

CLIA Regulations and Toxicology

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DESCRIPTION:

Sandy Pearson will begin the workshop with the CMS regulatory perspective for toxicology testing, presenting:

- A basic overview of CMS regulations as they apply to Toxicology/ Drugs of Abuse (DOA) Testing
- An overview of the problems identified through the CMS survey process and CLIA application process

About the Speaker:

Sandy Pearson is a Registered Medical Technologist. She is currently a Laboratory Consultant for the CMS Dallas Regional Office of the CLIA Survey Branch. Sandy also has an M.B.A., with emphasis in the public health sector.

She has been an M.T. since 1972, with 11 years clinical experience based in hospitals, Peace Corp, and university research settings. She worked with the State of Texas Health Department from 1983 to 1992, as a laboratory consultant surveyor for the Medicare Program. Her duties consisted of health surveys and administrative responsibilities.

Sandy began her career as a Federal employee with the Centers for Medicare and Medicaid Services (CMS) for the Dallas Regional Office in 1992.

When she is not working Sandy enjoys quilting and taking care of her ranch animals.

CMS Regulatory Perspective: Toxicology



Sandy Pearson, MBA, MT(ASCP), CMS Dallas RO

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Symposium for Clinical Laboratories
Las Vegas, NV



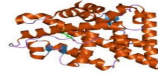
CLIA

Objectives

- ▶ Basic overview of CMS regulations as they apply to Toxicology/ Drugs of Abuse (DOA) Testing
- ▶ Overview of the problems identified through the CMS survey process and CLIA application process



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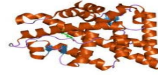


In the beginning.....



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In the beginning.....



- Since 2013....Increase in the # of app
- 2013 = total of 11 applications
- 2014 = total of 51 applications
- 2015 = total of 106 applications
- 2016 (as of 03/21/16) = 44 applications
- Total of 212 applications for drug testing labs



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CLIA Regulations: 116 Application

- Each certificate type has specific certification/application requirements
 - Subpart A – 42 CFR 493.35 – 493.37: Certificate of Waiver
 - Subpart C - 42 CFR 493. 43 – 493.53: Registration Certificate, PPMP, Certificate of Compliance
 - Subpart D – 42 CFR 493.55 – 493.63: Certificate of Accreditation



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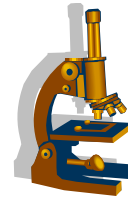
What is the RO looking for in the Review of Application.....

Lab Director: 116 system

- > than 5 labs**** major issue
- Do they have a current State Medical License; board certification; documentation of clinical experience
- Do they have State Laboratory License (LA)

Location of lab: 116 system

- How many other labs located at same location



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What is the RO looking for in the Review of the Application.....

Test list /equipment:

- Compare the tests/instruments with FDA website for test complexity
 - Is the Analyzer /test method FDA approved for Drugs of Abuse?
 - Also review the instrument / reagent combo for test categorization
 - Lin-Zhi rghts (research & development use only)
 - Immunalysis Corp., Carolina reagent (some forensic use only)
 - So if instrument is moderate, the reagents and/or QC are labeled "forensic, research, not for use in US, this makes the test system high complexity, then
 - Becomes a Laboratory Developed Test (LDT)



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What is the RO looking for in the Review of the Application.....

Test list /equipment:

- Compare with FDA website -test complexity
 - Analyzer may be FDA approved for routine chemistry tests; but not for Drugs of Abuse, this is a modification of FDA approval method
 - Becomes high complexity; Laboratory developed test
 - GC/MS Analyzers are not FDA approved for diagnostic purposes; only used for research and forensics
 - Becomes high complexity;
 - Laboratory developed test(LDT)



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What we were finding out....



Labs were obtaining CLIA certificates when:

- Based on 116 review and/or survey findings: The labs were not ready for patient testing
- The equipment manufacturer's were requiring a CLIA # before selling equipment to lab
- The lab had no location
- The lab had not received in house equipment /reagents
- The lab had received equipment /reagents, but still crated
- Staff had not been hired; or trained



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What we were finding out....



Labs were obtaining CLIA certificates when:

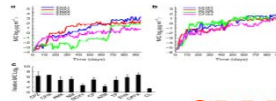
- LD did not have a State Medical License or State Laboratory License
- Staff did not have a State Laboratory License
- The laboratory had not performed studies
- The laboratory was performing verification/establishment studies simultaneously while testing patients or the studies were incomplete
- Equipment used for patient testing was modified
 - Did not perform establishment studies nor did not know they had to
- Personnel not qualified: LD or TS or testing personnel



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Equipment Used

- Mindray BS 200/Microgenics – routine chemistry
- Beckman Coulter Olympus AU 480/640
 - Olympus 400E – moderate – DOA- rgt combo?
- Synermed IR 500 – routine chemistry
- AB Sciex 4500 LC/MS – research only
 - Research only – not for diagnostic purposes
 - Triple Quad 3500, 4500, 5500, 6500 LC/MS
 - API 3200, 4000, 3200 LC-MS



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Equipment Used.....

- Carolina Liquids Chemistry - CLC 720
 - Biolis i24 (CLC 480)
 - BS200 chemistry (Mindray)
- Medica EasyRA w/Lin Zhi Reagents
- Siemens Viva-E w/Lin-Zhi Rgts
- Indiko Plus – Thermo Scientific
- There are some Beckman AU's that are moderate
 - If rgts used that are listed on the FDA website
 - Syva emit reagents



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High Complexity Toxicology Testing



Diatron Pictus 400
(all analyzers may be badged with
different name and vendor)



ImmTOX



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High Complexity Toxicology Testing



Vital Diagnostics Envoy
500



Medica EasyRA



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What has been found on survey.....



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Multiple CLIA #'s /labs in one location.....

- Each CLIA # must stand on its own and demonstrate its own compliance
- Tour of the locations; adequate space for testing/storage (refrigerators, freezers, counter space); questions asked about how patient specimens come in/accessioned; who processes specimens, screening vs confirmatory, work flow.
- Even more critical, each CLIA # /lab must maintain separate records to demonstrate CLIA compliance
 - Even if the instruments are the same;
 - Even if the instruments are all in the same room;
 - Can not share documents



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What is looked at on survey.....

- Drugs of Abuse – Nonregulated analytes
 - Enrollment in Proficiency Testing or twice a year assessment
 - Adulterant Testing/Validity Testing – urine
 - Creatinine, SG, pH, oxidants, etc.
 - If required by manufacturer, must be done
 - 42 CFR 493.1236, 493.1239
- Personnel: based on instrument/reagent combo
 - Mostly high complexity; AU/syva emit moderate
 - Training/competency of staff
 - Credentials, job description, delegation of responsibilities



What is looked at on survey.....

- Specimen types
 - oral, urine
 - Each specimen type must undergo their own establishment studies
- Record review
 - Out-of-state specimens
 - CA, FL, NY – require State License



What is looked at on survey.....

Preanalytic systems

- If high complexity, establishment studies on collection, storage, handling, shipping of specimens
- to develop lab policies
 - should include urine plastic container in use, collection swabs for orals (forensic use only)
- If moderate complexity, use the requirements on collection, storage, handling, shipping – must follow exactly the MI/PI
- If modified; must do establishment studies
- All scientific literature must be included that is used to support the studies



What is looked at on survey.....

Preanalytic systems

- Pay close attention to PI/MI, because not all drug tests have the same requirements
- Observe specimen processing to ensure all staff understands the requirements
- If reference lab; must have client service manual
- Rejection criteria – based on actual studies performed by the lab in-house



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What is looked at on survey.....

Preanalytic systems

- 42 CFR 493.1232,
- 42 CFR 493.1240,
- 42 CFR 493.1241
- 42 CFR 493.1242,
- 42 CFR 493.1249



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What is looked at on survey.....

- Package inserts (PI/MI): methods, QC, calibrators
- Lab policies and procedures
- 42 CFR 493.1250-493.1289
- Post-Analytic (42 CFR 493.1290-1299)
 - Acceptable ranges (cut off for positive/negative)
 - Name/address of testing lab
 - Correct collection, test, reporting dates
 - If disclaimer on report – screening vs c
 - LIS verification



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What is looked at on survey.....

Verification Studies: Moderate Complexity

- Protocol on how performed (Performance Spec)
- Accuracy; Precision; Reportable Range (linearity), method comparison
- Reference normal range (usually cut off for +/-neg)
- Establishment/verification of QC ranges
- Summary of results
 - Compare to PI to see if the lab can demonstrate performance specifications
- Data analysis; summary Signed by LD
- Performed prior to patient testing



All PI/MI, scientific literature, must be kept



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What is looked at on survey...

Establishment Studies: high complexity

- Everything listed on Verification Slide (21)...PLUS
- Analytic sensitivity – minimum detectable limits (LOD, LOQ)
- Analytic specificity – can the lab measure the analyte; interfering substances
 - Interfering substances: related drugs, endogenous compounds (Bili, ethanol, NaCL, NaFL, etc)
- Turbidity, adulterants
- Other studies: carry over; retention time stability



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What is looked at on survey...

Establishment Studies:

- Reportable Ranges (linearity), cut off points for positive/negative
 - Immunalysis Corp calibrator set (for forensic use only)
- Establishment of QC ranges
 - If using calibrators for QC, different lot number of calibrator or different working stock from same calibrator
- Raw Data and Summary of results
 - Reviewed and signed by Lab Director
 - Many of the labs use EP Evaluator
- Performed prior to patient testing



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What is looked at on survey...

Verification / Establishment Studies:

- 42 CFR 493.1252
- 42 CFR 493.1253
- 42 CFR 493.1254
- 42 CFR 493.1255
- 42 CFR 493.1256



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What is looked at on survey.....

- If multiple labs in one location, but different suite #s or in same suite;
 - Verify each location did their own study and not copied, all specimens types on each instrument
 - If multiple analyzers, verify each analyzer has a study, not a copied version with the name of the analyzer changed
 - Verified that studies actually performed in the lab with the lab staff and not performed in another lab or by the manufacturer



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Hints...



- Follow package insert for each drug;
- Urine adulteration: methods use to ID
 - temperature (normal urine 32.5 – 37.7 degree C)
 - pH (normal urine 4.7 – 7.8)
 - specific gravity (normal urine 1.003 – 1.035)
 - Creatinine (normal urine 80-200 mg/dL)
 - value of <20 indicates sample adulterated
 - value of <2 indicates a substitution of a non-urine sample urine
 - Oxidant-detect test – ID Oxidizing agents
 - Compounds: nitrite, chromate, iodine, bleach, horse radish, peroxidase, vinegar, baking soda, detergent
 - Fluid intake affects urine sample



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Hints...



- How does lab handle adulteration of urine sample?
 - Obtain a new sample and send both for confirmation?
- K2 (synthetic Cannabinoids-1) urine enzyme immunoassay PI “forensics use only” Marijuana will show + results w/oxidant on screen, but negative on confirmation/mass spec
- Specimen collection – plastic or glass, however some plastics adsorb drugs – what did the lab do about this?
- Samples w/high turbidity; centrifuge (at what speed and for how long? Did lab address?



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Hints...



- Some PI have very defined temperature requirements for shipment; handling, storage
 - If not tested immediately, refrigerate up to 7 days
- Samples w/in normal pH; no pretreatment needed
- DRI Ethyl Glucuronide Assay – Thermo Scientific
 - Not approved for use in the US. For export only. Do we allow the lab to use?
- Preliminary analytical test result
 - GC/MS, LC/MS/MS confirm with per package inserts
 - Some labs use table analyzers/modified, or the AUs modified as confirmation. These are screening methods



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Hints...



- Look at specimen handling/processing
 - Lab = cups were stored at RT up to 30 days; containers not closed leaking onto other containers – not an acceptable specimen
- Incomplete studies: establishment, preanalytic
- Screening vs confirmatory:
 - Screening will have adulterant test done;
 - If lab is only doing confirmatory testing, adulterant tests should be done
 - Storage, cleaning, rinsing of glassware; volumetric glassware
 - Perform Lot to Lot comparisons: compare peaks, internal stds, etc
 - Track and document lot #s of reagents, calibrators, QC, etc.



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Information obtained from MI/PI



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High Complexity Toxicology Testing

Problems seen:

- ▶ QC ranges used for "accuracy" are so large almost cannot be unacceptable (ex: Level 1: 324–1670 & Level 2: 511–2210)
- ▶ Mean, SD range and all results of precision study are so far above or below cutoff that they may be precise but are not accurate
- ▶ Linearity may not be performed
- ▶ "Cherry-picked" results so only the "best" results are used (Ex: Ran cutoff 40 times but only used 10 "best" results)
- ▶ Do not calculate mean and range for QC
- ▶ Gap in validation dates (part of validation performed at another lab)
- ▶ Method comparison
 - Only tested against waived method
 - Method comparison only uses negative samples
 - Not all drugs tested are compared
 - Discrepancies not investigated
- ▶ No disclaimer on patient test results
- ▶ Results not reported as "Positive" or "Negative" (Ex: "Normal" and "High")



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High Complexity Toxicology Testing

Examples:

The manufacturer's package insert for the Lin-Zhi International, Inc. Cocaine Metabolite Enzyme Immunoassay states, "If the specimen can not be analyzed immediately, it may be stored refrigerated for up to 3 days. For longer storage keep sample frozen and then thaw before use."

- ▶ Make sure validation includes RT, refrigerator and freezer storage.

The Immunalysis manufacturer's package inserts for Amphetamines, Barbiturates, Benzodiazepine, Carisoprodal, Methamphetamines, Methadone, Opiates, Tramadol and Zolpidem state, "THE IMMUNALYSIS (drug name) EIA KIT IS INTENDED FOR FORENSIC USE ONLY".



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High Complexity Toxicology Testing

Examples:



The package inserts for the Immunalysis analytes Amphetamines, Barbiturates, Benzodiazepine, Carisoprodal, Methamphetamines, Methadone, Opiates, Oxycodone, Tramadol and Zolpidem state, "The...Kit provides only a preliminary analytical test result. A more specific alternate chemical method must be used in order to obtain a confirmed analytical result."

"The Immunalysis Oxycodone Urine Enzyme Immunoassay Kit provides only a preliminary analytic test result. A more specific alternate chemical method must be used in order to obtain a confirmed analytic result. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the preferred confirmatory method."
▶ Not all labs are sending out for a confirmed result, not even the positives.



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High Complexity Toxicology Testing

What the manufacturer says:

The package inserts for the Immunalysis analytes Amphetamines, Barbiturates, Benzodiazepine, Carisoprodal, Methamphetamines, **Methadone**, Opiates, Oxycodone, Tramadol and Zolpidem state, "Results and Expected Values...Qualitative Results...A specimen that exhibits a change in absorbance...value, equal to or greater than the value obtained with the cutoff calibrator is considered positive."

From the Validation:

For Methadone, the mean of the 10 runs of the 300 ng/mL cutoff calibrator was 277.1. All 10 runs were below 300 ng/ml, and the acceptable +/-2SD range of 258.2 - 296.0 ng/mL was below the value of the cutoff calibrator.

Was cutoff adjusted?



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Example:

The package insert for Lin-Zhi International, Inc. Cocaine Metabolite Enzyme Immunoassay states, "Urine samples within the normal pH range of 5-8 can be tested without any pretreatment."

How do they test pH and adjust if needed?

Example:

The manufacturer's package insert for the Immunalysis Amphetamine Urine Enzyme Immunoassay states, "Fresh urine specimens should be used."

What is "fresh"?



High Complexity Toxicology Testing

Example:

The waived drug test method used for the comparison testing did not include the drugs Tramadol or Carisoprodol.

- ▶ Make sure all drugs have comparisons, negative and positive if possible and with the appropriate method.

Example:

The package insert for Lin-Zhi International, Inc. Cannabinoids (cTHC) 50 Enzyme Immunoassay states, "Specimen Collection and Handling...Some plastics may adsorb drugs." Polypropylene and polyethylene containers at different temperatures may cause the loss of THC in urine specimens. The package insert for the Immunalysis Oxycodone Urine Enzyme Immunoassay states, "Urine specimens should be collected in polypropylene or glass containers."

- ▶ Did they validate for the type of tube used and for extended storage?



High Complexity Toxicology Testing

Example:

The manufacturer's package insert for the Immunoanalysis Opiates Urine Enzyme Immunoassay states, "Ensure that the samples are free of gross debris. Highly turbid specimens should be centrifuged before analysis."

- ▶ Make sure lab has a centrifuge and uses it!



The manufacturer's package insert for the Immunoanalysis Benzodiazepines Urine Enzyme Immunoassay states, "Adulteration of urine specimens can cause erroneous results."

- ▶ Response from lab: "LD does not want to test for adulterants due to cost concerns"

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Examples:

The manufacturer's package insert for the Immunoanalysis Methamphetamine Urine Enzyme Immunoassay states, "Interpretation of results must take into account that urine concentrations can vary extensively with fluid intake and other biological variables."

- ▶ Does lab check for specific gravity and/or creatinine?

Method comparison results not evaluated

- ▶ The results for Opiates revealed the laboratory obtained a result of "POS" for 8 of the 20 specimens and the reference laboratory results showed 1 of the 8 specimens were positive. There was no documentation that the discrepancies had been reviewed and evaluated.

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High Complexity Toxicology Testing



Examples:

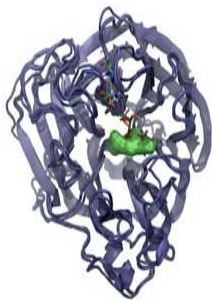
The package insert for Biochemical Diagnostics, Inc. Detectabuse 9 Panel Liquid Control Urine states, "Although target values are provided with the Detectabuse liquid controls, each laboratory should run these controls as unknowns to establish "in-house" assay values for them."

The package inserts for Lin-Zhi International, Inc. Cannabinoids (cTHC) 25 Drug of Abuse Calibrators and Lin-Zhi International, Inc. Cannabinoids (cTHC) 50 Drug of Abuse Controls state, "Values are provided only as guidelines and that laboratories should determine the ranges based on their own test system and tolerance."

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QUESTIONS.....



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