**GC & LC/MS/MS Approaches to Forensic Drug Testing**

CAT Course, Las Vegas, August 2005

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**Drug Analysis Disparity**

- Toxicology (forensic, employee screening, police)
  - Preliminary screen (TLC, immunoassay)
  - Confirm with GC/MS or GC/MS/MS
  - Some LC or LC/MS
- Pharma
  - Extensive use of LC, LC/MS and LC/MS/MS
  - Relatively little GC or GC/MS

*Strong preference by laboratory type*

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**Trends in 2005**

- Toxicology laboratories
  - Increased use of LC/MS
    - Excellent LOD
    - Cheaper (still expensive)
    - Much more robust
    - Solves many "limitations" of GC/MS
    - Simple sample preparation
- Pharma laboratories
  - Increased (although still limited) use of GC/MS
    - Less FDA inspection issues (helium vs. LC mobile phases)
    - Significantly lower cost than LC/MS

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**Factors to Consider**

- Experience and preference of users
- Existing methodologies
- Budget constraints
  - GC/MS $50K - $150K
  - LC/MS $100K - $250K – what can you afford?
  - Sample prep, labor, and material costs
- Analytical requirements
  - Molecular weight, volatility and polarity of analytes
  - Sensitivity and linearity
  - Matrix
  - Sample preparation requirements
  - Analytical requirements by regulatory agencies

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**Presentation Outline**

- Analytical requirements
- GC/MS – evolution, strengths, weaknesses
- GC/MS as the method of choice
- LC/MS – evolution, strengths, weaknesses
- LC/MS as the method of choice
- GC/MS or LC/MS? Practical comparisons

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**Polarity, MW and Volatility**

MS Applications

<table>
<thead>
<tr>
<th></th>
<th>GC/MS</th>
<th>GC/MS or LC/MS</th>
<th>LC/MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW &lt; 700</td>
<td>100 &lt; MW &lt; 800</td>
<td>50 &lt; MW &lt; 50k</td>
<td></td>
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<tr>
<td>Highly volatile</td>
<td>Moderately volatile</td>
<td>Non-volatile</td>
<td></td>
</tr>
<tr>
<td>Non-polar</td>
<td>Moderately polar</td>
<td>Thermally labile</td>
<td></td>
</tr>
<tr>
<td>Moderately polar</td>
<td>Highly polar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocarbons</td>
<td>Most pesticides</td>
<td>Proteins/peptides</td>
<td></td>
</tr>
<tr>
<td>Flavors</td>
<td>Many drugs</td>
<td>DNA</td>
<td></td>
</tr>
<tr>
<td>Fragrances</td>
<td>Many industrial cpds</td>
<td>Oligosaccharides</td>
<td></td>
</tr>
<tr>
<td>Pesticides</td>
<td>Some vitamins</td>
<td>Surfactants</td>
<td></td>
</tr>
<tr>
<td>Some drugs</td>
<td>With derivatization</td>
<td>Drug glucuronides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Many more!</td>
<td>Chlormequat</td>
<td></td>
</tr>
</tbody>
</table>

Ionization Techniques

<table>
<thead>
<tr>
<th></th>
<th>GC/MS</th>
<th>GC/MS or LC/MS</th>
<th>LC/MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC/MS EI 70eV</td>
<td>Hard</td>
<td>Large number of fragments</td>
<td>(best fingerprint); M+ varies, maybe zero</td>
</tr>
<tr>
<td>GC/MS PCI</td>
<td>Soft -</td>
<td>M+H dominant; fragments with “harder” reagents</td>
<td></td>
</tr>
<tr>
<td>GC/MS NCI</td>
<td>Very soft</td>
<td>M- dominant; may fragment to yield electroneg groups</td>
<td></td>
</tr>
<tr>
<td>LC/MS ESI</td>
<td>Very soft</td>
<td>Mol ion and adducts (+ or -)</td>
<td>Few fragments</td>
</tr>
<tr>
<td>LC/MS APCI</td>
<td>Soft -</td>
<td>Mol ion and adducts (+ or -)</td>
<td>Few fragments</td>
</tr>
</tbody>
</table>

Method Considerations

- Sample Preparation
  - Complexity, time and cost
  - Final “cleanliness”
  - Recovery and precision
- Instrumental Method
  - Detection limits, linearity and precision
  - Consider the instrument alone and the complete method with sample preparation
  - SIM, full scan, MS/MS, EI, NCI, ESI, etc.
  - Robustness, reliability
  - Cost - purchase price and daily operational costs
- Do both methods give all the required results?

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Evolution of GC Technology

- Fused silica capillary columns (late 70’s)
  - Inert
  - Flexible (not fragile after polyimide coating)
  - Easy to cut and install (naturally straight)
- Cross-linked, bonded phases
  - Reduced column bleed (siloxanes)
  - Longer column life and stable MS transfer lines
  - Lower chemical noise
  - Increased variety of phases
- Electronic flow/pressure control
  - Simple to use and complete method documentation
  - Programmable flows
  - Constant flow mode for stable flow into the MS

Evolution of GC Technology

- Temperature programmed injectors (mid 80’s)
  - Thermally labile
  - Larger volume injection
- Pressure pulsed splitless
  - Higher transfer efficiency (better detection limits)
  - Minimized diffusion losses and surfaces interaction
- Inert liners/inserts
  - Improved deactivation techniques
  - Silica coated
- Better septa (injector and vials)
  - Reduced siloxane artifact peaks
  - Solvent compatibility
Evolution of GC/MS Technology

- Simplified GC maintenance
  - Insert replacement and injector connections
  - Column
  - Temp stable phases allow better “bake out”
  - Cut off end of fused silica and reinstall
  - Retention gap with unions (press-fit or inert metal)
- Simplified MS maintenance (MS anxiety gone!)
  - Improved, new transfer line connections
  - EZ-Grip™ columns, No-Vent™ connectors, inert valves
  - Saturn Ion Trap offers “no tool” removal of the analyzer
  - Higher analyzer temperatures (stay clean longer)
  - Vacuum interlocks for rapid changes of ion volumes
  - Low pressure ion trap PCI (no reagent contamination)

GC/MS Handles a Wider Range of Applications Today Than Ever Before!

GC/MS Strengths

- No mobile phase preparation - just helium
  - No pH meters, no electronic balances, no stability issues
  - No waste reservoir to dispose
    - Disposal cost higher than cost of pure solvents
  - Low gas consumption
    - Helium is expensive in most of the world
- Simple “gradient” analysis
  - Remarkably precise retention times
  - Fast temperature increase - fast cool down
  - No reagent impurity peaks (but there is column bleed)
  - No proportioning process, seals, check valves to fail
  - No Gradient composition effects
  - Simple column switching configuration

GC/MS Strengths

- High Efficiency Columns
  - 30 m (ID 0.25 mm), 4000 plate/m = 120,000
  - A single, high efficiency phase can be used for many applications
- Ideal MS “Front end”
  - Low volume gas (1-2 ml/min) into a vacuum
  - Lower pumping requirements translate into reduced cost
    - Vacuum is a significant % cost for any MS
  - No liquids, salts or buffers
  - Significantly Less Expensive

GC/MS Strengths – EI Libraries

- Commercial EI Libraries
  - NIST 02 data base
    - 147,194 compounds with structures
    - 174,948 spectra (27,750 replicate)
  - Wiley Library, 7th Edition
    - 161,724 compounds with structures
    - 338,000 spectra (48,467 replicates)
  - PMW library (Pfleger-Maurer-Weber library)
    - Over 6300 spectra of drugs and pesticides
  - Adams Flavors and Fragrances library
    - Over 500 spectra

GC/MS Weaknesses

- Derivatization
  - Required to improve injection or chromatography
  - Time & cost
- Injection process
  - Improved but still troublesome
  - Less precise
- Extra sample preparation
  - Hydrolysis of glucuronides
- Compound dependent molecular ion intensity
  - Some compounds fragment too easily/too much
GC/MS or LC/MS: the Best Solution?

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GC/MS: Method of Choice

- Volatile components
  - Hydrocarbons, solvents, etc.
- Unknown identification
  - Non-target compounds
- Large number of analytes to be monitored
- Switching between different modes of ionization in the same run

Drug Monitoring in EI Full Scan:
241 Analytes in 28 minutes

1200 GC/MS & GC/MS/MS

Introduced 3/01

Ion Source - Exploded View

Source
Hexapole
Ion Guide
Q1 Mass Filter
Q2 semi-circular Collision Cell
Q3 Mass Filter
Detector
+/− ions
Interlock
Dual Stage Turbo Pump
Heater cartrdige (4)
Aluminum support for stainless steel lens
Mass filters (Q1 and Q3)

- Pre-guide (pre-filter)
- Post-guide (post-filter)

Mass Analyzer With Lens

Ions with the same m/z and energy, but different initial radial position and angle will have different radial positions at the exit of the field.

Lens-less Mass Analyzer

Ion energy: 3.0 ev

Pre-filter ion guides reduce the radial displacement in the mass filter and improve the peak shape and resolution.

1200 Collision Cell

“Square” geometry - flat surfaces

Collision Cell

- 180 degree path
- 40 degree pre-guide (pre-filter) section
- 100 degree collision cell (185 mm path)
- 40 degree post-guide section
- Collision cell without lenses
- Decreased ion losses
- Curved for low noise and high sensitivity
- Removes neutrals from the CID process
- Positions the detector in off-axis from the source
- Long path for wide CID energy range
- Efficient dissociation of stable ions
- Square geometry with flat surfaces
- Larger cross sectional area for ion transmission

- Square geometry with flat surfaces
- Higher order multipole moments in field reduce “noding” of product ions
Collision cell without lens
- No Apertures
- No noding
- Decreased ion losses
- Higher sensitivity

MS/MS Scan Functions

EI MS/MS THC
Neg Cl (NH₄⁺) THC-COOH

Analytical Conditions Neg Cl

Analytical Conditions:
- GC: Injector 1177, 250 degrees
- Flow: 0.8 ml/min, Precone Pulse 45.0 for 0.8 min.
- Column: 100.0 deg. hold for 0.5 min, program to 275 deg. at 15.0 deg. min. 0.5 hold program to 315 deg. at 60 deg. min. 2.0 min hold.
- MS: Transfer line: 250 degrees
  - MS/MS THC: 419-313 = 15V 419-343 = 8V
  - 419-319 = 15V 419-353 = 8V
  - 419-349 = 15V
  - MS/MS THC/COD: 599-362 = 15V 599-409 = 15V
  - 599-402 = 15V 599-425 = 15V
  - 599-422 = 15V

THC and THC-COOH in Whole Blood

Ammonia Negative Mode CI

Comparison of Low Level, Mid Level, and Unextracted THC (not normalized)

THC and THC-COOH in Whole Blood

Extracted Blood Standard 0.5 ng/ml

Calibration Curves

THC - d3 10.0 ng/ml
THC 0.5 ng/ml
THC-COOH 0.5 ng/ml
Analytical Conditions EI

**Analytical Conditions:**

- **GC:** Injector 1177: 240 degrees
  - Flow: 1.0 ml/min, Pressure 30.0 for 0.5 min
  - Column: 1300 deg. hold for 0.2 min, program to 360 deg. at 25.0 deg./min; 5.0 hold.

- **MS:** Transfer line: 280 degrees
  - MS/MS THC: 380-374 – 20V
  - 374-374 – 15V
  - 374-289 – 20V
  - MS/MS THC+COOH: 488-297 – 20V
  - 488-374 – 20V
  - 488-488 – 10V

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Evolution of LC Technology

- Improved column phases
  - Inertness - improved peak symmetry
  - Stability and reproducibility - lot-to-lot consistency
  - pH stability - purified silica, polymers, zirconium
- Increased variety of phases
  - Better control of separation selectivity
  - Particle size and pore dimensions
  - High efficiency 3 µm - readily available
- Column dimensions and flow rates
  - 4.0 - 4.6 mm: 800 - 2000 µl/min
  - 2.0 mm: 200 - 400 µl/min
  - 1.0 mm: 30 - 60 µl/min
  - 0.18 - 0.32 mm: 1 - 10 µl/min

Evolution of LC Technology

- High precision micro to macro (auto)injectors
  - Accurate, precise, simple
  - Injection solvent compatibility critical for large volumes
- Improved solvent delivery systems
  - Micro to prep flows (using different pumps)
  - Compositional accuracy and precision
  - Seal, check valve lifetime
- Splitters (pre- and post-Column)
  - Precise and robust
  - High pump flows for gradient precision/performance
  - Lower flows to detectors like the MS
  - Expensive micro-flow pumps not required

Evolution of LC/MS Technology

- Low flows and small ID columns
  - Less mobile phase = less pumping, less heating, less contamination
  - Electrospray is a concentration dependent detector
- Dramatic improvements in LC to MS interfaces
  - Robust with faster, easier optimization
  - Sensitivity comparable to GC/MS
  - ESI (Electrospray)
    - Ion evaporation - heat assisted, pneumatic nebulization
  - APCI (Atmospheric Pressure Chemical Ionization)
    - Solvent mediated CI - heat assisted, pneumatic nebulization

1200L LC/MS/MS Analyzer

- Spray Chamber
- Dual Stage Turbo
- Multiplier +5kV post acceleration
- Curved 185 mm Path
- Q1
- Q2
- Q3
- Capillary Plug Quadrupole Ion Guide
- Divertor
The API Interface

Transition from HPLC Liquid to MS Vacuum

Cross-Section of ESI Interface

- Spray needle assembly
- Drying gas heater
- Quadrupole ion guide
- Skimmer cone
- Sampling capillary
- Drain

Dual Off-Axis Orientation

- Needle off-axis from the capillary
- Capillary 6° off-axis from the ion guide
- Drain aligned with capillary

Excess liquid goes to drain to reduce chamber contamination

Off-axis spray needle minimizes contamination of capillary orifice and extends maintenance cycle

Capillary 6° off-axis from the ion guide

Off-axis capillary minimizes transfer of micro-droplets and contaminants to Q1
Fully Adjustable Spray Needle

Adjustment of the inner, liquid capillary needle to maximize nebulization efficiency

X-Y adjustment of spray needle to optimize sensitivity and maximum robust operation

Easy Cleaning

Hinged spray chamber opens easily to clean internal surfaces

Electrospray

Ionization, desolvation, excess droplet removal

Drying gas promotes rapid desolvation and blows large droplets away from capillary inlet

LC/MS Handles a Wider Range of Applications Today Than Ever Before!

LC/MS Strengths

- Precise, accurate injections
- No losses from vaporization process (discrimination)
- No losses from active injector surfaces
- Ideal for thermally unstable compounds
- Ideal for non-volatile compounds
  - Eliminate derivatization
  - High molecular weight range possible
  - Highly polar structures common to biological matrices
- Ideal for polar metabolites
  - Acids, glucuronides, etc.

LC/MS Strengths

- Intense molecular ions
- Large volume injections are simple
  - Must be careful to avoid matrix inhibitions of ionization
- Unretained matrix easily diverted from the MS
  - Extends time between maintenance
  - Can increase extra column variance
- A higher degree of automation is possible including on-line sample preparation
**LC/MS Weaknesses**

- Very "soft" ionization processes
  - Minimal fragments without secondary dissociation
- Sensitivity highly dependent upon mobile phase conditions
  - Sometimes troublesome adduct ions
- May require monitoring of both (+) and (-) ions
  - Separate analyses
  - Compromised sensitivity if run simultaneously
- Ion suppression artifacts (especially in ESI)
- No commercial libraries
  - None for MS or MS/MS

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**LC/MS: Method of Choice**

- Non-volatile components
  - Too polar for GC
  - Thermally unstable
- Target compound identification
  - Confirmation
- Reasonably large number of analytes
  - Assuming adequate MS selectivity to compensate for lower chromatographic resolution
- Compatible with one of the atmospheric pressure ionization (API) processes

**Norchem LC/MS/MS Analyses Using the Varian 1200L**

**Analysis of Amphetamines by GC/MS and LC/MS**

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**Sympathomimetic Amine Drugs**

- Wide range of pharmacological uses
  - CNS stimulants, anorectics, anti-Parkinsonians, nasal decongestants
  - Mild depression, obesity, narcolepsy
- Among the most frequently abused recreational drugs in the world
  - Amphetamine and methamphetamine
  - MDMA (“Ecstasy”, “Adam”) and MDEA (“Eve”)
  - Small compounds, easily manufactured in illicit drug labs
- Wide number of over-the-counter drugs in this category
  - Ephedrine, pseudoephedrine, phenylpropanolamine
- Toxic impact on CNS and cardiovascular system

**Amphetamine Structures**

- Amphetamine
- Methamphetamine
- MDMA (“Ecstasy”, “Adam”)
- MDEA (“Eve”)
- Phenylpropanolamine
- Ephedrine

- Small compounds, easily manufactured in illicit drug labs

**Structural Isomers**

- Methamphetamine
- Phentermine

**Amphetamine – EI Spectrum**

- No molecular ion
- Base peak - too low m/z

**Derivatized Amphetamine Spectrum**

**Amphetamines – GC/MS Analysis**

- Long list of literature references
- Full range of samples
  - Urine, blood, saliva, sweat, hair, nails, tissues
- Sample preparation
  - Liquid-liquid extraction
  - Solid phase extraction
- Derivatization
  - Off-line from the GC/MS
  - PFPA, BSTFA, 4-carboxyhexafluorobutyl chloride
  - On-column with a hot injector
    - TFAA, PFPA, HFBA
  - Direct on-fiber SPME
    - TFAA
Dilute 2 mL urine with PO4 buffer; adjust pH
Oxidize interfering compounds with Na2IO4
Heat for 15 minutes at 50-60°C
SPE
Apply sample to conditioned Certify cartridge
Wash with HOAc and MeOH
Elute with MeCl2/MeOH/NH4OH (78:20:2 v/v)
Partial evaporate; add MeOH/HCl; evap to dryness
Derivatization
Add 4-carbethoxyhexafluorobutyryl chloride in 1-chlorobutane and heat 30 minutes at 50-60°C
Add anhydrous EtOH and heat 30 minutes at 50-60°C
Evap to dryness and reconstitute in 50 µL EtOAc
Inject 1 µL, 280°C, split 10:1 onto a 15-m CP Sil-8 column

Linearity
100-5000 ng/mL \( (r^2 = 0.9982) \)
Urinary cutoff 500 ng/mL
LOD not approached for urine method
Lowest standard 100 ng/mL
Detection Limits
(2 mL urine \times 100 \text{ ng/mL} \times 1 \mu\text{L inj}) \div 50 \mu\text{L reconst.}
= 4 \text{ ng injected} \div 10 \text{ split ratio}
= 400 pg on column with S/N (pk-pk) > 400
LOD in low pg on column possible

Long list of literature references
Full range of samples
Urine, blood, saliva, sweat, hair, nails, tissues
Sample preparation is sample dependent
Organic precipitation
Liquid-liquid extraction
Solid phase extraction
No problem with injector “activity”
Concern focused on column plugging and interferences
No derivatization
ESI and APCI
MS and MS/MS

Plasma and oral fluid
50 µL sample and 200 µL MeOH with Int Stds
Vortex, centrifuge, inject 10 µL (solvent strength high)
Varian Pursuit C18 column (2.1 x 100 mm, 3.5 µm)
Isocratic: 10 mM NH4OAc and MeCN (75:25 v/v)
Optional gradient: same mobile phase components

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Collision Energy</th>
<th>Product Ion (m/z)</th>
<th>Precursor Ion (m/z)</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-Methamphetamine</td>
<td>-25</td>
<td>179</td>
<td>179</td>
<td>15.0</td>
</tr>
<tr>
<td>(+)-MDA</td>
<td>-25</td>
<td>916</td>
<td>916</td>
<td>17.0</td>
</tr>
<tr>
<td>(+)-Ephedrine</td>
<td>-25</td>
<td>1014</td>
<td>1014</td>
<td>17.5</td>
</tr>
<tr>
<td>(+)-Amphetamine</td>
<td>-25</td>
<td>129</td>
<td>129</td>
<td>19.0</td>
</tr>
<tr>
<td>(+)-MDMA</td>
<td>-25</td>
<td>1016</td>
<td>1016</td>
<td>19.5</td>
</tr>
<tr>
<td>(+)-MDEA</td>
<td>-25</td>
<td>1116</td>
<td>1116</td>
<td>21.0</td>
</tr>
</tbody>
</table>

LC/MS/MS Method

<table>
<thead>
<tr>
<th>Injection Volume</th>
<th>10 µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Solvent</td>
<td>80% MeOH</td>
</tr>
<tr>
<td>Mobile Phase Components</td>
<td>10 mM NH4Ac in water, Acetonitrile</td>
</tr>
<tr>
<td>Time (min)</td>
<td>T1</td>
</tr>
<tr>
<td>0.00</td>
<td>1.0</td>
</tr>
<tr>
<td>1.00</td>
<td>1.0</td>
</tr>
<tr>
<td>3.00</td>
<td>1.0</td>
</tr>
<tr>
<td>5.00</td>
<td>1.0</td>
</tr>
<tr>
<td>8.00</td>
<td>1.0</td>
</tr>
</tbody>
</table>

GC/MS or LC/MS: the Best Solution?
**Breakdown Curve and Spectra**

4.5V

7.5V

32.5V

14.5V

**Calibration: Amp. & Methamp.**

**Result (Isocratic)**

<table>
<thead>
<tr>
<th>Analytes</th>
<th>LOD (ppb)</th>
<th>Varian 1200</th>
<th>LOD (ppb in injection solution)</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(±)-Methamphetamine</td>
<td>0.5</td>
<td>0.0</td>
<td>0.01</td>
<td>3.0</td>
</tr>
<tr>
<td>1(±)-Methamphetamine-D5</td>
<td>0.5</td>
<td>0.0</td>
<td>0.01</td>
<td>3.0</td>
</tr>
<tr>
<td>21S,2R(+)-Ephedrine</td>
<td>0.4</td>
<td>0.0</td>
<td>0.01</td>
<td>2.0</td>
</tr>
<tr>
<td>21S,2R(+)-Ephedrine-D3</td>
<td>0.4</td>
<td>0.0</td>
<td>0.01</td>
<td>2.0</td>
</tr>
<tr>
<td>1(±)-Amphetamine</td>
<td>0.2</td>
<td>0.0</td>
<td>0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>1(±)-Amphetamine-D5</td>
<td>0.2</td>
<td>0.0</td>
<td>0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>1(±)-MDA</td>
<td>0.2</td>
<td>0.0</td>
<td>0.01</td>
<td>1.0</td>
</tr>
<tr>
<td>1(±)-MDA-D5</td>
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<td>0.0</td>
<td>0.01</td>
<td>1.0</td>
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<td>1.0</td>
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</table>

**Gradient Chromatogram (LOD)**

**Amphetamines: GC/MS or LC/MS?**

- Detection limits approximately equal
- GC/MS
  - Lower instrumentation cost than LC/MS
  - Derivatization required (especially for EI/MS)
  - Time, error and reagent cost
- LC/MS
  - Simple methods
  - All compounds compatible with LC injection and separation
  - Very robust method

5 ppb sample:
5 ng/mL x (50 µL/250 µL) x 0.010 mL inj = 10 pg on column
GC/MS or LC/MS or Both?

- Consider the costs
- Consider the complexity
- Be sure you have all of the tools you need to get the job done!
- Both are getting easier to use and more affordable
- Plan both for the future!