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Assessment of Bioequivalence with Dropout Subjects in 3×3 and 3×2 Crossover Design

Seoung-gon Ko[1] and Hyun Sook Oh[2]

ABSTRACT

Oh et al.(1999) proposed 3×2 crossover design for assessing bioequivalence when two new generic drug formulations and an innovator are simultaneously considered. This design is not only more efficient than 3×3 one, proposed by Lee et al.(1998), in practical sense, but also more ethical in medical sense. However, the general statistical methods are not directly applicable to both designs when subjects are dropped out in the experiment, even though it is always possible in bioavailability and bioequivalence studies because of some administrative and economic reasons. In this research we propose an inference to drug effects when subjects are dropped out in the planed-for 3×3 and 3×2 crossover experiments. An example is given for illustration.

Key Words : Bioequivalence, Crossover Design, Balanced Incomplete Block Design, Dropout subjects

1. INTRODUCTION

A crossover design is a modified randomized block design in which each subject receives more than one treatment at different periods and favourably recommended by the U.S. and Korean Food and Drug Administration(FDA). Currently, 2×2 crossover design is the standard method to assess bioequivalence between two drug products, for example, generic(test :T) versus innovator(reference :R), and is described as follows. Subjects are randomly assigned to each of two sequences of drug formulations. Subjects in sequence 1 receives a drug or drug formulation R at the first dosing period and then cross over to receive a drug or drug formulation T at the second dosing period, while subjects in sequence 2 receive treatments in the order of T and R at two dosing periods.

[1]Department of Applied Statistics, Kyungwon University, Sungnam 461-701, Korea
[2]Department of Applied Statistics, Kyungwon University, Sungnam 461-701, Korea

In recent years the developments of the drugs with the different dosage containing the same active ingredients are widely accepted in pharmacokinetic area. Since assessing bioequivalence of a generic drug with the innovator is required prior to distribute in markets, bioavailablity/bioequivalence studies in comparing several generic drugs simultaneously with the innovator is highly interested in. In such circumstance, the KFDA announces officially the partial acceptance regulation with the bioequivalence results from 3×3 Latin-squred crossover design when the generic drugs containing the same active ingredients and produced by the same company are compared with an innovator in an experiment.

Lee et al.(1998), motivated from this new policy, proposed an example for assessing bioequivalence using 3×3 crossover design which is a simple extension of the standard 2×2 one and suggested $k \times k$ experiments as a further extension. Oh et al.(1999) discussed Lee et al.'s work in both statistical and medical point of view and propose new 3×2 one with an idea of balanced incomplete blocks(BIB) allowing not only shorten total experimental period of human entry by using just one washout period but also less blood samples from a human subject by using just two periods. However, both designs have analytic drawback with dropout subjects(Oh et al.(1999)).

The purpose of this paper is to suggest a statistical analysis for incomplete or unbalanced data, mainly caused by dropout subjects, from both 3×3 and 3×2 crossover designs. The main results are described in section 2 and section 3. Section 4 includes an example which demonstrates derived results.

2. 3×3 Crossover Design

For two new test drugs or drug formulations(say, T_1 and T_2, respectively) and a reference drug(R), y_{ijk} denotes the bioavailability of i^{th} subject in k^{th} sequence or group and j^{th} period and assume that $n_k, k = 1, 2, 3$, subjects in k^{th} sequence are available as indicated in [Table 1] where $y_{.jk} = \sum_{i=1}^{n_k} y_{ijk}$, $y_{.j.} = \sum_{k=1}^{3} y_{.jk}$, $y_{..k} = \sum_{j=1}^{3} y_{.jk}$, and $y_{...} = \sum_{j=1}^{3} \sum_{k=1}^{3} y_{.jk}$ for $j = 1, 2, 3$ and $k = 1, 2, 3$. We assume that there is no carryover effects, since it is possible to set washout period long enough. Then, the observed data can be described as model (2.1) where μ, G_k, P_j , $F_{(j,k)}$ denote overall mean, sequence effect, period effect and drug effect,respectively, and satisfy (2.2) and (2.3).

$$
\begin{aligned}
y_{ijk} &= \mu + G_k + S_{i(k)} + P_j + F_{(j,k)} + \epsilon_{ijk}, \qquad (2.1)\\
&\quad i = 1, 2, \ldots n_k,\ j = 1, 2, 3,\ k = 1, 2, 3\\
&\quad \text{where } S_{i(k)} \sim iid\, N(0, \sigma_S^2),\ \epsilon_{ijk} \sim iid\, N(0, \sigma_e^2),\\
&\qquad \text{and independent each other for all } i, j, k
\end{aligned}
$$

$$
F_{(j,k)} = \begin{cases} F_R & \text{for (j,k) = (1,1), (2,2), (3,3),} \\ F_{T_1} & \text{for (j,k) = (2,1), (3,2), (1,3),} \\ F_{T_2} & \text{for (j,k) = (3,1), (1,2), (2,3)} \end{cases} \qquad (2.2)
$$

$$
\sum_j P_j = 0,\ \sum_k G_k = 0,\ \sum_j \sum_k F_{(j,k)} = 0 \qquad (2.3)
$$

Table 1 : 3 ×3 Crossover Design

Sequence \ Period	I	II	III	Total
I	R $y_{111}, \cdots, y_{n_1 11}$ $(y_{.11})$	T_1 $y_{121}, \cdots, y_{n_1 21}$ $(y_{.21})$	T_2 $y_{121}, \cdots, y_{n_1 21}$ $(y_{.21})$	$y_{..1}$
II	T_2 $y_{112}, \cdots, y_{n_2 12}$ $(y_{.12})$	R $y_{122}, \cdots, y_{n_2 22}$ $(y_{.22})$	T_1 $y_{132}, \cdots, y_{n_2 32}$ $(y_{.32})$	$y_{..2}$
III	T_1 $y_{113}, \cdots, y_{n_3 13}$ $(y_{.13})$	T_2 $y_{123}, \cdots, y_{n_3 23}$ $(y_{.23})$	R $y_{133}, \cdots, y_{n_3 33}$ $(y_{.33})$	$y_{..3}$
Total	$y_{.1.}$	$y_{.2.}$	$y_{.3.}$	$y_{...}$

When $n_k \neq n$ in the model (2.1), $E(MS_{Intra}) \neq \sigma_e^2$, so that analysis of variance procedure recommended by FDA and KFDA is not applicable to assess bioequivalence(Oh et. al(1999)). Recall that MS_{Intra} is an estimator of σ_e^2 derived in usual ANOVA Table for model (2.1). Confidence interval approaches for pairwise differences among drug effects, $F_R - F_{T_1}$, $F_R - F_{T_2}$ and $F_{T_1} - F_{T_2}$, are another possibility and $F_{T_1} - F_{T_2}$, however, is not our main interests because it shows for bioequivalence of two new formulations which is not certified for usefulness and/or safety. The expected values of $\bar{F}_R$, $\bar{F}_{T_1}$, and $\bar{F}_{T_2}$, sample means

of respective drugs in an experiment, are given in [Table 2] and the distributions of unbiased estimators for $F_R - F_{T_1}$ and $F_R - F_{T_2}$ are defined in (2.4) so that they are linear combinations of $\bar{y}_{.jk}$. Note here that estimatiors are variance balanced.

Table 2 : Estimators of drug effects and their expected values in 3x3 Crossover Design

Drug Effects	Estimator	Expected Value
R	$\bar{F}_R = \frac{1}{3}(\bar{y}_{.11} + \bar{y}_{.22} + \bar{y}_{.33})$	$E(\bar{F}_R) = \mu + F_R$
T_1	$\bar{F}_{T_1} = \frac{1}{3}(\bar{y}_{.13} + \bar{y}_{.21} + \bar{y}_{.32})$	$E(\bar{F}_{T_1}) = \mu + F_{T_1}$
T_2	$\bar{F}_{T_2} = \frac{1}{3}(\bar{y}_{.12} + \bar{y}_{.23} + \bar{y}_{.31})$	$E(\bar{F}_{T_2}) = \mu + F_R$

$$\hat{F_R} - \hat{F_{T_i}} = \bar{F}_R - \bar{F}_{T_i} \sim N(F_R - F_{T_i}, \frac{2m}{9}\sigma_e^2),\ i = 1, 2 \qquad (2.4)$$

$$\text{where } m = \frac{1}{n_1} + \frac{1}{n_2} + \frac{1}{n_3}$$

Based on the result (2.4), the bioequivalence is assessed by comparing between relative 90% confidence interval for each difference and equivalence interval, for example, (−20%, 20%). However, σ_e^2 is generally unknown and the estimator σ_e^2 from usual ANOVA table, call it MS_{Intra}, is biased in part from the fact that MS_{Intra} is a biased estimator of σ_e^2(Oh et. al(1999)). Therefore, our first claim is to find an unbiased estimator of σ_e^2.

The expected value of sum of square of all possible pairwise difference is defined as in (2.5) by the fact that $E(y_{ijk} - y_{ij'k})^2 = (P_j - P_{j'} + F_{(j,k)} - F_{(j',k)})^2 + 2\sigma_e^2,\ 1 \le j \ne j' \le 3$(Koch(1967)).

$$E(\sum_{k=1}^{3}\sum_{i=1}^{n_k}\sum_{j\neq j'}\frac{(y_{ijk} - y_{ij'k})^2}{3n_k}) = 6\sigma_e^2 + (P_1 - P_2)^2 + (P_2 - P_3)^2 + (P_1 - P_3)^2 \qquad (2.5)$$
$$+ (F_R - F_{T_1})^2 + (F_{T_1} - F_{T_2})^2 + (F_R - F_{T_2})^2$$

Also, it is easily verified that mean square of the period effect, MS_P, and mean square of the drug effect, MS_D are as in (2.6) and their expected values are as in (2.7) with $\bar{P}_j = \frac{1}{3}\sum_{k=1}^{3}\bar{y}_{.jk}$. Hence, unbaised estimator of σ_e^2 is defined as in (2.8) and it is further simplified to (2.9) with $d_{i1k} = y_{i1k} - y_{i2k}$, $d_{i2k} = y_{i2k} - y_{i3k}$, and $d_{i3k} = y_{i1k} - y_{i3k}$.

$$
\begin{aligned}
MS_P &= \sum_i \sum_j \sum_k (\bar{y}_{.j.} - \bar{y}_{...})^2 \\
&= \frac{3}{2m}[(\bar{P}_1 - \bar{P}_2)^2 + (\bar{P}_2 - \bar{P}_3)^2 + (\bar{P}_1 - \bar{P}_3)^2] \qquad (2.6) \\
MS_D &= \frac{3}{2m}[(\bar{F}_R - \bar{F}_{T_1})^2 + (\bar{F}_{T_1} - \bar{F}_{T_2})^2 + (\bar{F}_R - \bar{F}_{T_2})^2] \qquad (2.7)
\end{aligned}
$$

$$
\begin{aligned}
E(MS_P) &= \sigma_e^2 + \frac{3}{2m}[(P_1 - P_2)^2 + (P_2 - P_3)^2 + (P_1 - P_3)^2] \\
E(MS_D) &= \sigma_e^2 + \frac{3}{2m}[(F_R - F_{T_1})^2 + (F_{T_1} - F_{T_2})^2 + (F_R - F_{T_2})^2] \qquad (2.8)
\end{aligned}
$$

$$
\hat{\sigma_e^2} = \frac{3}{18 - 4m}[\sum_{k=1}^{3} \sum_{i=1}^{n_k} \sum_{j \neq j'} \frac{(y_{ijk} - y_{ij'k})^2}{3n_k} - \frac{2m}{3}(MS_P + MS_D)] \qquad (2.9)
$$

$$
\begin{aligned}
\hat{\sigma_e^2} &= \frac{1}{18 - 4m}[\sum_{k=1}^{3} \sum_{l=1}^{3} \frac{S_{lk}^2}{n_k} + mSS_c], \qquad (2.10) \\
&\text{where } S_{lk}^2 = \sum_{k=1}^{3} (d_{ijk} - \bar{d}_{lk})^2,\ \bar{d}_{lk} = \frac{\sum_i^{n_k} d_{ilk}}{n_k},\ l = 1, 2, 3 \text{ and} \\
&SS_C = \frac{1}{3m}[(\bar{d}_{31} - \bar{d}_{22} - \bar{d}_{13})^2 + (\bar{d}_{21} - \bar{d}_{12} - \bar{d}_{33})^2 + (\bar{d}_{11} - \bar{d}_{32} - \bar{d}_{23})^2]
\end{aligned}
$$

SS_C in (2.9) denotes sum of squares of two orthogonal contrasts in [Table 3] and therefore it has chi-square distribution with 2 degrees of freedom. Above all, it is equal to sum of square for carryover effects in the model with it(Ko and Oh(1999)). [Theorem 1] shows the independence of SS_C and the term, $\sum_{k=1}^{3} \sum_{l=1}^{3} \frac{S_{lk}^2}{n_k}$.

Table 3 : Coefficients of $\bar{y}_{.jk}$ in two contrasts

Sequence	Period			Period		
	I	II	III	I	II	III
I	-1	-1	2	1	-1	0
II	-1	2	-1	-1	0	1
III	2	-1	-1	0	1	-1

Theorem 1. $\sum_{k=1}^{3}\sum_{l=1}^{3}\frac{S_{lk}^2}{n_k}$ and $\bar{d}_{lk}$ are independent for $l = 1,2,3$ and $k = 1,2,3$.

Proof. For each k,

$$\begin{aligned}\sum_{l=1}^{3} S_{lk}^2 &= \frac{3}{2}\sum_{i=1}^{n_k}(d_{i1k}-\bar{d}_{1k})^2+\frac{1}{2}\sum_{i=1}^{n_k}[(d_{i2k}+d_{i3k})-(\bar{d}_{2k}+\bar{d}_{3k})^2]\\ &\equiv \frac{3}{2}S_{1k}^2+\frac{1}{2}S_{(2k+3k)}^2\end{aligned}$$

The term $\frac{3}{2}S_{1k}^2$ and $\bar{d}_{1k}$ are independent. Although S_{1k}^2, S_{2k}^2, and S_{3k}^2 are not independent each other, $d_{i2k}+d_{i3k}$ and $\bar{d}_{2k}+\bar{d}_{3k}$ are independent with $\bar{d}_{1k}$ for all i. Similarly, $\sum_{l=1}^{3} S_{lk}^2$ is also decomposed into the form of $S_{2k}^2+S_{(1k+3k)}^2$ and it can be shown that $\bar{d}_{2k}$ and $\bar{d}_{3k}$ are independent with $\sum_{l=1}^{3} S_{lk}^2$. Since this is true for any k, the result follows. □

The estimated unbiased estimator in (2.9) has chi-square distribution by [Theorem 1] and the approximate degree of freedom f by Satterthwaite approximation is given in (2.10).

$$f = \left[\frac{(18-4m)\hat{\sigma_e^2}}{\sum_{k=1}^{3}[\frac{(\frac{3}{2n_k}S_{1k}^2)^2}{n_k-1}+\frac{(\frac{1}{2n_k}S_{(2k+3k)}^2)^2}{n_k-1}]+\frac{mSS_C{}^2}{2}}\right] \tag{2.11}$$

where$[\cdot]$denotes the nearest integer.

Theorem 2. $\hat{\sigma_e^2}$ and $\bar{F}_R-\bar{F}_{T_i}$, $i = 1,2$, are independent.

Proof. By [Table 2] and (2.9), $\bar{F}_R-\bar{F}_{T_i}$, $i = 1,2$, are a linear function of $\{\bar{d}_{lk}, l = 1,2,3, k = 1,2,3\}$, for example, $\bar{F}_R-\bar{F}_{T_1} = \frac{1}{3}(\bar{d}_{11}+\bar{d}_{22}-\bar{d}_{33})$. Therefore, the first term in (2.9) and $\bar{F}_R-\bar{F}_{T_i}$, $i = 1,2$ are independent by the result of [Theorem 1]. The second term in (2.9), SS_C is also independent of $\bar{F}_R-\bar{F}_{T_i}$, $i = 1,2$ because SS_C is a function of orthogonal contrasts in [Table 3] and these orthogonal contrasts is independent of $\bar{F}_R-\bar{F}_{T_i}$, $i = 1,2$. Then, the result follows clearly. □

By the above theorems, $(1-\alpha)100\%$ confidence intervals for Dunnett's mul-

tiple t-test is given in (2.11) where $d(\frac{\alpha}{2}, 2, f)$ is the value for Dunnet's multiple comparison at significance $\frac{\alpha}{2}$ and degree of freedom 2 and f.

$$|\bar{F}_R - \bar{F}_{T_i}| \pm d(\frac{\alpha}{2}, 2, f)\sqrt{\frac{2m}{9}\hat{\sigma}_e^2}, \quad i = 1, 2 \tag{2.12}$$

3. 3 × 2 BIB Design

The three-sequence two-period crossover design is obtained by considering only first two periods in 3 × 3 crossover design and can be described by model (2.1) except $j = 1, 2$ instead of $j = 1, 2, 3$ and the dosing drug formulations of sequence I, II and III are (R, T_1), (T_2, R), and (T_1, T_2), respectively. Since the efficiency of this design is discussed in Oh et al.(1999), the confidence interval approaches with dropout subjects are mainly discussed in this section. In section 2, an unbiased estimator of the drug effect is simply the weighted sample mean of corresponding sequence-period cells, but in this case some adjustments are needed because drug effects and period effects are confounded each other. Firstly, the estimators of pairwise differences among drug effects and their distributions are defined as (3.1) with $\delta_k = \bar{y}_{.1k} - \bar{y}_{.2k}$. Notice here that this design is not variance balanced, in other words, the precision of the estimators for pairwise difference among drug effects are not equal. It suggests to us that more careful administration is needed for 3 × 2 crossover design. However, the precision of assessing bioequivalence may not be much different when the number of subjects are large and the number of dropout subjects are relatively small.

$$\begin{aligned}
\hat{F}_R - \hat{F}_{T_1} = \frac{1}{3}(2\delta_1 - \delta_2 - \delta_3) &\sim N(F_R - F_{T_1}, \frac{2\sigma_e^2}{9}(\frac{4}{n_1} + \frac{1}{n_2} + \frac{1}{n_3})) \\
\hat{F}_R - \hat{F}_{T_2} = \frac{1}{3}(\delta_1 - 2\delta_2 + \delta_3) &\sim N(F_R - F_{T_2}, \frac{2\sigma_e^2}{9}(\frac{1}{n_1} + \frac{4}{n_2} + \frac{1}{n_3})) \\
\hat{F}_{T_1} - \hat{F}_{T_2} = \frac{1}{3}(-\delta_1 - \delta_2 + 2\delta_3) &\sim N(F_R - F_{T_1}, \frac{2\sigma_e^2}{9}(\frac{1}{n_1} + \frac{1}{n_2} + \frac{4}{n_3}))
\end{aligned} \tag{3.1}$$

Now, consider the expected value of i^{th} subject's difference between each period for deriving an unbaised estimator of σ_e^2.

$$E\left(\sum_{k=1}^{3}\sum_{i=1}^{n_k}\frac{(y_{i1k}-y_{i2k})^2}{3n_k}\right) = 2\sigma_e^2 \quad + \tag{3.2}$$
$$(P_1-P_2)^2+\frac{1}{3}(F_R-F_{T_1})^2 \quad + \quad \frac{1}{3}(F_R-F_{T_2})^2+\frac{1}{3}(F_{T_1}-F_{T_2})^2$$

In (3.1), $E(\hat{P}_1-\hat{P}_2)^2=(P_1-P_2)^2+\frac{2m}{9}\sigma_e^2$ since the unbiased estimator of P_1-P_2 is $\frac{1}{3}\sum_{k=1}^{3}(\bar{y}_{.1k}-\bar{y}_{.2k})$ and it's variance is $\frac{2m}{9}\sigma_e^2$. The estimators of remaining drug effects are similarly done and the resulting unbiased estimator of σ_e^2,$\hat{\sigma_e^2}$, is given in (3.2) and it is further simplified to (3.3) with $d_{i1k}=y_{i1k}-y_{i2k}$.

$$\hat{\sigma_e^2} = \frac{3}{(6-2m)}\left\{\sum_{k=1}^{3}\sum_{i=1}^{n_k}\frac{(y_{i1k}-y_{i2k})^2}{3n_k}\right\} - \tag{3.3}$$
$$\frac{1}{9(6-2m)}\left\{4\sum_{k=1}^{3}(\bar{y}_{.1k}-\bar{y}_{.2k})^2+5\sum_{k=1}^{3}\sum_{k<k'}(\bar{y}_{.1k}-\bar{y}_{.2k})(\bar{y}_{.1k'}-\bar{y}_{.2k'})\right\}$$

$$\begin{aligned}\hat{\sigma_e^2} &= \frac{1}{(6-2m)}\left[\sum_{k=1}^{3}\sum_{i=1}^{n_k}\frac{d_{i1k}^2}{n_k}-\sum_{k=1}^{3}\bar{d}_{1k}^2\right] \\ &= \frac{1}{(6-2m)}\sum_{k=1}^{3}\frac{S_{1k}^2}{n_k}\end{aligned} \tag{3.4}$$

As before, $\hat{\sigma_e^2}$ is approximately distributed as chi-square with degree of freedom f' given in (3.4). Also, $\hat{\sigma_e^2}$ is independent to all of pairwise differences among drug effects because S_{1k}^2 is independent to $\bar{d}_{11}$, $\bar{d}_{12}$ and $\bar{d}_{13}$.

$$f' = \left[\frac{(6-2m)\hat{\sigma_e^2}}{\sum_{k=1}^{3}\frac{(S_{1k}^2/n_k)^2}{n_{k-1}}}\right] \tag{3.5}$$
where $[\ \cdot\ ]$ denotes the nearest integer.

Finally, Dunnett's $100(1-\alpha)\%$ confidence intervals are as in (3.5)where $d(\frac{\alpha}{2},2,f')$ is similarly defined as in (2.10).

$$|\hat{F}_R - \hat{F}_{T_i}| \pm d(\frac{\alpha}{2}, 2, f')\sqrt{\hat{Var}(\hat{F}_{T_i} - \hat{F}_R)}, i = 1, 2 \tag{3.6}$$

4. An Example and Concluding Remarks

[Table 4] shows Ondensetron example (Lee et al.(1998)) with Zofran Tablet (4mg) as a reference drug and Vominon 4mg and Vominon 8mg as test drugs. In this experiment, twenty one healthy Korean male subjects received each formulation at the Ondansetron dose of 8mg and plasma concentrations of Ondeansetron

Table 4 : AUC values for Ondensentron example (Lee et al.(1998), P40)

Sequence \ Period	I	II	III
	R	T_1	T_2
	12176	11424	14319
	10913	12114	11640
	11004	11802	11234
I	14377	15322	13700
	15110	18308	18598
	21644	23917	24176
	11367	10524	13224
	T_2	R	T_1
	12153	9771	12794
	14121	12292	18396
	6339	7860	7907
II	20062	17667	23253
	12306	17170	15114
	19123	15472	17058
	20043	15816	19540
	T_1	T_2	R
	8261	11015	9030
	16785	15493	19305
	14847	13936	12399
III	6692	6938	7677
	11060	13337	12348
	13196	11538	12685
	14008	12906	14744

were monitored by HPLC for over a period of 12 hr after the administration. In this experiment, all planed-for data are actually observed and both test drugs were are bioequivalent to a control one. We assume here, however, last two subjects in sequence II and the last subject in sequence I are dropped out for the purpose of demonstrating derived results.

[Table 5] summarizes relative 90% confidence intervals for differences between each test drug effects and the reference one and the bioequivalence could be determined by comparing each with equivalence interval (-20, 20) based on 20/20 rule, which admits the bioequivalence of two drug formulations when the average bioavailability of the test formulation is within ±20% of that of the reference one with a certain assurance. It shows all intervals are within $(-20, 20)$ except the estimated confidence interval for $F_R - F_{T_2}$ in 3×2 unbalanced case. Although this results depends on which and how many subjects are missing, we should notice that imbalance is more critical to 3×2 case than 3×3 one.

Table 5 : Bioequivalence Results for Ondensatron example

Designs	Unbiased $\hat{\sigma}_e^2(df)$	Dunnett's 90% C.I.
3 × 3 (Balanced Data)	2217135 (38)	T_1 : (-0.24, 15.54)
		T_2 : (-2.41, 13.36)
3 × 3 (Unbalanced Data)	2403350 (13)	T_1 : (-2.92, 16.82)
		T_2 : (-4.50, 15.23)
3 × 2 (Balanced Data)	2634156 (18)	T_1 : (-1.41, 17.27)
		T_2 : (-0.70, 17.98)
3 × 2 (Unbalanced Data)	2637570 (12)	T_1 : (-9.38, 19.74)
		T_2 : (-7.56, 22.68)

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