Commutability of quality control materials: the way forward

Ferruccio Ceriotti

Diagnostica e Ricerca S. Raffaele, Milano

Definition of **EQA**

System for objectively checking laboratory results by means of an external agency ……. the main objective being the establishment of **trueness.**
(ISO/REMCO N231, 1991)

To accomplish this task we need:

- Commutable control materials
- Reference methods based target values

Commutability

The equivalence of the mathematical relationship among the results of different measurement procedures for an RM and for representative samples of the type intended to be measured.

CLSI C53-A

Model of Lab Measurements for an EQA material

$$Y_p = a_p + b_p X + d_{p,s}$$

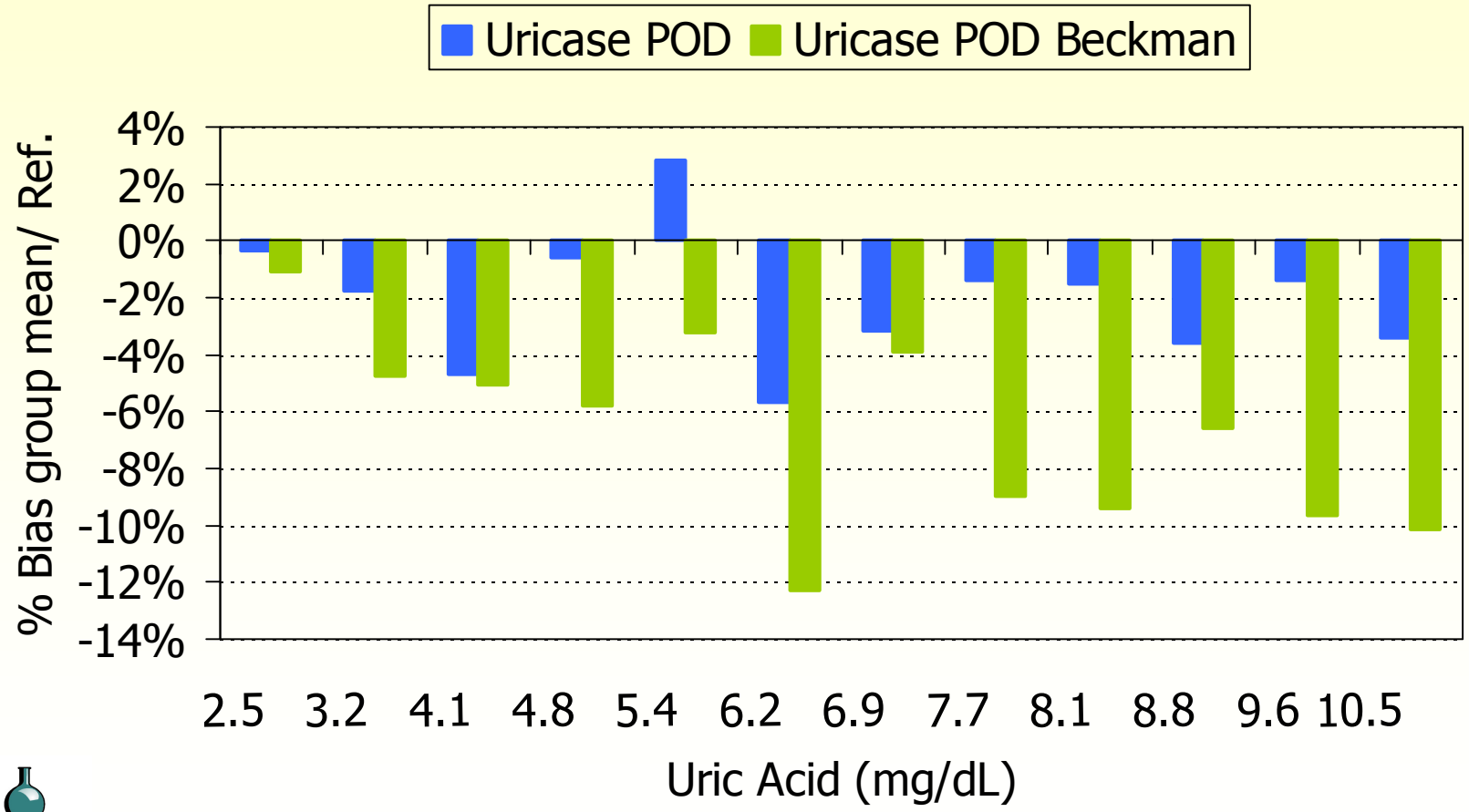
Y_p = mean result of a peer group p

X = true (e.g. IDMS) concentration of the analyte

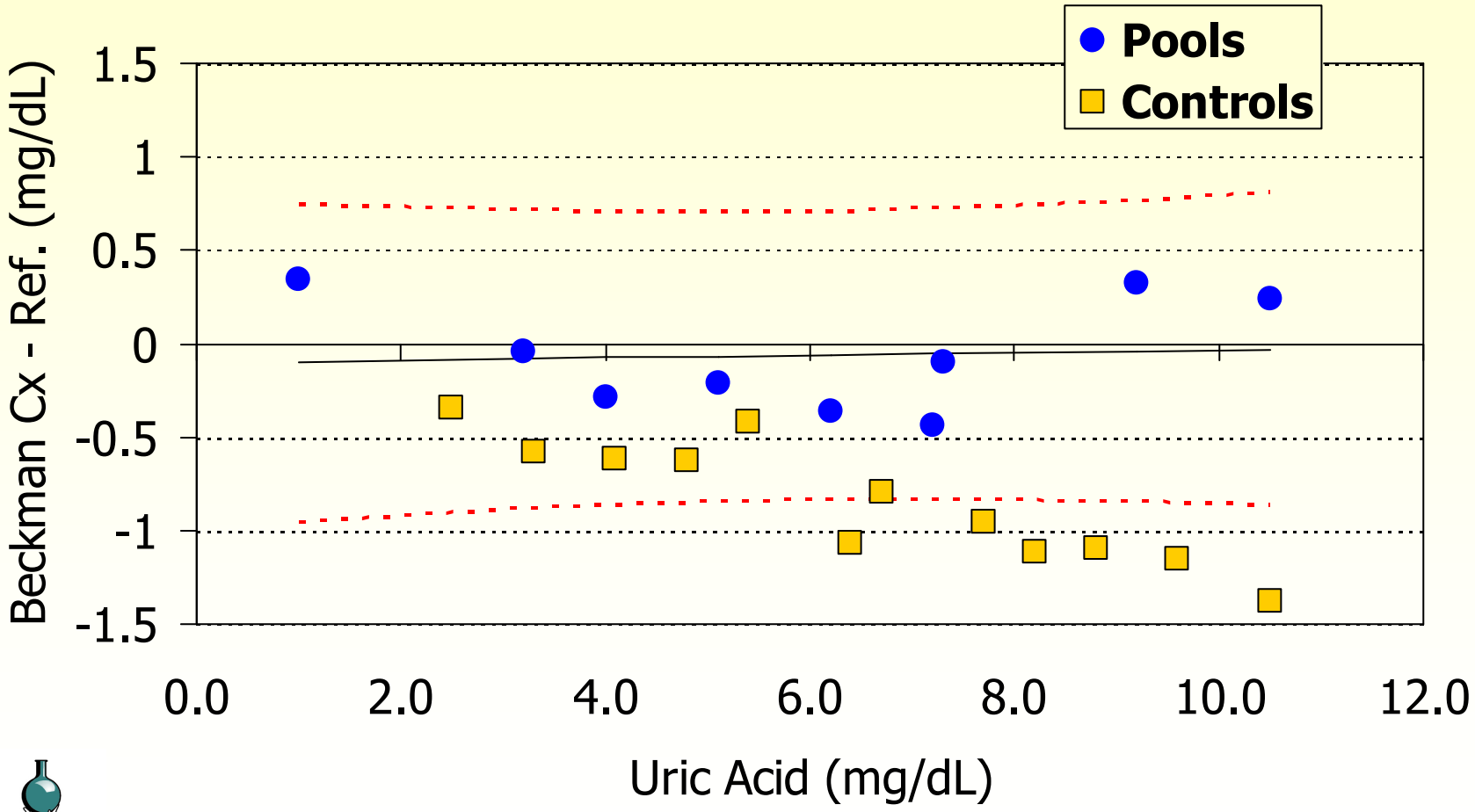
a_p, b_p = "calibration error" of the peer group (obtained on native sera)

$d_{p,s}$ = "matrix bias" (group p, material s)

Uric acid: bias of group means from reference method value



Uric acid: commutability verification of Beckman systems



Assessing commutability of CM (according to CLSI C53-A)

- Select 20 single donor samples spanning the relevant concentration range
- Analyze both CM(s) and patients' samples with the pair of methods (e.g. reference and routine method) trying to minimize the random errors (single run, adequate replication of measurements).
- Elaborate the data using regression analysis and calculate if the CM(s) fall within the 95% prediction interval defined by the patients' samples

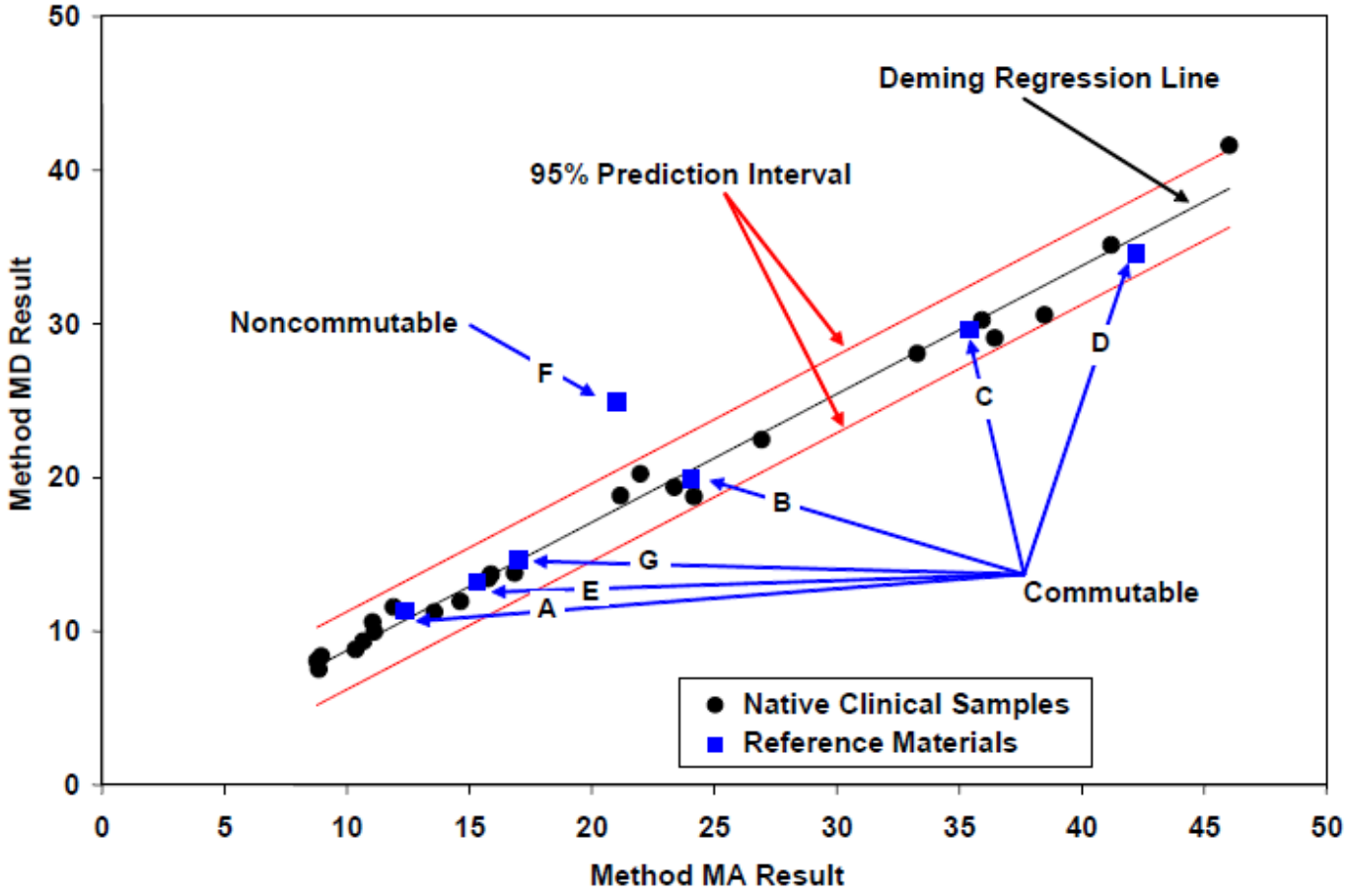
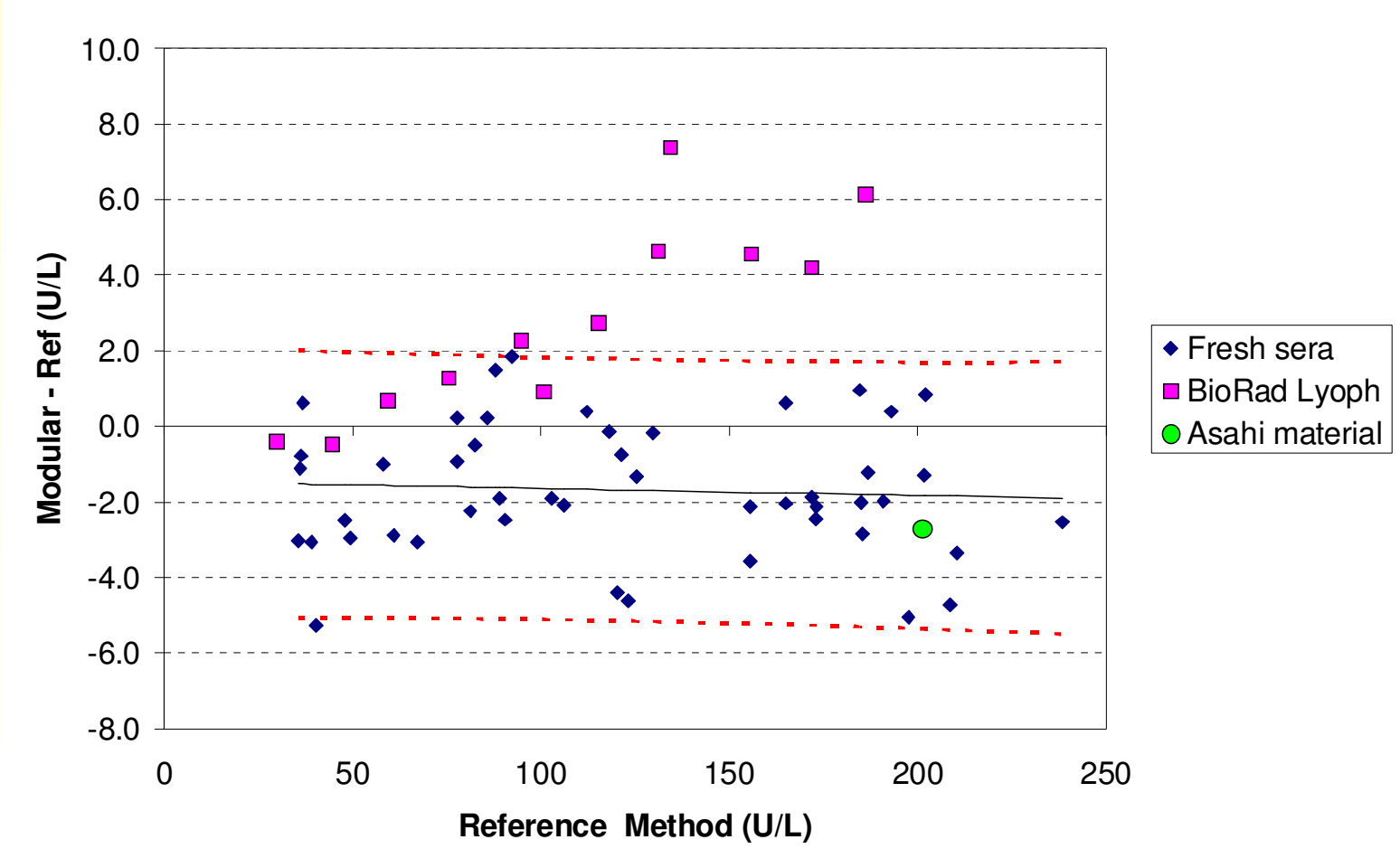
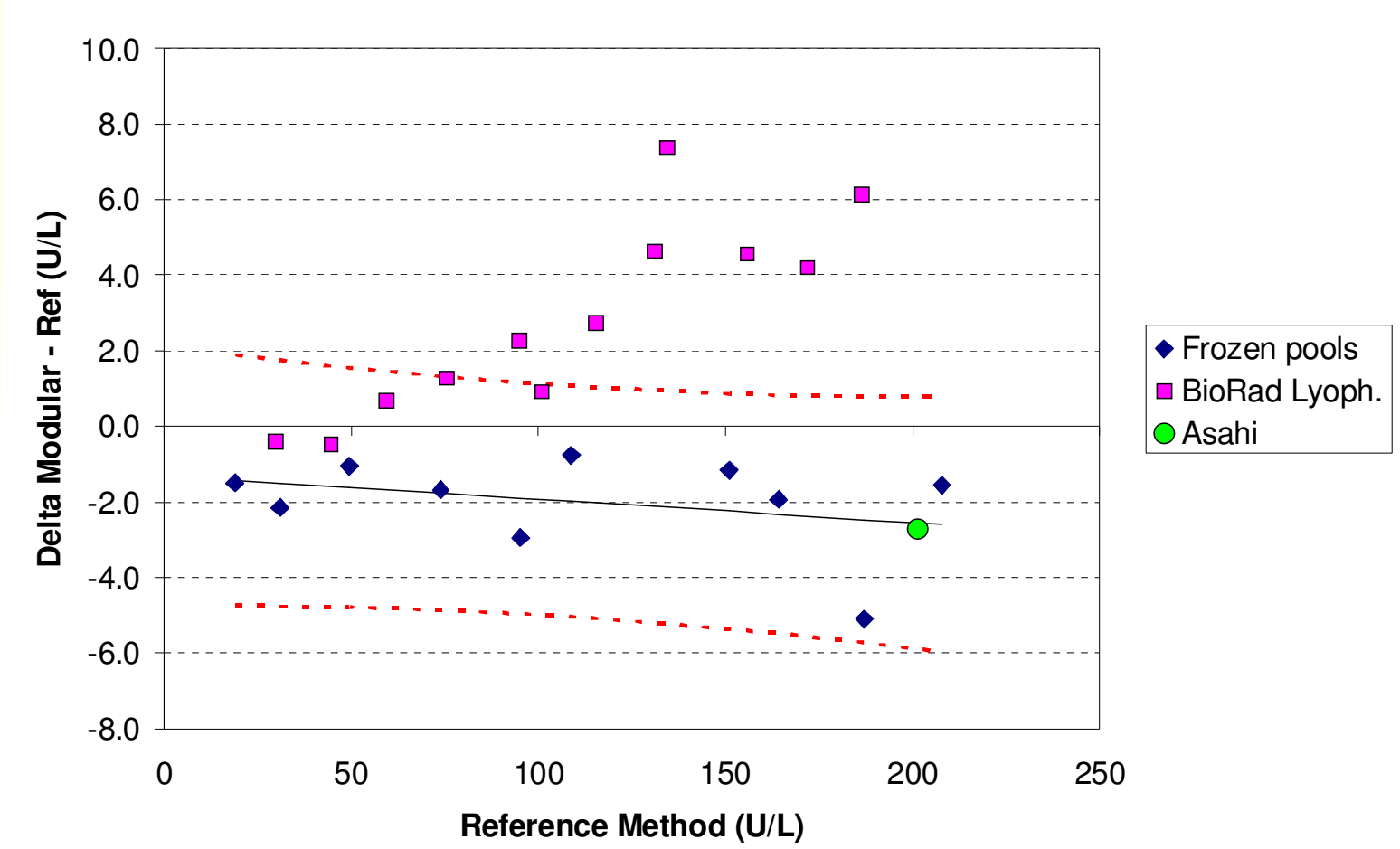


Figure 1. Use of the Regression Protocol and 95% Prediction Interval to Evaluate Commutability Between Methods MA and MD in Appendix B

AST commutability
40 fresh samples



AST commutability
10 frozen pools



Non-commutability

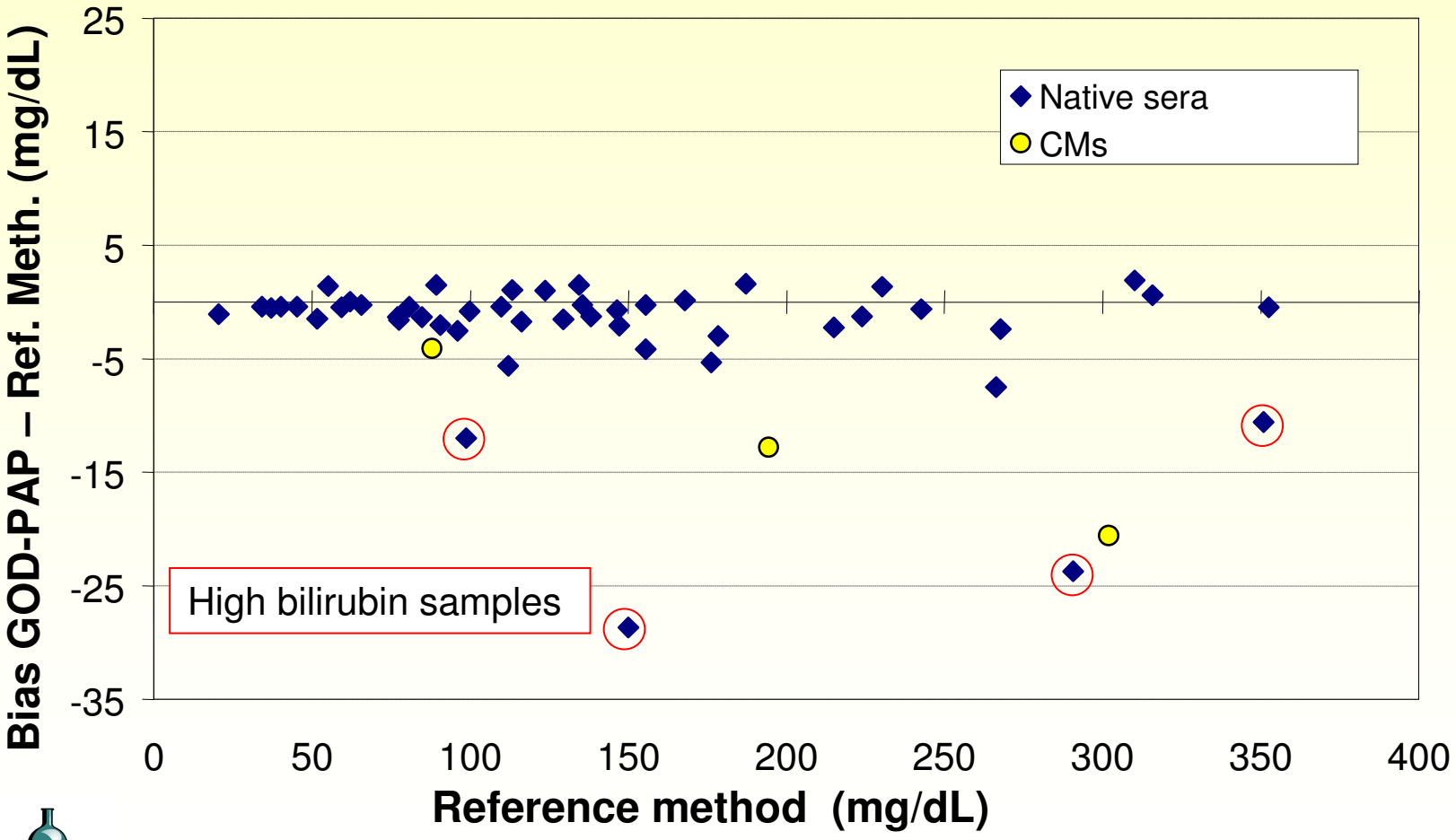
- Undesired byproduct of materials preparation combined with the nonspecificity limitations of some routine clinical laboratory methods. (W.G. Miller)
- Depends upon an abnormal material – method interaction

Non - commutability

- Important to distinguish between
  - **non – commutability**: problems only when analyzing CMs
  - **non – specificity** of the method: problems also with patients' sera

When specificity problems exist non – commutability is much more probable

Glucose


Native sera
CMs
High bilirubin samples
Bias GOD-PAP – Ref. Meth. (mg/dL)
25
15
5
-5
-15
-25
-35
0
50
100
150
200
250
300
350
400
Reference method (mg/dL)

Commutability verification experiment (hypothesis)

- 6 analytical systems
- 12 EQAS control materials
- 10 fresh frozen serum pools
- Triplicate analysis of both pools an control materials
- 20 common general chemistry analytes

TOTAL: 7920 routine analyses, 1320 Reference method analyses

Limits of commutability evaluation

- Can be applied only to "homogenous" analytical systems
- Impossible to check every analytical system
- Very expensive for immunochemical methods
- Complex organization, need for collaboration with manufacturers and / or many laboratories

Commutability assessment in a "twin study"

- Pairing laboratories two by two.
- Every pair of laboratories is asked to split six fresh patient samples with concentrations covering the analyte measurement range,
- to exchange them with the partner laboratory, and to assay them the next day (within 24 h after collection).
- Until analysis, specimens are stored at 4 °C.
- In total, 12 patient specimens are assayed in duplicate by each laboratory in a single analytical batch with the Control materials randomly interspersed between the fresh patient specimens.

Causes for non-commutability

Matrix

- Turbidity
- pH
- Higher or lower viscosity
- Presence of exogenous substances
- Absence of trace elements

Analyte

- Enzymes / proteins of animal origin
- Unusual isoenzyme composition
- Partially denaturated proteins
- Non glycosilated proteins

Alternative ways to assess commutability

Matrix problems

Check the methods

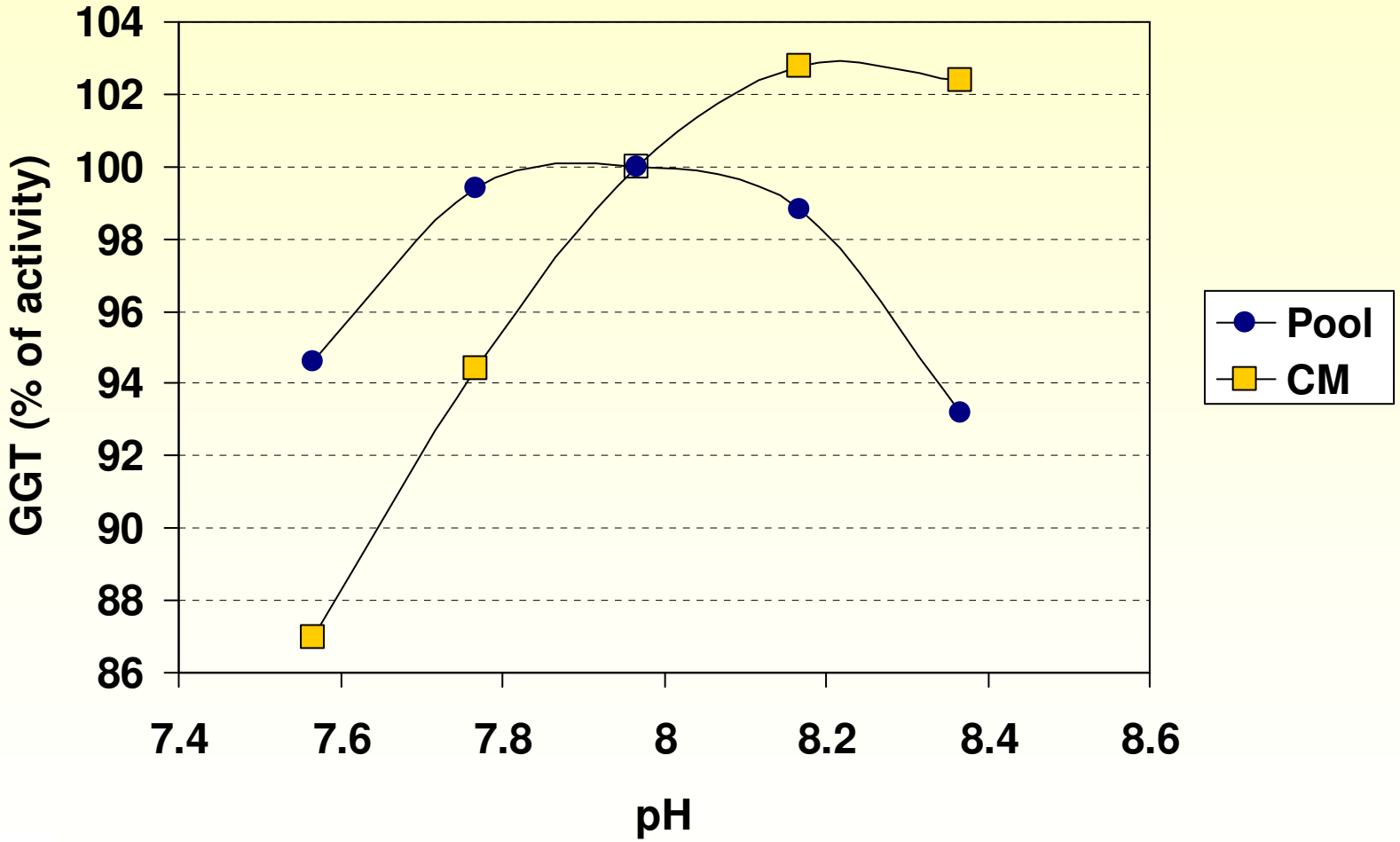
- Influence of:
  - Turbidity
  - Bilirubin
  - pH of the sample
  - Stabilizers
  - Etc.

Analyte problems (enzymes)

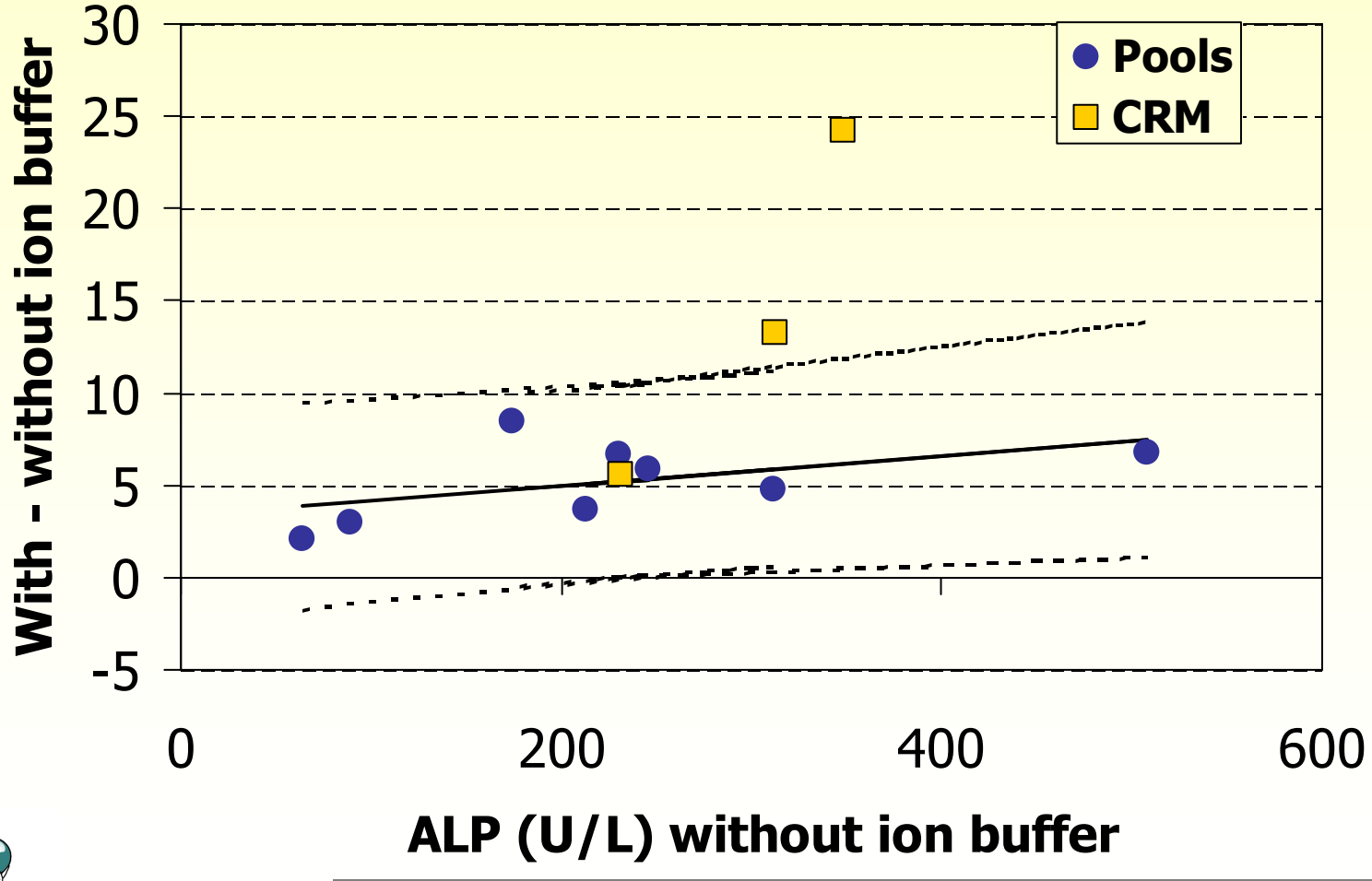
Check the CM

- Km
- Effect of activators – inhibitors
- pH optimum
- Buffer type / conc.
- Substrate type / conc

γGT pH optimum



ALP effect of the ion buffer



How to obtain commutability?

- Frozen materials collected according to CLSI C37-A
- Specialized materials dedicated to small groups of analytes (e.g. lipids, enzymes etc.)
- Use of recombinant enzymes / proteins
- Factors to correct the matrix bias

Model of Lab Measurements for an EQA material

$$Y_p = a_p + b_p X + d_{p,s}$$

Y_p = mean result of a peer group p

X = true (e.g. IDMS) concentration of the analyte

a_p, b_p = "calibration error" of the peer group (obtained on native sera)

$d_{p,s}$ = "matrix bias" (group p, material s)

Usefulness of the Matrix Bias Correction Factor

Measurement of a CM → Result affected both by "matrix bias" and "calibration error"

Matrix bias correction → Result affected only by "calibration error"

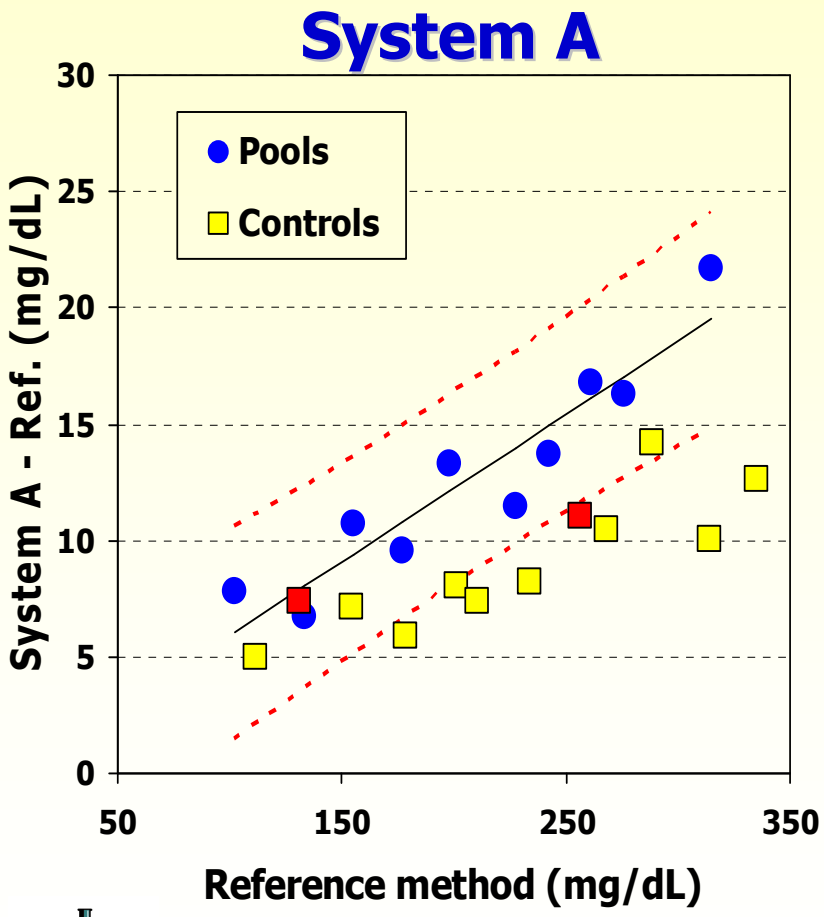
Calculation of the Matrix Bias Correction Factor (MBCF)

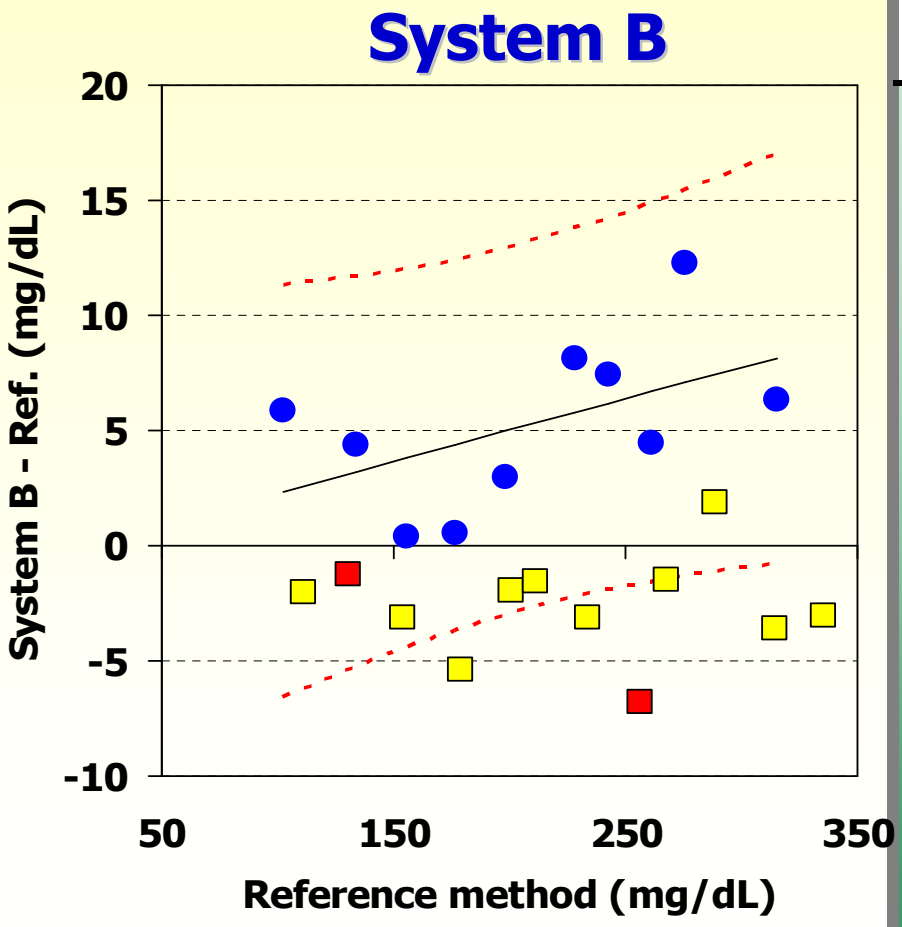
1. Analysis of CMs and 10 fresh frozen serum pools both with Reference and routine methods
2. Calculation of MBCF (material-Peer Group specific) according to the following formula:

$$\mathbf{MBCF = [(b_p C_L) + a_p] / Y_{pL}}$$

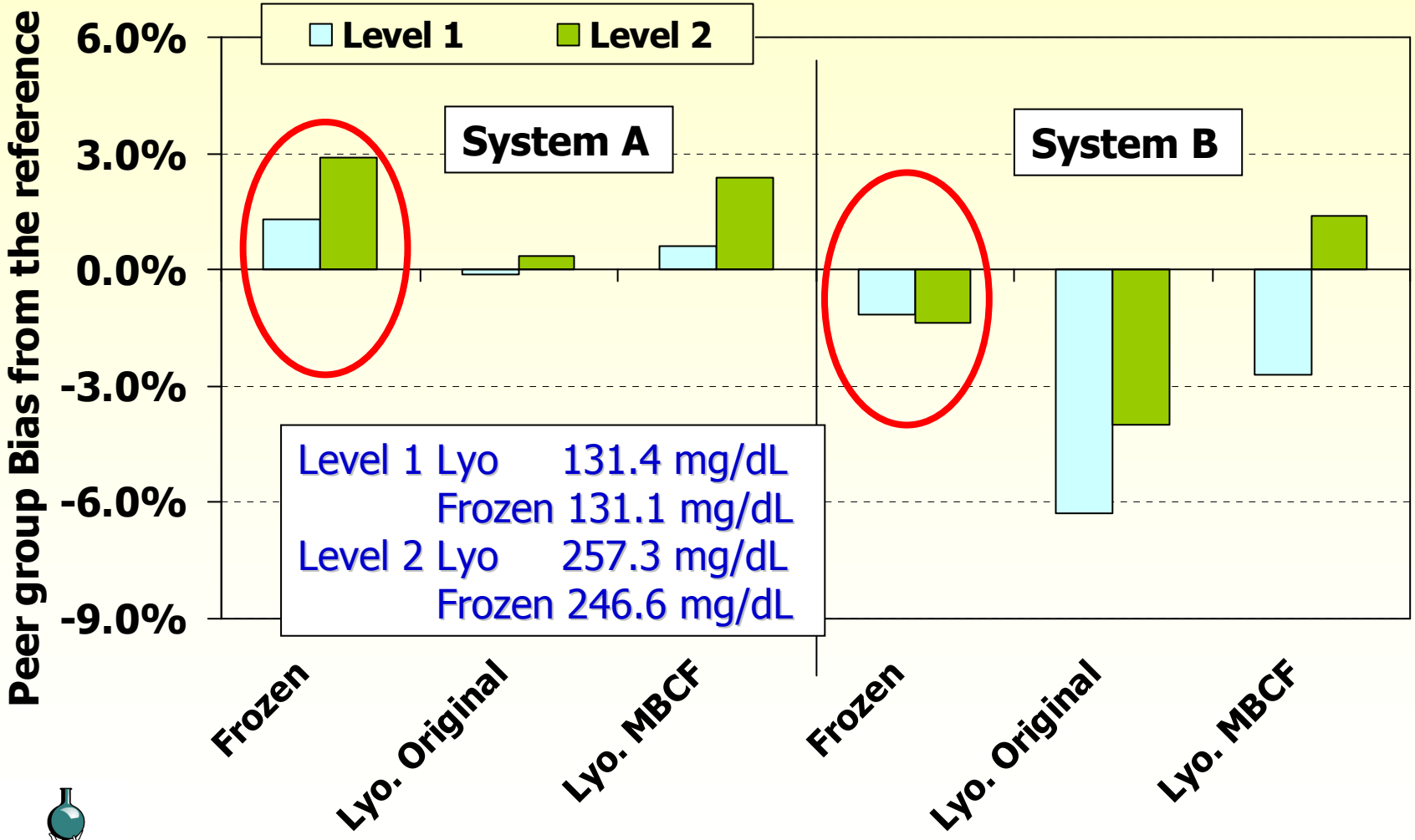
a_p, b_p = parameters of regression line vs. Ref. Meth (fresh frozen serum pools)
C_L = true value of control serum (Ref. meth)
Y_{pL} = mean value of control serum for P group

Cholesterol: commutability verification





Cholesterol: behavior of two analytical systems in a PT scheme



Conclusions

- Without commutable materials EQAS have very limited utility and Reference Method values are useless or even dangerous (wrong conclusions).
- The evaluation of commutability of the CMs requires a relevant effort, but can be performed.
- Fresh frozen pools are expensive to distribute and usually have narrow concentration ranges.
- Matrix bias correction factors can be an intermediate solution while developing better CMs

Amylase: method comparison