

Tools to Assess Compliance With CLIA

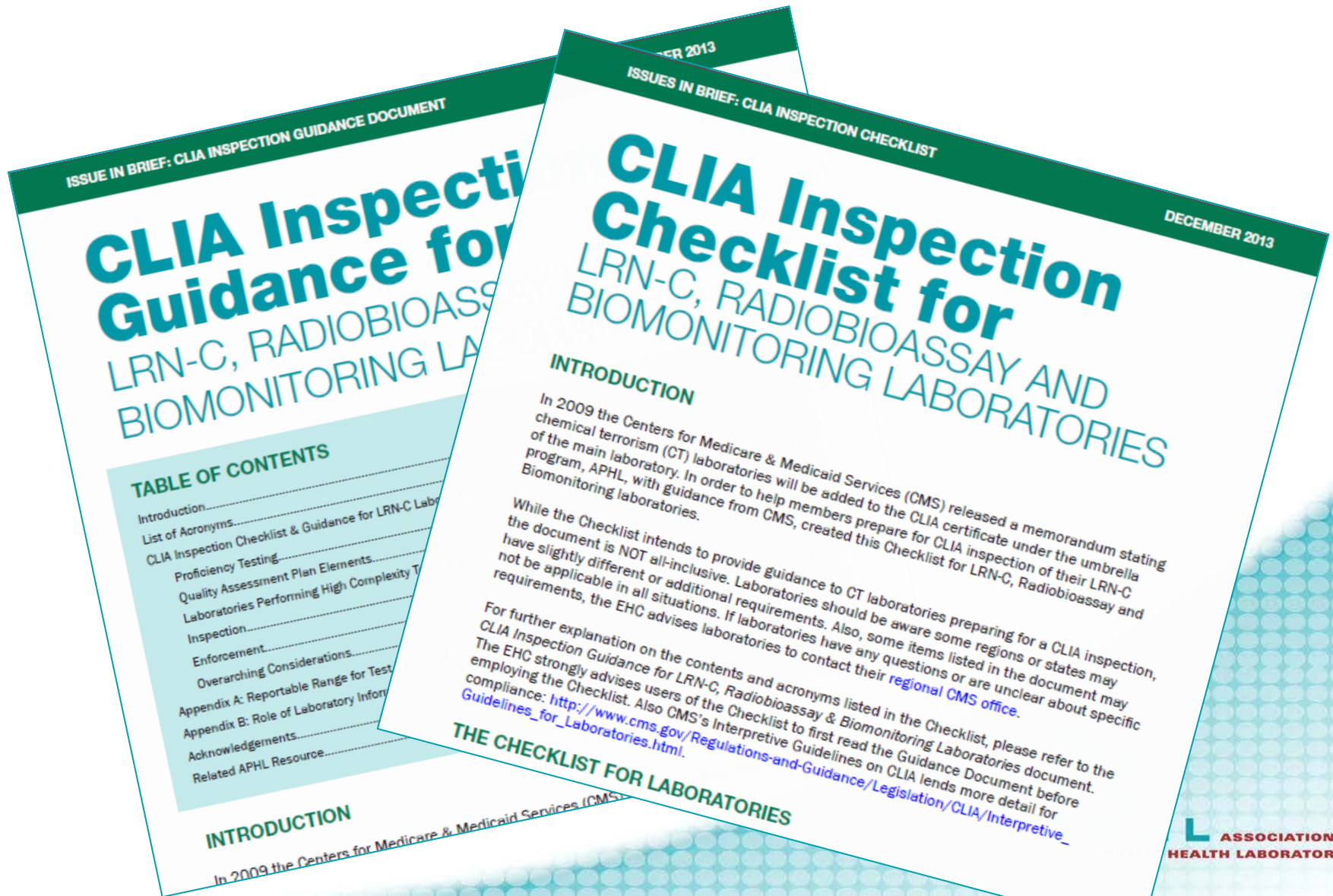
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CLIA Inspection Checklist

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

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

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

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.				

CDC Specifications for Demonstration of Analytical Performance (QC Characterization)

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

CDC Specifications for Successful Performance in Proficiency Testing

HNPA 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

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						
	VM 2						
	VM 3						
	matrix blk (CO,RI, INT)						

LRN-C Method Validation Design OUTCOME

LRN-C Analytical Methods Validation Report

Analyte: MFA

Performance Characteristic	Specification	Experimental Protocol	Results				Status
accuracy	12% maximum allowable inaccuracy	Accuracy was measured using five determinations per validation specimen over five different runs performed over three days. Three validation specimens prepared to contain analyte at 3 x LOQ, mid-range and 80% x ULOL were used.	Validation Specimen ID	Target (ng/mL)	Grand Mean (ng/mL)	Bias (%)	Acceptance (Y / N)
			VM1	150	150.8	0.5	Y
			VM2	1500	1504.7	0.3	Y
			VM3	4000	4081.5	2.0	Y
<p>Comments: The bias of results from the prepared concentrations of analyte is well within the performance specification for total allowable inaccuracy of 12%.</p>							

LRN-C Method Validation Design

NEXT STEP

Test...

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

Refine...

Thank you!

QUESTIONS & FEEDBACK