Module #4–
Risk-based Analytical and Sample Method Selection

- Purpose and objectives of Sampling & Inspections-Risk Based Selection paradigm
- Analytical Method Selection based on the Residue Risk Matrix
- Method Suitability and Qualification Approach
- Justification of Total Organic Carbon and Non-Specific Analysis

ICH Q9 Quality Risk Management (June 2006) Definitions:

- ***Detectability**: The ability to discover or determine the existence, presence, or fact of a hazard.*
- **Harm**: Damage to health, including the damage that can occur from loss of product quality or availability.
- **Hazard**: The potential source of harm (ISO/IEC Guide 51).

ASTM E3106-18 Cleaning Risk Assessment

6.6 Risk Analysis, Cont.

- 6.6.15 Hold Time Studies
- 6.6.16 Cleaning Control Strategy
- 6.6.17 Operator Training
- ***6.6.18 Sampling***
- ***6.6.19 Selection of Analytical Methods***
- 6.6.20 Using Risk Analysis for Master Planning

6.7 Risk Evaluation:

Inspection/Sampling Plan-
How and Where to Inspect to Get Representative Data

- Why? Purpose of sampling
- What analysis?
- How? Swab vs. Rinse vs. Visual
- Where? Random vs. “Hot Spots” vs. All surfaces
- Utilizing Rinse Sampling
- Visual Inspection

6.6.18 *Sampling-* In statistics, the purpose of sampling is to select a representative subset of individuals from a population that can reliably characterize the whole population. In cleaning, this means selecting representative samples from cleaned
equipment that can reliably characterize the cleanliness of the equipment.

6.6.18.1 *Sampling Strategy-* The risk assessment and prior experience should be used to determine the sampling locations,number of samples, and sampling methods for each piece of equipment. Sampling locations should consider the equipment design, accessibility, and materials of construction. Sampling locations should include those determined to be most difficult to clean and where there is a likelihood of contamination or carryover to the next product. Sampling strategies should have a statistical basis

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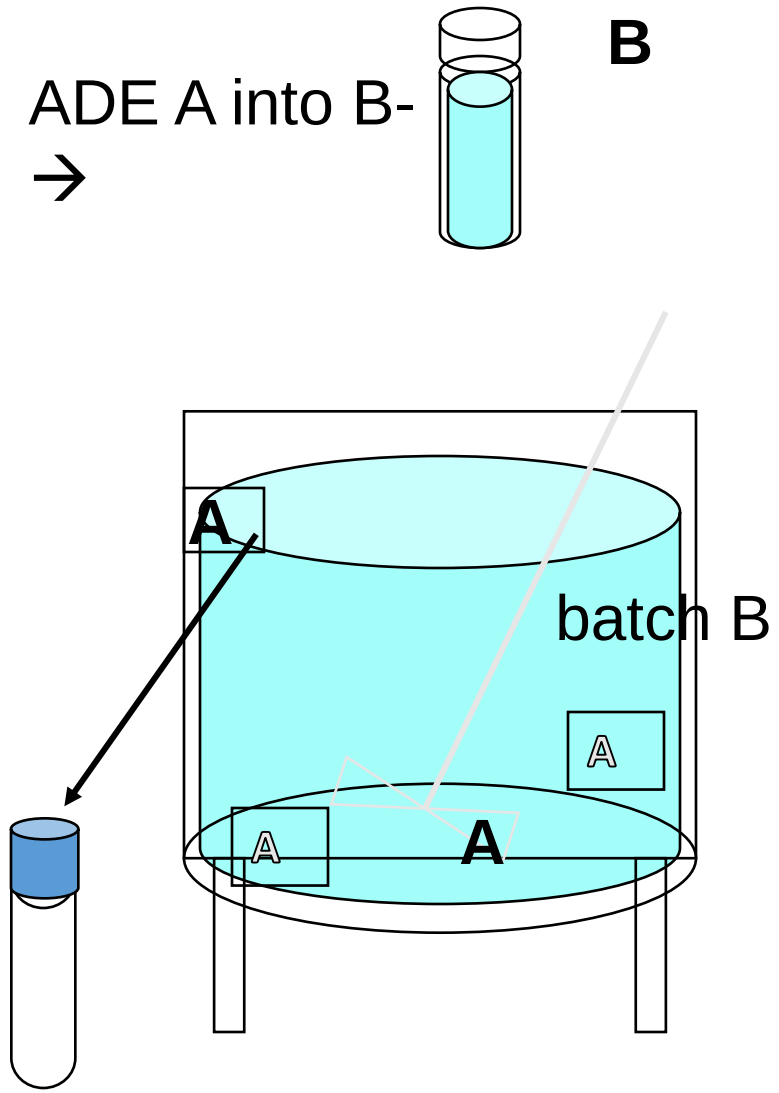
Purpose of Inspection using Samples

- Accurately measure surface residues
  - *Only meaningful in combination with analytical method*
  - Must have basis for quantitation of hazard residues
  - Must be within required sensitivity (LOD) for CQA/MSSR.
- Allow determination of overall surface quality
  - Rigorous justification of discrete locations
  - Cannot pass inspection of dirty equipment (>MSC, ARL/MSSR)

Converting Limits to Acceptance Criteria, for two product system

- **L1:** Allowable level of A in next product
  (ADE mcg A/daily dose Mg B
- **L2 MSC** in Equipment,next batch
  (mcg A/mg daily dose B X batch size B)
- **L3 Equipment surface limit** ARL/MSSR
  =MSC/shared equipment surface area
  = mcg/cm2
- **Sample acceptance criteria in ppm** =
  L3 Surface Limit (μg/cm2)
  X area sampled(cm2)÷ sample vol (ml)



Inspection Checklist

- *Residues analyzed for must indicate levels and risks for those not analyzed for*
- Locations sampled must indicate conditions of locations not sampled.
- Recovery, precision and reliability of combined sampling and analytical method must be demonstrated

Case: Blender Cleaning Plan

SOPs	Challenge Products	Cleaning Methods	OQ	PQ	Analytical Methods
5	5	5	5	15	5
5	5	1	1	15	5
1	*1*	*1*	*1*	*3*	*1*
1	5	1	1	15	5
2	2	1	1	6	2

Analytical methods for which products and contaminant residues?

- “Each and every” API, ingredient
- Most Potent or “critical” API
- Worst case only, or for a grouping
- Representative/indicator for group
- Only when HBEL based MSSR is below Visual detection level

Evaluation per Q7A

	A	B	C	D	E
Product Type					
Solubility					
“Cleanability”					
Potency					
Toxicity					
Stability					

Does Solubility Index predict relative residue removal rate?

Case: Blender Cleaning Plan

Equipment	Residues	Method	Procedure
Blender	**A,B,C,E** **Test w/C**	**Immersion** **Agitation** **CP-700**	**CIP** **Automatic**
	D, **Test w/D**	**Immersion** **Agitation** ***CP-400 Acid***	**CIP** **Automatic**

Lilly Case: Dose A>B: (0.001)I/J x K/L x M

10 ppm A>B: 10 x S/L x M

I = dose strength A; J= doses/day B
K=Batch size B (dose units); S= kg /batch B
L= common surface area (in2);
M= sample area (in2/swab)

ADE mcg/day	A J=1 K=40000 S=16 kg		B J=6 K=65000 S=13 kg		C J=3 K=90000 S=36 kg		D J=4 K=30000 S=15 kg		E J=8 K=35000 S=26 kg	
A			4500	0.481	6500	0.923	4500	0.333	4500	0.194
50 mg/day				0.116		0.222		0.133		0.231
B	4500	0.533			4500	0.400	4500	0.100	5500	0.048
15		0.142				0.320		0.133		0.189
C	6500	0.369	4500	0.144			4500	0.100	4500	0.058
15		0.098		0.116				0.133		0.231
D	4500	7.111	4500	1.926	4500	5.333			4500	0.778
200		0.142		0.116		0.320				0.231
E	4500	35.556	5500	7.879	4500	26.667	4500	6.667		
1000		0.142		0.095		0.320		0.133		

What analytical methods are needed to demonstrate L3 residue limits are met,? to address risk? What was identified with ADE?

- Whole composite vs. Single components
  - ***Actives***, excipients, impurities, degradants
  - most prevalent? most toxic? most adherent?
- Process aids
  - cleaning agents
  - lubricants, gaskets
- Microbiological

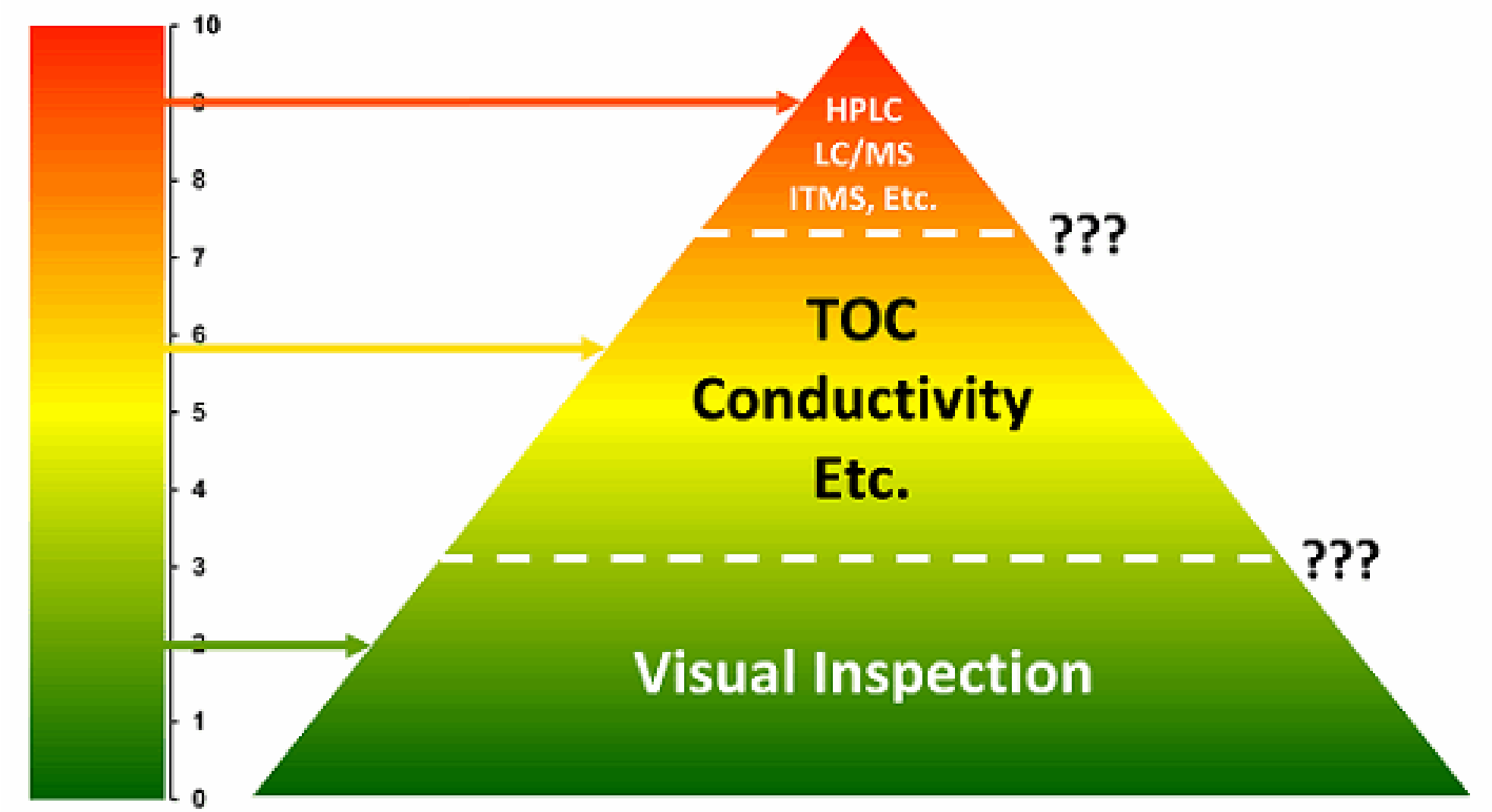
Analytical Methods

- Identification vs. quantitation
- *Non-Specific vs. Specific method*
  - Remember: The FDA does not require use of “specific” method. They require that your methods will respond to your specific residue matrix and target. The problem cited for many firms was that there was no data to show their residues would be detected by the USP water tests, conductivity or pH testing.

A Swab Limit-Derived Scale For Assessing The Detectability Of Total Organic Carbon Analysis

Pharmaceutical Online; January 24, 2018

By Andrew Walsh; Thomas Altmann; Alfredo Canhoto, Ph.D.; Ester Lovsin Barle, Ph.D.; et al



6.6.19 ***Selection of Analytical Methods*** -The choice of methods should be science and risk based. The goal should be to use the simplest technique that is appropriate and can be justified. Analytical methods fall into two general categories: specific and non-specific.

6.6.19.1 ***Specific Analytical Methods*** -Specific methods, such as high performance liquid chromatography (HPLC), are capable of identifying and quantifying specific process residues in the presence of potential contaminants. Specific methods
should be considered for high-hazard products or high-risk situations.

6.6.19.2 ***Non-Specific Analytical Methods-*** Non-specific methods, such as total organic carbon (TOC), UV, conductivity, pH, and visual inspection detect the presence of multiple ingredients which can be acceptable in certain situations.

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Whole product vs. specific component
Biotech example

Residue	Assay					
	HPLC	**PAGE, ELISA**	**Lowry**	**Micro**	**Cond.**	**TOC**
Active proteins	X	X	X			X
Denatured Protein and fragments; Amino acids; Peptides, Nucleotides, Sugars, nutrients, Org.Buffers		X	X			X
Inorganics, salts					X	
Endotoxin				LAL		X
Viable Micro				X		X
Cleaning Agents					X	X

Drug Formulation Example
What analytical methods are needed to demonstrate L3?

	HPLC	Other Assay	TOC	Conduct.
Active D				
Active C				
Excipient 1				
Excipient 2				
Excipient 3				
Cleaning agent 1				
Viable micro.				

Specific Analytical Methods

Can distinguish specific chemical or specific analyte-

- Thin Layer Chromatography (TLC)
- Gas Chromatagraph (GC)
- High Performance Liquid Chromatography **(HPLC)**
- Infrared, IR/FTIR
- Atomic Absorption (AA)
- Immunoassays
  - ELISA, Enzyme-Linked Immunosorbent Assay
  - RIA-radioimmunoassay
- Polyacrylamide Gel Electrophoresis (PAGE)
- Specific Ion Probes
- Endotoxin-LAL
- chemical assays
  - Spectrophotometric
  - titration

Analytical Methods (continued)

The FDA has said that non-specific methods can be employed if you have the data for your particular residue matrix.

- Non-Specific-
  - **Total Organic Carbon (TOC)**
  - **Conductivity**
  - pH
  - Calorimetric protein assays- Biuret, Bradford, Lowery
  - UV/VIS Absorbency

USING TOC ANALYSIS IN CLEANING VALIDATION

Andrew Walsh, M.S.

- "Non-specific" analytical method can work, even for drug active
- Even water insoluble residues can be measured
- Very practical analytical tool when correlated to HPLC

Comparison of TOC and HPLC

HPLC	TOC
• Product specific	• Not specific
• Need many methods	• One method
• Sensitive	• Sensitive (0.05 ppb)
• Detect Insolubles	• Cannot detect Insolubles?
• Accepted Practice	• Not well accepted

Definitions of Solubility

(

Very Slightly Soluble	1 part to 1000 to 10,000 parts	< 1000 ppm
Practically Insoluble to Insoluble	1 part to more than 10,000 parts	< 100 ppm

Recovery of Insolubles in Water

Active	Solubility (Merck Index)	Actual Solubility	(as TOC)	Recovery (HPLC)	Recovery (TOC)
Sulfacetamide	Sparingly Soluble	10,000 ppm?		91.0%	93.1%
Sulfabenzamide	Substantially Insoluble	300 ppm	127 ppm	71.2%	78.0%
Sulfathiazole	Substantially Insoluble	600 ppm	254 ppm	82.4%	86.5%
Recovery from coupons @ μ4g/cm^2 level (~2 ppm TOC in 20 mL sample)					

Suitability: Test and verify Sensitivity, Specificity, Recovery in Solution

- Compare known quantity to measured quantity for range of concentrations- Spiked recovery in solution/solvent
- Find Limit of Quantitation (LOQ); Limit of Detection(LOD)
- Ruggedness- stress the method conditions, use various analysts
- **Interference**- Will you get the same result with pure target substance and with target in residue mixture?

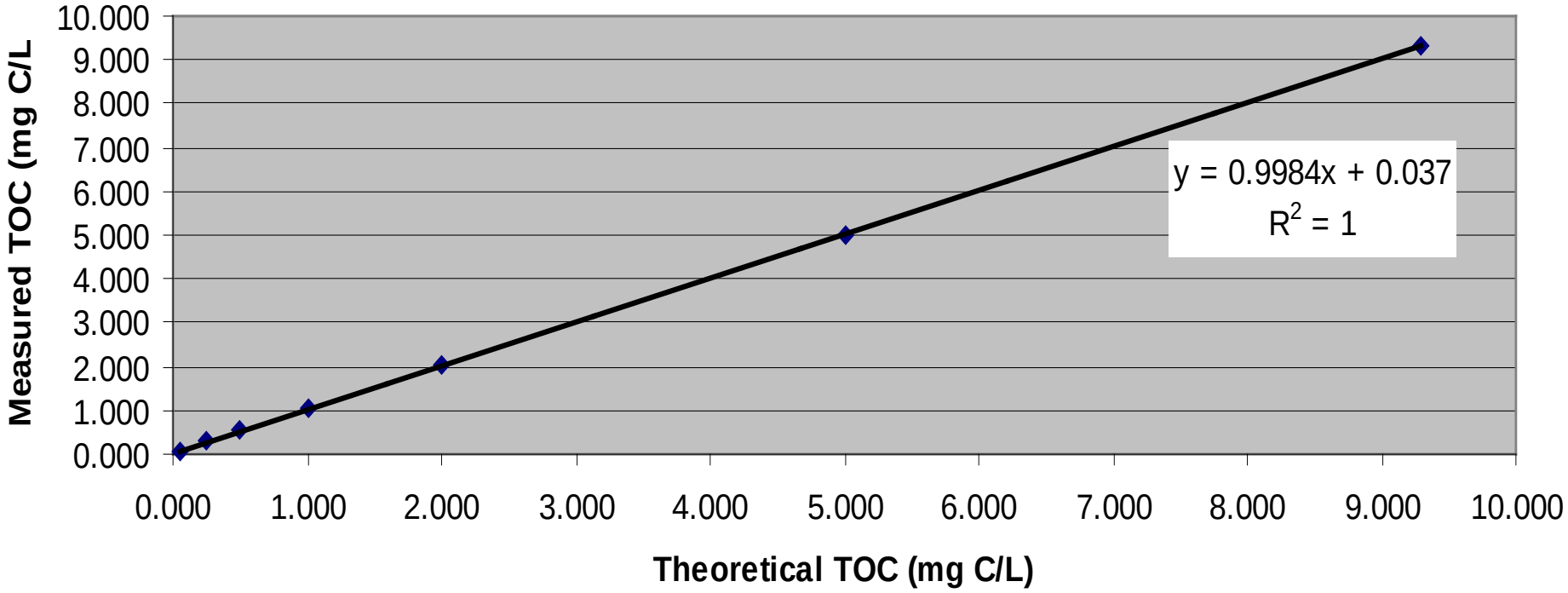
Analytical Method Suitability -

Carl Craig, Ph.D.;Pharmaceutical Resource Associates, Arvada, CO

- Quantitate residual Target residue directly in solvent, dried in sample vials, and dried on stainless steel at equivalent levels
- Analyze with TOC and evaluate method
- A positive outcome is defined by meeting or exceeding the data quality objectives
  - Accuracy > ± 10%
  - Recovery > 85%

Spiked recovery of target compound in solution

Graph 4.
TOC Instrument Linearity
using Heparin as Carbon Source



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Carbon Content Calculation from Formulation

Chemical Formula for Sucrose = $C_{12}H_{22}O_{11}$

Molecular weight = 342.3

To Calculate Percent Carbon:

1) mw carbon X number of carbons

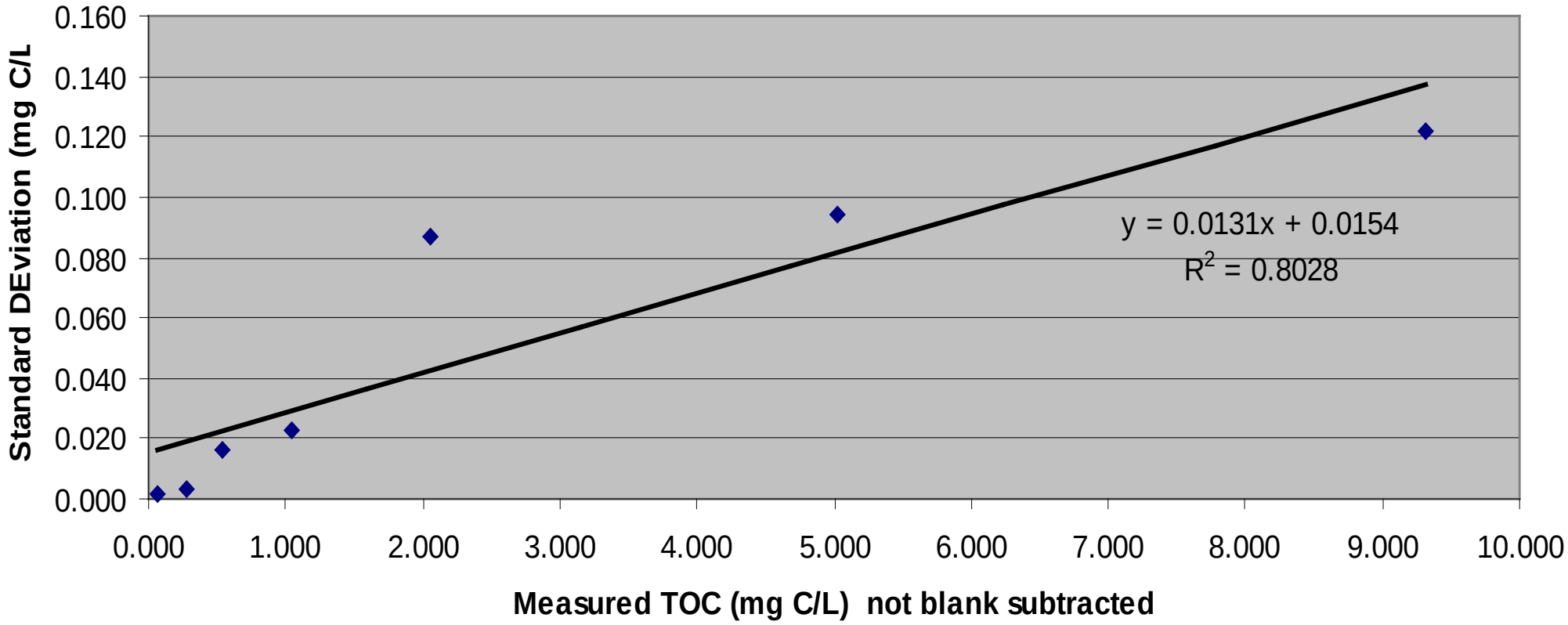
12.01 X 12 = 144.12

2) weight carbon/molecular weight

144.12 / 342.3 X 100 = 42.10 % C

Spiked recovery of target compound in solution

Graph 5.
Extrapolated Standard Deviation at "Zero" Concentration using Heparin Solutions



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Accuracy, Linearity and Sensitivity

	Accuracy	Linearity	Sensitivity
TOC CRMs*	101%	(r) = 1.0	MDL = 0.008 mg C/L LOD = 0.024 mg C/L LOQ = 0.080 mg C/L
TOC Drug	99%	(r) = 1.0	MDL = 0.015 mg C/L LOD = 0.045 mg C/L LOQ = 0.150 mg C/L

*Certified Reference Material

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