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R-based Solution for PK/ADA Simulated Data

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ABSTRACT

When preparing for a dry run in blinded studies related to PK or ADA, it is crucial to use simulated data for PK/ADA to avoid potential unblinding risk. This paper introduces a comprehensive R-based tool designed for generating PK/ADA simulated data. In the PK section, the tool leverages the well-established PKPDsim package renowned for its capabilities in simulating and visualizing PK models. While the data is simulated, it is designed to be representative of realistic scenarios. The simulated PK data provides the concentration changes that reflect the processes of drug absorption, distribution, metabolism, and excretion. In the ADA section, the tool independently generates simulated ADA data from scratch, which is modeled on actual ADA result scenarios, providing a robust foundation for further analytical exploration.

INTRODUCTION

Simulated Pharmacokinetic (PK) and Anti-Drug Antibody (ADA) data play a crucial role in blinded studies. There are two primary reasons for this necessity: Firstly, using actual data in blinded studies introduces the potential risk for unblinding, which can compromise the integrity of the study. Simulated data are employed as an effective safeguard against this risk, ensuring the blind is maintained throughout the study period. Secondly, PK and ADA testing is inherently complex, often resulting in a longer wait for data compared to other data types. This lag can affect the dry run timeline. Historically, vendors have supplied simulated PK or ADA data, but this approach has encountered several challenges. On one hand, the simulation process itself is time-consuming and has not substantially reduced the waiting period for these data, which can impact the dry run schedule. On the other hand, the quality of the simulated data often was poor. These data may not adequately represent all the potential scenarios encountered with real data, thereby providing insufficient support for code development and preparation. Based on these considerations, it becomes a priority to investigate alternative methods for generating simulated PK or ADA data to address these issues. Effective simulated PK and ADA data not only accelerate the initial phase of coding preparation by reducing the waiting time for real data, but they also enable the team to thoroughly examine the output format. This early review facilitates the identification and resolution of potential issues, minimizing the need for significant modifications when the actual data becomes available. Adopting this approach promotes a more streamlined and reliable analysis process in clinical trials.

This paper delves into PK simulation, exploring how to use R packages to create simulated PK concentration, discussing the characteristics and special considerations of PK data, and introducing a strategy for simulating ADA data rooted in analysis-driven approach.

PK SIMULATION

During the PK simulation process, the R package PKPDsim is utilized to generate raw PK data that closely reflects the structure of authentic PK data. The core variable in this simulation is the PK concentration, which varies across different time points and subjects. To accurately represent the overall trends in PK data, from overall trend of PK changes, it is essential to consider that variations in PK concentration over time. And at the individual level, while there is a consistent trend in PK concentrations among individuals, each subject has a distinctive concentration profile. To create a realistic representation of these scenarios, simulated PK concentration data is generated using a PK model that accurately reflect the complexities of concentration dynamics. This approach enhances the precision of the simulations, ensuring that the PK data is represented both thoroughly and accurately. The following section will introduce the relevant R package and explore additional considerations for effective simulation practices.

PKPDSIM PACKAGE USAGE

PK simulations are conducted using the PKPDsim package, an R package that offers functionality for model simulation and exploration, to simulate dosing regimens for pharmacokinetic-pharmacodynamic (PK-PD) models described by differential equation (DE) system. Current package version is 1.3.0, and it requires an R version of 3.02 or higher. Within this package, two primary functions, new_regimen () and sim (), are utilized.

The first function, new_regimen (), is responsible for creating dosing regimens. To establish a unique regimen, certain treatment information is necessary. Below are the four key factors that determine a distinct dosing regimen, and all these factors will be applied to the new_regimen():

1.Unique Drug Component: All PK simulations are based on the unique drug component. If a drug contains multiple components, the PK concentration should correspond to each unique component. The total number of unique components will determine how many regimens need to be defined in new_regimen().

2.Dosage: Listing all possible dosages for a single subject within a study is essential. When dosage changes occur, the unique subject becomes the unit for determining whether the changes constitute the same regimen. If dosage adjustments happen within the same subject, it remains part of the same regimen. However, if dosage changes occur across different subjects, they are treated as separate regimens. The value of dosage will be directly used in new_regimen(), with the argument "atm" referring to the dosage.

3.Dose Frequency: The dose frequency determines whether a study involves a single dose or multiple doses over time. This factor manifests in new_regimen() by combining with the number of doses and dosing time to describe the administration characteristics.

4.Administration Method: The chosen administration method dictates which PK model will be selected for the simulation. The type of information will also utilize the 'type' argument in new_regimen() for capturing.

Considering these factors and function arguments, users can customize dosing regimens to align with their study design. In the simulation process, there are four key arguments in this function are selected, including amt, interval (times), n, and type. These arguments are detailed in Table 1. This function includes an example that demonstrates how to define a dosing regimen. Details of the coding can be found in Example 1.

Arguments	Description	Function
amt	Dosing amount, the unit is ‘mg’, either a single value (which will repeated for multiple doses), or a vector with doses for each administration	new_regimen()
interval	Dosing interval, the unit is ‘hour’ (requires n as argument)	new_regimen()
n	Number of doses (requires interval as argument)	new_regimen()
times	Vector describing dosing times	new_regimen()
type	Either ‘infusion’, ’bolus’, ’oral’, ‘sc’(subcutaneous),or ‘im’(intramuscular)	new_regimen()

Table 1. new_regimen() Arguments

Example 1:

```
r1 <- new_regimen(
        amt=c(rep(100,4),rep(50,16)),
        times=c(0:19)*12,
```

```
        type="oral"
        )
r2 <- new_regimen(
        amt=50,
        interval=12,
        n=20,
        type="infusion"
        )
```

In this example, the dosing regimen in r1 begins with four doses of 100 mg, followed by sixteen doses of 50 mg, totaling twenty doses. Each dose is administered orally at 12-hour intervals. The dosing regimen in r2 consists of twenty doses of 50 mg at 12-hour intervals over 10 days.

After defining the dosing regimen, the simulation begins by sim() function with a PK model. The sim () function is used to carry out the simulation, which may utilize either a system of ordinary differential equations (ODEs) or an analytical solution.

In this tool's simulation process, an ODE system is selected, as the choice of PK model is crucial for accurate simulations. Two models are applied:

1. pk_1cmt_iv: This model represents a one-compartment system with intravenous (IV) administration. For the ODE system, the essential parameters include clearance rate (CL) and volume of distribution (V).

2. pk_1cmt_oral: This model also represents a one-compartment system but with oral administration. For the ODE system, the required parameters for this PK model include CL, V, bioavailability (F), and absorption rate (KA).

PK results can significantly differ between oral administration and other routes. The selection of these two PK models aims to provide comprehensive coverage for all potential IP administrations. It's worth noting that, apart from oral administration, the IV model will be applied to all other IP administrations. Based on these two PK models, some key arguments involved in sim() include 'parameters', 'regimen', 'n_ind', and 't_obs' are used. These relevant arguments are detailed in the sim () function's list, as outlined in Table 2. The output of this function is a data frame containing compartments with associated concentrations at specific time points. Example 2 provides a sample code that illustrates how to use the sim() function in practice.

Arguments	Description	Function
ode	The function describing the ODE system	sim()
parameter	Model parameters	sim()
n_ind	Number of individuals to simulate	sim()
regimen	A regimen object created using new_regimen	sim()

Table 2. sim() Arguments

Example 2:

```
P <- list(CL = 38.48,v=7.4)
r1 <- new_regimen(
        amt=100,
        times=c(0,24,36),
        type="infusion"
        )
mod <-new_ode_model("pk_1cmt_iv")
dat <-sim(
      ode=mod,
      parameters=p,
      n_ind=20,
      regimen=r1
```

)

This example defines using pk_1cmt_iv model to simulate r1 (dosing regimen) pk concentration.

PK SIMULATION LINK TO VISIT

The simulation of PK concentration relies on specific time points (hours) relative to the first dose. These time points are crucial for linking VISIT data to PK concentration. To determine this information, The determination of this information involves the utilization of several protocol-scheduled variables: 'VISIT,' 'PROTSCHD' (protocol scheduled description), 'PSCHDAY' (protocol scheduled day), 'PSCHHOUR' (protocol scheduled hour), and 'PSCHHMIN' (protocol scheduled minute). By comparing each visit time point to the first dose date, it is possible to obtain information at the hour level. For example, if the first dose date is known, and the PK sample collection dates, based on protocol design, are scheduled for day 1, day 2, day 4, and day 6 after the first dose, the calculation of PK hours will involve subtracting the corresponding visit date from the date of the first dose, multiplying by 24, and combining with the minutes information to obtain the hours elapsed after the first dose.

In real-world scenarios, sample collection times may not always align precisely with the scheduled times. To address this, a time-shift strategy is employed. The actual hour is calculated based on the protocol's scheduled hours and minutes, using the first dose date as the anchor time. For pre-dose visits, the shift occurs forward from this time point, while for post-dose visits, the shift occurs after this time point. The extent of the shift depends on the PK sample collection type. If the protocol defines the PK sample collection as intensive—where samples are collected multiple times in a short duration—the shift occurs at the minute level, minimally impacting pre-visit or post-visit times. However, if the protocol's scheduled hour is not intensive, the shift occurs within hours, which may still adequately support the adjustment.

ADDITIONAL CONSIDERATION OF PK SIMULATION

In addition to the PK concentration sample collection time shift strategy, it is crucial to address inter-subject variability in PK concentrations. While the PKPDsim package performs well in generating unique PK concentrations for specific time points, it cannot account for subject-specific variations. To enhance its functionality, it is recommended to incorporate a mechanism that considers subject-specific variations in concentration shifts.

The algorithm involves constraining the concentration not to exceed the range between preceding and succeeding values. It is assumed that for different subjects at the same time point, changes in concentration will be minimal, and the shift won't significantly impact the overall concentration trend. To derive this shift, the process can be simplified it into two steps: Step 1, calculate the difference between three consecutive records. Step 2, select the minimum absolute difference value based on Step 1 and derive the shift value from a normal distribution to ensure minimal influence on the PK concentration trend.

In addition to considering specific criteria for reporting PK summary statistics, it is addressed the scenario where more than 50% (but not all) of the concentrations are 'NQ' (not quantifiable) (FDA-2001-D-0197 (2022). When this occurs, the geometric mean (gmean), coefficient of variation (CV), arithmetic mean, and standard deviation (SD) are reported as 'not calculable' (NC). To simulate this scenario, the following algorithm is applied: for the final visit of each dosing regimen, an 'NQ' (Not Quantifiable) concentration value is deliberately assigned to over 50% of the records to ensure adherence to the specified criteria.

ADA SIMULATION

ADA simulation differs slightly from PK simulation. Unlike PK, there isn't a readily available R package for ADA simulation. Instead, the ADA simulation algorithm relies on simulating all possible ADA results scenarios. Additionally, since neutralizing antibodies (NAbs) falls under the broad definition of ADA, it is included in the ADA simulation. The output generated by ADA simulation is like PK, providing data for each subject's specific time points.

The ADA is categorized into two types depending on their interaction with antigen binding sites: those that do not neutralize the antigen, known as non-neutralizing antibodies (non-NAbs), and those that do, referred to as NAbs (Sundaram, Maruthavanan, & Seagen Inc., 2023). To get the ADA results, the Food and Drug Administration (FDA), has released specific guidelines for the immunoassays that are used to detect antibodies targeting biologic medications (FDA-2009-D-0539, 2019). Blood samples are to be

collected and analyzed for ADA levels at predetermined timepoints throughout the study. The process begins with an initial ADA screening; if needed, this is followed by a series of detailed tests to refine the analysis, which includes confirmatory ADA testing and the evaluation for the presence of NAbs. Simulated ADA results are approached from an ADA analysis perspective, ensuring coverage of as many ADA reporting scenarios as possible.

ADA REPORTING SCENARIOS

For analytical purposes, characterizing ADA facilitates the presentation of ADA data. Analysis strategy of ADA often focus on results such as ADA-positive, ADA-negative, treatment-emergent ADA positive, ADA positivity at baseline only, persistently positive ADA and transiently positive ADA. The primary focus for NAbs is on the ADA-positive population, including NAbs positivity at any point during the study. The simulation aims to cover all relevant ADA reporting scenarios. The possible ADA reporting scenarios are listed in Table 3.

Category	Scenario	Description
ADA Positive	1	ADA positive (A positive sample at any time)
ADA Negative	2	ADA negative (Negative samples at all timepoints)
TE-ADA Positive	3	TE-ADA positive Treatment-induced ADA positive (ADA negative at baseline and at least one post-baseline titer is >=1 dilution factor than the MRD*) MRD* stands for minimum required dilution. Treatment-boosted ADA positive (ADA positive at baseline and baseline titer is boosted by greater than the variability of the assay)
Non-TE ADA Positive	4	ADA positive but not fulfilling the definition of TE-ADA positive
Only Baseline Positive	5	ADA positive at baseline and all post-baseline assessments are either negative or missing (or a mixture of negative and missing)
ADA Persistently Positive	6	ADA negative at baseline and either of the following conditions: 1.ADA positive results at the last post-baseline assessment 2.At least 2-post-baseline ADA positive assessments (with >=16 weeks between the first and last positive)
ADA Transiently Positive	7	ADA negative at baseline, having at least one post-baseline ADA positive assessment

Table 3. ADA Reporting Scenarios

ADA SIMULATION LINK TO VISIT

Compared to PK sample collection, ADA collection involves two distinct models based on dosing scenarios: single dose and multiple doses. In a single-dose study, the ADA collection model consists of one pre-dose measurement followed by a post-dose measurement. For multiple doses studies, there are three types of ADA collection models:

i. Every Pre-dose ADA Collection + Post-dose ADA Collection:

This model guarantees that each administered dose is paired with a pre-dose record, and every pre-dose record is matched with a subsequent post-dose ADA collection.

ii. Multiple Doses with Single Baseline ADA collection:

For this collection model, the pre-dose ADA collection occurs before the initial dose, while the post-dose ADA collections are associated with subsequent doses, which may include the first dose.

iii. Multiple Pre-dose ADA Collections + Post-dose ADA collections:

In this case, ADA measurements are collected before dosing on multiple occasions, and post-dose ADA measurements only occur after the last dose.

The resulting records for these three scenarios are listed in Table 4.

Type	PROTSCHD	Visit
Every Pre-dose ADA Collection +Post-dose ADA collection	Pre-dose	Dosing1
	Post-dose	Dosing1
	Pre-dose	Dosing 2
	Post-dose	Dosing 2
	Pre-dose	Dosing 3
	Post-dose	Dosing 3
Multiple Doses with Single Baseline ADA Collection	Pre-dose	Dosing 1
	Post-dose	Dosing 1
	Post-dose	Dosing 2
	Post-dose	Dosing 3
Multiple Pre-doses and post-dose ADA Collections	Pre-dose	Dosing 1
	Pre-dose	Dosing 2
	Pre-dose	Dosing 3
	Post-dose	Follow-up

Table 4. Multiple ADA Collection Types

For NAbs, two scenarios are also encountered. The first scenario aligns the NAbs collection with the same visit model as the ADA. In this case, visit information is directly inherited from ADA. However, the second scenario involves a different NAbs collection model compared to ADA, since the IP is an immunotherapeutic agent rather than a virus or pathogen. In this context, NAbs may represent the body's own ADAs that are generated in response to the administered therapeutic antibody. Here, the timing of NAbs measurements is reconstructed to fit the specific scenario. Beyond these specific collection types, other VISIT derivations for ADA and NAbs follow a similar approach as in the PK section. The approach for time shifting considers using the date of the first dose as the anchor point, from which the shifting algorithm is applied, like the method utilized for PK simulation.

CONCLUSION

The PK/ADA simulated data generator is a versatile R-based tool equipped with an R Shiny application, designed to create simulated PK and ADA data. For PK simulation, the tool utilizes the PKPDsim package, which employs an ODE system to model PK concentrations realistically. The simulation process carefully considers PK models, aiming to closely approximate real-world scenarios. Furthermore, the tool integrates details of the study design along with various impact factors to facilitate the preparation of dry run coding. When it comes the ADA simulations, the tool analyzes critical scenarios to characterize ADA results, ensuring their suitability for clinical trials. This R Shiny application enhances the quality of simulated PK/ADA data, enabling study teams to plan and execute dry runs more efficiently.

REFERENCES

Sundaram, S., Maruthavanan, J., & Seagen Inc. (2023). Handling Anti-Drug Antibody (ADA) Data for Efficient Analysis.

FDA-2009-D-0539 (2019) Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection.

FDA-2001-D-0197 (2022) Draft Guidance for Statistical Approaches to Establishing Bioequivalence

Tools for Performing Pharmacokinetic-Pharmacodynamic Simulations, available at

https://cran.r-project.org/web/packages/PKPDsim/index.html

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