

# FDA/CDRH Public Meeting: Blood Glucose Monitoring

**Industry Perspective:  
Tighter Performance  
Criteria Are Achievable  
and Appropriate**



**Barry H Ginsberg, MD, PhD**  
Diabetes Technology Consultants



# Barry H Ginsberg, MD, PhD

## Credentials

72	MD	Einstein COM	
71	PhD	Einstein COM	Molecular Biology
72-74	Residency	Harvard	Beth Israel Hosp
74-77	Fellow	Diabetes	NIH (Diabetes Br)
77-90	Professor	Internal Med	Univ Iowa
		Biochemistry	Univ Iowa
	Clin Assoc	VA Med Cntr	Iowa City
	Research Assoc		
83-90	Princ Investig	DCCT	Univ Iowa
90-07	VP Medical	WW Diabetes	Becton Dickinson
07-	Consultant	Diabetes Technology	Consultants

# Current Conflicts

## Direct

Consulting Medical Director  
Speaker  
Consultant

Agamatrix  
Bayer  
JDRF

## Indirect

Consultant  
Consultant

Roche  
LifeScan



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# Overview

## ■ Background

- Measurements of inaccuracy
- Necessary accuracy, outliers
- Sources of error

## ■ Current technology

- Accuracy
- Methods to improve

## ■ Testing and reporting

- Internal vs external
- Periodic

## ■ Consumer product

- Labeling



# Accuracy and Precision

Need both

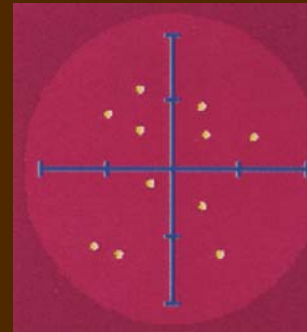
One number

MARE

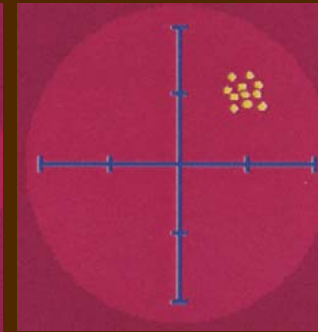
➤ Mean Absolute Relative Error

➤ Several other names  
MAE, MAD

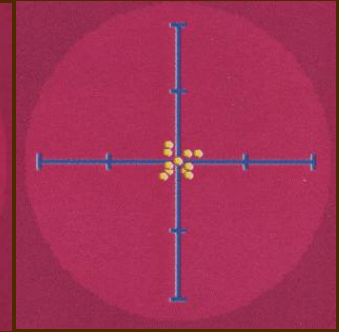
Bias



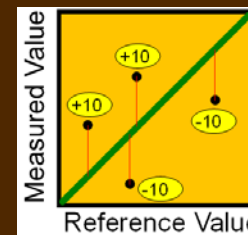
Accurate



Precise



Accurate  
and Precise



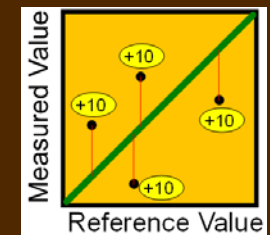
Accurate

(Mean)

Error

0

10



Accurate/ Precise

(MARE)



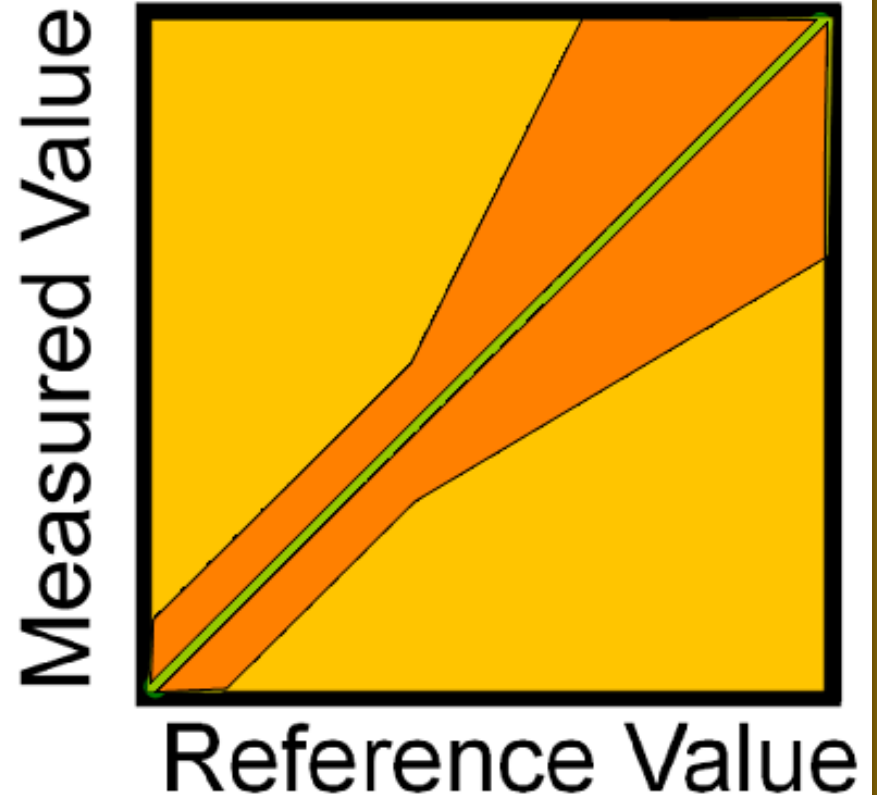
# ISO 15197 (Orange)

## International Standard

- Clinical and laboratory
- Study design

## 95% of values within:

- 20% of reference for  $BG > 75$
- 15 mg/dL of reference for  $BG < 75$



# Extended ISO 15197

## 🔥 Accuracy

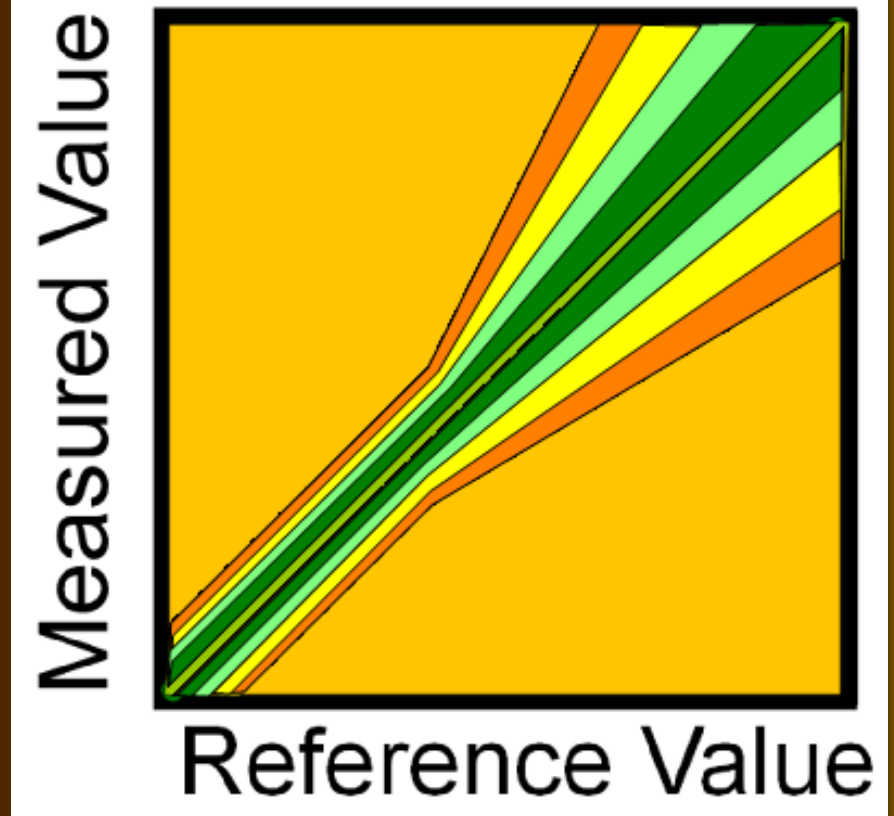
% of values falling within:

mg/dL

<75	3.8	7.5	11.3	15 mg
>75	5	10	15	20 %

🔥 At 70 mg/dL:

ISO	55-85
15%	59-81
10%	62-78
5%	66-74



# Error in Diabetes Control

## ■ Selecting insulin dose

Error	Likely	High
CHO cnt	15	25
Constants	10	25
Ins absorp	20	30
<b>Total</b>	<b>27% (<math>\pm 68\%</math>)</b>	<b>46% (<math>\pm 115\%</math>)</b>

■ BGM only adds 1-3% to this

■ Hypoglycemia: At 70 mg/dL:

<b>ISO</b>	<b>55-85</b>
<b>15%</b>	<b>59-81</b>
<b>10%</b>	<b>62-78</b>
<b>5%</b>	<b>66-74</b>

# Desired Accuracy

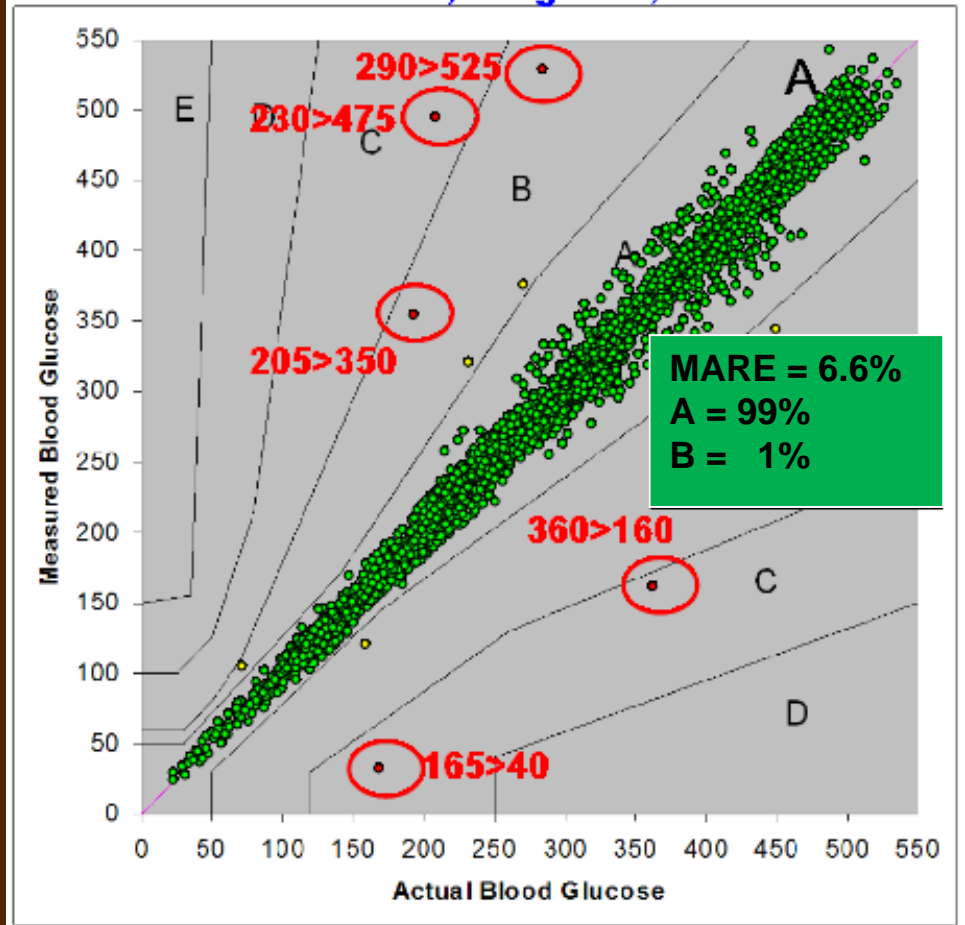
Meter/ Standard	<5%	<10%	<15%	20%
Type 2 Diet/Orals				95%
Type 2 Insulin			95%	
Type 1 Insulin		95%		
Laboratory	95%			
MARE	2%	4%	6%	8%

# Outliers

## Error Grid

- C, D and E are outliers
- Serious outliers  
~0.03-0.1%  
(100-300 mg/dl)
- Dangerous

Clarke Error Grid, Integrated, Patients



For illustrative purpose only

# Sources of Error

## 🔥 Intrinsic

- Manufacturing variation:  
well, enzyme, age, mediator oxidation

## 🔥 Physical location

- Temperature, Altitude

## 🔥 Interfering substances

- Intrinsic: urate, triglycerides, oxygen
- Extrinsic: GO: Ascorbate, Acetaminophen, L-Dopa, Tolazimide  
GDH-PQQ: Maltose, Icodextrin, Xylose

## 🔥 Patient factors

- Medical: Hematocrit
- Education: Technique, Coding, Handwashing



# ISO 15197 Data

TABLE 1. BG MONITORING SYSTEM ACCURACY RESULTS







FRECKMANN ET AL.

BG monitoring system	ISO 15197 C Requirements fulfilled <sup>a</sup>	BG concentration $\geq 75$ mg/dL			
		$\pm 20\%$	$\pm 15\%$	$\pm 10\%$	$\pm 5\%$
Accu-Chek Active	Yes	100% (170/170)	98% (166/170)	88% (149/170)	52% (88/170)
Accu-Chek Aviva	Yes	100% (164/164)	99% (162/164)	95% (156/164)	71% (117/164)
Ascensia Contour	Yes	98% (161/164)	91% (149/164)	74% (121/164)	44% (72/164)
FreeStyle Freedom	Yes	100% (162/162)	100% (162/162)	94% (152/162)	69% (111/162)
FreeStyle Lite	Yes	100% (164/164)	99% (162/164)	87% (142/164)	53% (87/164)
GlucoCard-X-Meter	Yes	100% (162/162)	93% (150/162)	82% (133/162)	52% (84/162)
OneTouch Ultra 2	Yes	100% (164/164)	96% (158/164)	76% (124/164)	43% (71/164)
OneTouch Ultra Easy	Yes	99% (162/164)	91% (150/164)	71% (116/164)	30% (50/164)
Optium Xceed (E)	Yes	99% (158/160)	93% (149/160)	78% (125/160)	44% (71/160)
		BG conce. $< 75$ mg/dL			
		$\pm 20$ mg/dL	$\pm 15$ mg/dL	$\pm 10$ mg/dL	$\pm 5$ mg/dL
Accu-Chek Active	Yes	100.0% (200/200)	100% (30/30)	93% (28/30)	47% (14/30)
Accu-Chek Aviva	Yes	100.0% (200/200)	100% (36/36)	83% (30/36)	69% (25/36)
Ascensia Contour	Yes	98.5% (197/200)	100% (36/36)	86% (31/36)	64% (23/36)
FreeStyle Freedom	Yes	100.0% (200/200)	100% (38/38)	92% (35/38)	66% (25/38)
FreeStyle Lite	Yes	100.0% (200/200)	100% (36/36)	89% (32/36)	47% (17/36)
GlucoCard-X-Meter	Yes	99.0% (198/200)	95% (36/38)	92% (35/38)	74% (28/38)
OneTouch Ultra 2	Yes	100.0% (200/200)	100% (36/36)	97% (35/36)	69% (25/36)
OneTouch Ultra Easy	Yes	99.0% (198/200)	100% (36/36)	94% (34/36)	75% (27/36)
Optium Xceed (E)	Yes	98.5% (197/200)	98% (39/40)	93% (37/40)	43% (17/40)

# ISO 15197 Data

Meter	<20%	<15%	<10%	<5%
Company A	99	91	68	35
Company B	96	91	82	52
Company C	99	95	84	53
Company D	100	98	88	52
Company E	99	98	92	63
Company F	98	97	89	61
Company G	98	95	79	41
Company H	99	98	92	65
Company I	99	98	93	71

# Methods to Improve Accuracy

 <b>Hematocrit</b>	AC impedance, dynamic electrochemistry
 <b>Temp / Altitude</b>	Thermistor, dynamic electrochemistry
 <b>Mfg variation</b>	QC, dynamic electrochemistry
 <b>Interferants</b>	Multiple electrodes, dynamic electrochemistry
 <b>Coding</b>	Code select, code on strip
 <b>Aging</b>	Date strip/cartridge

# Clinical Testing

## You can trust device manufacturers clinical trials

- If EU certified, ask for NB testing (independent)
- ISO 15197 specifies clinical protocol
- Pass
  - ❖ 95% of values are within 20% (15 mg for <75 mg/dL)
  - ❖ Can also find out how many are within 15%, 10%, 5%

# Testing: Internal or External

## Information is king in a consumer product

- Need to create informed consumers
- Best way: standardized information

## External testing

- Standard protocol for clinical testing random lots
- Standardized analysis
- Standardized labeling
- Fifth grade reading level
- “Batting average”
- Standard protocol for outlier analysis



# Testing: Periodic

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- Clinical testing every 6-12 months
  - ❖ Random lots
  - ❖ Reasonable failures require correction not recall
- Outlier testing – continuous
  - ❖ May be performed by manufacturer

# Recommendations

## ■ Accuracy:

- Substantial majority of users only require ISO 20%
  - ❖ Keep ISO 20% as minimal acceptable clinical accuracy with random lots.
- Labeling:
  - ❖ Strip container labeled with MARE & extended ISO
  - ❖ ?label as group appropriate

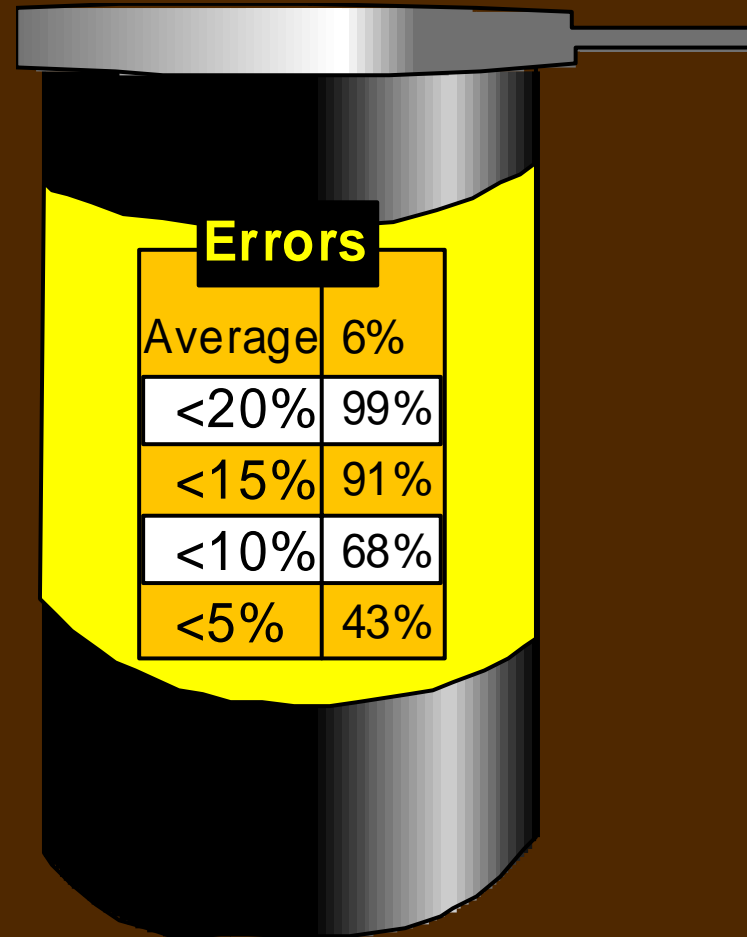
## ■ Testing:

- Initial random lots, external control (Notif. Body-like)
- Periodic testing of random lots
- Better testing of outliers

# Recommendations (2)

## ■ Labeling:

- Develop standard label
- MARE
  - ❖ A “batting average” would be even better
- Extended ISO
- ?Intended consumers



# Summary

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- Blood glucose monitoring is currently accurate enough for a substantial majority of patients (by number, not usage)
- Better accuracy is achievable but not necessary for everyone
- Since it is a consumer product, better labeling is essential
  - External testing with standard protocol
  - Periodic testing
  - Standard label, like nutritional labeling

Questions?

