Quality Planning: Principles and Practices

A new role for Risk Analysis in developing Analytic QC Plans?

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“A rose is a rose is a rose!”

But, is a glucose a glucose a glucose?

Or, a glucose a BMG glucose or an e-glucose from HbA1c?

Or, an INR an INR an INR?

Harmonization is a major issue for medical laboratories today!

- "Improving Clinical Laboratory Testing Through Harmonization: An International Forum", Oct 26-27, 2010, NIST, Gaithersburg MD
  - "The AACC is hosting an **invitation only** conference on global harmonization of results from clinical laboratory testing procedures for which no reference measurement procedure exists or is likely to be developed. The two-day conference will seek to strengthen quality of laboratory measurements and improve patient care by developing consensus on technical and organizational processes to achieve harmonization of clinical laboratory results.

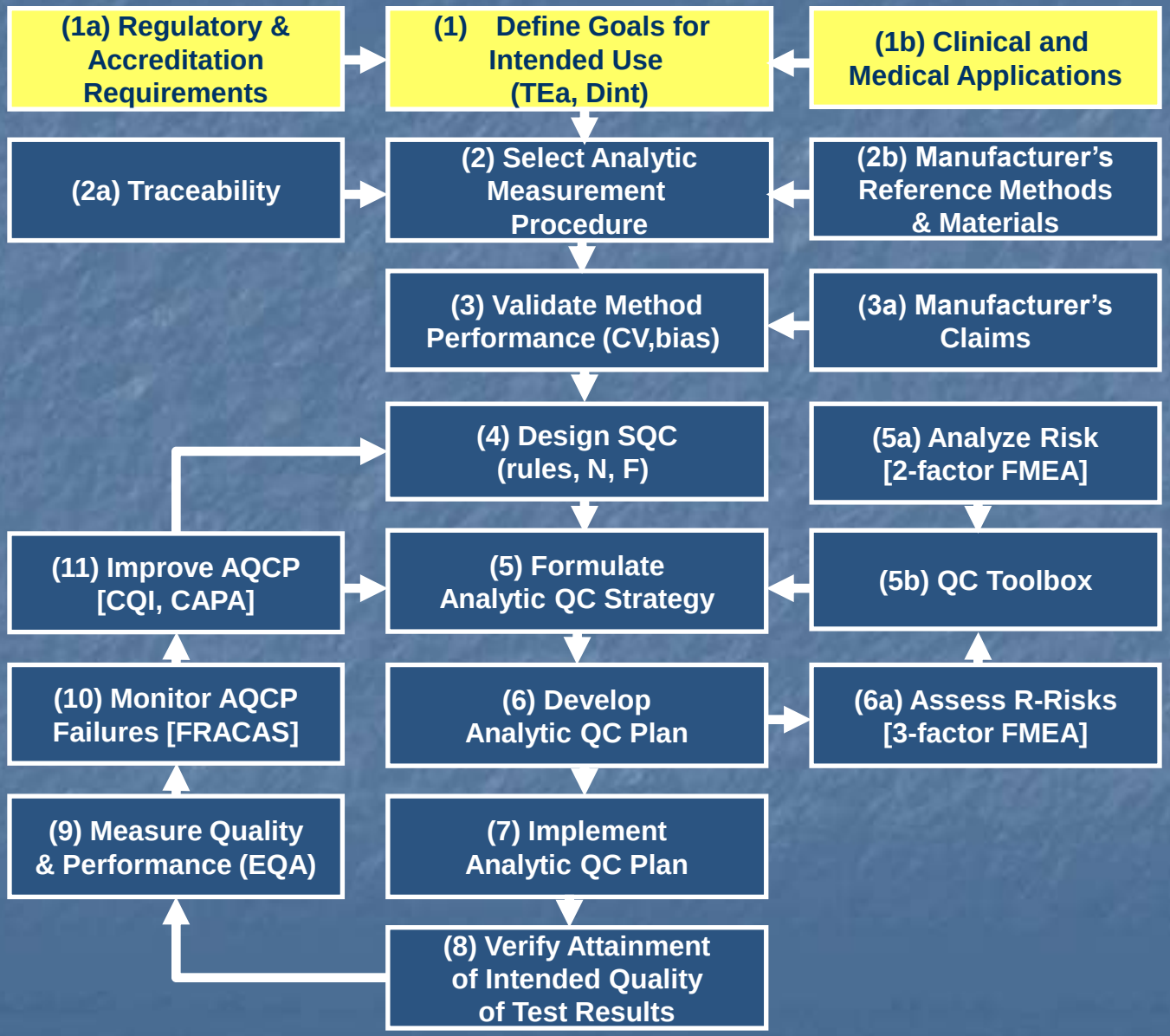
Harmonization

- CLSI definition: **harmonization** in glycohemoglobin (GHB) testing, the process by which GHB test results among laboratories are made comparable to a common reference.
  - Harmonization is a process!
  - Comparability is a measure of the outcome!
  - Are HbA1c test results comparable today?

How assure comparability?

- Traceability
  - In principle, laboratory methods should have common reference materials and methods to establish the correct or true test values
- Analytical Quality Management (AQM)
  - Quality systems, method validation, QC design, Analytic QC Plan, Risk Analysis
- External Quality Assessment
  - In practice, test performance must be monitored to demonstrate comparability

What's the plan for AQM?

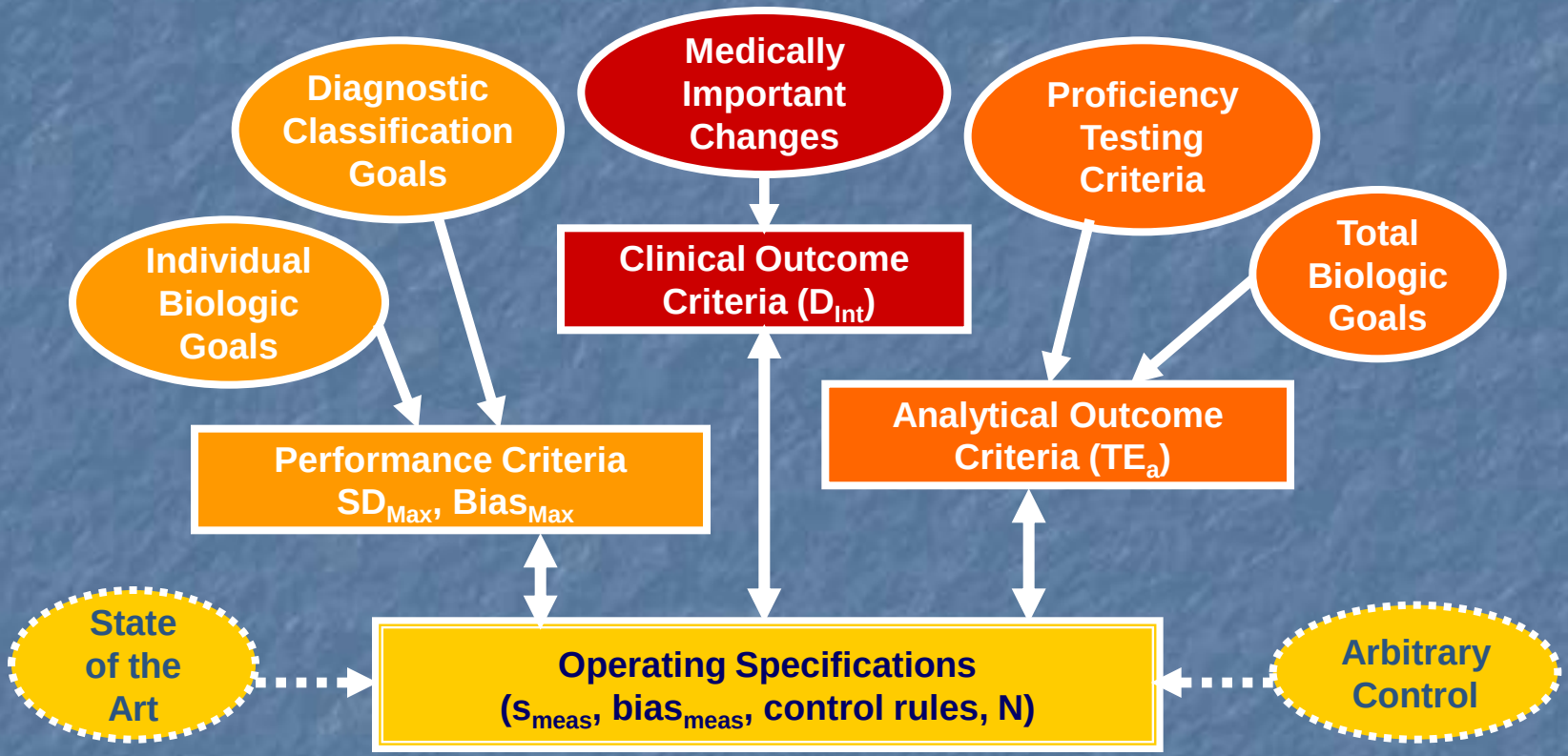


1999 Stockholm Conference Global Analytical Quality Specifications

- "Hierarchy" of quality specifications
  - Quality required for specific clinical applications
  - Quality required generally to monitor individual subjects based on intra-individual biologic variation
  - Quality recommendations from experts and expert groups (e.g., NCEP, NACB, etc)
  - EQA or PT quality requirements (e.g, CLIA)
  - "State of the Art" requirements

Reference: Strategies to Set Global Analytical Quality Specifications in Laboratory Medicine. Scand J Clin Lab Invest 1999;59:No.7(Nov)

"Systems" Perspective

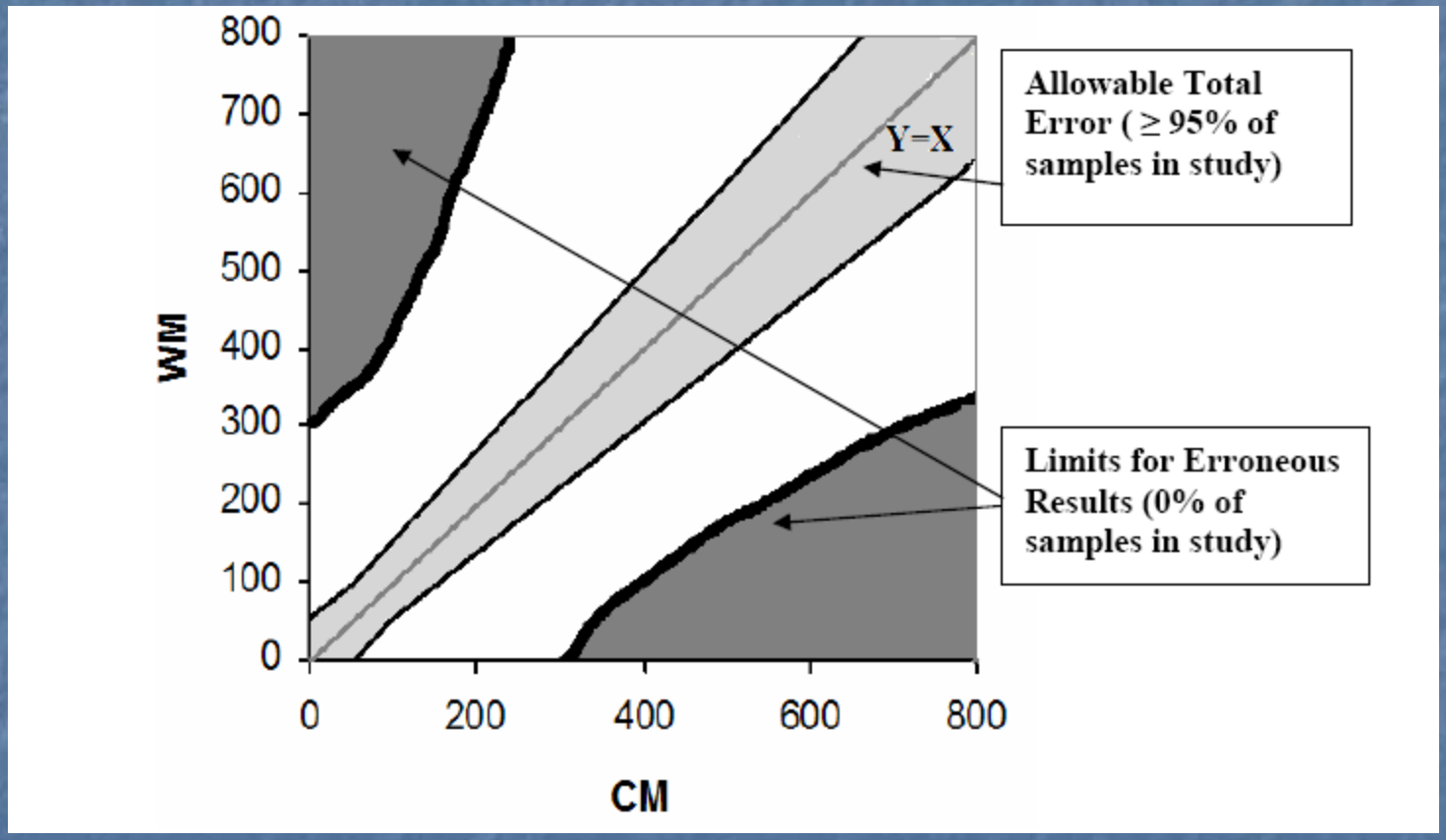


- Ref: Westgard JO. The need for a system of quality standards for modern quality management. Scand J Clin Lab Invest 1999;59:481-486.

Progress with Quality Goals

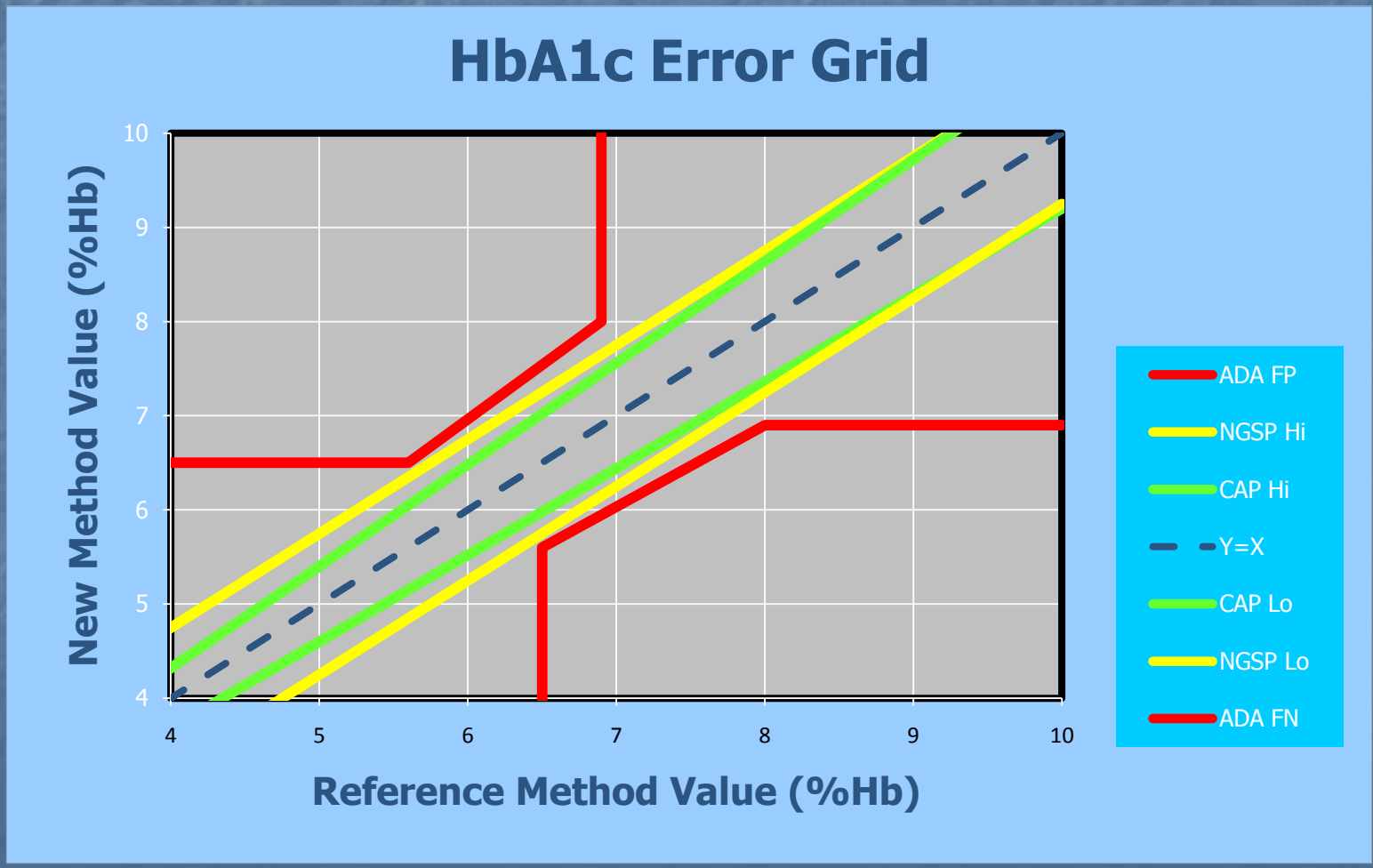
- FDA supports use of Allowable Total Error to validate quality of "waived" tests
- Recommends use of "error grids"
  - Clarke et al. Diabetes Care 1987;10:622-8
  - Parkes et al. Diabetes Care 2000;23:1143-8
- CLSI EP27P published late 2009
  - "How to Contruct and Interpret an Error Grid for Diagnostic Assays"

FDA Guidance (2008)
Allowable Total Error Grid

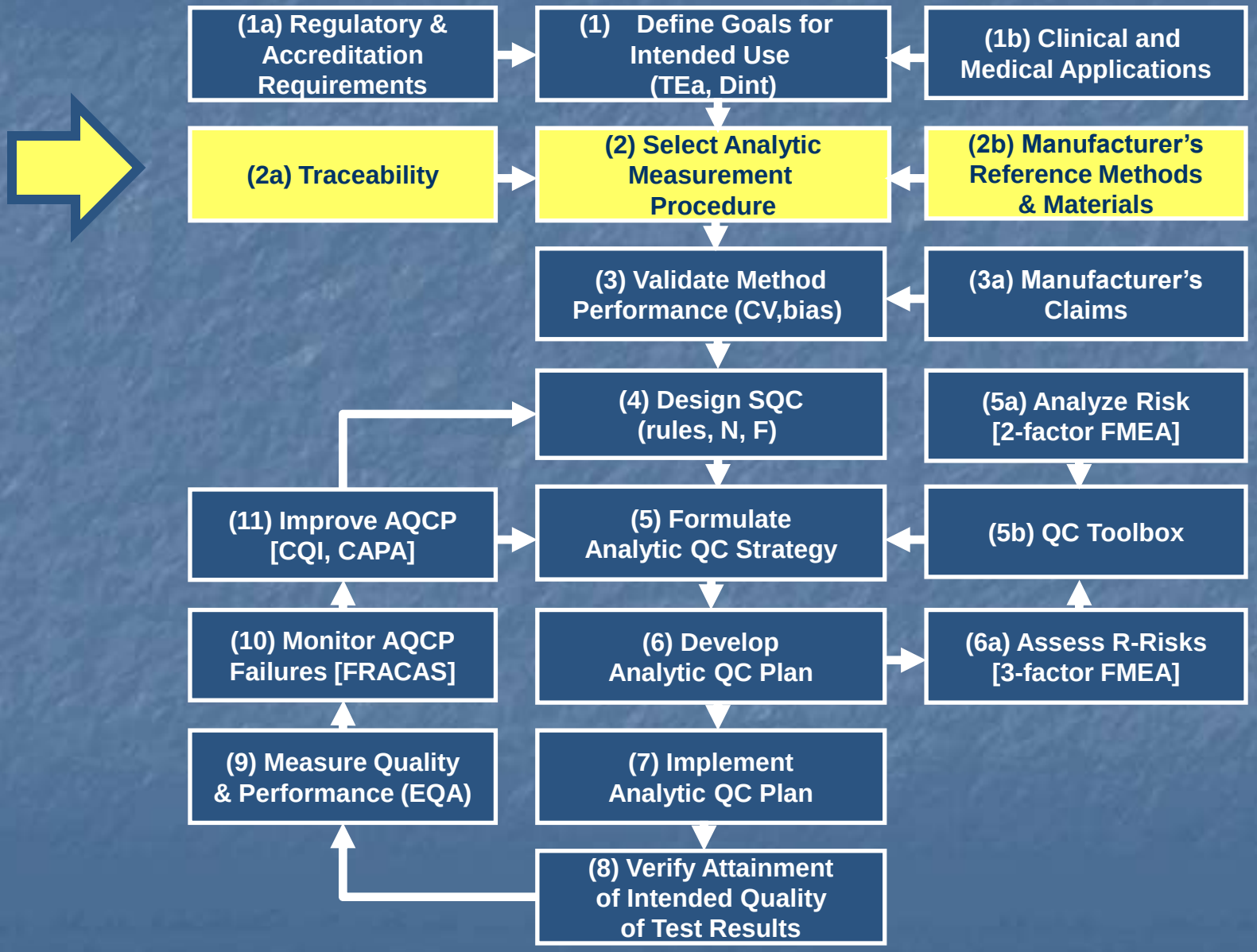


Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers' of Invitro Diagnostic Devices. Jan 30, 2008, Food and Drug Adminstration

HbA1c Diagnostic (Δ0.8%Hb) and Monitoring (Δ1.0%Hb) Goals vs NGSP Certification vs CAP PT



What's the plan for AQM?



Metrological Standards for Quality Measurement Processes

- Traceability
  - Property of the results of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an ***unbroken chain of comparisons*** all having stated uncertainties
- Uncertainty of measurement
  - Parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand

Traceability Chain

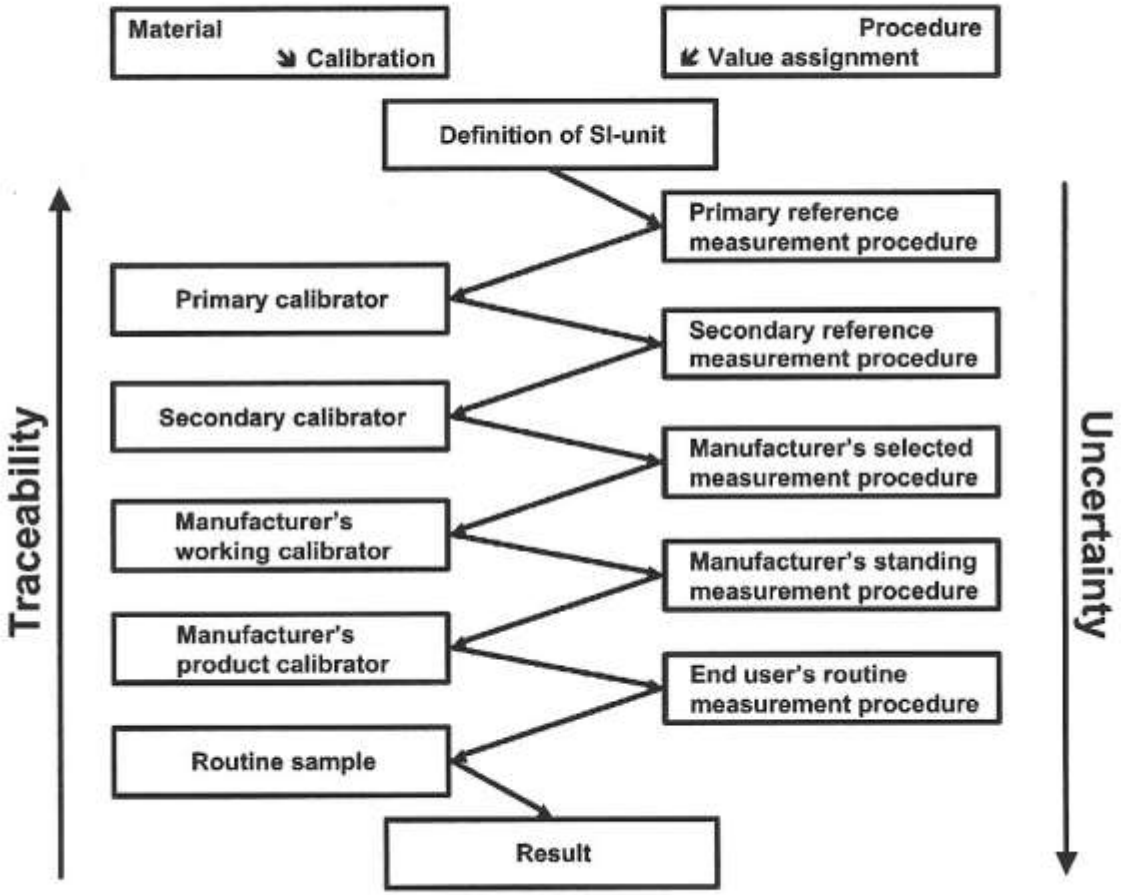


Figure 1 Extensive calibration hierarchy to ensure metrological traceability to the SI (adapted from EN/ISO 17511).

Issues with Traceability

- Definition of analyte and units
  - "Physico-chemical complexity" of biologic measurands and matracies
- Lack of Primary Reference Materials
- Lack of Primary Reference Methods
- Lack of Secondary Calibrators
- Lack of Secondary Reference Methods
- Need for Reference Laboratory Services

"Medical Traceability"

- Thienpont et al. Clin Chem Lab Med 2004;42:842-850
  - "Physio-chemical complexity"
    - Complex biologic matrices
    - Analyte may be a class of substances
    - Lack of specificity in measurement procedures
  - Need for traceability models that utilize "accepted" reference materials and methods, value-assignment protocols, laboratory networks as base of reference

Model II: International Reference Method and Calibrator

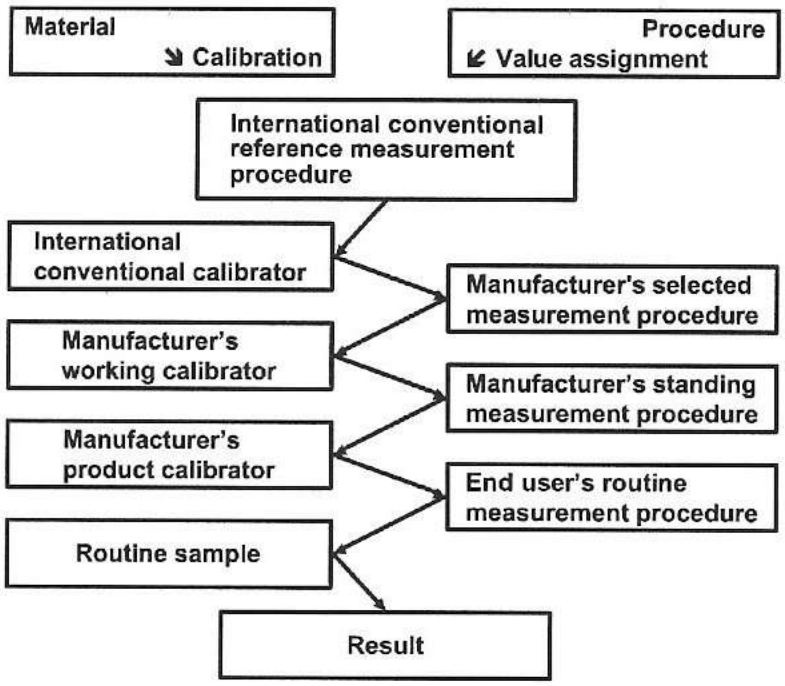
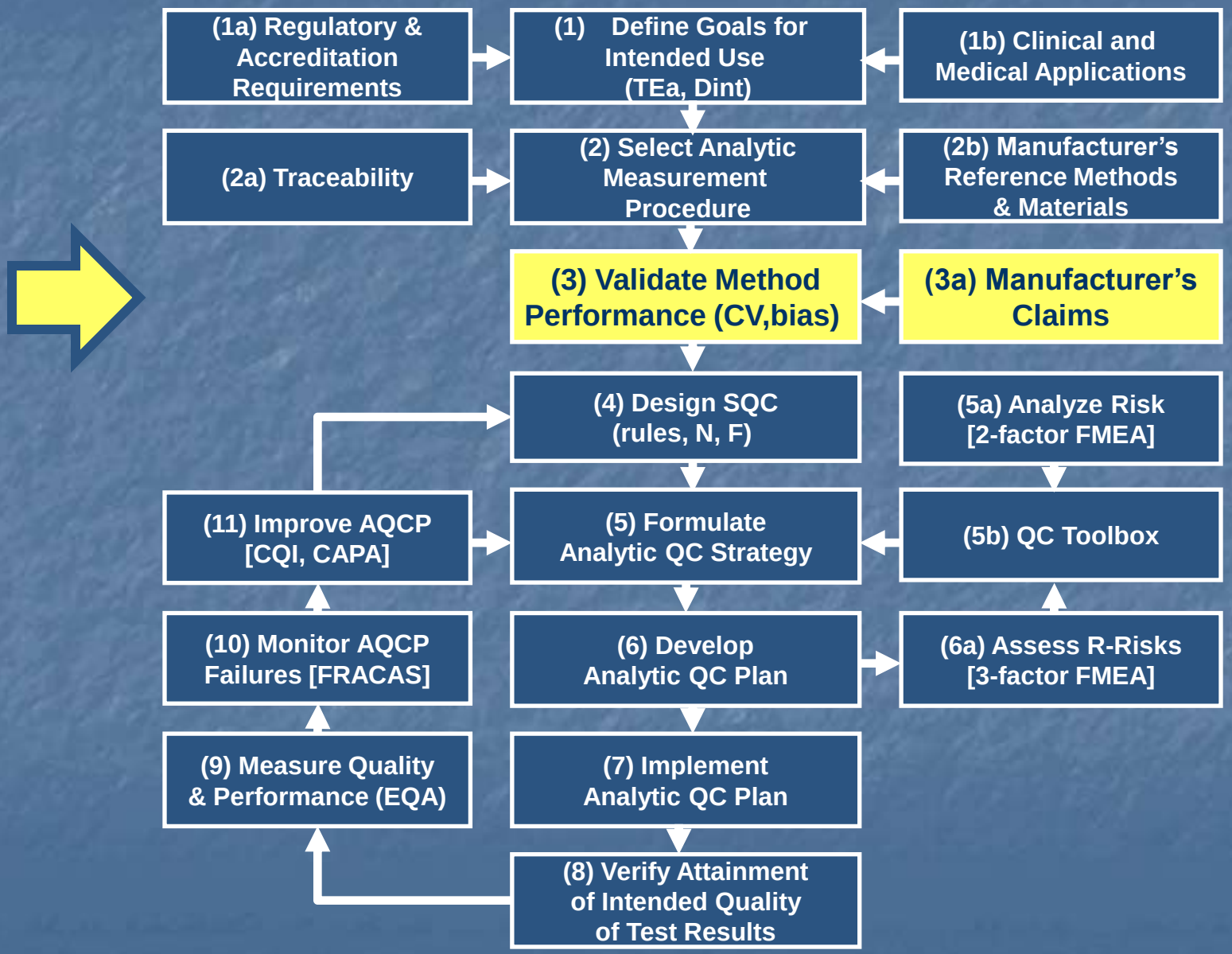


Figure 2 Calibration hierarchy and metrological traceability to an international conventional reference measurement procedure and international conventional calibrator (applies, e.g., to the measurement of the amount-of-substance concentration of hemoglobin (Fe)).

What's the plan for AQM?



Method Validation in the Real World: HbA1c example

- Lenters-Westra E, Slingerland RJ. Six of Eight Hemoglobin A1c Point-of-Care Instruments Do Not Meet the General Accepted Analytical Performance Criteria. Clin Chem 2010;56:44-52.
- Bruns DE, Boyd JC. Few Point-of-Care Hemoglobin A1c Assay Methods Meet Clinical Needs. Clin Chem 2010;56:4-6.

Precision results from Lenters Study

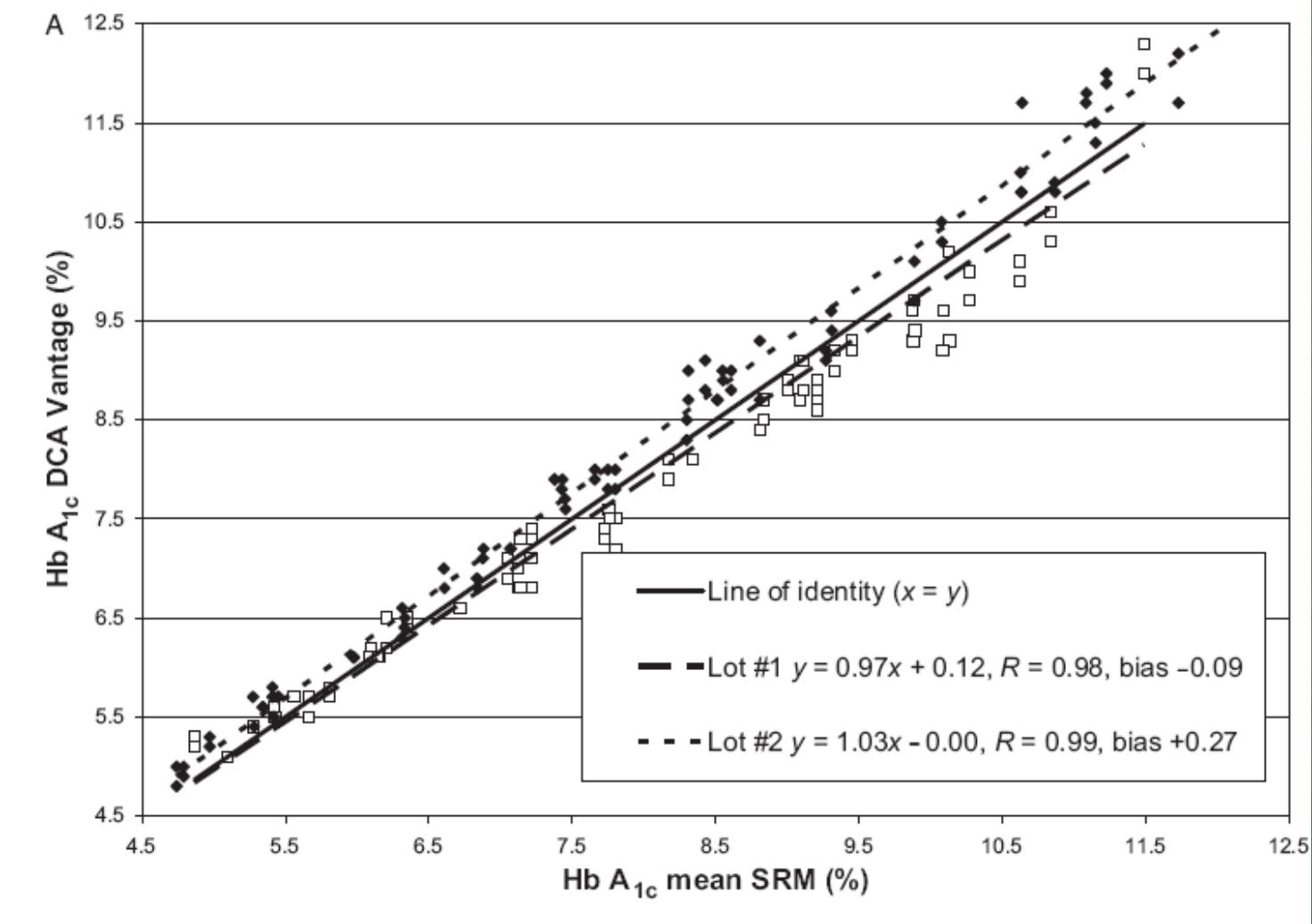
Table 1. EP-5 total CV imprecision results from the different POC instruments.

	In2it	DCA Vantage	Clover	InnovaStar	Nycocard	Afinion
Patient sample 1	4.9% (5.1%)[a]	1.8% (5.1%)	4.0% (5.0%)	3.2% (5.2%)	4.8% (4.8%)	2.4% (4.7%)
Patient sample 2	3.3% (11.2%)	3.7% (11.2%)	3.5% (11.9%)	3.9% (11.5%)		
Nycocard normal control					5.3% (6.1%)	
Nycocard abnormal control					5.2% (11.6%)	
Afinion control CI						1.4% (6.3%)
Afinion control CII						1.8% (8.2%)

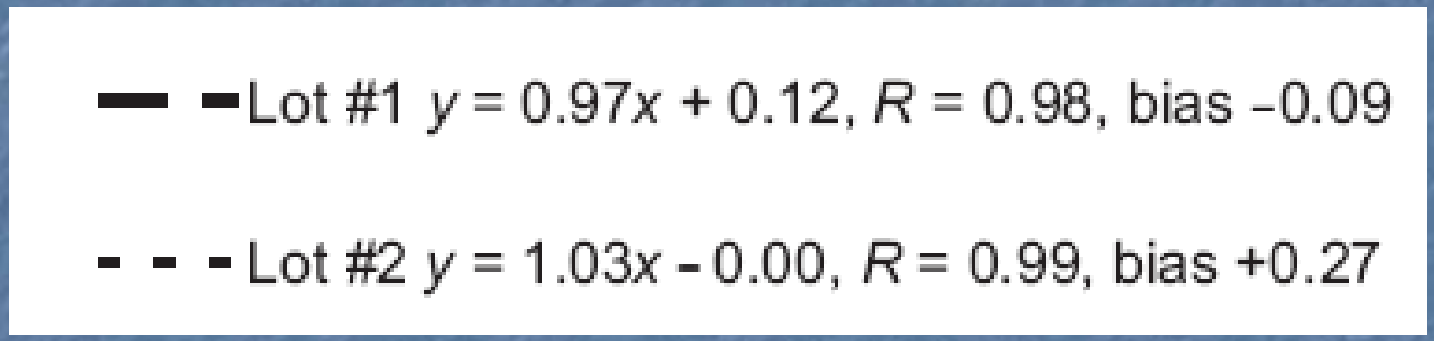
[a] Hb A_{1c} value of the sample/control are in parentheses.

Lenters-Westra E, Slingerland RJ. Six of Eight Hemoglobin A1c Point-of-Care Instruments Do Not Meet the General Accepted Analytical Performance Criteria. Clin Chem 2010;56:44-52.

Accuracy results - Comparison with avg of 3 reference methods



What do the statistics tell us about the size of errors?



- For Xc=7.0 %Hb
  - Yc = 0.97*7.0 + 0.12 = 6.91
    - SE = 6.91–7.0 = -0.09 %Hb or 1.3%Bias
  - Yc = 1.03*7.0 – 0.0 = 7.21
    - SE = 7.21 – 7.0 = +0.21 %Hb or 3.0%Bias

What quality is needed in a medical laboratory for the intended clinical use of HbA1c?

- CAP criterion was 10% in 2009, 8% in 2010 (8%) and will be 6% in 2011
- NGSP 2010 criterion of ±0.75 %Hb corresponds to TEa of 10.7% @ 7.0 %Hb;
- CLIA criterion for acceptable performance of glucose is 10%

What's sigma?

- Estimate precision midrange as average of observed CVs at 5.1 and 11 %Hb
  - CV = ~ (1.8+3.7)/2 = ~ 2.75%
- Calculate sigma for each lot #
  - **Sigma = (%TEa-%Bias)/(%CV)**
  - Sigma = (10%-1.3%)/2.75% = 3.16
  - Sigma = (10%-3.0%)/2.75% = 2.55

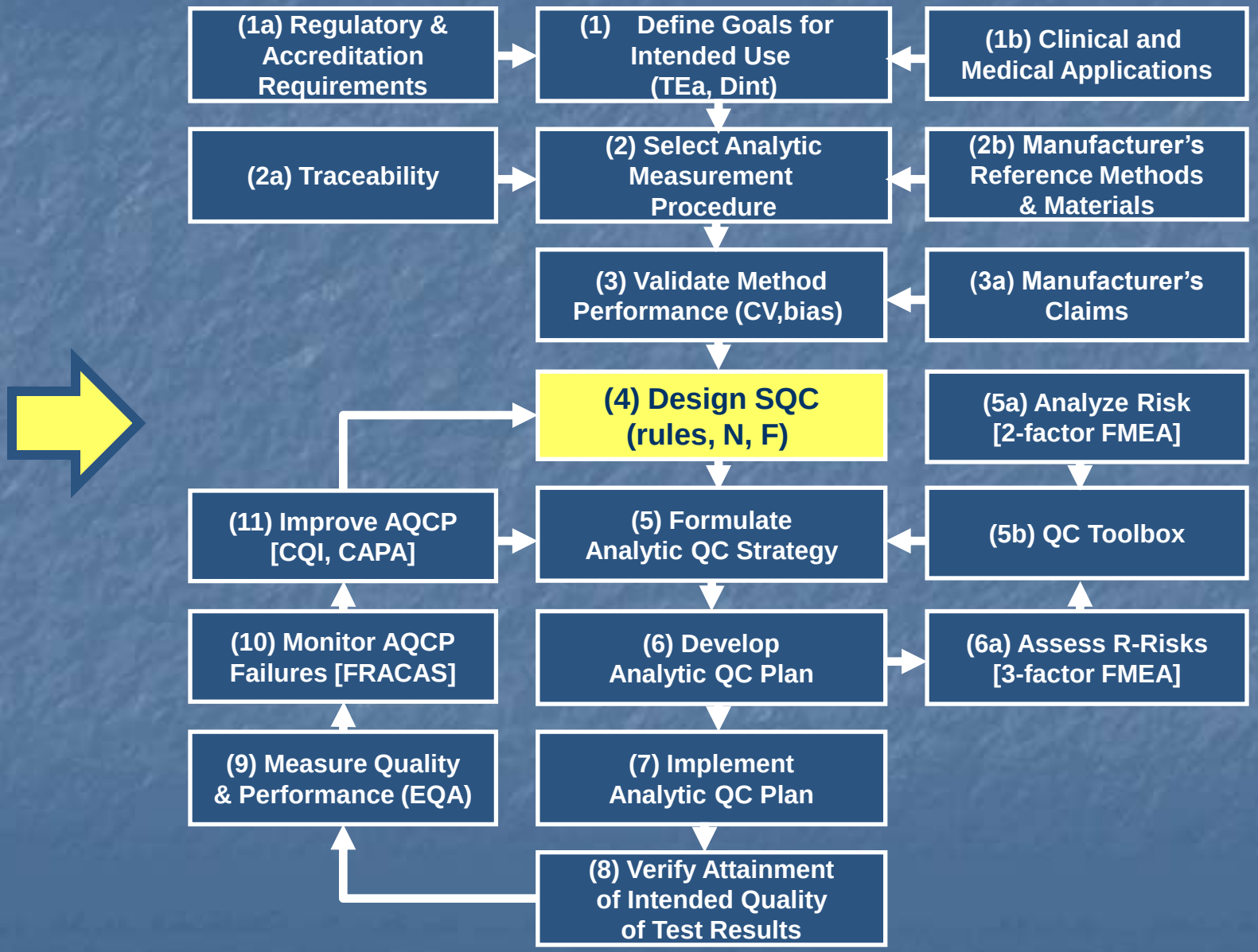
Houston – We have a problem! Or maybe not???

- Waived test doesn't have to meet US CLIA minimum QC of 2/day, nor EQC of 2/week or 2/month!
- Just follow manufacturer's instructions and recommendations
- Not required to validate method performance!
- Not required to participate in PT!

What's the point?

- 1st issue is whether the device can achieve the necessary quality when it is working correctly?
  - Method validation is critical, but not required!
  - Quality is controlled by FDA when device is approved as "waived"
- 2nd issue is that QC only monitors the stable performance achieved
  - Of little use if device can't achieve desired performance

What's the plan for AQM?



ISO 15189
Assuring the quality of examination procedures

- Performance specifications for each procedure used in an examination shall relate to the **intended uses** of that procedure.
- The laboratory shall design internal quality control systems that verify the attainment of the **intended quality of results**.

Where find Guidance to design QC? CLSI C24-A3 (2006)

- 3rd edition published in June 2006
  - Updates QC planning process
  - Adds "Sigma-metric QC selection" tool
  - Define quality requirement as allowable total error (TEa)
  - Calculate sigma as (TEa – bias)/SD
    - Where bias represents inaccuracy of method
    - SD represents imprecision of method

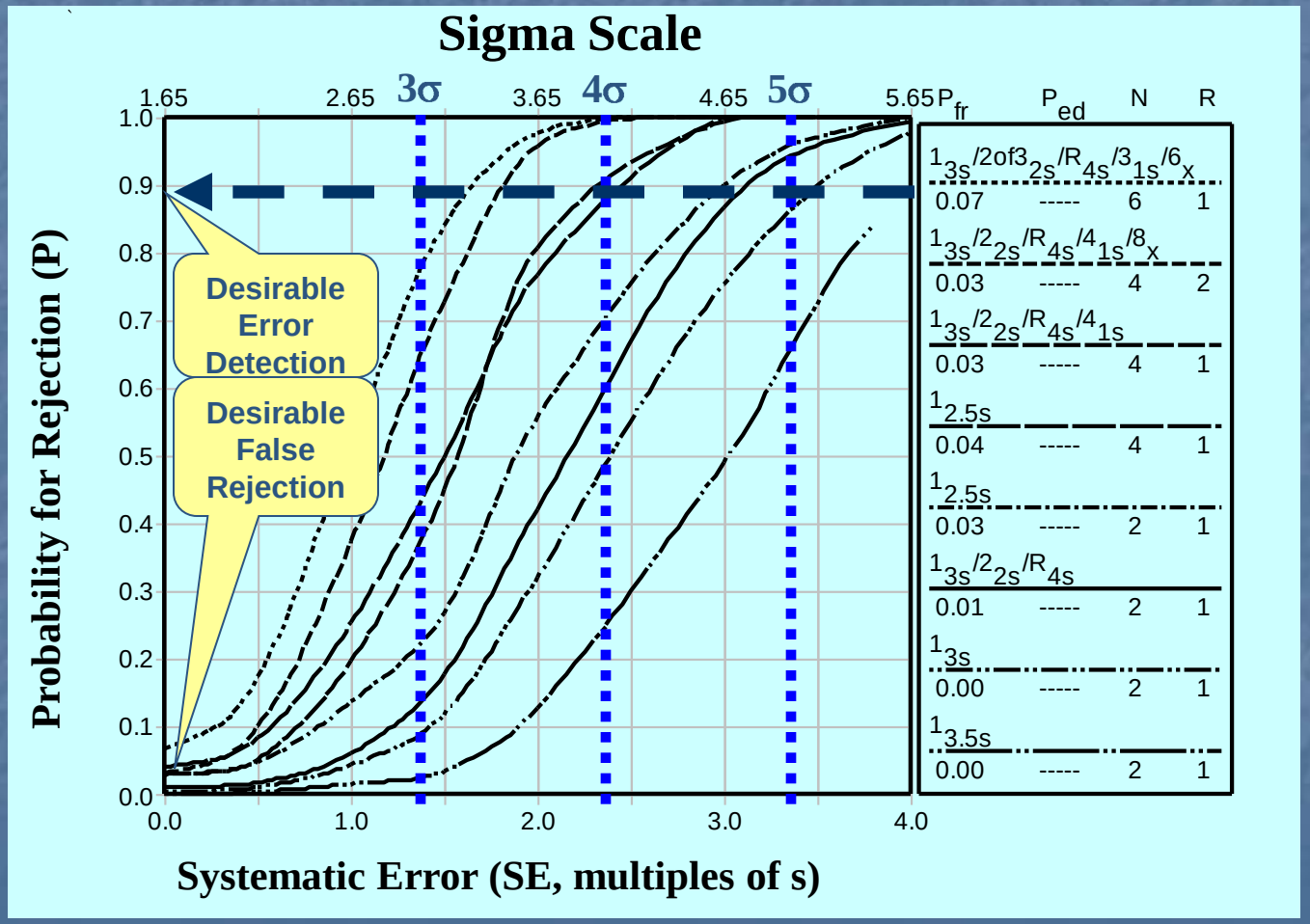
Relationship of Sigma to QC

- Critical Systematic Error (ΔSE_{crit})
  - Index used to describe size of error that needs to be detected by QC procedure
  - $\Delta SE_{crit} = [(TEa - Bias)/CV] - 1.65$

Sigma

  - $\Delta SE_{crit} + 1.65 = Sigma$
  - Can relate ΔSE to rejection characteristics of QC rules and numbers of QC measurements using known power curves

Sigma-metrics QC Selection Tool 2 Levels Control

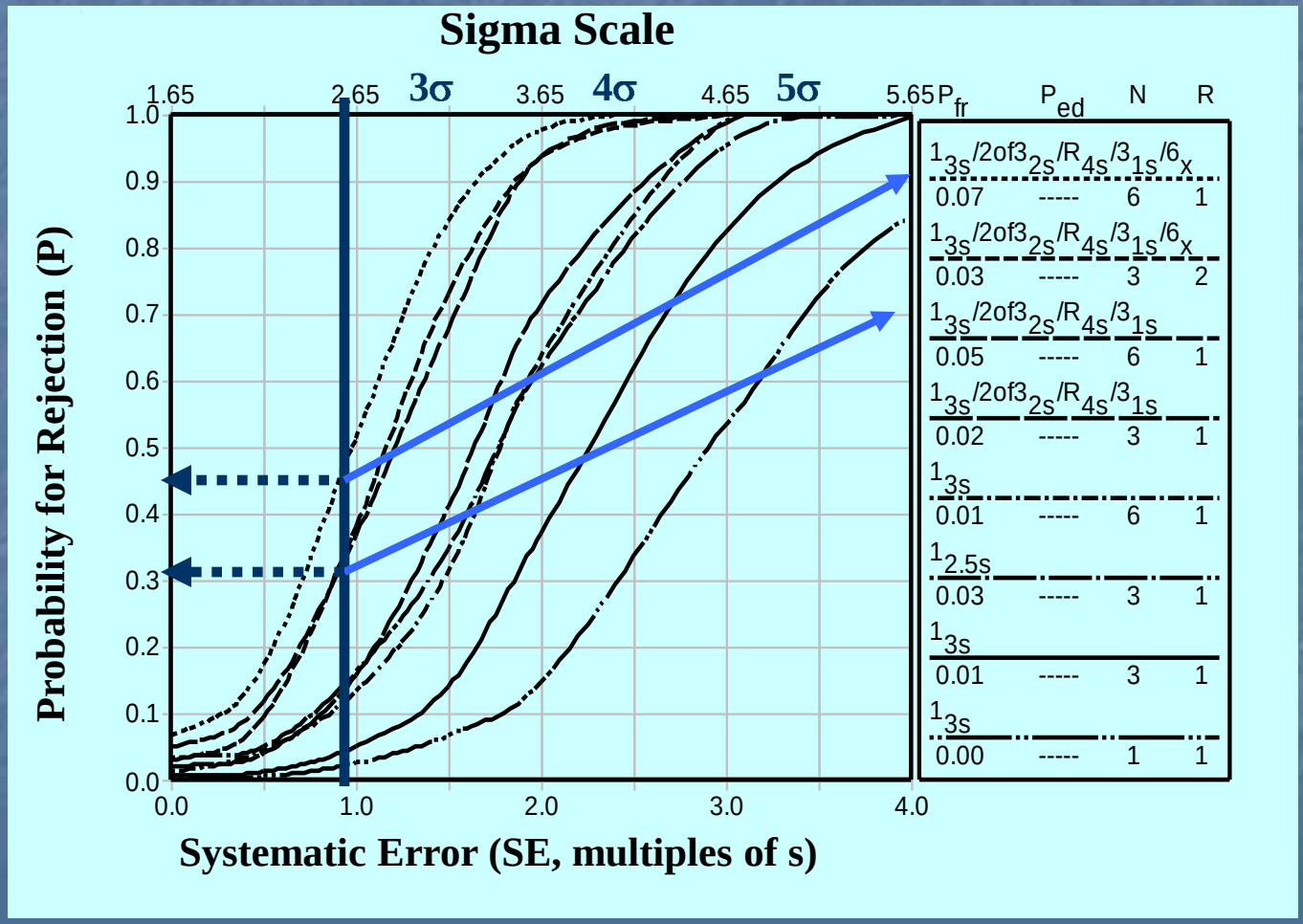


What's the point?

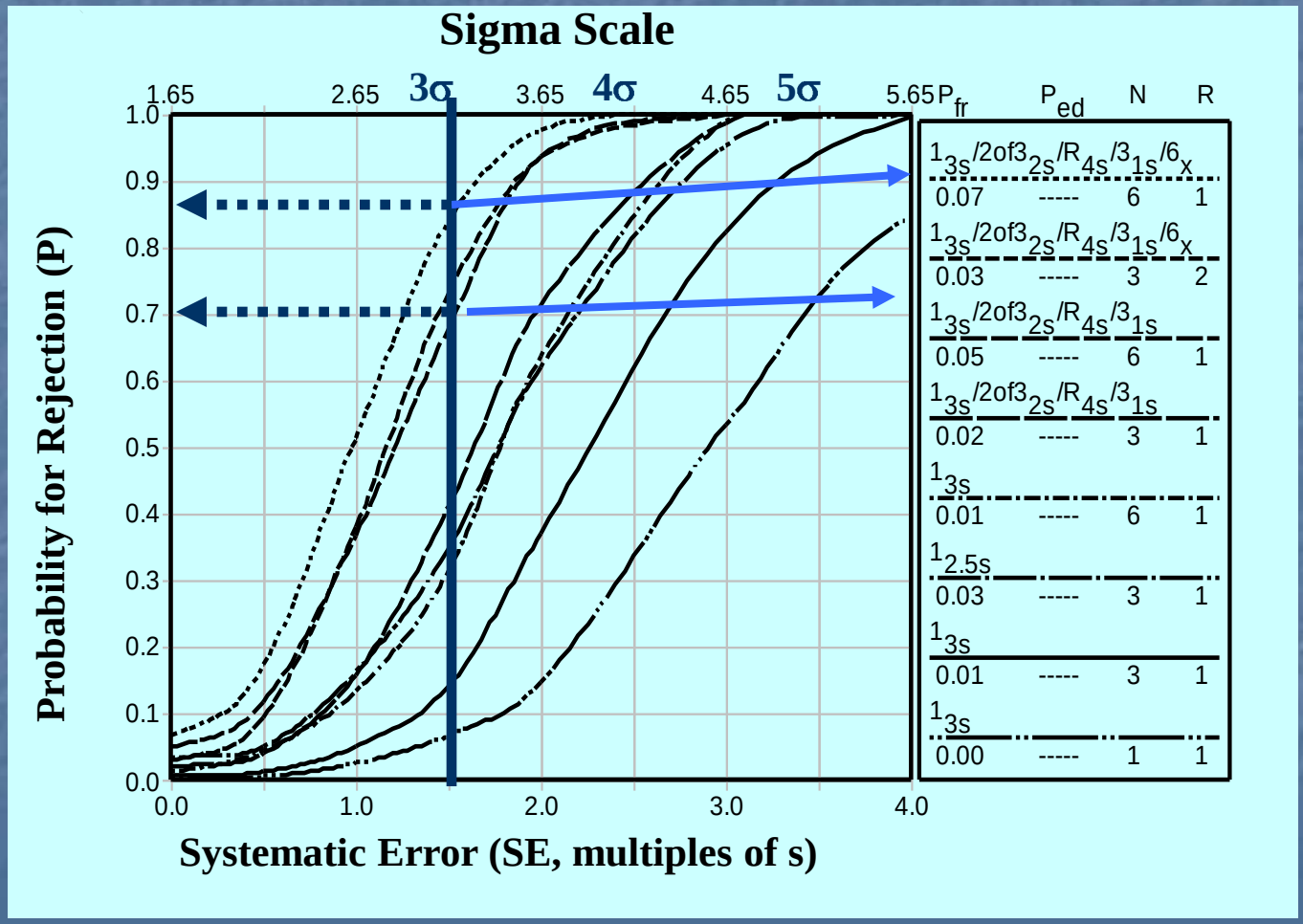
QC needed for a test depends on sigma performance of method!

- **6 sigma process** - any common single rule QC will do!
- **5 sigma process** - single rule QC with 2.5s limits and N of 2-3
- **4-sigma process** – single rule QC with 2.5s limits or multirule QC with Ns of 3-6
- **3-sigma process** – do all QC possible Ns of 6-8
  - Can't afford to run enough controls to detect medically important errors!

What QC is needed?
3 Levels Control (2.55 Sigma)



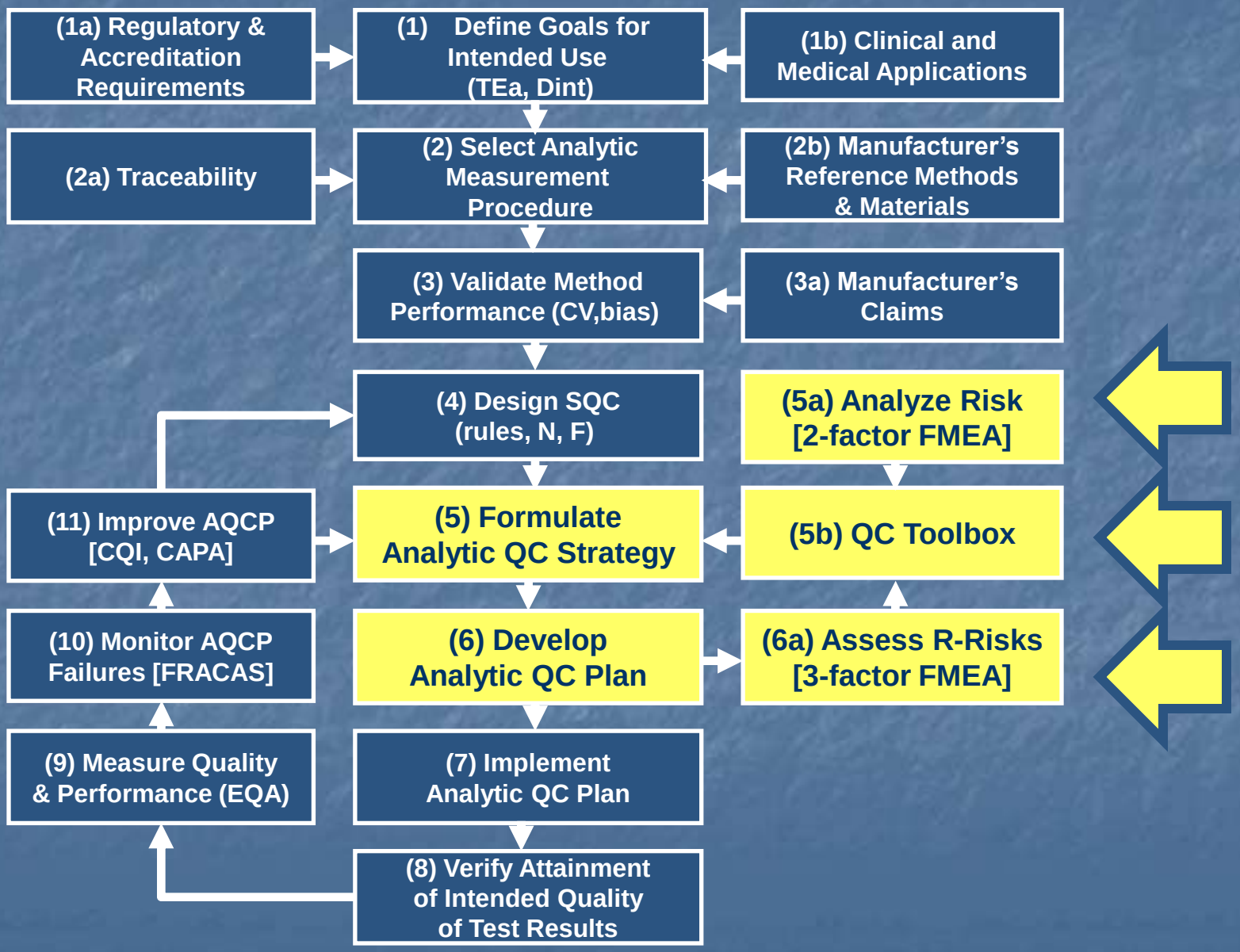
What QC is needed?
3 Levels Control (3.16 Sigma)



Example Application

Method Performance Characteristics and QC Design				
Test (Units)	*Glycated Hemoglobin (%Hb)*			
Method (Analyzer)	*DCA Vantage*			
Medical Decision Levels	Concentrations	LOW Xc	MID Xc	High Xc
		5.0	*7.0*	*9.0*
CLIA Quality Criterion	%TEa	*10%*	*10%*	*10%*
Precision (Replication or QC Data)	SD			
	Mean	*5.1%Hb*		*11.2%Hb*
	%CV	*1.8%*	*~2.75%*	*3.7%*
Bias (Comparison, PT, Peer Data)	Calculated Bias			
	%Bias		*1.3-3.0%*	
Sigma-Metric	(%TEa)/%CV			
	(%TEa - %Bias)/%CV		*3.16-2.55*	
SQC from Sigma tool, Control Rules	*Multi-rule QC*			
Total Number Measurements, N	*All the QC you can afford!*			
Analytical QC Strategy	*Hope and pray nothing goes wrong!*			

What's the plan for AQM?



Risk Management Approach for Developing QC Plan

Recommended by ISO, adopted by manufacturers

- Accepted by CLSI & CMS for "Alternate QC"
  - EP18 "Risk management techniques to identify and control laboratory error sources"
  - EP22 "Presentation of manufacturer's risk information"
  - EP23 "User Quality Control Plans based on risk management"

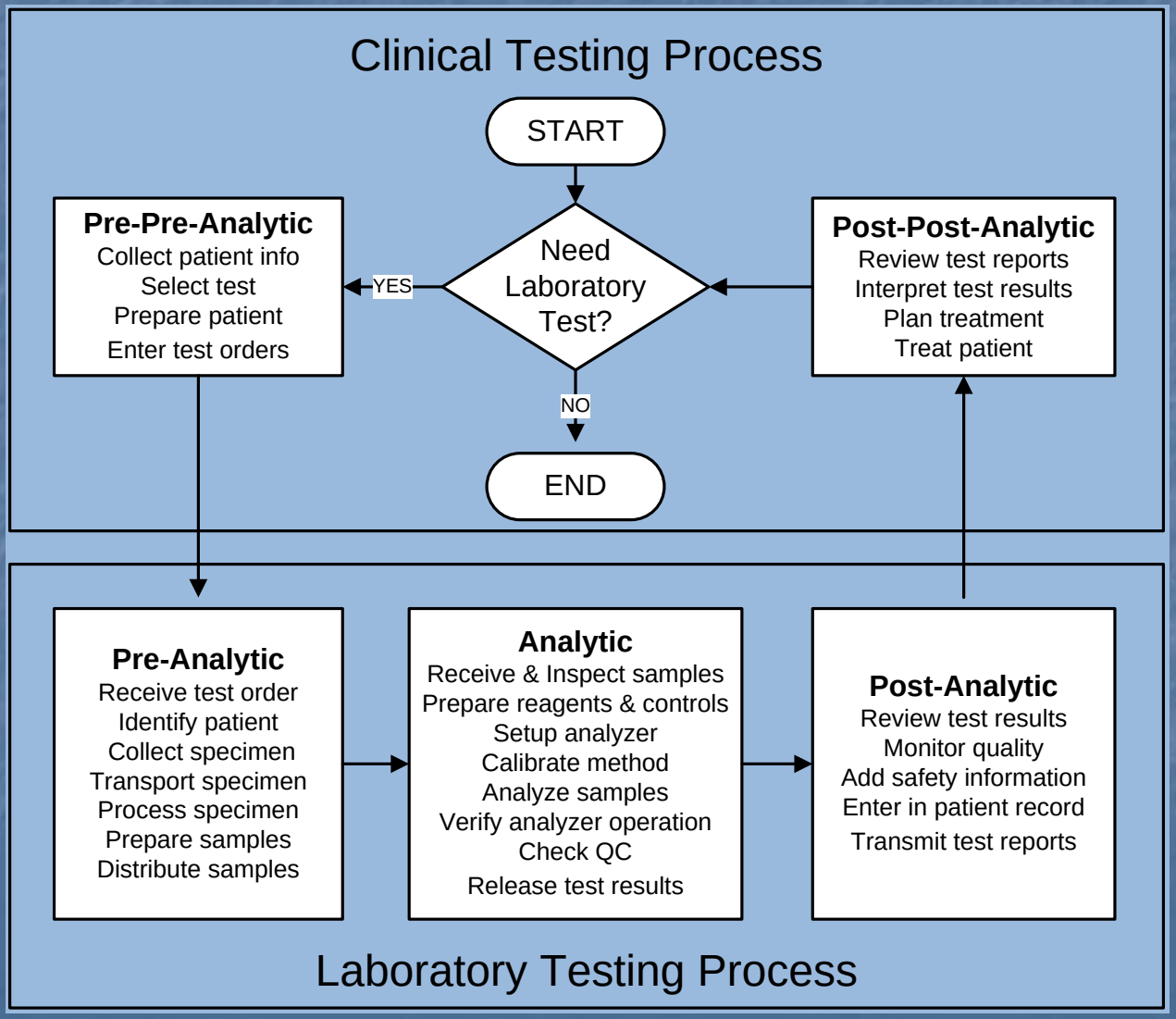
Risk Analysis

- Manufacturer's expected to perform "Failure mode effects analysis" FMEA on all new products during design and before release
- FMEA is a standard risk management tool that has been widely used in industry
- Process much like quality improvement project and uses many of the same tools

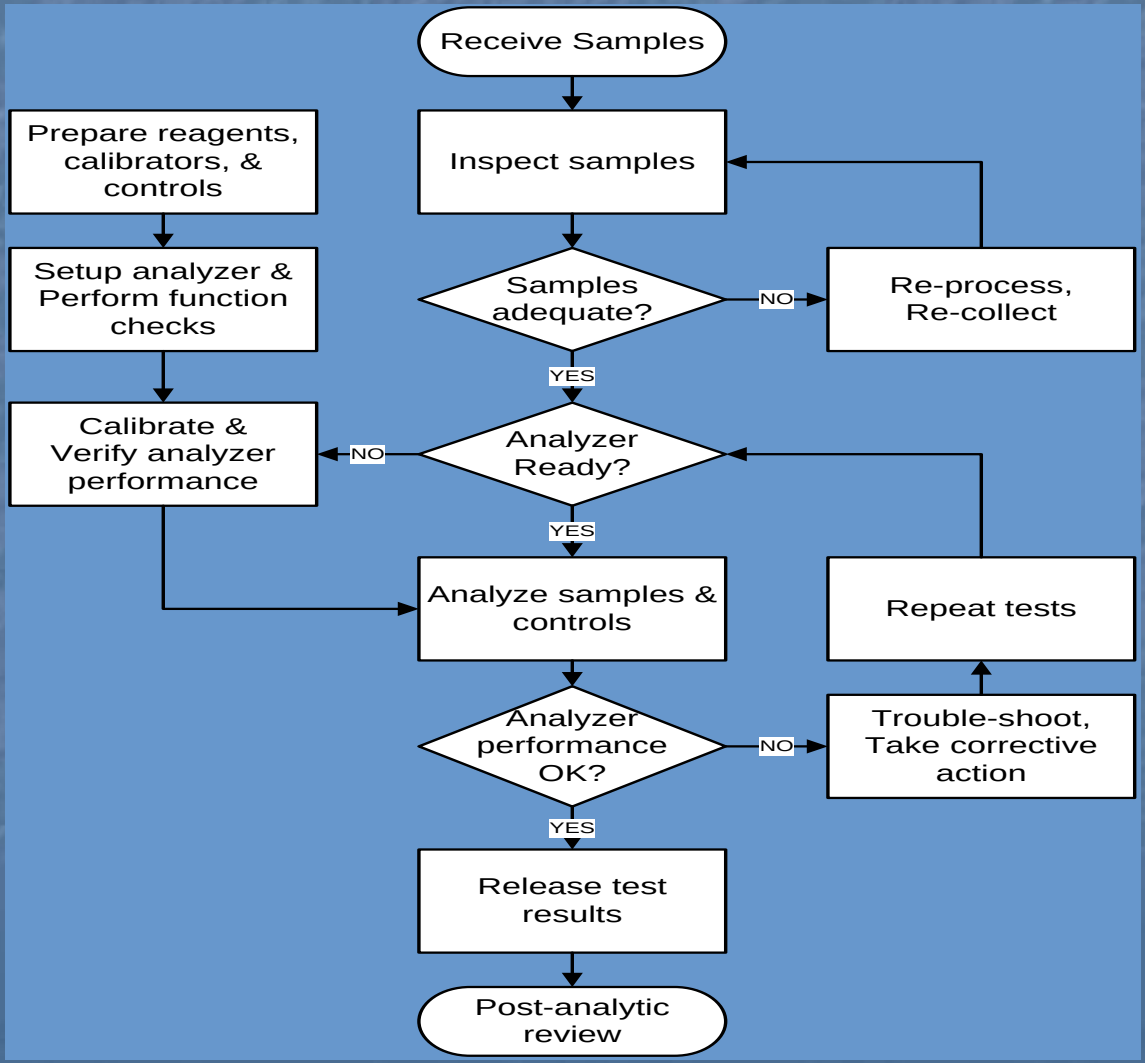
FMEA Applications

- Map process
- Identify potential sources of error (failure modes)
- Estimate risk
- Prioritize risks
- Implement improvements to reduce risks
- Identify controls to monitor "residual risks"
- Evaluate residual risks

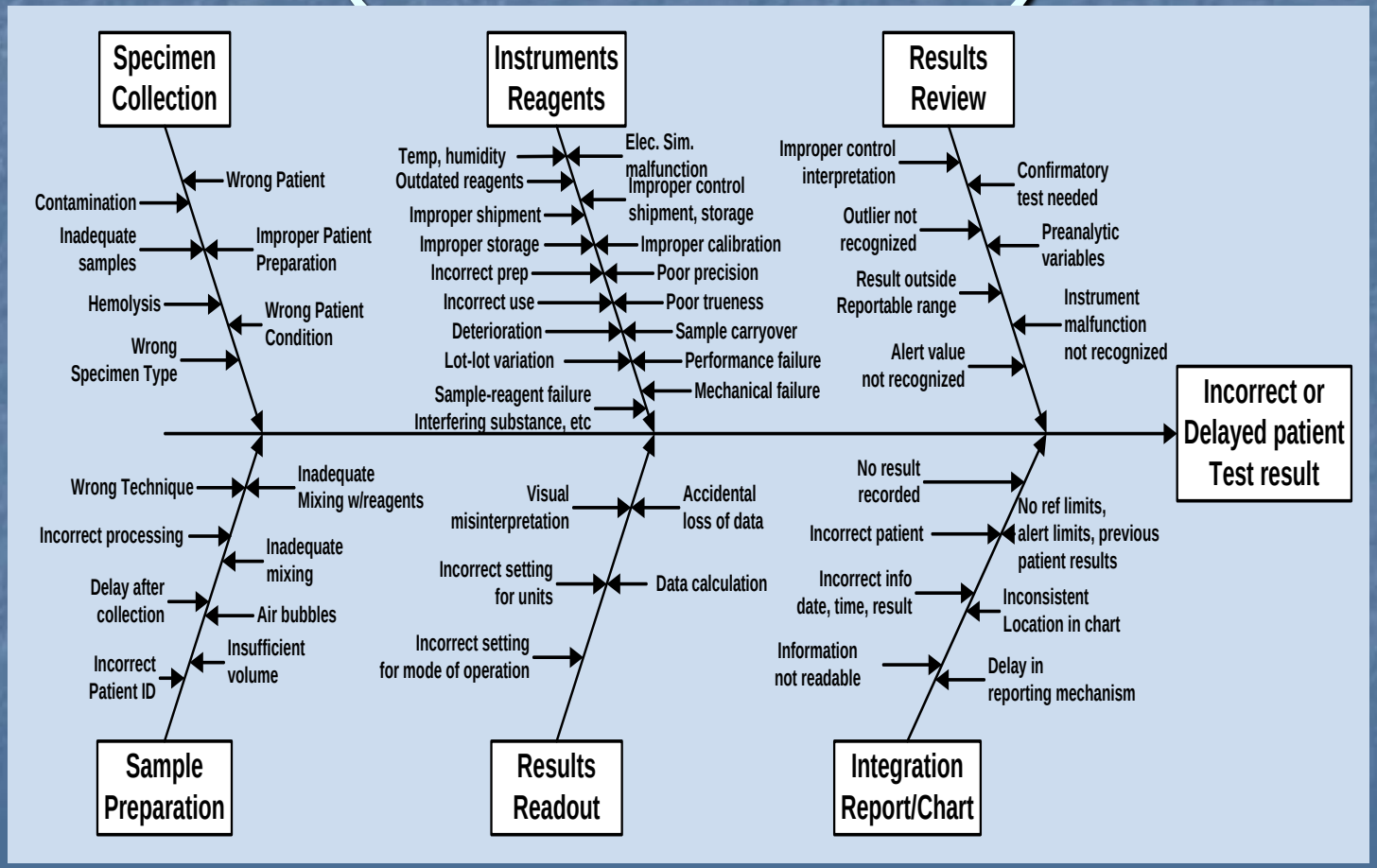
Patient Testing Process



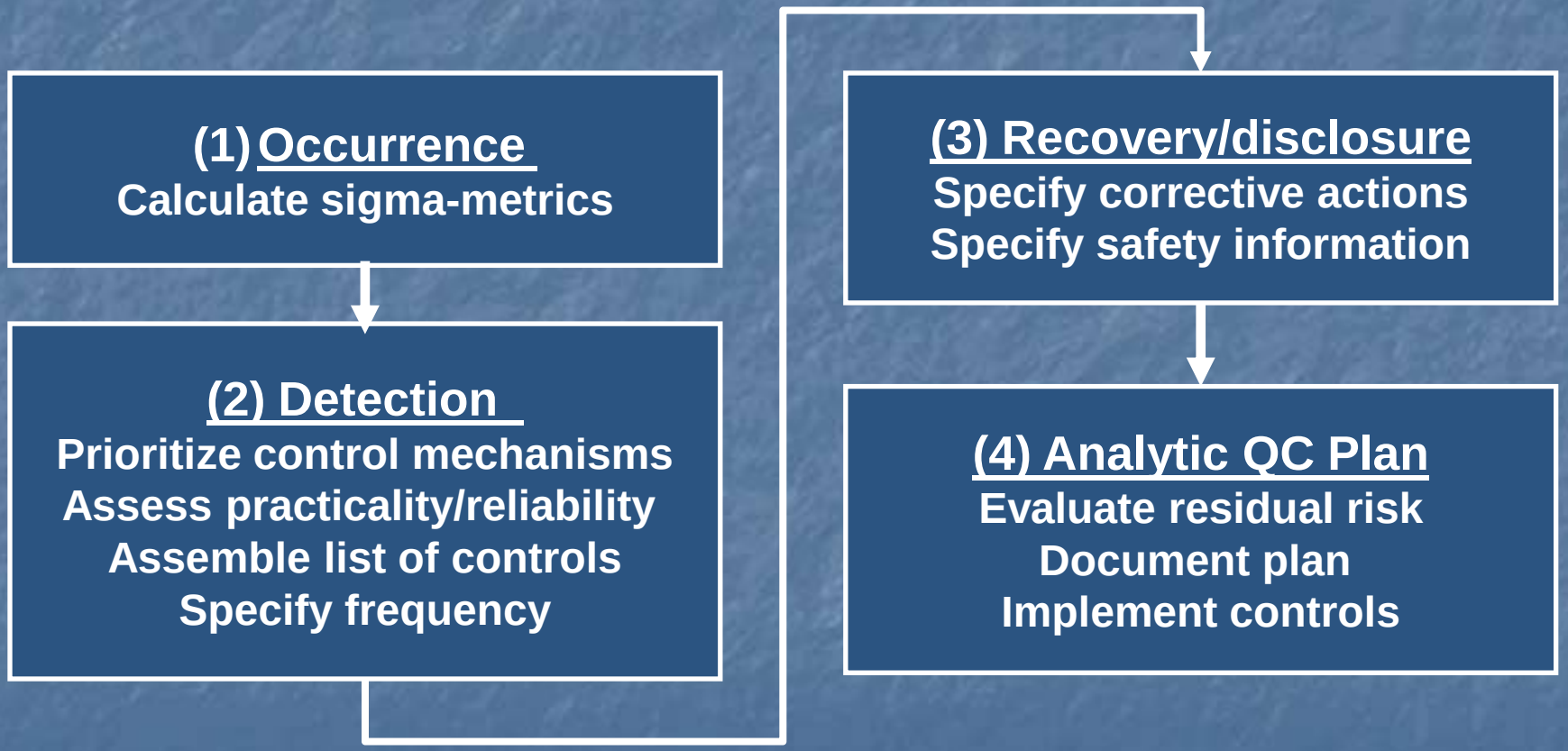
Analytic Testing Process



Potential Failure Modes Incorrect or Delayed Test (CLSI EP18A3)



Risk Mitigation Strategies for Analytic QC Plan



Possible Control Mechanisms (CLSI EP23 QC Toolbox)

Recommended QC Tool	Control Objective	Coverage	Detection
Analyst/operator controls			
Standard Operating Procedure	Process for safe use	Multiple runs	Unknown
Operator training	Correct performance	Total testing process	Unknown
Operator checklists	Proper operation	Single runs	Unknown
System maintenance	Proper operation	Multiple runs	Unknown
Operator competency	Correct performance	Total testing process	Unknown
Built-in analyzer controls			
Electronic checks	Analyzer components	Single runs	Unknown
Function tests	Analyzer components	Single runs	Unknown
Process tests	Process steps	Single samples	Unknown
Calibration checks	Analyzer stability	Single runs	Unknown
Integrated controls	Analyzer stability	Single runs	Unknown
Stable control materials			
Statistical QC	Method stability	Single runs	Known
SQC with peer comparison	Method stability	Multiple runs	Knowable
Periodic EQA, PT	Method accuracy	Multiple runs	Knowable
Trueness controls	Method accuracy	Multiple runs	Knowable
Patient data analysis			
Implausible values	Random errors	Single patients	Unknown
Delta checks	Random errors	Single patients	Knowable
Correlation algorithms	Random errors	Single patients	Knowable
Repeat patient testing	Short-term stability	Single runs	Knowable
Population statistics (AoN)	Long-term stability	Single runs	Known

Example Analytic QC Plan

QC Plan	Frequency	Recovery	Disclosure
Analyst/operator controls			
Standard Operating Procedure	Yearly SOP review	Director review	No
Operator training	Every operator	Supervisor review	No
Operator checklists	Daily	Supervisor review	No
System maintenance	Manuf. Schedule	Manuf. Repair	No
Operator competency	Yearly	Re-train	No
Built-in analyzer controls			
Electronic checks	Manuf.	Manuf. Instructions	No
Function tests	Manuf.	Manuf. Instructions	Sample condition
Process tests	Manuf.	Manuf. Instructions	No
Calibration checks	Manuf./Reg.	Supervisor review	No
Stable control materials			
Statistical QC	Startup + Monitor	TS guidelines	No
Trueness control	Calibration	TS guidelines	No
Periodic EQA, PT	3/year	CA plan	No
Patient data analysis			
Implausible values	Each sample	Repeat test	Yes

Evaluation of Residual Risks

- Adopt 3 factor risk model
  - Occurrence, Severity, and Detection
- Express occurrence as "defect rate"
- Express severity on scale 0 to 1.0
- Express detection as 1-Ped
  - Where Ped is the Probability of error detection
- Express residual risk as number of harmful test results in defined time period
  - Residual Risk = OCC*SEV*(1-Ped)

Expressing Occurrence as Defect Rate

Lab Process	Parameters	Rating	Description		Defects/Year	OCC (Defect rate)
Samples/run	50	V. frequent	1	sample/day	312	0.0100
Runs/day	2	V. frequent	1	run/day	15600	0.5000
Wdays/week	6	Frequent	1	sample/week	52	0.0017
Weeks/year	52	Frequent	1	run/week	2600	0.0833
Months/year	12	Probable	1	run/month	600	0.0192
Wkday/year	312	Probable	1	day/month	1200	0.0385
Samples/year	31200	Occasional	1	day/year	100	0.0032
3 year factor	0.33	Remote	1	day/3 years	33	0.0011
5 year factor	0.2	Improbable	1	day/5 years	20	0.0006

Example FMEA Table for Evaluating Residual Risks

FMEA to Evaluate Residual Risk

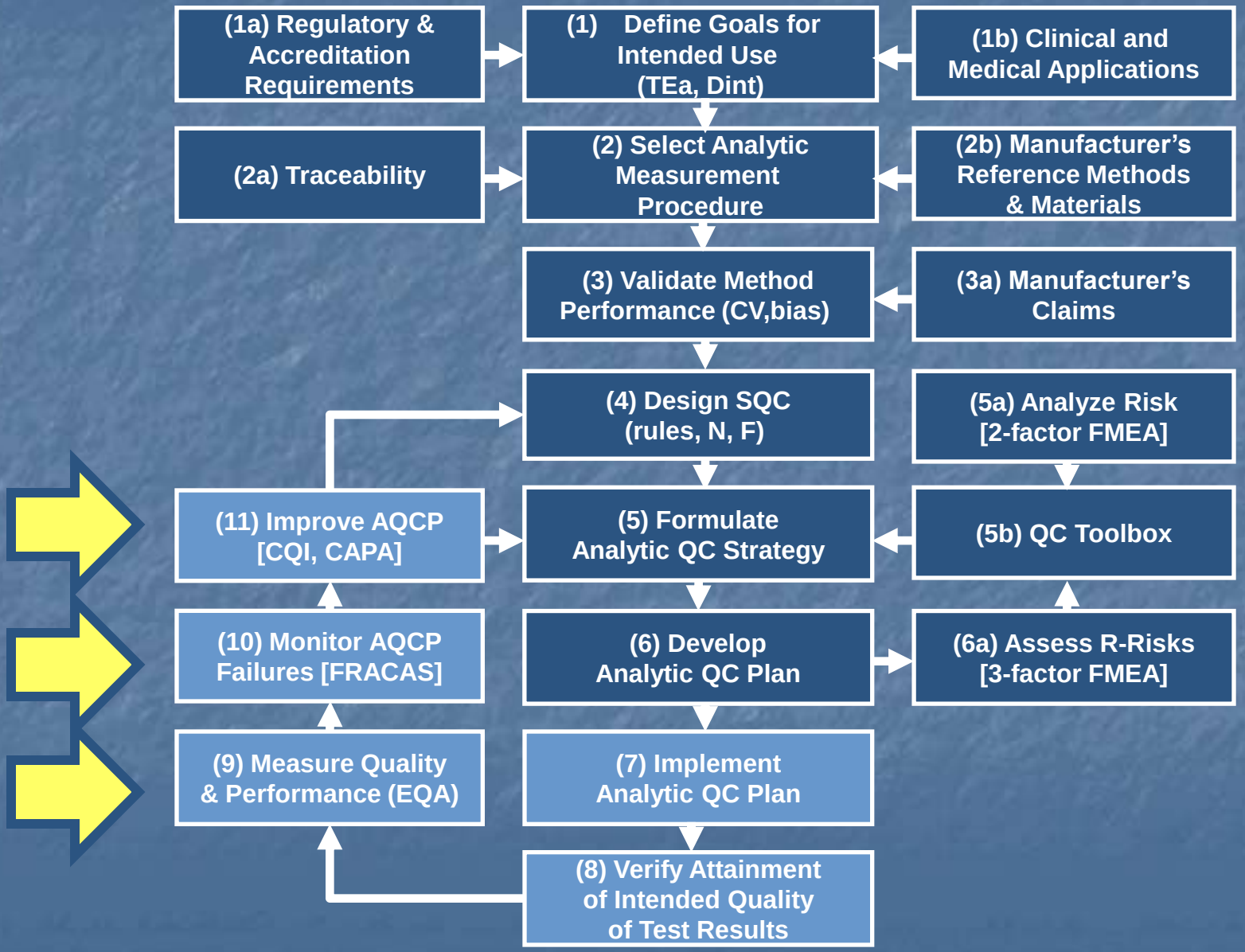
Analytic phase of laboratory testing process (Figure 11-2)

#	Step	Failure mode	Effect	SEV	Apparent cause	Rate	OCC	Control	Ped	DET	Risk	R-Risk
1	Sample	Hemolyzed	Delay	0.50	Wrong collection	1sam/day	0.0100	Visual	0.50	0.50	0.0025	8
2	Sample	Bubbles	Error	1.00	Wrong collection	1sam/day	0.0100	Analyzer	1.00	0.00	0.0000	0
3	Sample	Clots	Error	1.00	Wrong processing	2sam/day	0.0200	Analyzer	?	1.00	0.0200	62
4	Analyzer	Poor maintenance	Delay	0.50	Workload/schedule	1run/week	0.0833	Checklist	?	1.00	0.0417	130
5	Analyzer	Reagent outdate	Delay	0.50	Workload/schedule	1run/mon	0.0192	Barcode	?	1.00	0.0096	30
6	Analyzer	New reagent	Delay	0.50	Workload/schedule	1run/mon	0.0192	Checklist	?	1.00	0.0096	30
7	Analysis	Photometric drift	Error	1.00	Electrical supply	1day/year	0.0032	Analyzer	?	1.00	0.0032	10
8a	Analysis	Degraded reagent	Error	1.00	Onboard instability	1day/mon	0.0385	SQC	0.90	0.10	0.0039	12
8b	Analysis	Degraded reagent	Error	1.00	Onboard instability	1day/mon	0.0390	Analyzer	?	1.00	0.0390	122
9	Analysis	Calibration error	Error	1.00	Operator setting	1day/year	0.0032	SQC	0.90	0.10	0.0003	1
10a	Analysis	Calibration drift	Error	1.00	Calibrator instability	1day/mon	0.0385	SQC	0.90	0.10	0.0039	12
10b	Analysis	Calibration	Error	1.00	Calibration cycle	1day/mon	0.0390	Analyzer	?	1.00	0.0390	122
11	Analysis	Operator error	Error	1.00	Workload/schedule	1day/mon	0.0385	SQC	0.90	0.10	0.0039	12
12	Analysis	High temperature	Error	1.00	Environment temp	1day/year	0.0032	Analyzer	?	1.00	0.0032	10
13	Analysis	Bias	Error	1.00	Calibration	1day/mon	0.0385	Tru.Ref.Mat.	0.90	0.10	0.0039	12
14	Analysis	Bias	Error	1.00	Calibration	1day/mon	0.0385	PT	0.33	0.67	0.0258	80
15	QC	Degraded control	Error	1.00	Deterioration	1day/year	0.0032	Peer Comp	?	1.00	0.0032	10
16	QC	Interpret wrong	Error	1.00	Operator	1run/mon	0.0192	Competency	?	1.00	0.0192	60
17	Release	Inconsistent results	Delay	0.50	Analysis	5sam/day	0.0500	Delta check	?	1.00	0.0250	78

Risks of Risk Analysis

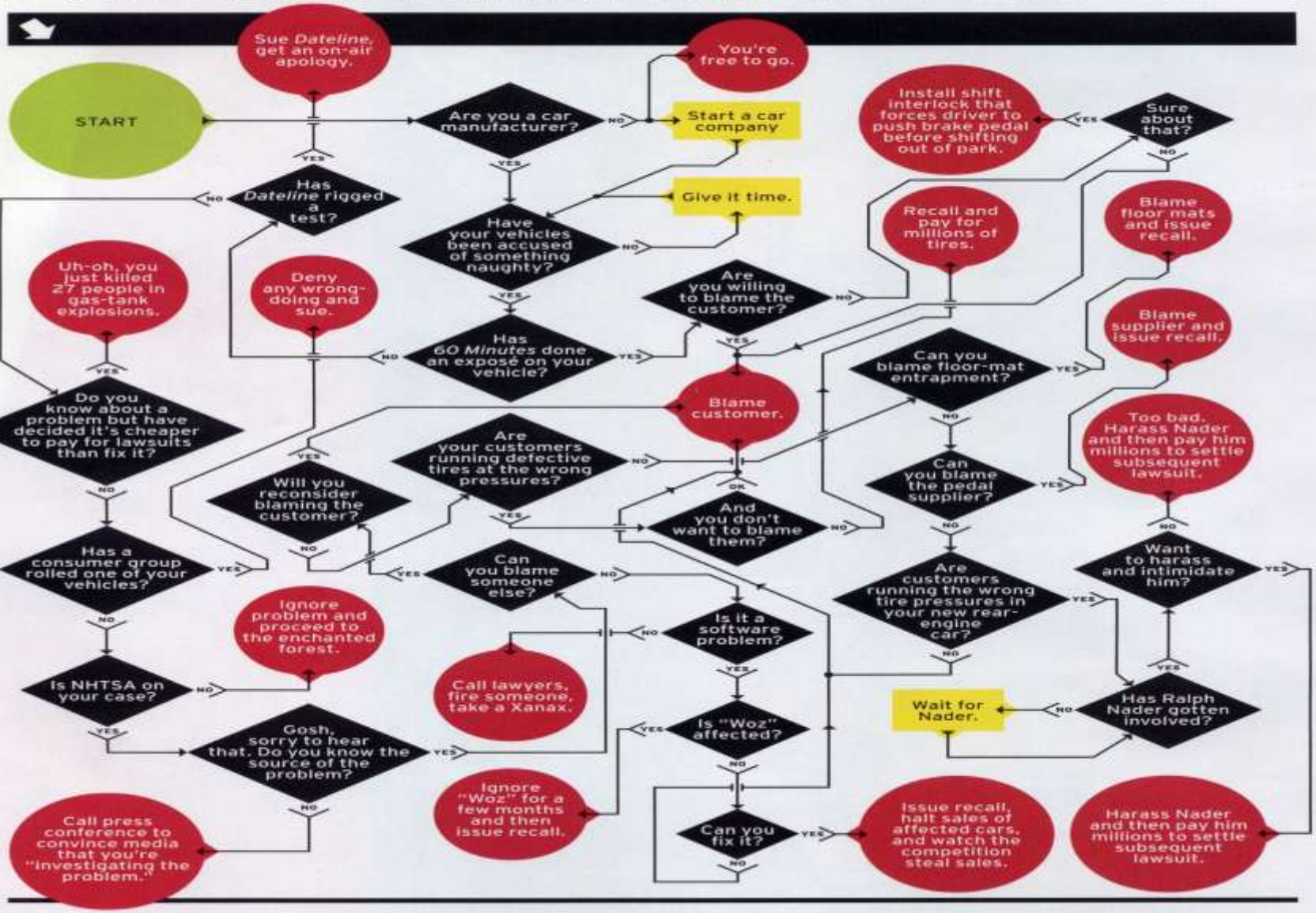
- FMEA is a new tool and requires education and training for proper applications
- Most guidelines describe qualitative applications that use an "acceptability matrix" for evaluating residual risks
- Most guidelines neglect DETECTION
- Looks scientific, but is subjective with arbitrary decisions about acceptability of residual risks and effectiveness of QC Plan

What's the plan for AQM?

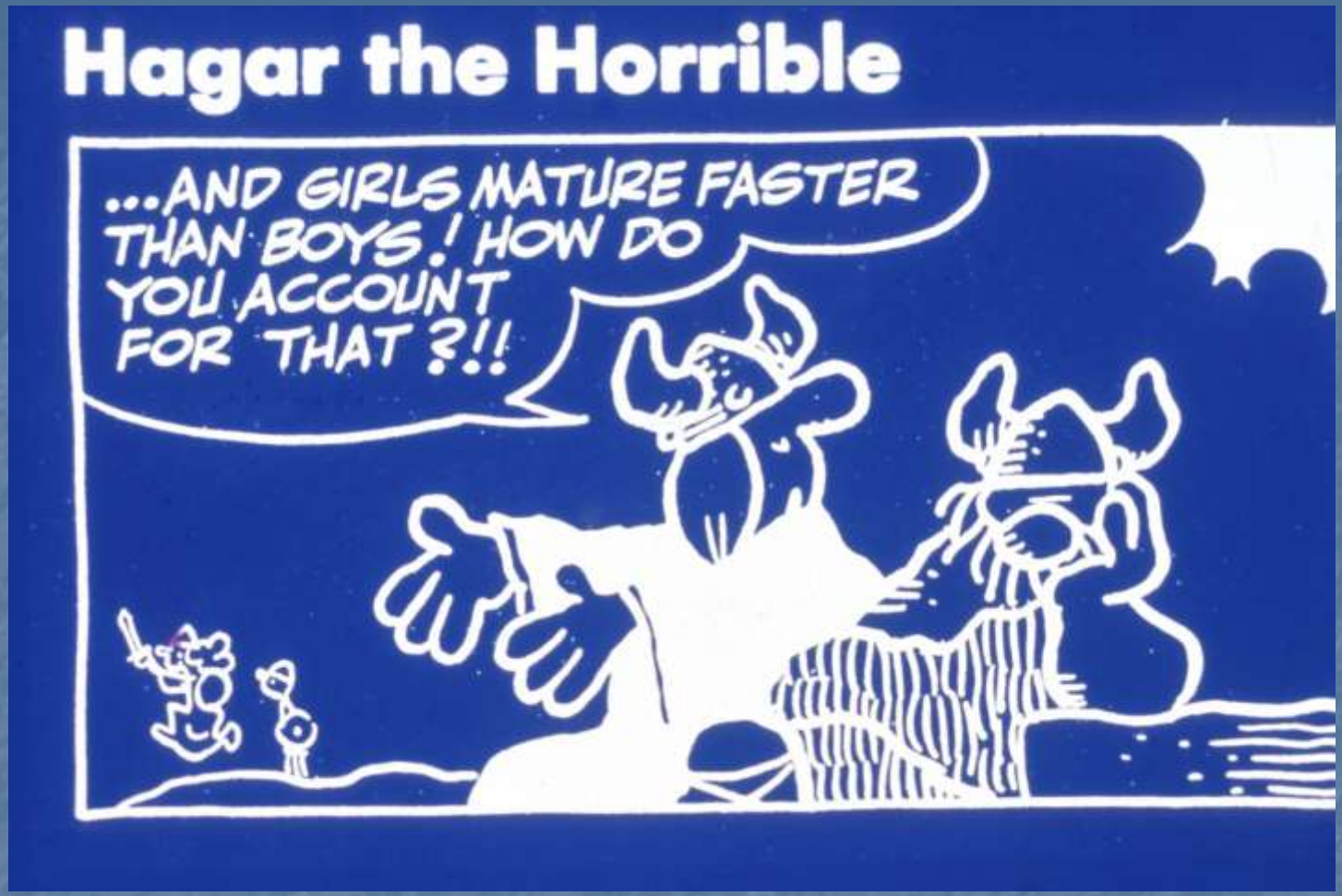


How to: DEAL WITH AUTOMOTIVE DEFECTS

Modern cars are complex machines, and, as the renegade computer, HAL, taught us in *2001: A Space Odyssey*, occasionally machines may try to kill us. Is another HAL loose at Toyota? Well, Toyota's not the first to have its feet put to the fire. Our flowchart chronicles the history of disastrous screw-ups and the resulting corporate responses. See if you can remember them. —TONY QUIROGA



GRAPHIC *by* WALTER C. BAUMANN



A process problem!

Can only be solved by upper management