Methods to Detect Non-Compliance and Minimize its Impact on Population PK Parameter Estimates

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Introduction

- Non-compliance is an important issue for many drugs with chronic outpatient administration;

- Concentration-time profiles of non-compliers (subjects who do not follow prescribed dosing pattern) cannot be adequately described by the model that assumes full compliance;

- Even a small fraction of non-compliant patients may significantly bias population PK parameter estimates as most estimation methods are sensitive to outliers (observations not consistent with the expected profiles or subjects with significantly different parameters);

- There are no commonly accepted and tested modeling methods to identify non-compliant patients and obtain unbiased estimates of population PK parameters.
Objectives

To propose and evaluate two methods (CM1 and CM2) that would allow:

- Detection of non-compliance and identification of non-compliant subjects using concentration-time data;
- Unbiased estimation of population PK parameters in a population with prevalent non-compliance;

CM1: Compliance Method 1; CM2: Compliance Method 2
Illustration of the problem (sparse data)

QD oral administration; steady-state trough values; proportional residual error (CV=20%); simulated with non-compliance; estimated assuming full compliance.

Observation: non-compliers have higher residual variability
CM1 Method: Motivation

Ref. [1] proposed to detect subjects with odd observations and reduce their influence on the population PK parameter estimates by introduction of the random effect ($\eta_e$) on the residual error. Example:

SD=IPRED ; proportional error model

$Y = \text{IPRED}+\text{SD} \times \text{EPS}(1)$ ; error model without random effect

$Y = \text{IPRED}+\text{SD} \times \text{EPS}(1) \times \text{EXP}(\text{ETA}(1))$ ; error model with random effect

We apply the same idea to detect non-compliant patients who can be distinguished by large fluctuations of their observed concentrations that are not explained by the model that assumes full compliance and time-independent parameters.

CM1 Method: Proposed Procedure

- Fit the model with the random effect $\eta_\varepsilon$ on the residual error;
- Identify subjects with strong non-compliance as those with high $\eta_\varepsilon$;
- Exclude non-compliant subjects from the dataset to obtain unbiased estimates of model parameters.

Three procedures for exclusion were tested:

- Exclude subjects with large residual error, e.g., $\eta_\varepsilon > 0$;
- Investigate $\eta_\varepsilon$ distribution to identify subjects with high error visually;
- Exclude 10%, 20%, etc., 60% of study subjects with the highest $\eta_\varepsilon$ from the data set while checking the parameter estimates and variance of $\eta_\varepsilon$. 
CM1 Method: Simulated Example

Model: two-compartment linear; once-a-day (QD) administration; relatively long (2 days) half-life, and significant drug accumulation ($C_{\text{trough}}$ accumulation ratio of about 5).

Non-compliance pattern:

- 50% of non-compliers;
- Non-compliers:
  - Missed 60% of doses (randomly);
  - Shortest drug holiday: 2 days; longest drug holiday: 6 - 18 days;
- In-patient doses (on sample days) assumed to be administered.

Subjects and samples:

- Sparse data from 400 subjects;
- All subjects: pre-dose samples on weeks 4, 6, 8, 10, 12, and 24;
- 80 PK subjects: Additional post-dose samples at about 3 and 6.5 hours post-dose on weeks 4, 6, 8, 10, 12, and 24
CM1 Results: $\eta_\varepsilon$ Distribution

The data were simulated with non-compliance and zero inter-subject variability of residual error.

The estimation assumed full compliance.

The random effect on the residual error was included and estimated by the model.
CM1 Results: Estimates of Clearance

Simulated data:

50% of non-compliers, 60% of missed doses

X% of all subjects (those with the highest $\eta_e$) were excluded from the dataset.
CM1 Results: Estimates of Clearance

Simulated data:

50% of non-compliers, 60% of missed doses.

X% of all subjects (those with the highest $\eta_c$) were excluded from the dataset.

When 50% of subjects were removed, parameters versus X curves flatten close to the true values.
CM1 Results: Estimates of $\eta_\varepsilon$ Variance

Simulated data:

50% of non-compliers, 60% of missed doses, 2-days drug holidays.

X% of all subjects (those with the highest $\eta_\varepsilon$) were excluded from the dataset.

When 50% of subjects were removed, $\eta_\varepsilon$ variance approaches zero.

Can be used for diagnostics: exclude subjects until $\eta_\varepsilon$ variance approaches zero.
CM1 Method: Range of Simulated Examples

Non-compliance patterns:
- 30%, 50%, or 100% of non-compliers
- 10 to 80% of missed doses.

Subjects and samples:
- Sparse data from 400 subjects;
- All subjects: pre-dose samples on weeks 4, 6, 8, 10, 12, and 24 or pre-dose samples on weeks 4, 8, and 24;
- In-patient doses (on sample days) assumed to be administered;
- 80 PK subjects: Additional post-dose samples randomly sampled for the time windows 2-4 hours and 5-8 hours post-dose.

Parameters of interest:
- Clearance and variance of the random effect on clearance.
CM1 Method: Summary of Results

- For the models that did not account for non-compliance, clearance estimates were biased, with bias approximately equal to the fraction of missed doses;
- Introduction of the random effect on the residual error reduced bias in many cases but did not eliminate it;
- When subjects with the highest $\eta_e$ were incrementally removed from the datasets, bias due to non-compliance was reduced or eliminated. At the same time, the variance of $\eta_e$ decreased towards zero;
- Most (but not all) removed subjects were non-compliers while most (but not all) retained subjects were compliant;
- Magnitude of bias and bias reduction using CM1 method depends on study design, fraction of non-compliers, and non-compliance patterns;
- As expected, for the datasets with all non-compliant subjects, CM1 method was not able to reduce the parameter bias.
Illustration of the problem: rich data

QD oral administration; steady-state trough values; rich data following the last dose; proportional residual error (CV=20%); simulated with non-compliance; estimated assuming full compliance.
CM2 Method: Motivation

Ref. [2] proposed to account for non-compliance using only data that follow the in-patient (compliant) doses:

- Considered a one-compartment model with absorption half-life much shorter than inter-dose interval

- In this case, concentrations that follow in-patient doses can be computed as

\[ C(t) \approx C_0 \exp(-k_e t) + A [\exp(-k_e t) - \exp(-k_a t)] \]

where the parameters \( C_0, A, k_e, \) and \( k_a \) can be estimated from only the reliable data that follow the in-patient doses. \( C_0 \) reflects the contribution of outpatient doses.

- The proposed procedure ignored all the data except those that immediately preceded or followed the in-patient (compliant) doses.

CM2 Method: Derivation

Linear Multi-Compartment Model

If the absorption half-life is short relative to the inter-dose interval, concentration-time profile following known dose can be presented as a superposition of the multi-exponential decay and concentration-time profile following the single dose:

\[
C(t) \approx \sum_i C_{0i} \exp(-k_i t) + A \left[ \sum_i \alpha_i \exp(-k_i t) - \sum_i \alpha_i \exp(-k_a t) \right]
\]

If the distribution half-lives are short relative to the inter-dose interval:

\[
C(t) \approx C_0 \exp(-k_{term} t) + A \left[ \sum_i \alpha_i \exp(-k_i t) - \sum_i \alpha_i \exp(-k_a t) \right]; \quad k_{term} = \min(k_i)
\]

Here \(k_{term}\) depends on model parameters while \(C_0\) depends on model parameters and preceding dosing history. In particular, it depends on compliance pattern of preceding doses.
CM2  Method: Key Idea

Linear Multi-Compartment Model

$C_0$ is also proportional to bioavailability of those doses.

**IDEA**

Assume full compliance for all doses, but estimate bioavailability of the outpatient doses. This would effectively estimate $C_0$.

**THEN**

- Estimation of bioavailability for ANY dosing history is equivalent to estimation of $C_0$!
- Knowledge of the specific dosing history, and analytical expressions for $C_0$ and $k_{term}$ are not required for implementation of the method. Nonmem and numerical equation solver can handle this part while required flexibility is provided by estimation of bioavailability of out-patient doses.
CM2 Method: Implementation

- Does not require an explicit expression for concentration;
- Use only data from samples immediately preceding or following the in-patient doses.
- Assume full compliance but introduce individual relative bioavailability (with high and fixed variance) for out-patient doses.
- If more than one sampling period with in-patient doses is available, allow separate bioavailability parameters for out-patient doses preceding each of these periods.

\[ F_1 = 1 \]

IF(outpatient dose) \( F_1 = 0.5 \times \exp(\eta_1) \)

....

$\text{OMEGA} 10 \text{ FIX} \quad ; \text{ETA-F1}$
CM2 Method: Advantages and limitations

- Can be applied to both linear and non-linear models when absorption and distribution half-lives are much shorter than inter-dose interval;
- Simple to implement without analytical solution of underlying equations;
- Relies on the availability of sufficient data following in-patient doses;
- For a one-compartment linear model, reduces to the method proposed in [2].
**CM2 Method: Simulated Example**

**Model:** two-compartment linear; QD administration; relatively long (2 days) half-life and significant drug accumulation ($C_{\text{trough}}$ accumulation ratio of about 5).

**Non-compliance pattern**

- 50% of non-compliers;
- Non-compliers:
  - Missed 40% of doses (randomly);
  - Shortest drug holiday: 6 days; longest drug holiday: 12 - 24 days;
- In-patient doses (on sample days) assumed to be administered.

**Subjects and samples:**

- 400 subjects;
- Pre-dose samples on weeks 1, 2, 3, and 4;
- Rich data following the last dose: 2, 4, 6, 12, 24, 72, and 144 hours.
Simulated data:

400 subjects, 50% of non-compliers, 40% of missed doses.

CM2 method was able to estimate all population model parameters without significant bias.
CM2 Method: Range of Simulated Examples

Non-compliance patterns:
- 50% or 100% of non-compliers;
- 10 to 80% of missed doses.

Subjects and samples:
- Rich data from 400 subjects;
- Pre-dose samples on weeks 1, 2, 3, and 4 (last dose);
- Rich data following the last dose: 2, 4, 6, 12, 24, 72, and 144 hours

Parameters of interest:
- All population PK parameters.
CM2 Method: Summary of Results

- CM2 method provided unbiased estimates of the population PK parameters in the datasets with any fraction of non-compliant subjects;
- CM2 method should be able to provide unbiased estimates of the individual PK parameters of all subjects, including non-compliers;
- CM2 method results do not depend on non-compliance patterns;
- Most (but not all) non-compliant subjects were estimated to have lower bioavailability during outpatient dosing.
CM1 and CM2 Methods: Comparison

CM1 and CM2 methods can be viewed as complementary, each with its own advantages and limitations:

CM2 Method:
- Provides unbiased parameter estimates for any non-compliance patterns;
- Can be applied only for the specific sampling schemes that include relatively rich data following in-patient (fully compliant) doses;

CM1 method:
- Is not based on any assumptions about the sampling schemes;
- More applicable to Phase 3 data (only sparse sampling usually available);
- Unlikely to account for the non-compliance if it is present in the majority of patients.
CM1 and CM2 Methods: Combination

- CM1 and CM2 methods can be combined for the datasets that contain mixture of sparse and rich data;
- Simulations confirmed that combined CM1/CM2 method provided better results than each of them separately;
- Possible extension: apply CM2 method only to subjects with high residual error (identified by CM1 procedure).
Conclusions

For a number of simulated datasets with various sampling schemes and various fractions of non-compliant patients, the proposed methods allowed to identify subjects with non-compliance and to obtain the unbiased estimates of model parameters;

These methods can be used to evaluate the influence of non-compliance on the population PK parameter estimates;

Real-life performance of the methods (especially CM1) can be influenced by the underlying PK model, inter-occasion variability of model parameters, dosing and sampling schedules, non-compliance prevalence and patterns.