, we were confident that the nonlinear functions for F, informed by both the available data and the meta-data from literature, could be used for both interpolation and extrapolation to clinically relevant dosing scenarios, which also facilitated the extension to the patient's PK in **Chapter 4**.

6.2.3 Simulation and re-estimation to assess parameter identifiability

Simulation and re-estimation approaches can help to assess parameter identifiability when there is a suspicion of limited information regarding certain model parameters in the data as a result of the associated study design. Model identifiability is categorized into two types; structural identifiability related to the structure of the model and deterministic identifiability related to the study design [3]. In **Chapter 5**, the absorption profiles after administration of the oral tablet in the semi-simultaneous oral and IV study showed absorption to not be fully completed when the IV dose was administered (Figure 1), leading to the suspicion that the sampling duration of the absorption phase might have been too short to support an accurate estimation of F. This would comprise deterministic identifiability issues. While there are limited software tools that are specifically created to evaluate structural identifiability, there is currently no dedicated software available for assessing deterministic identifiability [3]. In Chapter 5, we therefore performed a simulation and re-estimation analysis to assess the deterministic identifiability. To implement the simulation and re-estimation approach, we simulated the design of the original study under scenarios of two different values for F, one scenario in which F was 50% and another in which F was 90%, in both cases, interindividual variability was 1.69 (variance) in the logit domain. Subsequently, the model was re-estimated based on the simulated datasets. The re-estimated F obtained with these datasets was 57% and 92.5%, indicating a percentage bias of 14% and 3%, respectively. This confirmed that in this case, the applied study design was sufficient to obtain an accurate estimate of F despite the limited observation period after oral dosing before the intravenous dose was given. Even though this approach allowed us to confirm the identifiability of fixed effect parameters in our analysis, parameter identifiability should be ideally considered in the design phase of a study. In addition to the existing software that has been

developed for an optimal design of experiments [4, 5], this proposed simulation and re-estimation approach can also be considered in helping select a design that fulfills the requirements for deterministic identifiability. It has to be noted that an appropriate model structure and appropriate parameter values are prerequisites for any approach, otherwise, the results can be misleading. A recently released design evaluator in NONMEM ($DESIGN) provides parameter estimability or expected model parameter uncertainty by assessing the Fisher Information Matrix [6], which can be a more efficient approach compared with the simulation re-estimation approach to investigate deterministic variability.

6.2.4 Close inspection of diagnostic plots

During model development, close inspection of diagnostic plots, including appropriate subsets of the data, is an indispensable addition to numerical diagnostics in model selection. In **Chapter 5**, we investigated the model fit when using the different numbers of transit compartments in describing the absorption profile of the fluconazole capsule. As shown in Figure 1 below, the lowest objective function value (OFV) was obtained with the model with six or seven absorption transit compartments. As expected, the parameter estimate of the first-order rate constant between absorption transit compartments (k_{tr}) increased with the increasing number of transit compartments, Yet during the absorption phase, these two models also showed time-related trends in the diagnostic plot of conditional weighted residuals *versus* the time after dose, which was not present in the model with three transit compartments. Based on these plots, the model with three transit compartments was selected, even though it had not reached the lowest statistically significant objective function value (see Figure 1). Of note is that the bias in the 2.5-hour absorption phase is easily overlooked when only examining the plots of the entire 48-hour time span of the study. This illustrates the importance of a detailed investigation of subsets of the data, as the absorption model selected based on a detailed investigation of the data in the absorption phase not only yielded an optimal description of the data in the absorption phase but also yielded more realistic estimates of the remaining PK parameters. For other drugs for which rich data is available in the absorption phase, it may be equally important to investigate and optimize the absorption model to achieve an unbiased fit, in which a lower OFV value does not always mean a more precise model fit and close inspection in diagnostic plots, like Figure 1, should be performed.

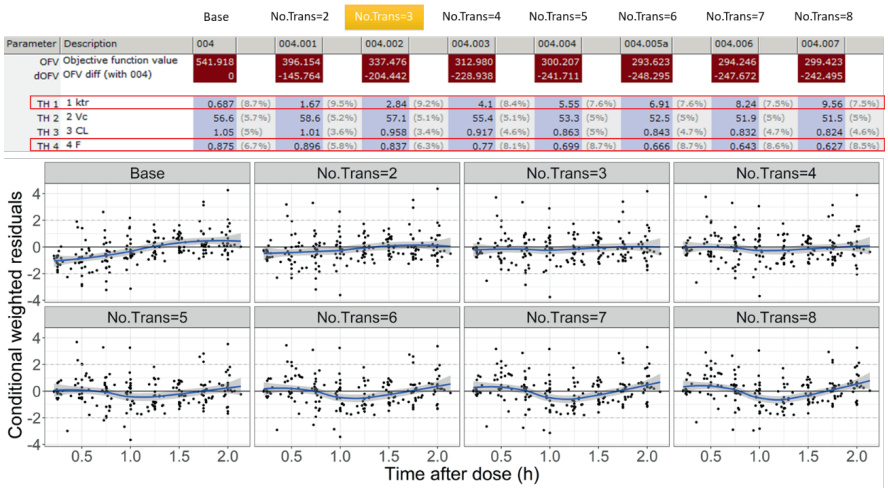

Figure 1 Overview of obtained fluconazole PK fixed effect parameter estimates (top) and the corresponding conditional weighted residuals *versus* the time after dose plots (bottom) in a first-order absorption model without transit compartment (Base) compared with those in models incorporating absorption delay using two to eight transit absorption compartments.

No.Trans = number of transit compartments, *OFV* = objective function value, *ktr* = first-order rate constant between absorption transit compartments (h^{-1}), *Vc* = volume of distribution in the central compartment (L), *CL* = clearance (L/h), *F* = bioavailability (-).

Stratifying diagnostic plots across different subgroups or strata of a population is also important to inspect for possible bias both during model development as well for final model validation. This is to ascertain an accurate description of the data obtained across the entire population. Incorporating stratification into the eta and goodness-of-fit (GOF) plots is crucial. Splitting the eta and GOF for separate strata or using different colors for data points of individuals or observations with specific characteristics, can expose bias in subgroups at an early stage during model development and indicate the direction for model improvement. If we find that the model fits well across all subgroups, then we can confirm a good description of the model for the population as a whole. If, on the other hand, we find that the model fits well in some subgroups, but not in others, we may need to modify the model or investigate further to understand why this is the case. Visual predictive check (VPC) and normalized prediction distribution errors (NPDE) plots are often used to provide a more comprehensive assessment of the final model's ability to predict the data and may not only reveal issues in the structural model but also in the stochastic model. In this context, these plots can also be stratified for subpopulations.

It is even more important in an integrated analysis to stratify the diagnostic plots, because the bias can be easily overlooked when data from various subgroups are assembled in the same diagnostic plot. In **Chapter 3**, we stratified our GOF and NPDE results into 3 separate figures based on formulation, and in **Chapter 4**,

we stratified them based both on formulation and population (healthy population *vs*. patients). In **Chapter 5**, we found that both total bodyweight and sex have a significant influence on fluconazole PK, therefore we wanted to look at the residuals separately for men and women, and obese and non-obese groups (Figure S1). By doing this, we confirmed that the model fits equally well across different subgroups.

6.2.5 The added value of shark-plot in a covariate analysis

In a covariate analysis, the goal is to identify patient or treatment-specific variables, such as demographics, disease-related variables, or concomitant treatments, that are correlated with the variability in PK parameters. These covariates are typically included in the PK model as fixed effects. However, not all patients contribute to the covariate relationship in the same way. In exceptional cases, one or two patients may have extreme covariate values or have a low-frequency covariate, while their individual PK parameters deviate from the rest of the patients. As a result, it may seem that the tested covariate is statistically significant, while in reality it can be ascribed to a multi-factor influence or other (unknown) reasons. In the covariate analysis, the OFV provides statistical evidence based on the whole population but does not take the sensitivity of the individual contributions to the OFV difference into account. Shark-plot can be used to illustrate the contribution of each individual to the overall OFV differences between the model with the new covariate included and the reference model without the covariate and establish how many individuals drive the statistical significance of the difference [7].

Identifying influential individuals that drive covariate selection, with shark-plot can be useful in two ways. It can pinpoint the influential individuals who largely contributed to the statistical significance during the covariate analysis, opening the opportunity for further investigation. When a shark-plot shows only one or very few individuals are driving the statistical significance, in many cases, one should not include such a covariate relationship. It can either be that the causal relationship is missing (otherwise the other individuals would follow the same trend), or the study design/included individuals are not sufficient to differentiate between true correlation and spurious patterns, whereby the data are not sufficient to support conclusions Ignoring the influential individual during covariate analysis may lead to a final model with a weakly supported covariate relationship, which may yield unnecessary recommendations for dose adjustments. For this reason, we urge modelers to consider using a shark-plot during the covariate analysis.

6.3 Perspectives

In this thesis, we fill a few PK knowledge gaps of posaconazole and fluconazole using a population modeling approach. While our work covers solely PK, during the analysis and literature study, we identified a few crucial components that are not adequately addressed in current antifungal PK/PD analyses, such as free target site

drug concentration, antifungal drug resistance, and host immunity. Furthermore, we recognize the potential utility of another PK modeling approach, i.e., physiologically-based PK (PBPK) modeling, in characterizing oral drug absorption and PK in obese individuals. Our objective in this section is to draw attention to these underexplored areas in antifungal PK/PD analysis and emphasize the unique value of PBPK modeling in exploring drug absorption and PK in special populations. Eventually, we can have a more comprehensive understanding of the pharmacology of antifungal therapy and improve treatment outcomes across diverse patient populations.

6.3.1 Free target site drug concentration

The free drug concentration at the site of action is the main determinant of drug activity and is therefore considered to be a more relevant measure of drug exposure than the total plasma concentration. In many cases, total drug concentration in blood or plasma is a good proxy for the free fraction at the target site, for instance when there is no saturation of plasma protein binding or specific tissue binding or accumulation at the target site. Therefore, they are commonly used to establish the total PK profile of a drug in plasma.

In the context of antifungal treatment, sufficient free drug concentration at the site of infection is a key determinant of antifungal efficacy. This is because only the free drug can penetrate the fungal cell wall and reach the target site to exert its fungicidal or fungistatic activity. Some antifungal agents (e.g. itraconazole, posaconazole, micafungin) exhibit significant drug accumulation in pulmonary epithelial lining fluid and alveolar cells which are common infection sites for invasive aspergillosis, causing plasma levels to be unpredictive for target-site exposure [8, 9]. For posaconazole, free posaconazole also accumulates and persists within the membranes and the endoplasmic reticulum of the A. fumigatus cells where the azole target enzyme CYP51a is located [10]. In this case, significant drug accumulation with high variability was observed in the target tissue, meaning drug concentrations in the plasma cannot reliably serve as a surrogate of the exposure at the target site. Compared with the free plasma drug concentrations, which have received increasing recognition in clinical practice [11, 12], measuring free target site drug concentration can be more challenging. Fortunately, recent advances in technology, such as microdialysis facilitating sample collection in the respiratory tract or subcutaneous tissues, as well as ultrafiltration, ultracentrifugation, and equilibrium dialysis, facilitating quantifying unbound concentrations, together enabled more accurate and sensitive measurements of free drug concentrations. Incorporating these measured free target site drug concentrations in future PK/PD and PBPK studies can be a viable and effective resolution to better predict antifungal efficacy and understand the antifungal mechanism.

6.3.2 Antifungal drug resistance

Antifungal drug resistance is a growing concern, while the antifungal treatment options are rather limited [13]. PK/PD indices based on minimum inhibitory concentration (MIC), such as AUC/MIC, peak concentration *versus* MIC (C_{max}/MIC), and duration of time during which the concentration exceeds MIC (T>MIC), link the fungal sensitivity to antifungal exposure and are widely used to predict the clinical effectiveness and required dose of the antifungals in treating IFDs. The MIC measurement obtained by the conventional broth dilution method, while still widely used, relies on a limited number of tested concentrations of antifungal agents, which can limit its accuracy. With this approach, a static threshold of one single value is provided to represent the sensitivity of the pathogen colony against antifungals, which does not account for the diversity of the fungal population nor for changes over time resulting from the dynamics of fungal growth. Additionally, using a static summary of exposure such as the AUC, $C_{max,}$ or T>MIC in the PK/PD indices, precludes the investigation of how the dynamic changes in antifungal exposure affect susceptibility and resistance development.

The recent progress of more advanced and dynamic assays, such as impedance-based assays, in determining antibiotic susceptibility, provides more accurate results within hours and therefore allows real-time monitoring, which cannot be achieved by the static broth dilution method [14]. The impedance-based assays utilize the change in impedance caused by bacterial growth or death as an indicator of antibiotic susceptibility and provide faster detection with higher sensitivity of microbial activity and the bacterial response to antibiotics, which allows monitoring bacterial growth in real-time [14]. Although primarily tested in bacterial infections, this approach has exhibited promising potential for application in fungal infections [15]. By incorporating dynamic antibiotic susceptibility data, as well as the dynamic systemic and target site drug exposure and response profile, into a mechanistic PK/PD model, the dynamic drug-pathogen interaction can be captured. This model enables valuable insights into effective antifungal treatment against resistance.

6.3.3 Host immunity in antifungal treatment

In Chapter 2, we pointed out that host immunity plays an indispensable role in controlling and eradicating fungal infections. Most of the pathogenic fungi are opportunistic and as a result, they mainly cause IFDs in individuals under immunocompromised conditions. Many antifungal exposure-response relationships are developed based on data from *in vivo* neutropenic animals aiming to mimic human immunosuppression [16]. In practice, while neutropenia is a common feature of many immunocompromising conditions, such as chemotherapy-induced immunosuppression or prior to stem cell transplantation, it is not a universal feature. Moreover, the level of immune response in a patient can vary widely. For example, some patients may have only a mild decrease in their neutrophil count with remaining

function, while others may have severe neutropenia with functional loss of immune response. Consequently, the findings based on the neutropenic murine models only cover one subgroup of immune suppression seen in actual patients, thereby they have their limits when extrapolating to humans. To address this issue, incorporating host immunity into *in vivo* antifungal PK/PD analysis is the key.

Some researchers have proposed using mechanism-based models to integrate the time courses of the host immune response (such as IL6, IL8, and TNF-alfa profiles) with the infection biomarkers and real-time antimicrobial PK exposure. Such an integrated approach not only captures the interaction between the antimicrobials and the invading pathogen, i.e., the conventional PK/PD model but also incorporates the interaction between the pathogen and host immune system [17, 18], allowing the quantification of the dynamic change in the infection biomarkers and the variability from host immune response and antimicrobial PK. This concept has already been applied in the field of antibacterial treatment, with one approach being to include measures of host immune status, such as the patient's neutrophils, white blood cell count, or immune biomarkers including cytokines and chemokines, in the model [19-21]. In a manner akin to bacterial resistance, the immune system can also interfere with the emergence and progression of antifungal drug resistance. This is because the immune system does not distinguish between a resistant fungus and a susceptible one, thereby eliminating the residual pathogenic fungus aside from the elimination via antifungal agents, irrespective of their susceptibility level, which should be considered in future antifungal drug resistance studies as well.

Overall, incorporating host immunity into antifungal PK/PD models has the potential to improve our understanding of how antifungal drugs exert their antifungal efficacy in patients exhibiting diverse immune system conditions. Consequently, this advancement may facilitate the optimization of treatment strategies for fungal infections.

6.3.4 PBPK modeling in characterizing oral absorption and PK in obese population

PBPK modeling takes into account both the physicochemical properties of the drug and the physiological characteristics of different tissues and organs in the body, to predict drug disposition [22]. It can account for intestinal and hepatic enzyme activity, transporters, and other permeability-limited processes, which can be highly valuable in predicting the rate and extent of drug absorption, as well as the impact of food and other factors on these processes [23, 24]. Additionally, this modeling approach can also account for the free antifungal drug accumulation at the target site, which is a viable solution for the challenge discussed in section 6.3.1. Early PBPK modeling can help researchers make more informed decisions by identifying potential issues with the drug's absorption and making necessary chemical modifications (e.g. prodrug design), or modifications in formulation or dosing regimen. As a result, it can

facilitate the drug development process and help get effective treatments to patients more quickly. While PBPK modeling of drug absorption processes provides multiple advantages, it is highly complex and requires the collection of data regarding drug characteristics and physiological data. Although the physiological data are system-specific and therefore transferable to different scenarios, missing, incomplete, or unreliable drug-specific parameters, e.g., total unbound intrinsic CL by one microgram of metabolic microsomes, significantly impede the development of PBPK models. To address this challenge, it is imperative to consider mandating the acquisition of these drug-specific measurements as a standard practice within drug development or routine experimental protocols, ensuring the availability of pertinent and reliable drug-specific properties. Furthermore, the PBPK modeling methodology should be continually refined in alignment with the evolving knowledge in the field.

The influence of obesity on drug PK exhibits substantial variability across drugs with different drug properties, rendering it impractical to make predictions for this population using a single overarching principle [25-27]. While the global incidence of obesity keeps increasing, the obese population is often underrepresented in clinical trials compared to other special populations such as patients with renal or hepatic impairment. In this particular case, PBPK modeling which quantifies the physiological changes in body composition, blood flow, and organ function, in obese individuals compared to non-obese individuals, can be employed to conduct *in silico* clinical trials for drugs lacking clinical data in obese individuals. Pioneer researchers have taken the lead in developing the PBPK modeling framework for the obese population based on existing knowledge and investigating the parameter sensitivity of the drug dispositions in a few representative drugs [28]. Promising validation results on drug exposure have been obtained in several drug classes [29]. As promising as this approach may sound, certain critical parameters identified by the sensitivity analysis are still not accurately quantified in this special population, such as adipose tissue distribution, the abundance, and potency of metabolic enzymes and transporters in different tissues and organs, gastric emptying, and intestinal motility. This increases uncertainty in model prediction and therefore still limits its current application in this population. Future studies filling these knowledge gaps are essential to expanding the application of drugs associated with more complicated PK features.

6.4 Conclusions

This thesis investigated the PK of two triazole antifungal drugs, i.e., posaconazole and fluconazole, using a population modeling approach. The study began with a comprehensive review of existing knowledge on posaconazole PK, PD, major toxicity, resistance patterns, clinical experiences in special populations, and new therapeutic strategies. Identifying gaps in this knowledge, we proceeded to compare the PK profiles of all available pharmaceutical formulations of posaconazole in healthy volunteers through an integrated analysis. The analysis demonstrated DR-tablet's superiority compared with the oral suspension under both fed and

fasted conditions. To minimize the potential risk of inadequate drug exposure, we recommend administering both posaconazole oral suspension and DR-tablet with food. When extending the analysis to patients, we found that even though the DR-tablet exhibited higher and more stable F than the suspension, it did not achieve exposure levels equivalent to the intravenous form. A substantial risk of inadequate exposure was identified in a considerable proportion of hematological patients receiving oral posaconazole at the standard dose, irrespective of prophylaxis or treatment. To mitigate this risk, the option of switching to the IV formulation or increasing the DR-tablet dose, alongside therapeutic drug monitoring, should be considered to ensure sufficient drug exposure in these patients. Furthermore, our analysis revealed that obesity alters fluconazole PK. Consequently, we proposed a dosing table for clinicians to treat *Candida* infections in obese adults, which adds to the growing body of evidence on optimal dosing strategies for this underrepresented special population. Based on the modeling and simulation results of posaconazole and fluconazole, we identified high-risk scenarios for ineffective antifungal treatment and provided alternative treatment options and dosing advice. This may contribute to improving patient outcomes, aligning with the overarching goal of all pharmacometric modeling exercises.

Throughout the analysis, we learned new lessons and shared our insights to serve as a reference for other modelers in their decision-making processes during PK analysis. Free target site drug concentration, antifungal drug resistance, and host immunity are all essential yet unexplored, elements in antifungal treatment. Incorporating them into PK/PD modeling frameworks may provide insight into effective antifungal treatment. Additionally, PBPK modeling may provide valuable insights into drug absorption and disposition in the obese population by accounting for physiological changes, which can be a powerful tool to facilitate early-stage drug development and support decision-making regarding the selection of drug formulation or dosage regimens for further clinical studies.

6.5 References

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