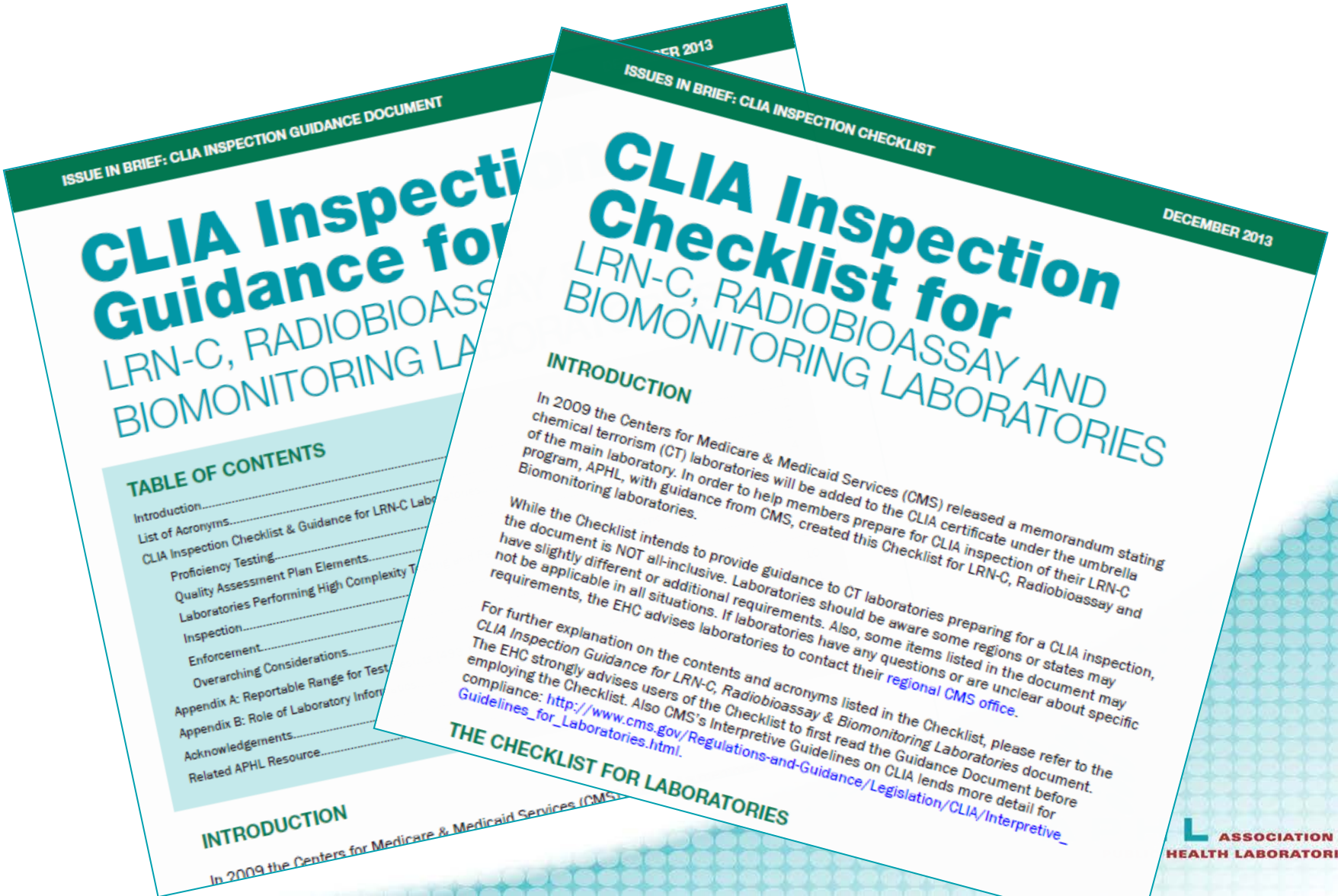
Tools to Assess Compliance With CLIA

Jeff Moran
Dick Jenny
Surili Sutaria Patel

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

CLIA Inspection Checklist

for LRN-C, Radiobioassay and Biomonitoring Laboratories



CLIA-Compliant Analytical Method Validation Plan

Objectives

- Good laboratory practice (SWGTOX, CLSI, FDA)
- Network consensus
- Regulatory compliance
- Informative of method performance

CLIA-Compliant Analytical Method Validation Design

Objectives

- Statistical rigor
- Efficient use of resources
- Support “Just-In-Time” Method validation
- Informative & concise report on performance characteristics

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

CLIA-Compliant Analytical Method Validation Design

Method Performance Characteristics

- Accuracy, precision
- Limits (upper, lower) of Quantification (sensitivity and reportable range)
- Interference and matrix effects (specificity, selectivity)
- Reference interval (None Detected) verification

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

LRN-C Analytical Method Validation Design

How well must our methods perform?

Specifications for Analytical Accuracy and Precision

- **Medical usefulness requirements** based on the effect of analytical performance on clinical decisions
- Published **professional recommendations**
- Performance goals set by regulatory bodies and agencies
- Goals based on the current state of the art, which include EQA or proficiency testing schemes

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

CDC Specifications for Demonstration of Analytical Performance (QC Characterization)

Performance Criteria Evaluation		
Method: Tetranitromethane Metabolite LC/MS/MS		
Material Batches: HNPAA2		

	HNPAA	
	QC Low	QC High
Mean Values	**ACCEPTED**	**ACCEPTED**
lower limit	29.5	292
upper limit	37.7	375
Standard Deviation	**ACCEPTED**	**ACCEPTED**
Upper limit	2.67	26.6

REFER TO THE LRN-C DEMONSTRATION OF ANALYTICAL PERFORMANCE (DAP) GUIDE

*****A minimum Bias and %RSD of 5.00% was employed for calculating the above limits.**

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

CDC Specifications for Demonstration of Analytical Performance (QC Characterization)

	CDC Performance Specifications			
	Laboratory Validation Exercise			
Analyte / Material	minimum bias (%)	Allowed inaccuracy (%)	Allowed CV (%)	TEa (%)
HNPAA QCL	10%	12.3	8.0	25.5
HNPAA QCH	10%	12.3	8.0	25.5

minimum bias(%) is the minimum bias, assigned by CDC, that is used to determine the range of acceptable means

allowable range of mean values = (TV-Bias) - SEE (2.093) < TV Mean < (TV +Bias) + SEE(2.093)

maximum allowable CV (%) is determined as (SPHL SD * 1.5912) / TV

TEa (%) is the total allowable error around TV determined as maximum allowable inaccuracy (%) + 1.65 * maximum allowable CV (%)

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

CDC Specifications for Successful Performance in Proficiency Testing

HNPAA 201301				
Sample	**mean** (ng/mL)	**SD**	**CV (%)**	**TEa (%)**
1	397	28.2	7.1	21.3
2	506	25.3	5.0	15.0
3	802	40.1	5.0	15.0
4	661	33.1	5.0	15.0
5	38	2.39	6.3	18.9
6	0			
7	246	12.3	5.0	15.0
8	101	5.54	5.5	16.5
9	79.6	3.98	5.0	15.0
10	9.46	0.5	5.3	15.9
			CDC LDAP Specification	25.50%

TEa(%) = 3 * CV(%); i.e., passing z-score = +/- 3

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

CDC Specifications for Demonstration of Analytical Performance

Laboratory demonstrates acceptable performance over a range of concentration specified by CDC:

- Lowest calibrator (S1) is the minimum lower limit of quantification (LLOQ)
- Highest calibrator is the upper reporting limit without dilution (ULOL)

Validation Materials Design

- **calibrators**, minimum 6 non-zero concentration, prepared in-house or supplied through CDC contract
- **VM1-3**, validation materials, prepared in matrix in-house or supplied through CDC contract. Prepared using certified drug standard. Target value assigned as weigh-in concentration
- **VM1 concentration** targeted at 3 x LOQ, **VM2** targeted at mid-reportable range, **VM3** targeted at 80% x ULOL.
- **blk (source 1-30)**, blank matrix specimens from minimum 15 sources (population) without the addition of internal standard.
- **QC_L, QC_M, QC_H:** externally supplied quality control materials

Validation Run Design

Five Analytical Runs Over Five Days

			Day 1		Day #2		Day #3	
			Run #1	Run #2	Run #3	Run #4	Run # 5	Makeup
Calibration (Reportable Range)	std 1 (LOD/LOQ)							
	std 2							
	std 3							
	std 4							
	std 5							
	std 6 (ULOL)							
Quality Control	QC_BLK (carryover)							
	QC_L							
	QC_M							
	QC_H							
Validation Materials	matrix blk (CO,RI, INT)							
	std 1 (optional)							
	VM1	**x5**						
	VM 2							
	VM 3							
	matrix blk (CO,RI, INT)							

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

LRN-C Method Validation Design OUTCOME

LRN-C Analytical Methods Validation Report

Analyte: MFA

Performance Characteristic	Specification	Experimental Protocol	Results				
accuracy	12% maximum allowable inaccuracy	Accuracy was measured using five determinations per validation specimen over five different runs performed over three days.	**Validation Specimen ID**	**Target** (ng/mL)	**Grand Mean** (ng/mL)	**Bias (%)**	**Acceptance (Y / N)**
		Three validation specimens prepared to contain analyte at 3 x LOQ, mid-range and 80% x ULOL were used.	VM1	150	150.8	0.5	Y
			VM2	1500	1504.7	0.3	Y
			VM3	4000	4081.5	2.0	Y

Comments: The bias of results from the prepared concentrations of analyte is well within the performance specification for total allowable inaccuracy of 12%.

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

LRN-C Method Validation Design NEXT STEP

Test…

- New York – nitrogen mustard
- Massachusetts – CVAA
- Arkansas – nerve agents

Refine…

Thank you!

QUESTIONS & FEEDBACK

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES