

# Analysis of Non-Pivotal Bioequivalence Studies Submitted in Abbreviated New Drug Submissions for Delayed-Release Drug Products

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**Abstract** - The US FDA's rule on "Requirements for Submission of Bioequivalence Data" requiring submission of all bioequivalence (BE) studies conducted on the same formulation of the drug product submitted for approval was published in Federal Register in January 2009. With the publication of this rule, we evaluated the impact of data from non-pivotal BE studies in assessing BE and identified the reasons for failed *in vivo* BE studies for generic oral delayed-release (DR) drug products only. We searched the Agency databases from January 2009 to December 2016 to identify Abbreviated New Drug Applications (ANDAs) submitted for DR drug products containing non-pivotal BE studies. Out of 202 ANDAs, 43 ANDAs contained 102 non-pivotal BE studies. Forty-nine non-pivotal BE studies were conducted on the to-be-marketed (TBM) formulation and 53 were conducted on formulations different from the TBM formulation. These experimental formulations primarily differed in the ratio of components of the enteric coating layer and/or amount (i.e., %w/w) of enteric coating layer. Of the 49 non-pivotal BE studies conducted on the TBM formulation, 41 failed to meet the BE acceptance criteria. The majority of failed non-pivotal BE studies on the TBM DR generic products had insufficient power, which was expected as these studies are exploratory in nature and not designed to have adequate power to pass the BE statistical criteria. In addition, among the failed non-pivotal BE studies on the TBM DR generic products, the most commonly failing pharmacokinetic parameter was  $C_{max}$ . The data from these non-pivotal BE studies indicate that inadequate BE study design can lead to failure of the BE on the same formulation. Also, the non-pivotal BE studies on formulations different from the TBM formulation help us link the formulation design to the product performance *in vivo*.

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## INTRODUCTION

In the United States, the applicants seeking approval to market a generic drug product must demonstrate that the to-be-marketed (TBM) generic formulation is bioequivalent to the corresponding reference listed drug (RLD) product and conduct the bioequivalence (BE) studies using the corresponding reference standard (RS) drug product listed in the Orange Book (1). Thus, bioequivalence (BE) testing is a critical component of Abbreviated New Drug Application (ANDA) submissions. The BE testing also plays an important role in the drug development process when the TBM formulations are selected. Prior to July 2009, to support the ANDA approval, the applicants were required to submit results of passing adequately powered pivotal BE studies conducted on the TBM generic formulation only, demonstrating that TBM generic formulation meets the BE criteria. Thus, the ANDA applicants typically did not submit non-pivotal

BE studies conducted on same drug product formulation, including studies that failed to demonstrate that the TBM generic formulation is bioequivalent to the corresponding RS drug product.

In January 2009, the United States Food and Drug Administration (US FDA) published the "Requirements for Submission of Bioequivalence Data" (the BE data rule) in the Federal Register with an effective date of July 15, 2009 (2). According to this rule, the ANDA applicants are required to submit data from all BE studies including those that failed on the "TBM formulation" and "formulations considered

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to be the same drug product formulation as the TBM formulation.” This requirement includes both *in vivo* and *in vitro* testing conducted to demonstrate BE. The data on non-pivotal BE studies must be submitted as either a complete study report or a summary report of the BE data. The term “same drug product formulation” means the formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval but are similar enough to be relevant to the Agency’s determination of BE (2, 3).

The BE data rule companion guidance [FDA Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs (May 2011)] provides information on the types of ANDA submissions covered by the BE data rule, a recommended format for summary reports of BE studies, and the types of drug formulations that FDA considers to be the “same” drug product formulation for different dosage forms based on differences in composition. The guidance explains that the following ANDA submissions must include all BE studies conducted on the same drug product formulation: (1) original ANDAs, (2) ANDA amendments, (3) ANDA supplements that require BE studies under 21 C.F.R. § 320.21(c), (4) ANDAs submitted under a suitability petition, and (5) ANDA annual reports. The guidance also addresses differences in composition to consider when comparing the drug product formulations to determine whether or not the experimental formulations used in non-pivotal BE studies are considered same as the TBM formulation (4). For specific differences in composition to consider when comparing the drug product formulations for various dosage forms (i.e., immediate-release, extended-release, and semisolid dosage forms), the readers are directed to above mentioned guidance.

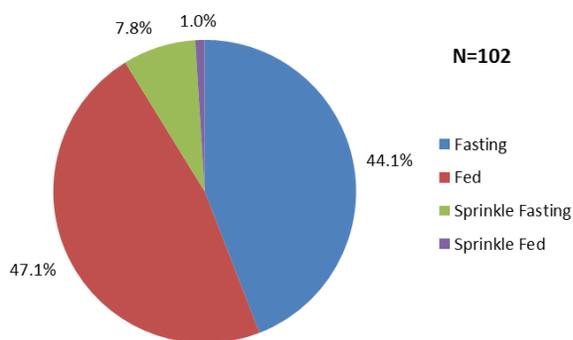
The data from non-pivotal BE studies is not only important to Agency’s assessment of BE for a specific generic drug product but is also helpful in increasing the Agency’s understanding of generic drug development and how changes in components and composition may affect formulation performance (5). This article focuses on the non-pivotal *in vivo* BE studies for generic oral delayed-release (DR) drug products only. The paper discusses the potential reasons for failed non-pivotal BE studies and the impact of non-pivotal *in vivo* BE studies in assessing the BE via selected case studies from ANDAs for oral DR drug products only.

## METHODS

With the publication of “the BE data rule” in Federal Register, the Agency databases were searched from January 2009 to December 2016 to identify the ANDAs submitted for DR drug products containing non-pivotal BE studies. Per FDA’s Submission of Summary Bioequivalence Data for ANDAs guidance, “the percentage (%) differences for non-release and release controlling excipients between the TBM formulation (A) and experimental formulation (B)” were calculated  $[(A-B)/A \times 100]$  to determine whether or not the formulations used in the submitted studies were considered the same as the TBM formulation. The potential reason (s) for failed non-pivotal BE studies conducted on the TBM were determined.

## RESULTS

The analysis of collected data showed that out of 202 ANDAs, 43 ANDAs contained 102 non-pivotal BE studies. The non-pivotal BE studies were designed as crossover studies evaluating 1-2 formulations/study under fasting, fed, sprinkle fasting, and sprinkle fed conditions. The number of subjects used in the non-pivotal BE studies ranged from 5-86. Out of 102 non-pivotal BE studies, 45 (44%) studies were conducted under fasting conditions, 48 (47%) were conducted under fed conditions, 8 (8%) were conducted under sprinkle fasting conditions, and 1 (1%) was conducted under sprinkle fed conditions (Figure 1).

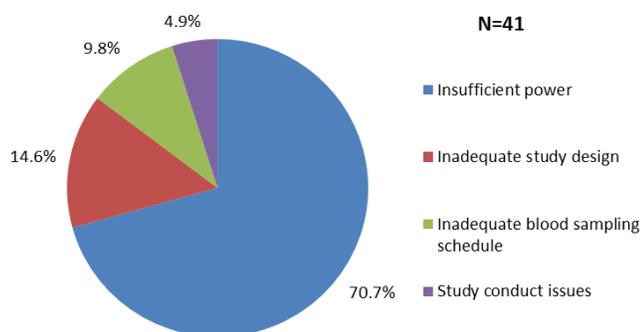


**Figure 1.** Distribution of non-pivotal BE studies based on the study type.

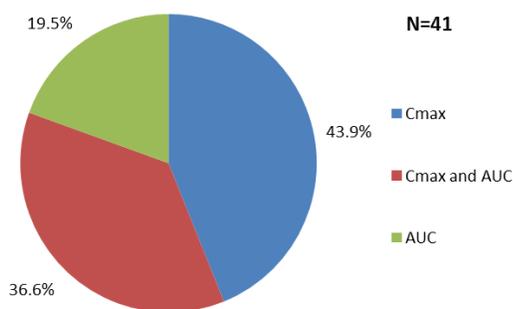
Of the 102 non-pivotal BE studies, 49 (48%) were conducted on the TBM formulation or formulations considered to be same as the TBM formulation, and 53 (52%) were conducted on formulations different from the TBM formulation. Fifty-three (53) BE studies evaluated 64 different experimental

formulations, which primarily differed in the ratio of components of the enteric coating layer and/or amount (i.e., %w/w) of enteric coating layer with respect to their core or seal coated pellet/tablet. Some of the experimental formulations identified as “same drug product formulation” by the ANDA applicants in these 53 BE studies are actually “not considered to be the same” based on the FDA guidance (May 2011) mentioned above.

Out of 49 non-pivotal BE studies conducted on the TBM formulation, 41 BE studies did not meet the BE criteria either due to (i) insufficient power (inadequate number of subjects) [29 studies (71%)], (ii) failure to use appropriate study design [6 studies (15%)], (iii) inadequate blood sampling schedule [4 studies (10%)], or (iv) study conduct issues (clinical and/or bioanalytical) [2 studies (5%)] (Figure 2). As shown in Figure 3, among the 41 failed BE studies conducted on the TBM formulation, 18 (44%) failed solely due to  $C_{max}$ , 15 (37%) failed due to both  $C_{max}$  and AUC, and 8 (19%) failed due to AUC only.



**Figure 2.** Distribution of failed non-pivotal BE studies conducted on the TBM formulation based on reasons of failure.



**Figure 3.** The percentage of failing PK parameter (s) for non-pivotal BE studies conducted on the TBM formulation

The reasons of failure of non-pivotal BE studies conducted on the TBM formulation are illustrated through the representative case studies below. In addition, we have presented the selected case studies conducted on the formulations different from the TBM formulation for generic DR products below, to illustrate how non-pivotal BE studies were used to guide the development of TBM formulation. It should be noted that data in below case studies has been blinded, while representing the actual scenarios observed in the submitted ANDAs.

### Case Study 1

In this case, the applicant conducted 2 pilot BE studies on the TBM formulation. The BE studies were designed as a single-dose, randomized, open-label, two-sequence, two-way crossover in 10-15 healthy adult subjects under fasting and fed conditions. The purpose of these pilot studies was to assess the BE and determine the number of subjects required to achieve sufficient power, before conducting the pivotal BE studies. In the pilot fasting study, the TBM formulation was found to be bioequivalent to the corresponding RS drug product. However, under fed conditions, the upper limit of 90% CI of  $C_{max}$  was marginally outside BE acceptance criteria of 80.0-125.0%. The results of power calculations showed that  $C_{max}$  had insufficient power due to fewer numbers of subjects completing the pilot fed BE study. Based on the promising results of the pilot BE studies, an exhibit batch was manufactured and evaluated in pivotal fasting and fed BE studies conducted on 45-55 healthy adult subjects. The pivotal BE studies met the BE acceptance criteria for  $C_{max}$  and AUC under both fasting and fed BE conditions.

### Case Study 2

To obtain approval for marketing of its generic drug product, the applicant submitted the results of pivotal fasting and fed BE studies conducted on the TBM generic formulation comparing it to the corresponding RS drug product. The results of pivotal fasting and fed BE studies were within acceptable BE limits. In addition, the applicant submitted the results of 2 failed fasting BE studies conducted on the TBM formulation.

The 1<sup>st</sup> failed fasting BE study was designed as a single-dose, two-treatment, two-way crossover study in 40 healthy adults subjects. A large number of subjects dropped out from the study, with 30 subjects completing both study periods. In this study, the 90% CI for  $C_{max}$  was not within acceptable BE limits. The failed fasting study showed good test (T)/reference

(R) ratios for AUC and  $C_{\max}$  with large intra-subject %CV (i.e., >30%). The observed power for  $C_{\max}$  indicated that the number of subjects included in the statistical analysis might not be sufficient to conclude BE.

Using the information obtained from the 1<sup>st</sup> failed fasting study, the applicant designed 2<sup>nd</sup> fasting BE study in 50 subjects with same study design. None of the subjects dropped from the study. The 2<sup>nd</sup> fasting study also failed to meet the BE limits for  $C_{\max}$  due to high intra-subject %CV observed in the study that lead to insufficient power. The data from these 2 failed fasting studies indicated that drug product under investigation is a highly variable drug product. Highly variable drugs or drug product are generally defined as those exhibiting intra-subject variability of 30% CV or greater in  $C_{\max}$  and/or AUC (6, 7).

Subsequently, the applicant conducted a 3<sup>rd</sup> fasting BE study using a partial-replicated three-way crossover design using the same number of subjects as in 2<sup>nd</sup> failed BE study. In a three-way partial replicate crossover design, the reference (R) product was given twice and the test (T) product was given once, with sequences of TRR, RTR, and RRT. In the analysis of a BE study using this design, the reference-scaled average BE (ABE) approach is used for a specific PK ( $C_{\max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ ) parameter that has a  $S_{WR}$  (within-subject variability of the reference)  $\geq 0.294$ , and unscaled ABE approach is used if  $S_{WR}$  is  $<0.294$  (6, 7). In the statistical analysis of 3<sup>rd</sup> fasting BE study, reference-scaled ABE approach was applied only for  $C_{\max}$  ( $S_{WR} > 0.294$ ), which met both acceptance criteria, as the 95% upper confidence bound was  $<0$  and the T/R geometric mean point estimate was within 0.80 and 1.25. The unscaled ABE was used for  $AUC_{0-t}$  and  $AUC_{0-\infty}$  ( $S_{WR} < 0.294$ ), for which 90% CIs met the 80-125% limits. Thus in this case, the TBM generic drug product that initially failed to meet the BE criteria using two-way crossover design under fasting conditions, subsequently met the BE limits when the power was increased by changing the study design to reference-replicated three-way crossover.

### Case Study 3

A failed BE study was conducted on the TBM formulation under fed conditions. The BE study was designed as a two-way crossover study in 45 healthy adult subjects. Per the RLD label, the  $t_{\max}$  under fed conditions is 10 hours. However, the  $t_{\max}$  range is not specified in the RLD label. Thus, the applicant collected only 2 blood samples between 10-24 hours in the failed fed BE study, which did not meet the BE

acceptance criteria for  $C_{\max}$ . The individual and mean plasma concentration profiles indicated that blood sampling times were insufficient to adequately cover the whole plasma concentration-time curve. As a result, the applicant repeated the fed BE study using the same design and number of subjects, with 7 additional blood sampling times collected between 10-24 hours to accurately capture the  $t_{\max}$  and  $C_{\max}$  of the test and reference products. The repeat fed BE study met the BE acceptance criteria for both  $C_{\max}$  and AUC. The results of this study confirmed that the 1<sup>st</sup> fed BE study failed due to an inadequate blood sampling schedule.

### Case Study 4

In this case, the applicant submitted a failed sprinkle fasting BE study conducted on the TBM formulation, which did not meet the BE acceptance criteria for both  $C_{\max}$  and AUC. The applicant mentioned that it was suspected that 1 subject took concomitant medication during ambulatory samples that could have affected the PK parameters of the study drug, leading to failure of the BE study. A definitive reason could not be determined for study failure, therefore, the applicant repeated the sprinkle fasting BE study with same study design and number of subjects, which met the BE acceptance criteria. The data from these two BE studies provided confidence that the test product formulation performance is robust *in vivo*, and the 1<sup>st</sup> study failed due to study conduct issues rather than test product formulation performance issues.

### Case Study 5

The applicant submitted two pilot BE studies evaluating 2 experimental formulations in 15-20 healthy adult subjects. The pilot BE studies were designed as three-way crossover studies, comparing the 2 experimental formulations to the corresponding RS drug product, under fasting and fed conditions. The experimental formulations differed from the TBM formulation in the ratio of excipients contained in the enteric coating layer or %w/w of enteric coat with respect to seal coated tablet. Per FDA guidance mentioned above, the experimental formulations are considered not to be same as the TBM formulation.

Prior to conducting *in vivo* BE studies, the applicant conducted *in vitro* dissolution testing on a number of experimental formulations differing in %w/w of enteric coating layer in the range of 5%-30%, comparing to the corresponding RS drug product. The results of *in vitro* dissolution studies showed a general trend of slowdown of drug release with increasing levels of enteric coating layer.

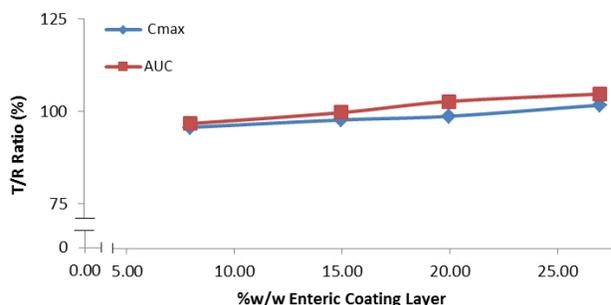
However, the *in vitro* drug release for investigated enteric coating levels (5-30% w/w) was within the acceptable ranges of applicant's proposed dissolution specifications.

From the formulations investigated during *in vitro* dissolution testing, 2 experimental formulations i.e., one closer to lower (T1) and one closer to higher (T2) range of %w/w enteric coating level were then evaluated in the pilot fasting and fed BE studies. Both experimental formulations met the BE acceptance criteria under fasting and fed conditions. However, under fed conditions, for experimental formulation T1, the 90% CIs for  $C_{max}$  and AUC were borderline. The results of pilot BE studies on experimental formulations showed that increasing the amount of coating layer improves the T/R ratio (i.e., closer to 1.0) under fed conditions for both  $C_{max}$  and AUC. The experimental formulation T2 was selected for further optimization. The TBM and T2 formulations had the same %w/w of enteric coating layer, however, these formulations differed with respect to the ratio of release and non-release controlling excipients contained in the enteric coating layer. The T2 formulation is considered not to be the same formulation as TBM formulation per FDA guidance mentioned above. The TBM formulation met the BE criteria under both fasting and fed conditions in the pivotal BE studies. The results of BE studies on the TBM and T2 formulations suggest that change in the ratio of excipients in the enteric coating layer in the studied range is unlikely to have an impact on the BE.

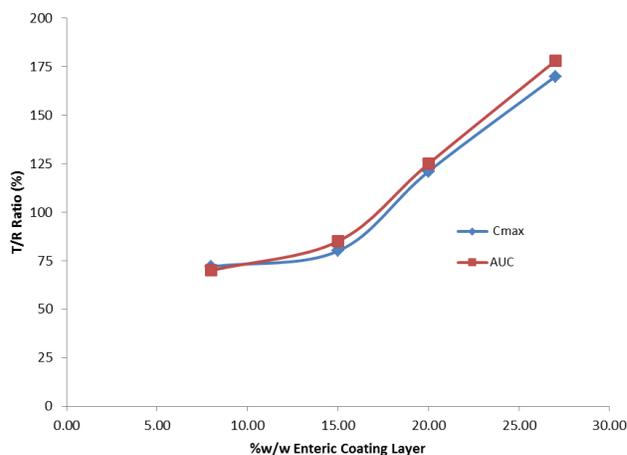
### Case Study 6

Eight pilot BE studies (4 fasting, 4 fed) conducted on 4 experimental formulations were submitted. Experimental formulations differed from the TBM formulation in the amount of excipients in the enteric coating layer and %w/w of enteric coat with respect to seal coated pellets. As opposed to Case Study 5, in this case, the applicant did not evaluate the performance of experimental formulations in the *in vitro* dissolution studies prior to conducting *in vivo* BE studies. The *in vivo* BE studies were conducted to understand the impact of change in %w/w of enteric coating layer on the PK parameters of the generic drug product, under fasting and fed conditions. No significant change in T/R ratios for  $C_{max}$  and AUC was observed with increase in %w/w of enteric coating layer in the studied range under fasting conditions (Figure 4 – not actual data from the ANDA). Whereas, a significant effect was observed under fed conditions with respect to T/R ratios of  $C_{max}$  and AUC (Figure 5 – not actual data from the ANDA). Based on the

results of pilot BE studies, the optimized TBM formulation with a %w/w enteric coating layer in the studied range having a  $C_{max}$  and AUC T/R ratios closer to 1.0 was selected. The optimized TBM formulation met the BE criteria under both fasting and fed conditions



**Figure 4.** Effect of %w/w enteric coating layer on T/R ratios of  $C_{max}$  and AUC under fasting conditions



**Figure 5.** Effect of %w/w enteric coating layer on T/R ratios of  $C_{max}$  and AUC under fed conditions

### Case Study 7

In this case also, the applicant conducted pilot fasting and fed BE studies to understand the impact of enteric coating weight on *in vivo* performance. The applicant used a slightly different approach than outlined in Case Study 6 above. Two sets of pilot BE studies were conducted. In the 1<sup>st</sup> set of pilot BE studies, two experimental formulations (T1 and T2) differing in %w/w of enteric coating layer were evaluated under fasting and fed conditions. Both experimental formulations did not meet the BE acceptance criteria under fasting and fed conditions. A significant impact of difference in enteric coating layer weight build up was observed only under fed conditions i.e., higher coating weight build up (T2) showed higher T/R ratios

for both  $C_{max}$  and AUC compared to lower coating weight build up (T1). Based on the outcome of the 1<sup>st</sup> set of fasting and fed BE studies, the applicant conducted a 3-way pilot crossover fed BE study, comparing experimental formulations, T3 and T4 to the corresponding reference product. The order of %w/w of enteric coating layer for experimental formulations was T4>T3>T2>T1. Only experimental formulation T3 met the BE acceptance criteria under fed conditions. Effect of difference in enteric layer coating weight build up was observed for both  $C_{max}$  and AUC. Based on the outcome of pilot BE studies, enteric coating weight build up was set in the range of that for T2 and T3 experimental formulations, for the optimized TBM formulation. The optimized TBM formulation met the BE acceptance criteria in pivotal BE studies.

It is worth mentioning that development of a biopredictive dissolution method i.e., an *in vitro* dissolution method that can predict *in vivo* performance of the drug product reasonably well and also discriminate between the formulations that perform differently, prior to conducting the *in vivo* studies can reduce the number of BE studies conducted on the experimental formulations to select the TBM formulation. This approach could have been taken by the applicants in Case Studies #5-7 mentioned above to reduce the number of *in vivo* BE studies conducted on experimental formulations. In addition, the biopredictive dissolution methods can increase the likelihood that the selected TBM formulation meet the BE criteria in pivotal BE studies in the very first attempt, without the need of conducting non-pivotal BE studies.

## CONCLUSIONS

The non-pivotal BE studies data is an important tool to gain better understanding of the product quality on *in vivo* performance of the generic drug products. The review of non-pivotal BE studies conducted on the TBM formulation provides added confidence in the Agency's BE determination. The scientific criteria have been consistently employed in assessing the acceptability of failed BE studies. The data from these non-pivotal BE studies indicate that inadequate BE study design can lead to failure of the BE on the TBM formulation. The majority of failed non-pivotal BE studies on the TBM DR generic products had insufficient power (inadequate number of subjects), which was expected as these studies are exploratory in nature and not designed to have adequate power to pass the BE statistical criteria. In addition, among the

failed non-pivotal BE studies on the TBM DR generic products, the most commonly failing PK parameter was  $C_{max}$ . The data from non-pivotal BE studies on formulations different from the TBM formulation help us link the formulation design to the product performance *in vivo*. In summary, these non-pivotal BE study data are essential for making an informed, scientifically based decision about BE determination of generic drug product.

## DISCLOSURE

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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