

# NKDEP, NIST, CAP Reference Material Commutability Study: A Preliminary Look at the Data

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# Presentation Objectives

- Describe how the commutability study was performed using NCCLS/CLSI EP14-A2
- Review the commutability findings with participating manufacturers
- Suggest and gather input on alternate approaches to quantifying a reference material's commutability

# NCCLS/CLSI EP14-A2

- Approximately 20 patient serum samples and various reference materials are analyzed by each field method in replicate (triplicate) in a single analytical batch
- Same set of patient samples and reference materials analyzed by a “reference method” (LC IDMS at NIST)
- Plot mean of field method (y-axis) vs. reference method result (x-axis)

# NCCLS/CLSI EP14-A2

## (continued)

- Compute least squares linear regression line and parameters including  $S_{y.x}$  from the patient samples data
- Compare location of reference material data points to the prediction intervals (PI) around the regression line for the patient sample means
- Define as commutable reference materials whose data points fall within the 95% PI defined by the patient serum data points (other PI's can be used)

# Patient and Reference Materials Evaluated

- 20 to 24 patient serum samples attending the Univ of MN Medical Center's diabetes, hypertension, and nephrology clinics
- CAP LN24 Linearity Survey reference material intended to be a PT/EQAS material (trueness controls) prepared from fresh frozen serum according to NCCLS/CLSI C37A
- NIST SRM 967 reference material intended to be a calibrator prepared from fresh frozen serum according to NCCLS/CLSI C37A

# Reference Material Preparation

- CAP LN24
  - CAP LN24-2 is a fresh frozen female serum pool without additives; this was used as the “base pool”
  - CAP LN24-7 is CAP LN24-2 base pool supplemented to ~4 mg/dL creatinine with reagent grade creatinine
  - CAP LN24-3 (and LN24-4, LN24-5, and LN24-6) are blends of LN24-2 and LN24-7
  - CAP LN24-1 is CAP LN24-2 diluted with phosphate buffered saline
- NIST SRM 967
  - Level 1 is a fresh frozen female serum pool without additives
  - Level 2 is Level 1 pool supplemented to ~4 mg/dL creatinine with reagent grade creatinine

Prediction Interval is Defined by the  
Following Equation

$$\bar{Y}_{\text{pred}} \pm t(0.975, n - 2) S_{y \cdot x} \left[ 1 + \frac{1}{n} + \frac{(\bar{X}_i - \bar{\bar{X}})^2}{\sum (\bar{X}_i - \bar{\bar{X}})^2} \right]^{1/2}$$

# Definition of PI Equation Variables

- $\bar{Y}_{\text{pred}}$  = the predicted value of  $y$  at  $X_i$  based on an estimated regression curve;
- $n$  = the number of fresh patient specimens (not total number of replicates);
- $S_{y \bullet x}$  = the standard error of regression =  
$$\left[ \sum (Y_{\text{pred}} - \bar{Y}_i)^2 / (n - 2) \right]^{1/2}$$
- $\bar{X}_i$  =  $i$ th value on the  $x$  axis (comparative method mean);
- $\bar{Y}_i$  =  $i$ th value on the  $y$  axis (evaluated method mean);  
and
- $\bar{\bar{X}}_i$  = the overall grand mean of the reference method means.



# Format of Slides to Follow

## Data Point Color Coding

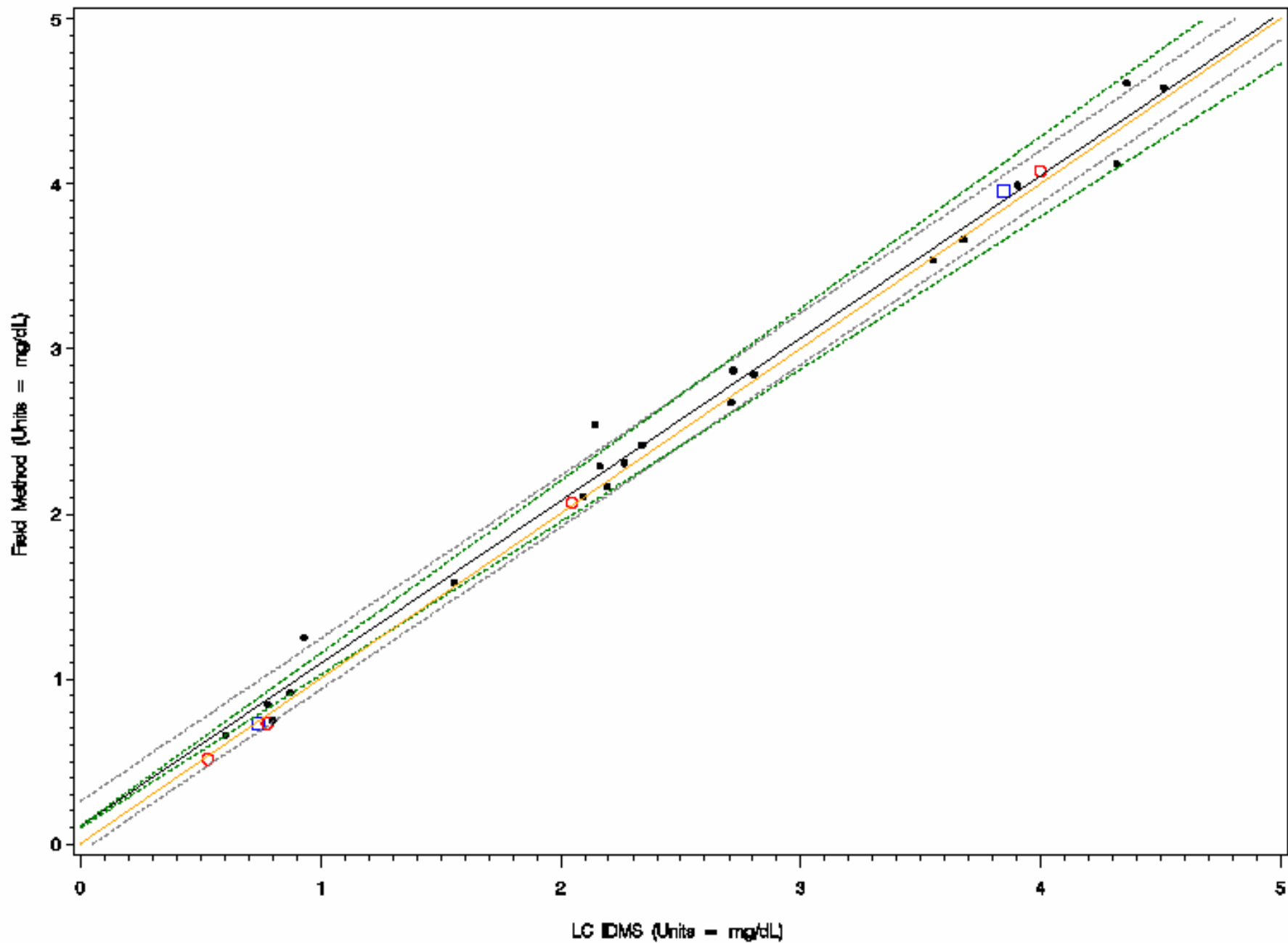
- Plots show x,y-scattergrams of field methods mean results (y-axis) vs. NIST LC IDMS results (x-axis)
  - Black points are patient specimens
  - Red points are CAP LN24 Linearity Survey specimens (left to right: LN24-1, LN24-2, LN24-4, and LN24-7)
  - Blue points are NIST SRM 967 (left to right: level 1 and 2)

# Format of Slides to Follow

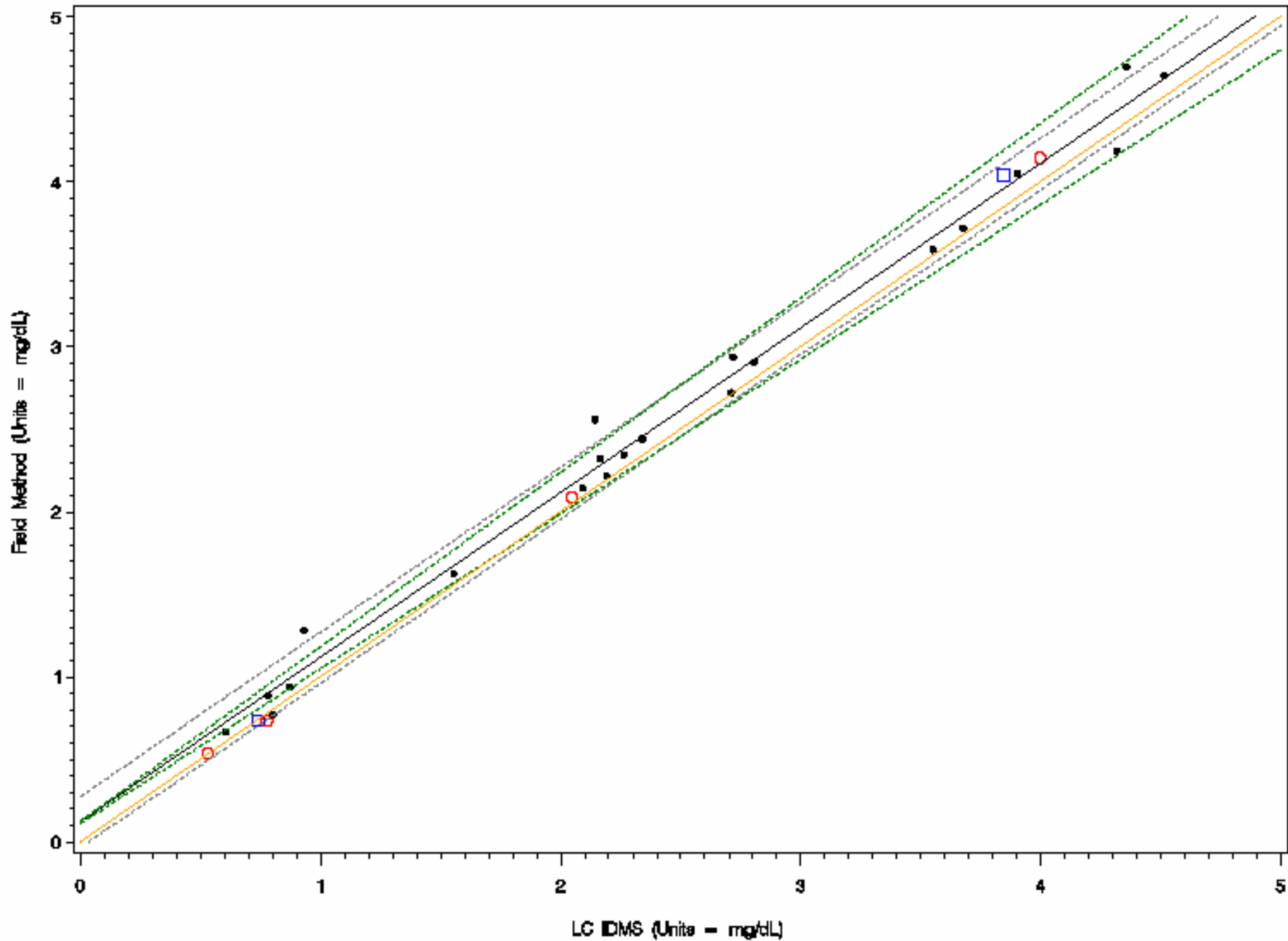
## Continued

- Black line is the linear regression line computed from the patient sample data points only
- Grey lines are statistically determined 95% prediction interval per NCCLS/CLSI EP14-A2
- Green lines are fixed limits based on +/- 6% from patient sample linear regression line.
- Red line is line of perfect correlation (i.e.,  $y=x$ )
- Shown are data for 18 “methods” from seven manufacturers

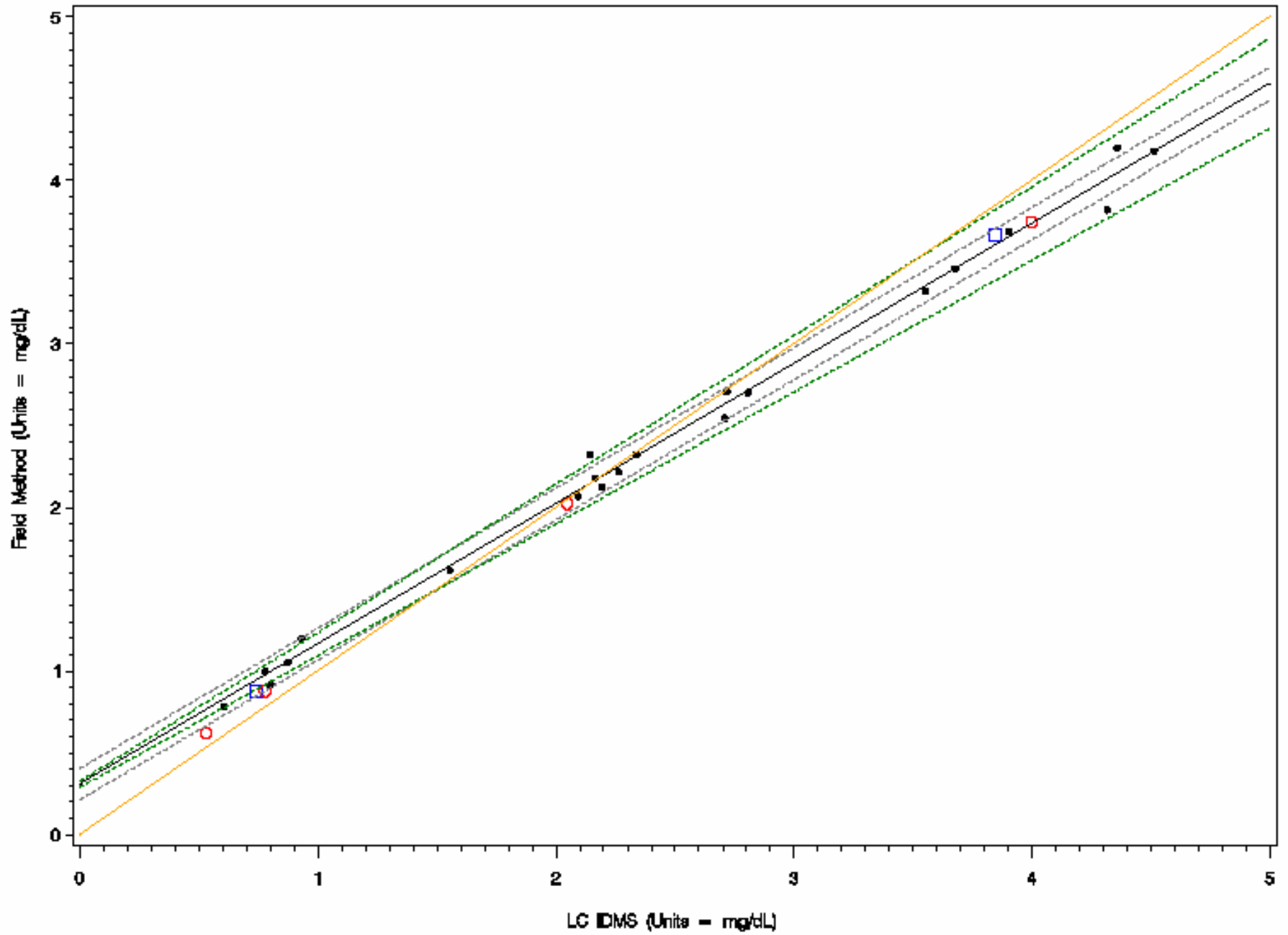
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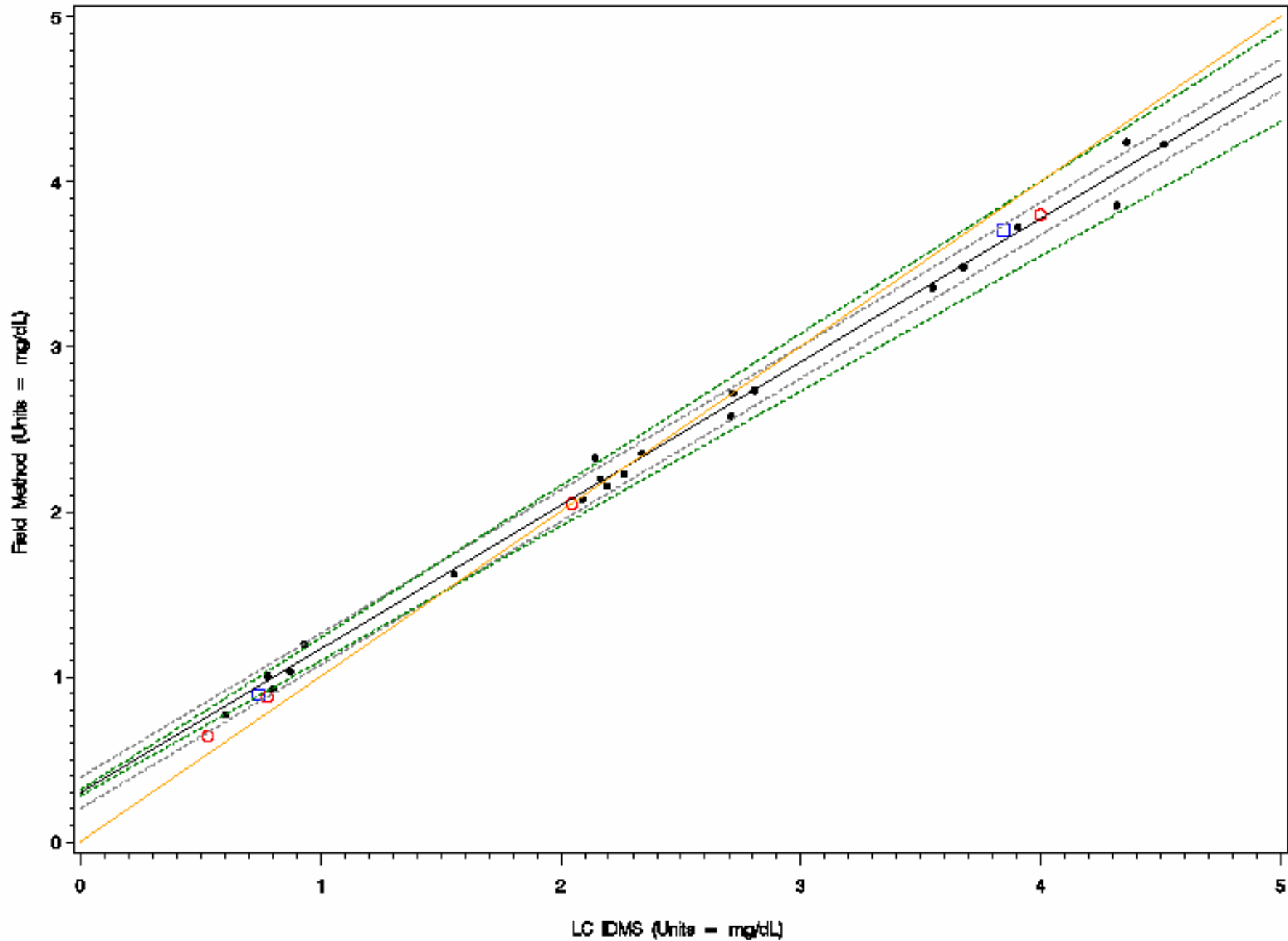
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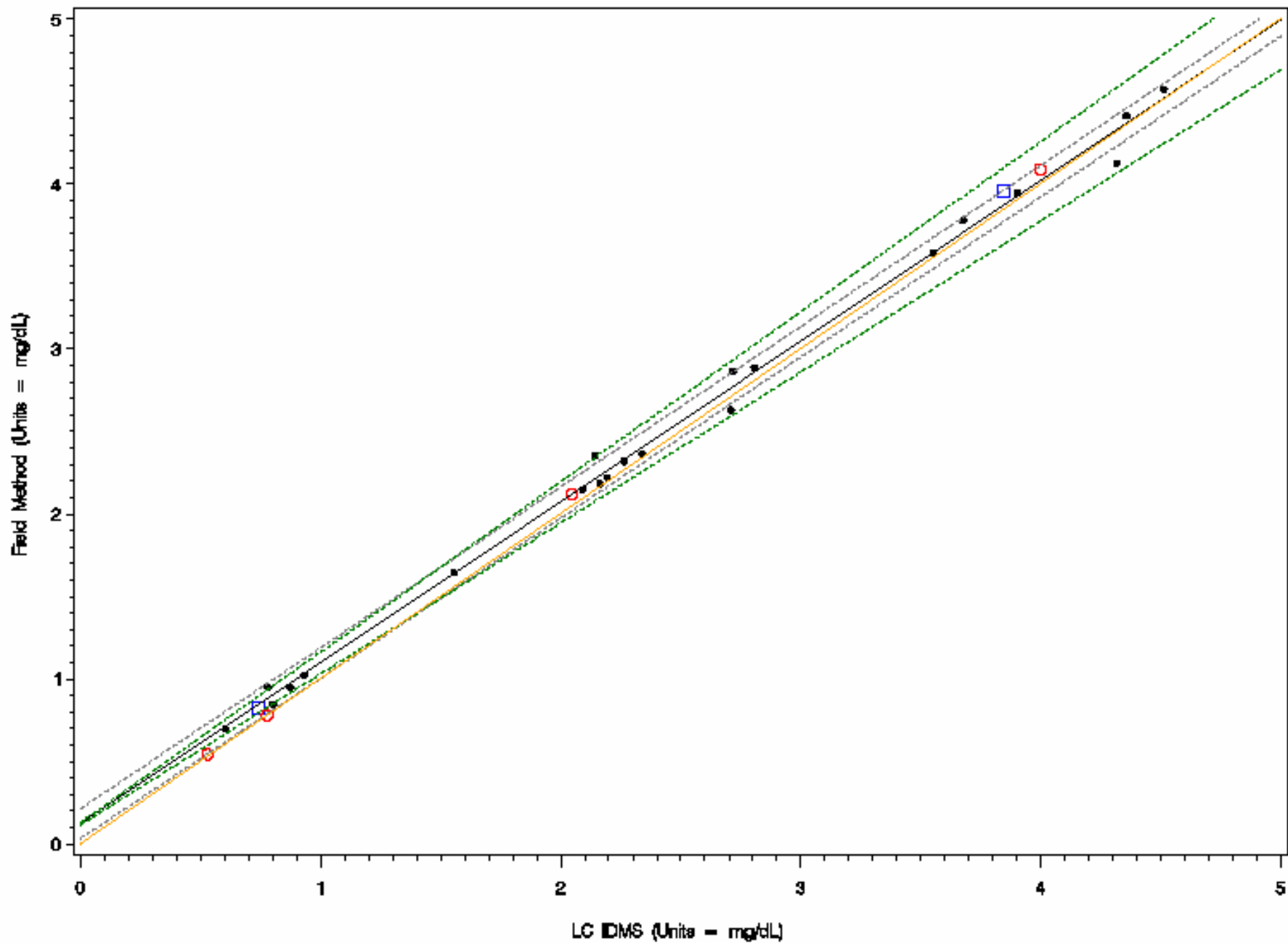
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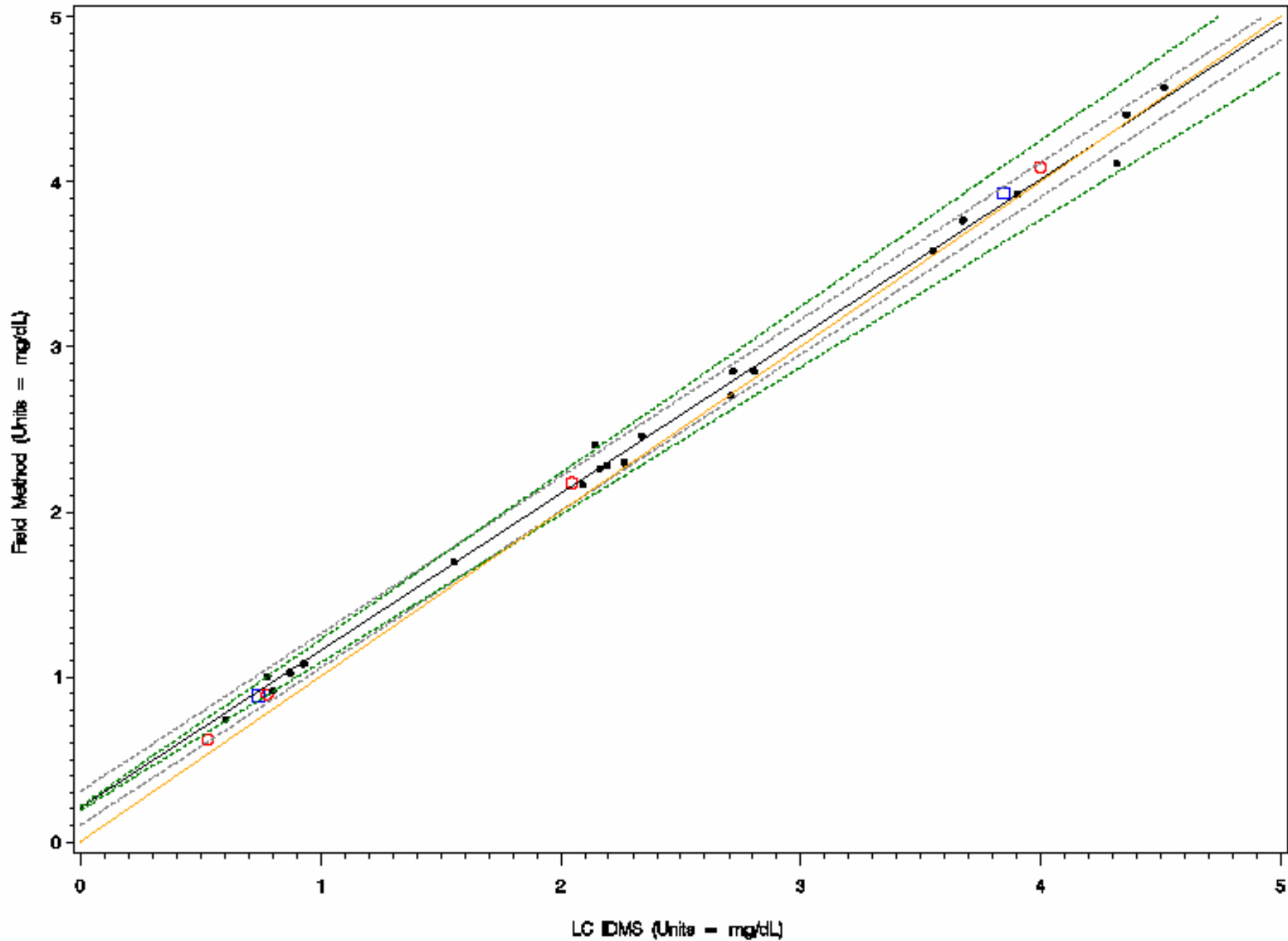
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Manufacturer = Method 2-1

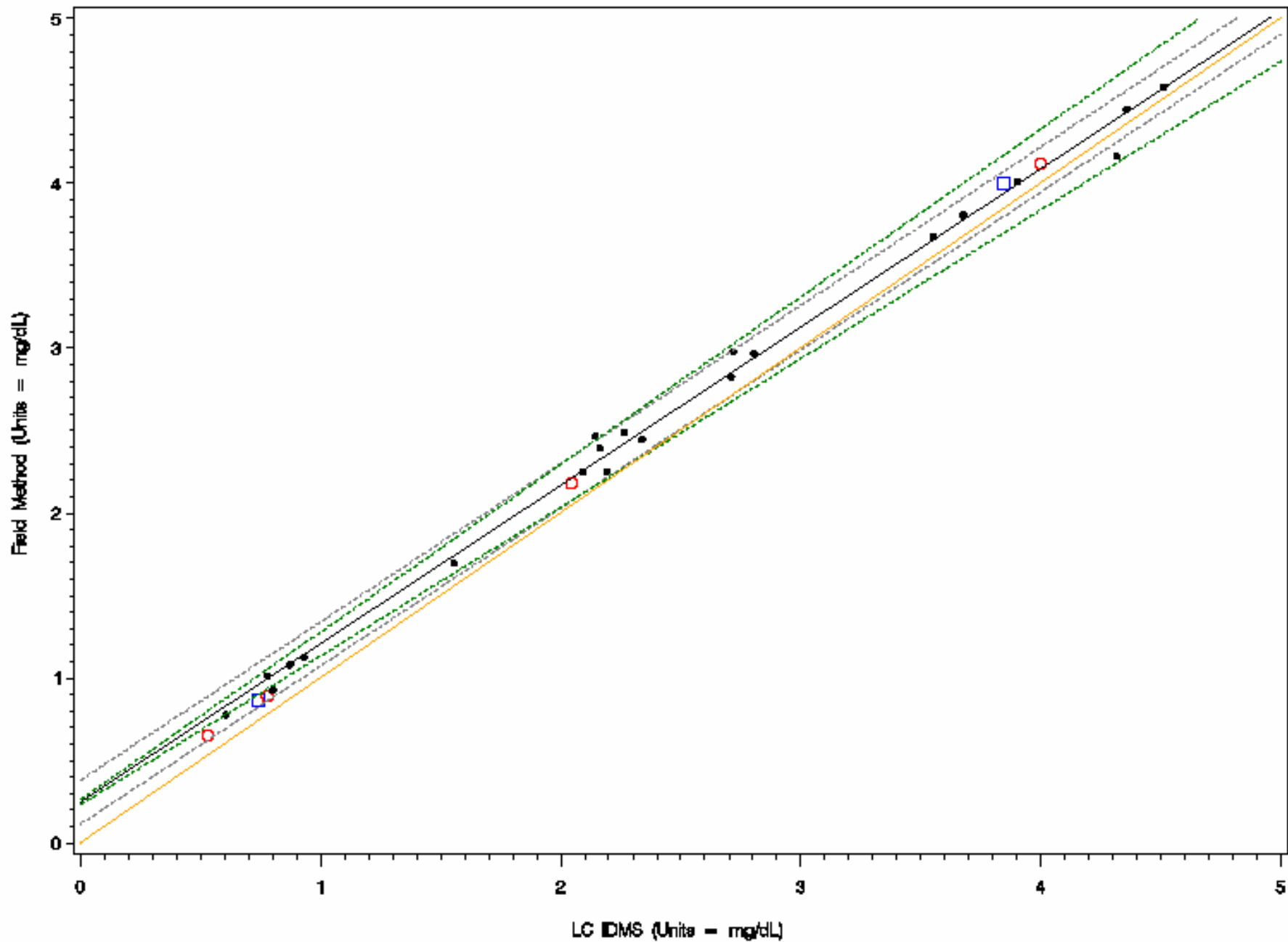


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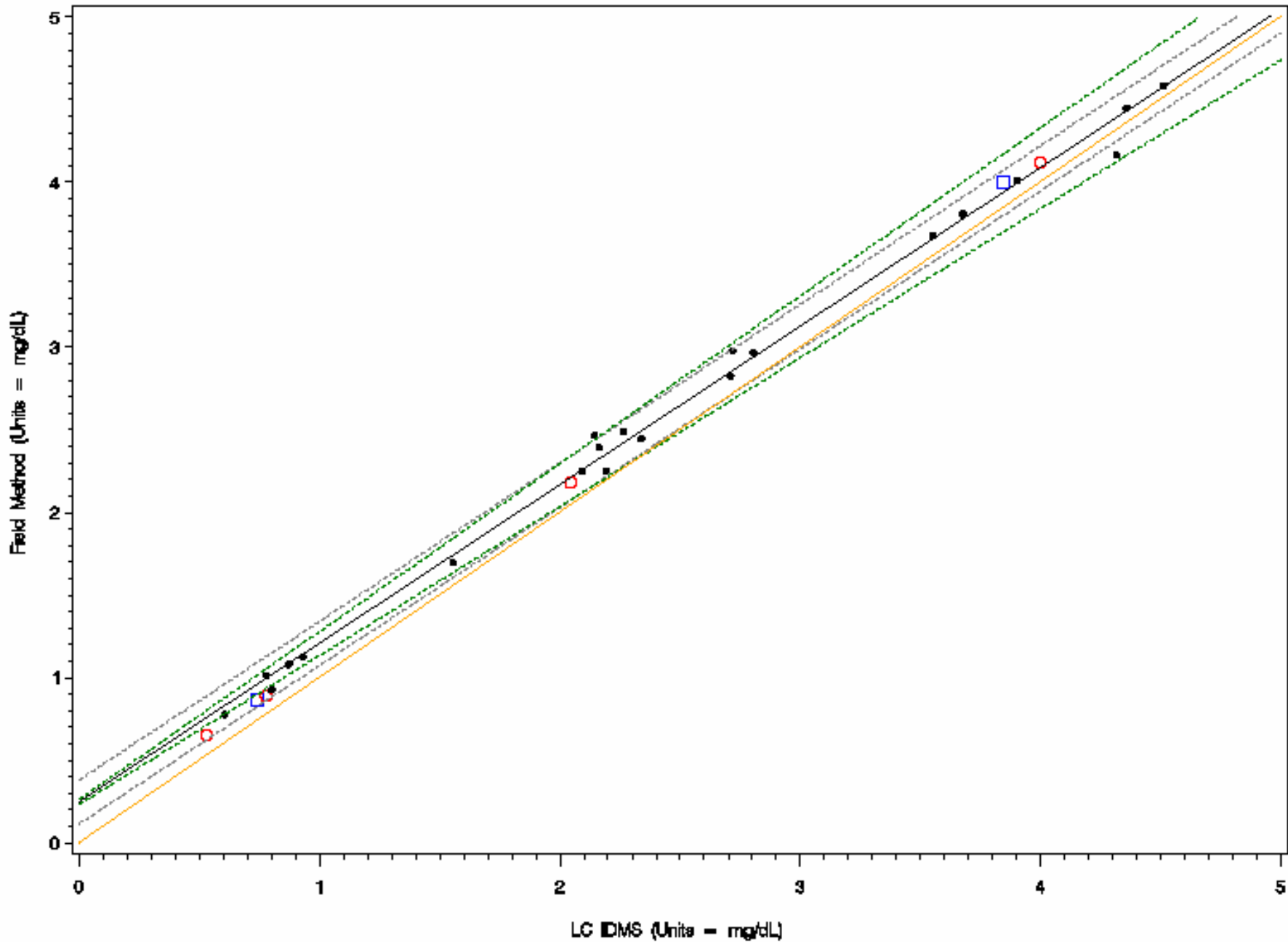




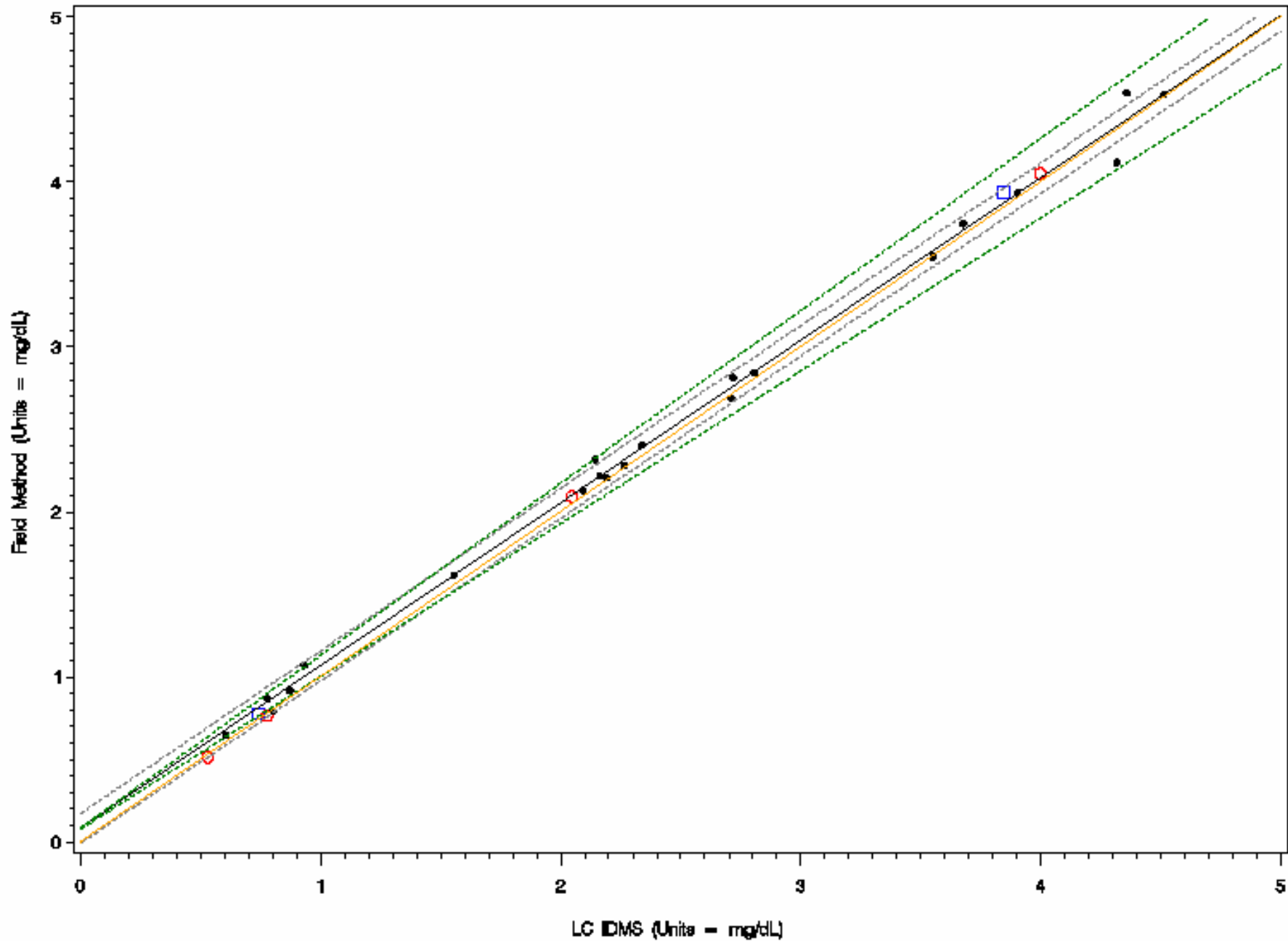
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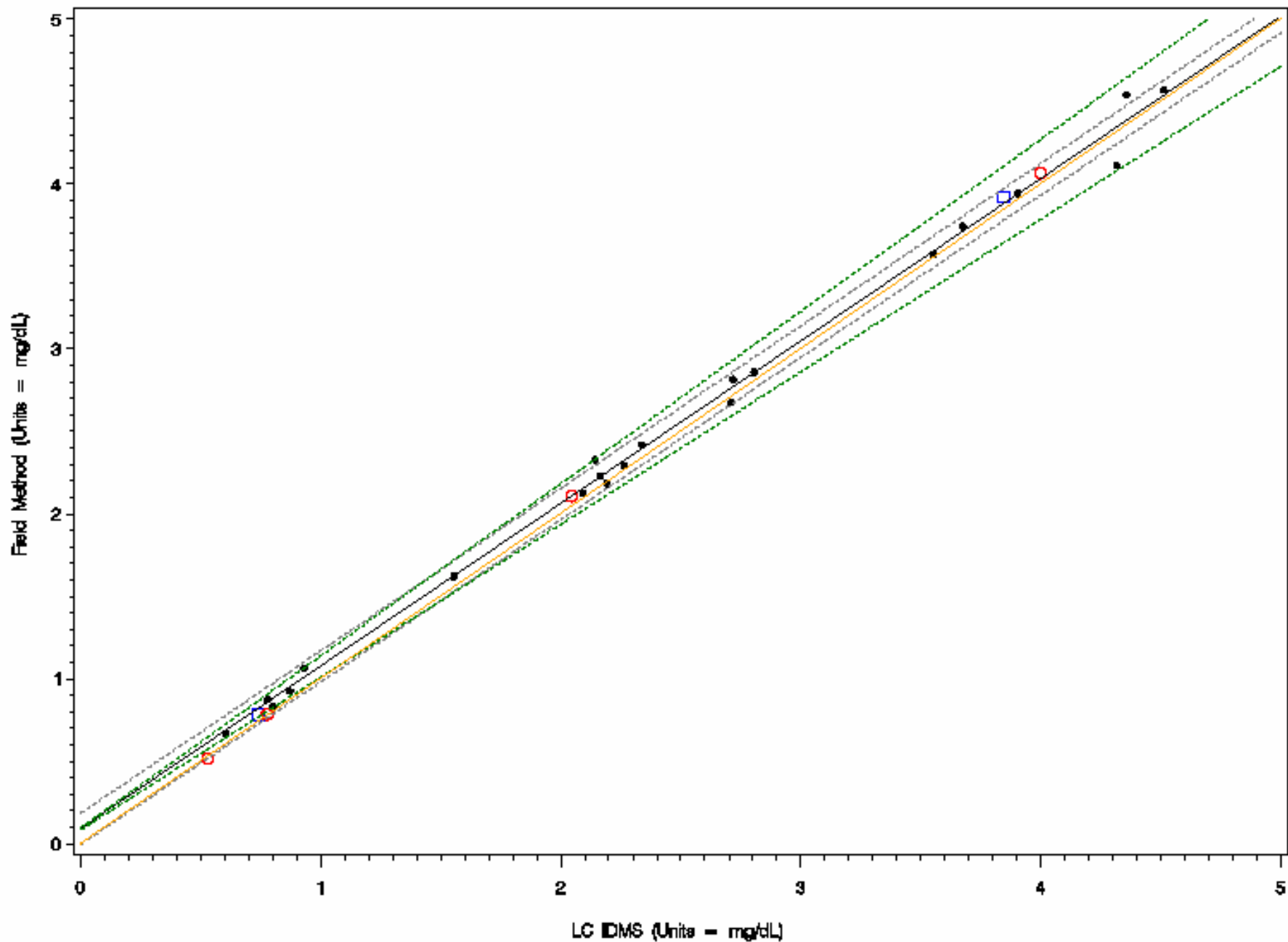
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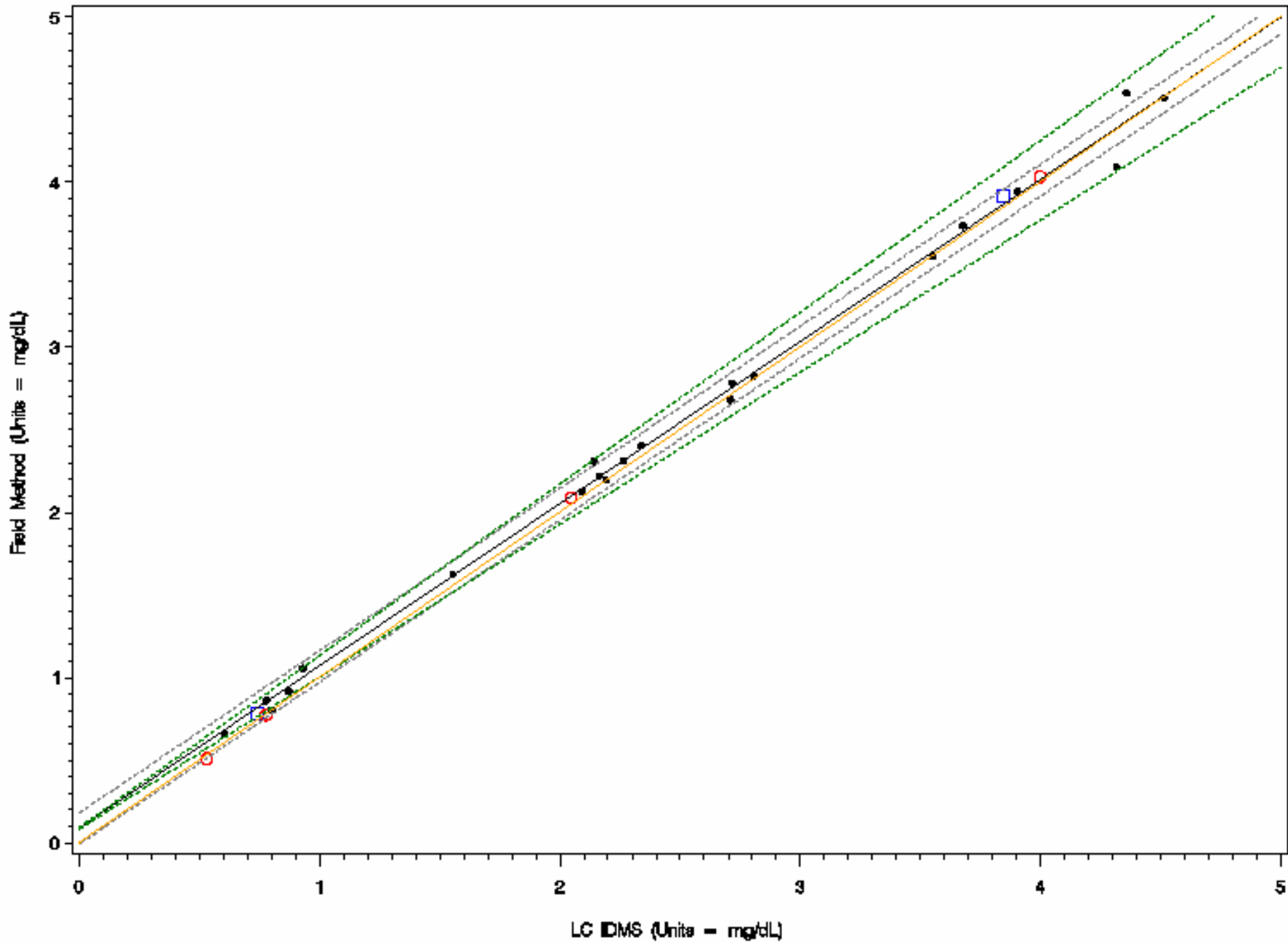
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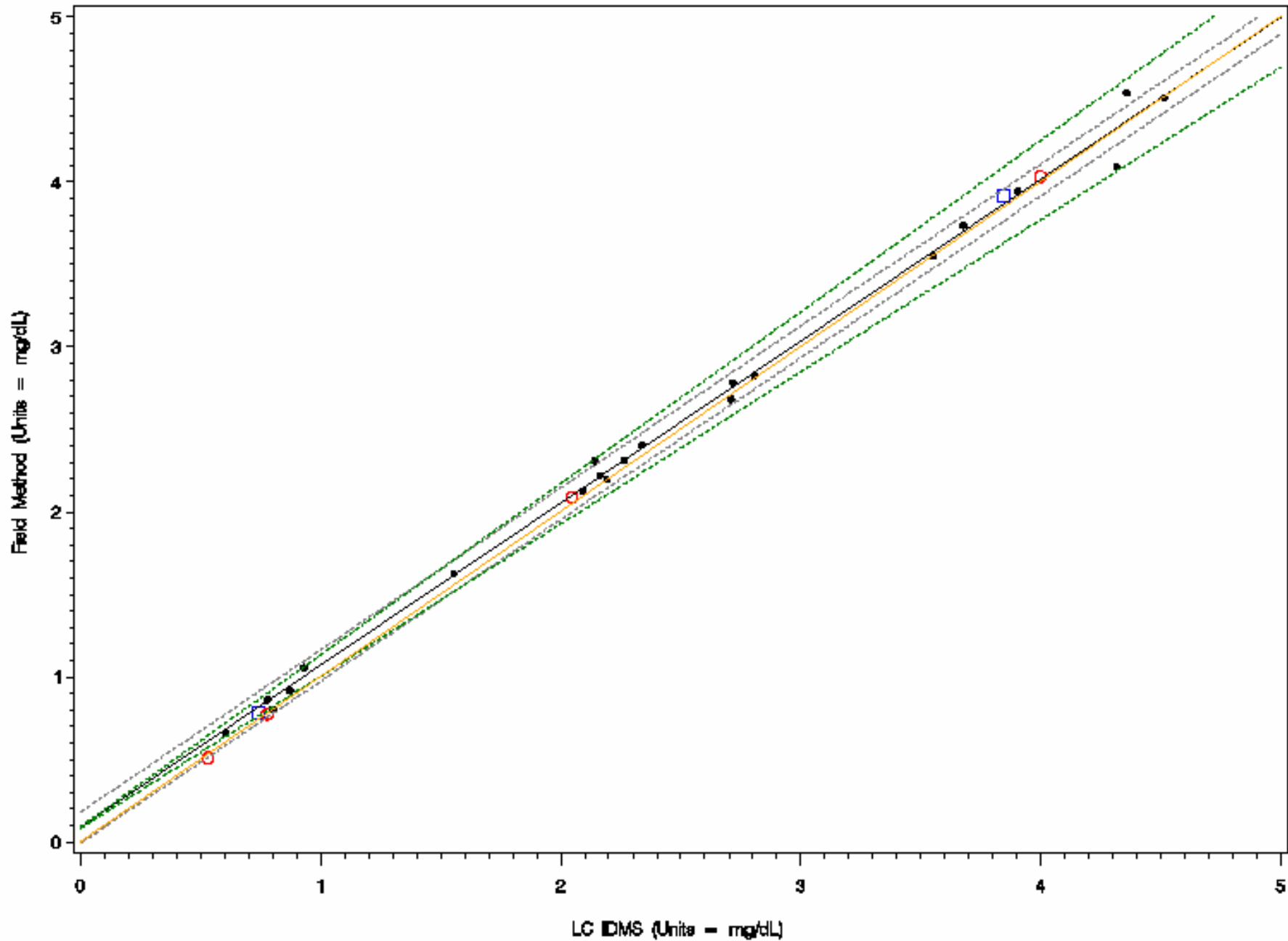
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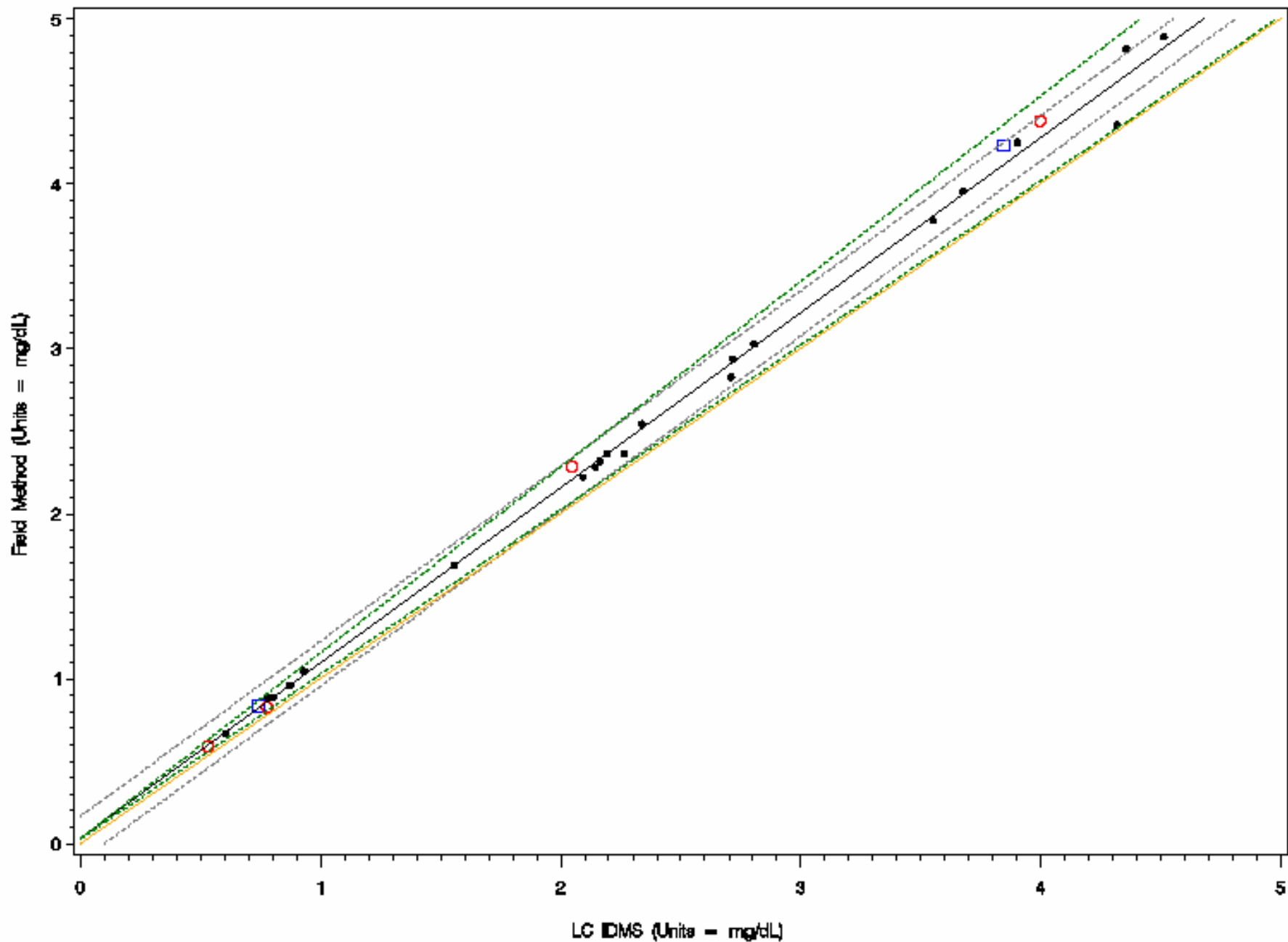
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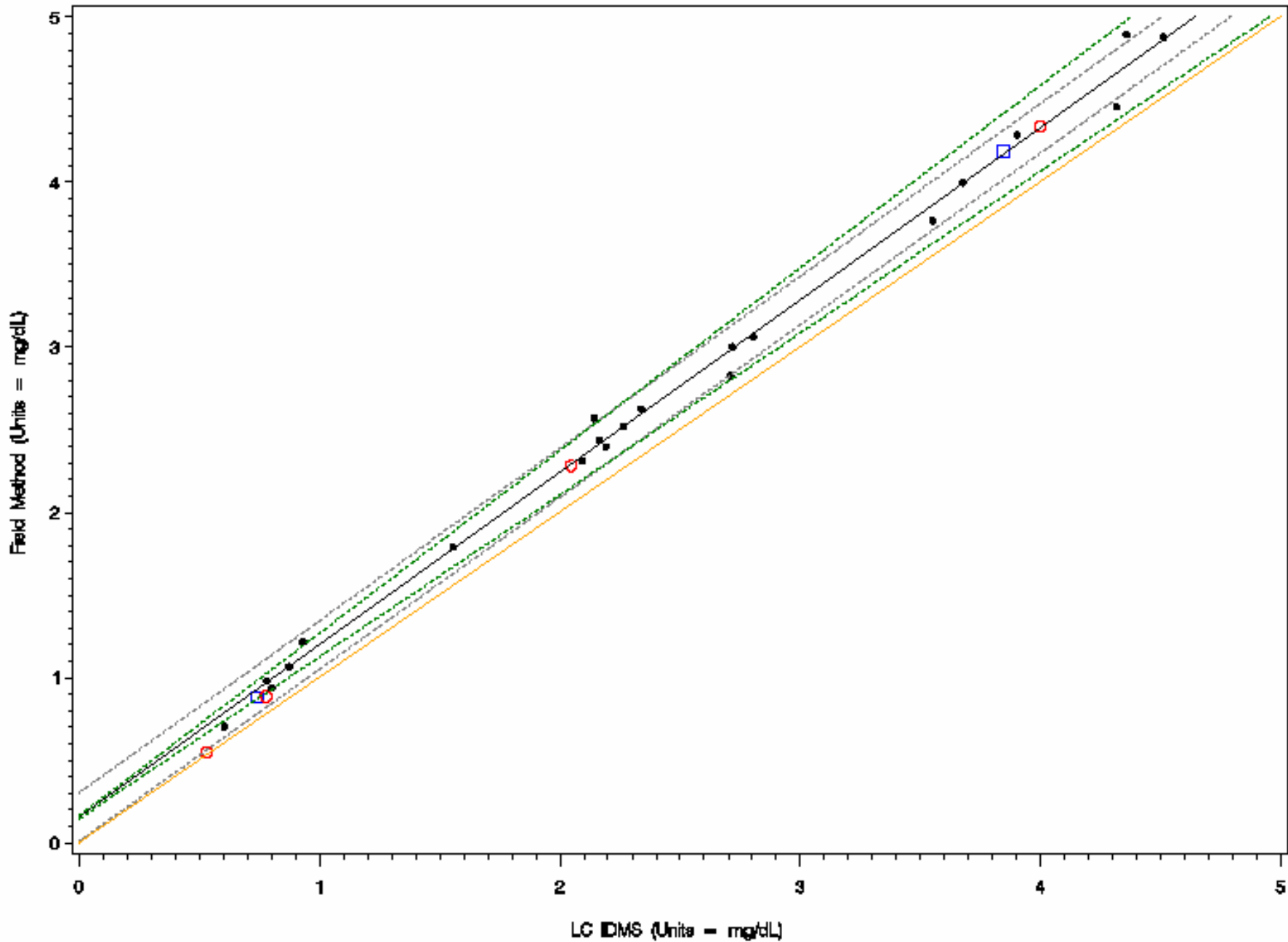
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Manufacturer= Method 4-1 Enzymatic

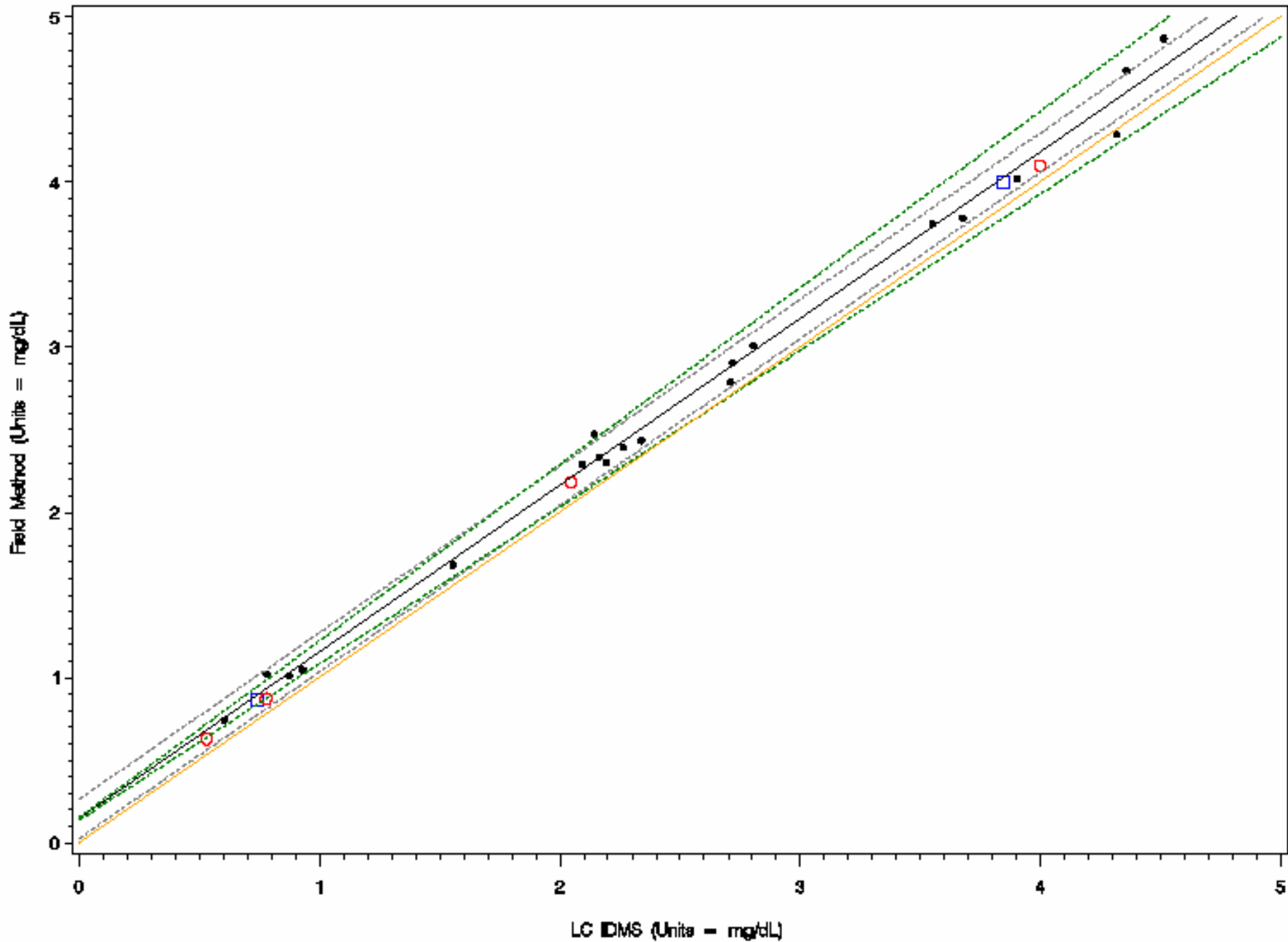


Manufacturer= Method 4-2

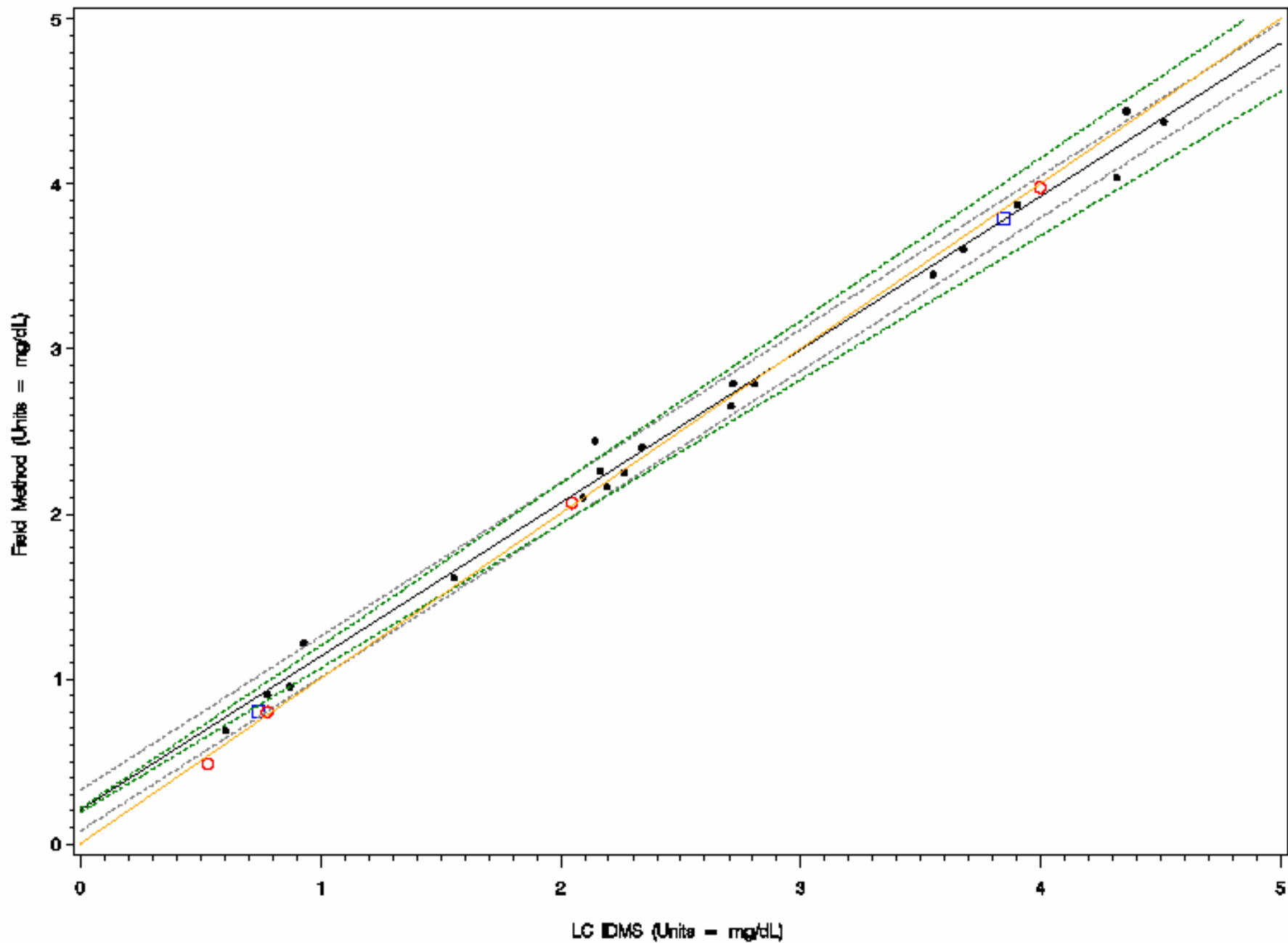




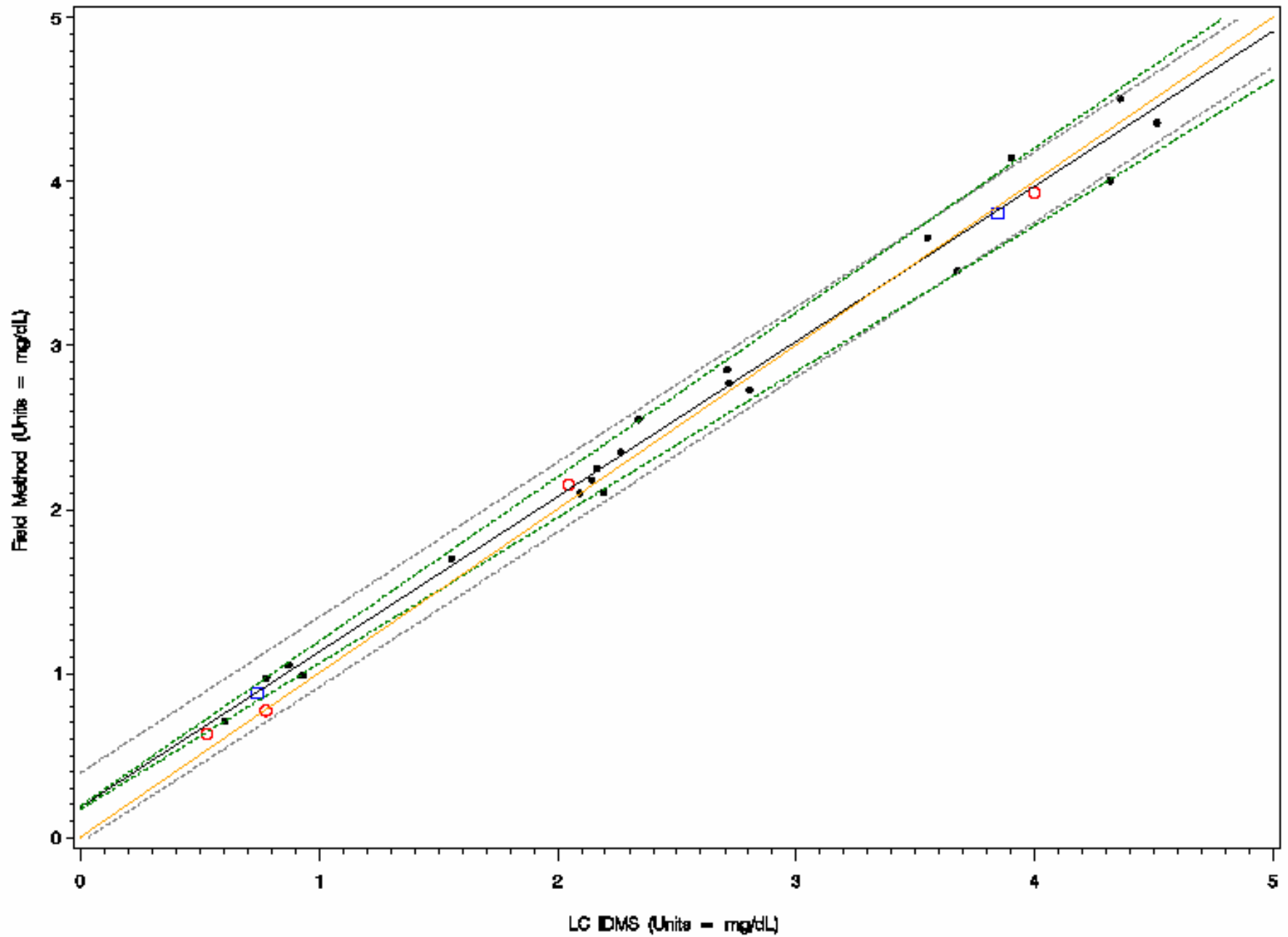
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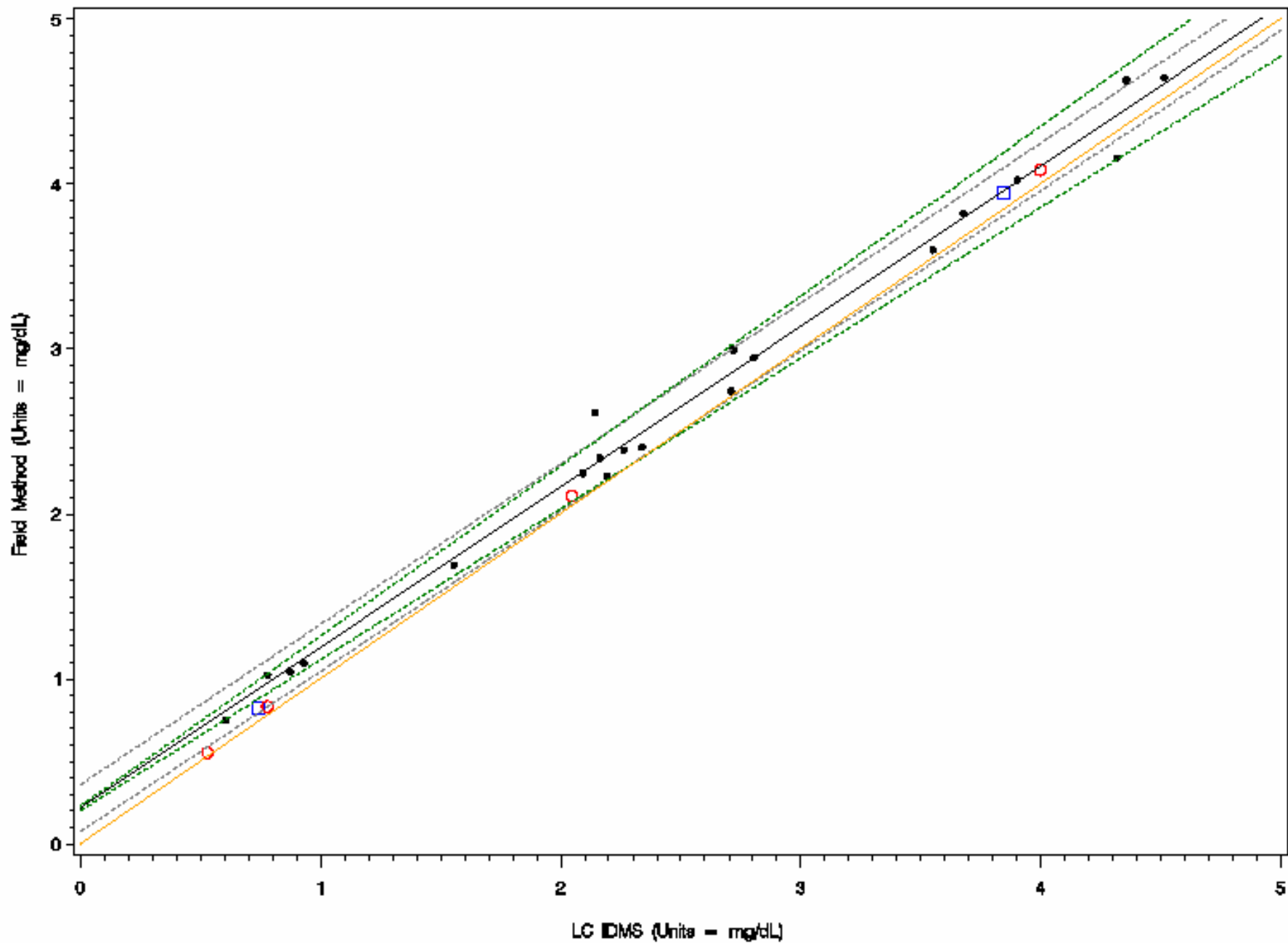
Manufacturer = Method 6-1



Manufacturer = Method 6-2 Enzymatic



Manufacturer = Method 7-1



# Issues to Consider

- How should we define commutability for a reference material:
  - Statistically defined 95% prediction interval (PI) - EP14-A2 approach
  - Fixed limit interval (e.g., +/- 6% as shown on scattergrams) about the regression line
- Statistically defined PI size is determined by how well correlated the field method values are to the reference method values for the patient samples
  - Methods with large specimen-specific, non-specificity biases have wider PI intervals
  - The EP 14-A2's 95% PI is rather large for many methods (e.g., >15% in many cases)

# General Conclusions

- Both SRM 967 and CAP LN24 samples appear to be commutable with virtually all methods using EP14-A2's +/- 95% PI criteria
- 95% PI appears to be a rather large a window of acceptability for determining non-commutability if NKDEP targets for traceability to IDMS-defined target values for bias (<8% at 1 mg/dL) are to be met
- Other limits for determining acceptable commutability should be considered

# General Questions and Discussion