

# **Impact of ICH M13A Implementation on Bioequivalence Assessment: Removal of Data due to Low Exposure**

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# Learning Objectives

- Provide an overview of the ICHM13A guidance recommendations regarding removal of bioequivalence (BE) study data due to low exposure
- Highlight case studies showing how the Office of Bioequivalence (OB) has implemented these recommendations, including how the scientific principles have been applied for non-immediate release (IR) products

# Previous Practice Regarding Low Exposure Data Removal



- Per the FDA draft Guidances for Industry: Bioequivalence (BE) Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (Aug 2021) and Statistical Approaches to Establishing Bioequivalence (Dec 2022), data should not be removed from bioequivalence studies due to identification of statistical outliers.
- Such data was generally only removed with real time documentation of a protocol deviation; otherwise, it is not clear if the anomalous data could be due to other factors such as product failure.
- In limited cases, an exception was made due to data below the limit of quantitation (BLQ) which precluded calculation of a subject period's pharmacokinetic (PK) parameters, i.e., if test/reference (T/R) ratio could not be calculated for the subject.

# Removal of BE Study Data Due to Low Exposure

- Section II.B. (Data Analysis for Non-Replicate Study Design) 1.a.
- Generally, data should not be removed from the statistical analysis of BE studies solely based on statistical tests that identify extreme values in the PK variables.
- An exception can be made for a subject without measurable concentrations or only very low concentrations.

## M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms

### Guidance for Industry

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

October 2024  
ICH – Multidisciplinary

# Removal of BE Study Data Due to Low Exposure

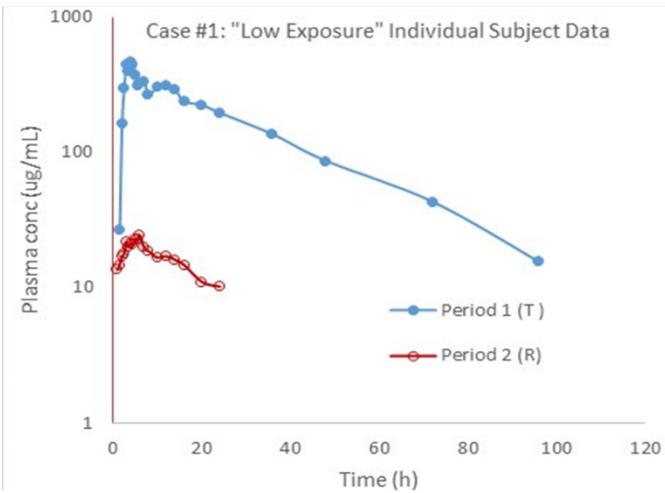


- May be applicable for the test (T) or reference standard (RS) product
- May be applicable when AUC for that period is less than 5% of the geometric mean (GM) AUC for the drug product, without inclusion of data from the low exposure subject
- Because this is considered to be the result of subject non-compliance, exclusion will only be accepted in exceptional cases (in general, with no more than one subject in each study)
- Applicants should minimize the potential for subject non-compliance in the conduct of the BE study (e.g., by mouth checks after dosing, etc.)
- All data should be submitted for assessment

# Case 1: Immediate Release (IR) Product Two-Way Crossover BE Study



- After RS treatment for one subject, the observed AUC<sub>t</sub> was 3.58% of the geometric mean AUC<sub>t</sub> for the reference standard overall (excluding the “low exposure” subject).
- With inclusion of this subject, both C<sub>max</sub> and AUC<sub>t</sub> failed to meet BE criteria.



Parameter	Low Exposure Data Excluded (N=35)		Low Exposure Data Included (N=36)	
	T/R	90% CI	T/R	90% CI
AUC <sub>t</sub>	0.995	95.22 - 103.98	1.0916	91.98 - <b>129.54</b>
AUC <sub>i</sub>	0.9885	94.15 - 103.79	0.9885	94.15 - 103.79
C <sub>max</sub>	1.0263	97.27 - 108.27	1.1099	95.57 - <b>128.89</b>

# Case 1: IR Product Two-Way Crossover BE Study

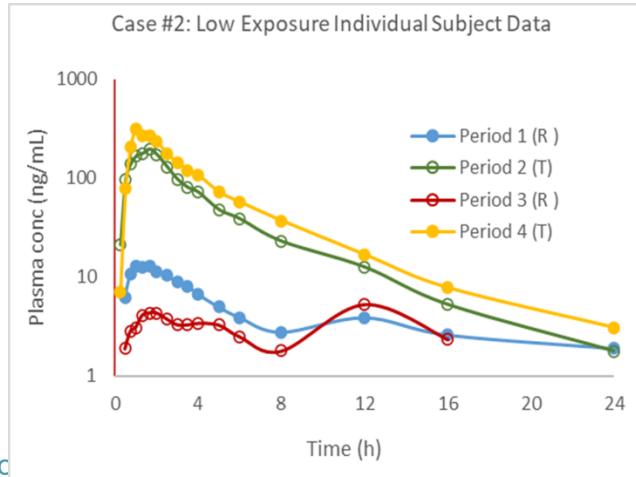


- The removal of the low exposure subject data in this case was considered acceptable because:
  - Scientific principles outlined in ICH M13A were met (i.e.,  $AUC_{t}$  < 5% GM  $AUC_{t}$ )
  - When the low exposure data is excluded, T/R ratio for  $AUC_{t}$ ,  $AUC_{i}$  and  $C_{max}$  is close to 1, and 90% confidence interval (CI) are within BE limits
  - Based on available data, such low concentration is not typical of the RS

# Case 2: IR Product Fully Replicated BE Study



- Reference-scaled BE approach was adopted due to high variability.
- AUCt/GM AUCt = 7.6% for period 3 after RS treatment.
- AUCt and Cmax results failed to meet acceptance criteria using the reference-scaled BE approach with the inclusion of low exposure data.



Parameter	T/R	90% CI	T/R	90% CI
AUCt	1.1432	100.34-130.25	1.2004	100.17 - 140.66
AUCi	1.1068	99.15-123.56	1.1061	99.15 - 123.56
Cmax	1.2418	104.11-148.11	1.3053	103.69 - 161.65
Reference-scaled BE	$S_{WR}$	Criteria Bound (N=28)	$S_{WR}$	Criteria Bound (N=29)
LAUCT	0.4069	-0.07015	0.409322	0.007195
LAUCi	0.3134	-0.04434	0.31345	-0.04434
LCMAX	0.4719	-0.06746	0.480911	0.080282

# Case 2: IR Product Fully Replicated BE Study

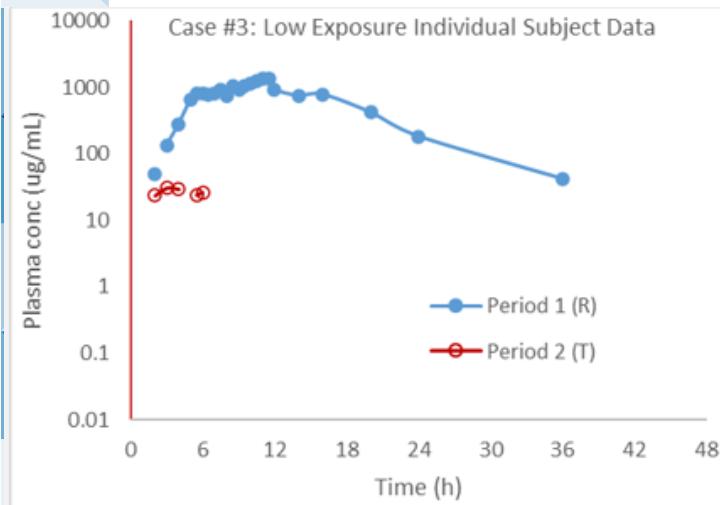


- The removal of the low exposure subject data in this case was unacceptable because:
  - $AUCt > 5\% GM AUCt$
  - Due to the highly variable nature of the drug product, similarly low concentrations were observed from other ANDAs and were not excluded from statistical analysis. This suggests the observed low exposure is not likely due to subject non-compliance.
  - The applicant was recommended to repeat the study.

# Case 3: Modified Release (MR) Product Two-Way Crossover BE Study



- $AUCt/GM AUCt = 1.57\%$  for one period after T treatment.
- With inclusion of this subject,  $AUCt$ ,  $AUCi$  and  $Cmax$  failed to meet BE criteria.



Parameter	Low Exposure Data Excluded (N=51)		Low Exposure Data Included (N=52)	
	T/R	90% CI	T/R	90% CI
AUCt	0.9897	85.09 - 120.36	0.9075	74.58 - 116.22
AUCi	1.0098	86.93 - 121.10	0.9478	79.72 - 116.60
Cmax	0.9707	81.10 - 113.26	0.9121	73.92 - 109.49

# Case 3: MR Product Two-Way Crossover Fasting BE Study

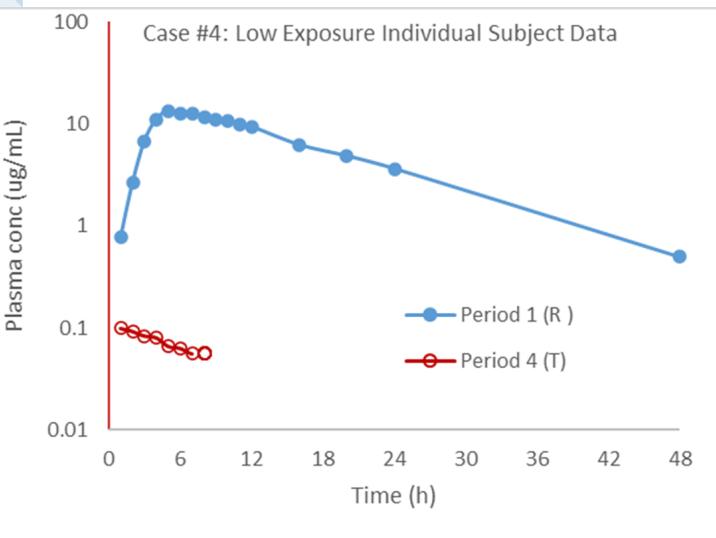


- Although the M13A guidance is not generally applicable for MR products, a risk-based approach using the scientific principles outlined in the guidance was evaluated for this product, including:
  - $AUC_{t_0} < 5\% \text{ GM } AUC_{t_0}$
  - Such low concentration was not expected based on the overall variability of the product
  - With exclusion of this subject, T/R ratios for  $AUC_{t_0}$ ,  $AUC_{i_0}$  and  $C_{max}$  are close to 1
  - Similar formulation between T and RS products with same type and grade of release-controlling excipients
  - Comparable dissolution profiles between test and RS product in quality control medium and multiple pH media
  - Taken once daily with evening meal, suggesting the acceptable fed BE study has more relevance

# Case 4: Narrow Therapeutic Index (NTI) MR Product Fully Replicated BE Study



- Acceptance criteria include 95% upper confidence bound from reference-scaled BE  $\leq 0$ , unscaled 90% CI within 80.00% - 125.00% and upper limit of 90% equal-tails CI for  $\sigma_{WT}/\sigma_{WR} \leq 2.500$ .
- AUCt/GM AUCt = 0.27 % for one period (P4) after T treatment.
- With inclusion of P4 PK data, AUCt, AUCi and Cmax failed to meet acceptance criteria from unscaled BE assessment, but still met the reference-scaled BE criteria.



Unscaled BE Results		Low Exposure Data Excluded (N=52)		Low Exposure Data Included (N=53)	
Parameter	T/R	90% CI		T/R	90% CI
AUCt	0.9903	96.45 - 101.67		0.8793	72.82 - 106.17
AUCi	0.9916	96.54 - 101.85		0.8933	75.69 - 105.41
Cmax	0.9825	96.03 - 100.52		0.8928	76.62 - 104.03
Reference-scaled BE Results (with or without low exposure data)					
Parameter	T/R Ratio	sWR (N=49)	sWT (N=49)	Criteria Bound	95% CI sWT/sWR
AUCt	0.9958	0.096339	0.126287	-0.00757	1.6704
AUCi	0.9967	0.098796	0.130056	-0.00799	1.6775
Cmax	0.9883	0.09538	0.107334	-0.0072	1.434

# Case 4: MR Product Fully Replicated BE Study



- Although the M13A guidance is not generally applicable for MR products, a risk-based approach was evaluated for this product, including:
  - $AUC_t < 5\% GM AUC_t$
  - 90% CI are in the range of 96-102% if excluding this subject.
  - Observed plasma concentrations are close to LLOQ (0.05  $\mu\text{g/mL}$ ).
  - Formulation and release mechanism of the test product are similar to the RS product with same type and similar grade of release-controlling excipients.

# Challenge Question #1

Which FDA guidance document contains information about an exception for removal of BE study data due to low exposure?

- A. Bioequivalence (BE) Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (Aug 2021)
- B. Statistical Approaches to Establishing Bioequivalence (draft Dec 2022)
- C. M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Oct 2024)
- D. M10 Bioanalytical Method Validation and Study Sample Analysis (Nov 2022)

# Challenge Question #2

**Which of the following statements is NOT true?**

- A. Low exposure data removal may be applicable if AUC for that period is less than 5% of the geometric mean (GM) AUC for the drug product, without inclusion of data from the low exposure subject.
- B. Data removal due to subject non-compliance may be applicable for the RS product only.
- C. Exclusion will only be accepted in exceptional cases (in general, with no more than one subject in each study).
- D. All data, including any data excluded from statistical analysis for low exposure, should be submitted for assessment.

# Summary

- The M13A Guidance, *Bioequivalence for Immediate-Release Solid Oral Dosage Forms*, introduced scientific principles for the exclusion of low exposure BE study data which is considered to be due to subject non-compliance.
- Removal of low exposure data will only be accepted in exceptional cases. For example, if more than one subject in a study shows low exposure, this could bring questions of dose administration reliability or product failure.
- Although M13A applies for IR products, the scientific principles of low exposure data removal may be considered for other types of products using risk-based approach to assess whether the low exposure data is likely due to subject non-compliance.

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