Development of the World’s Most Sensitive Triple Quad MS

LC/MS Division
and Agilent Labs
Agilent Technologies
Santa Clara, CA
New 6490 - World’s Most Sensitive LC/QQQ

**iFunnel Technology**
- Agilent Jet Stream
- Hexabore capillary
- Dual-stage ion funnel

**Collision Cell – hexapole**
- Tapered structure for increased ion acceptance
- Reduction of background noise

**Improved Quad Drive Electronics**
- Higher RF power capability
- Quad drive frequency increased to 1.4 MHz
iFunnel Technology captures 10X more ions

**Agilent Jet Stream**
- Thermal confinement of ESI plume
- Efficient desolvation to create gas phase ions
- Creates an ion rich zone

**Hexabore Capillary**
- 6 capillary inlets
- Samples 6X more ion rich gas from the source
- Captures the majority of the gas from the source region

**Dual Ion Funnel**
- Removes the gas but captures the ions
- Removes neutral noise
- Extends turbo pump life
Enhanced efficiency nebulizer

Super-heated sheath gas

Nebulizing gas

Heated drying gas

Resistive sampling capillary

The super-heated sheath gas collimates the nebulizer spray and creates a dramatically “brighter source”
Agilent’s Hexabore Atmospheric Sampling….. The Most Sensitive…. By Far.

- Nearly **6x** the amount of atmospheric gas sampled compared to a single capillary system

  AND

- **5 - 10x** more ions into the high vacuum region

**But how do we handle all the extra gas molecules?**
Need for Greater Ion Sampling Capacity

• Many ions formed in the collimated Agilent Jet Stream plume are still not captured by the MS system

• Ions sampled by a single capillary with a 600 µm i.d.

• Maximum ion generation occurs across a 3-5 mm horizontal region at the center of the plume.
Hexabore Sampling Capillary

- Hexabore sampling capillary increases ion sampling efficiency about 6X compared to single bore.

Ion sampling gains are most dramatic with the combination of both Agilent Jet Stream technology with the hexabore sampling capillary.
Agilent’s Two Stage Ion Funnel Can Handle the Gas Load

Stage 1 offset breaks up the high pressure gas exiting the Hexabore Capillary
How Does an Ion Funnel Work?

The RF Voltage focuses the ions to the center.

Unfocused Ions and Gas Enter

The DC Voltage accelerates the ions to the exit.

Focused Ions Out
How is an Ion Funnel Constructed?

Previously, with many metal plates....

... resulting in a large capacitive load and relatively large RF power electronics.

The 6490 design uses printed circuit board technology with only a small conductive rim resulting in a reduced capacitance load. This makes +/- ion switching possible.
Improved Ion Sampling Efficiencies with iFunnel

Agilent Jet Stream positive ion

Agilent Jet Stream negative ion

6490

6460
6490 with iFunnel vs 6460 in positive ion mode

1 pg Reserpine (7X)

1 pg Alprazolam (6X)
New 6490 Increases Signal but also Reduces Noise

6X gain in signal shown in previous slide translates into 10X gain in signal-to-noise for alprazolam relative to the 6460 as shown below.

6460

\[ \text{S/N} = 1,157:1 \]

where noise = 1xRMS

6490

\[ \text{S/N} = 11,640:1 \]

where noise = 1xRMS
6490 with iFunnel vs 6460 in negative ion mode

- **1 pg Chloramphenicol (8X)**
  - 6490: Relative Increase in Signal
    - Triton: 0.9
    - BB1-CAT CC only: 0.3

- **1 pg Acid red 4 (9X)**
  - 6490: Acquisition Time (min)
    - 0.2, 0.4, 0.6, 0.8, 1.0

Acquisition Time (min)

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Agilent Technologies
New iFunnel Technology Revolutionizes Atmospheric Sampling

The combined result of all three elements of iFunnel Technology is a dramatic gain in sensitivity.
Novel Curved and Tapered Collision Cell Design

Efficient Ion Transmission over wide mass range
Reduces transmission of ionizer generated noise

RF & DC Voltages Set Confinement and Axial Acceleration

Smaller (3.5mm) Exit Aperture Focuses Ions into MS2

Larger (5 mm) Entrance Aperture Accepts more Ions
New 6490 LC Triple with iFunnel Technology

“Unrivaled Quantitative Excellence”

1290 Infinity LC/6490 Triple : Clearly Better Together
Agilent Triple Quads: 2006 – 2010
Relentless increase in signal-to-noise specs

SNR 1 pg reserpine

<table>
<thead>
<tr>
<th>Year</th>
<th>SNR 1 pg reserpine</th>
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<tbody>
<tr>
<td>2006</td>
<td>6410</td>
</tr>
<tr>
<td>2007</td>
<td>6430</td>
</tr>
<tr>
<td>2008</td>
<td>6460</td>
</tr>
<tr>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>6490</td>
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</tbody>
</table>
New 6490 Triple installation Spec:  S/N > 10,000:1
so the 6490 should be able to detect 1 fg?

1 pg reserpine on-column
S/N > 22,605:1
6490 Triple - Attogram Sensitivity for Reserpinine

1 fg of reserpinine injected on-column

S/N scales as expected
NO gaming the noise spec
6490 Achieves Zeptomolar Detection Limits

+ MRM (455.3 -> 164.9)

200 zeptomoles
verapamil
Injected on-column

Acquisition Time (min)
Unprecedented Six logs of Linearity with 6490

100 Attogram to 100 Picogram varapmil on-column

\[ Y = 65283 x - 0.390412 \]

\[ R^2 = 0.9976 \]

Area Response

<table>
<thead>
<tr>
<th>Femtograms</th>
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<tbody>
<tr>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>10</td>
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50 pg/mL Fluticasone in plasma with 6460

25 Femtogram on-column
Area RSD = 23.7% (n=6)
Mean accuracy = 104

Fluticasone propionate

MRM unit / unit resolution
(0.7 amu / 0.7 amu)
5 pg/mL Fluticasone in plasma with new 6490

2.5 Femtogram on-column
Area RSD = 8.7% (n=5)
Mean accuracy = 104

Fluticasone propionate

MRM enhanced / unit resolution
(0.4 amu / 0.7 amu)

Agilent Technologies
The Value of Enhanced Resolution on 6490

*Fluticasone propionate (inhalant) in human plasma 2.5 fg on-column*

Enhanced Resolution gives increased selectivity for analytes in complex matrices.
Ultra Trace Levels of Pesticides in Potable Water

Triazine herbicides analyzed at **50 parts per quadrillion**

- **Atraton** S/N = 819
- **Simazine** S/N = 18
- **Simetryn** S/N = 9
- **Secbumeton** S/N = 51
- **Prometion** S/N = 40
- **Atrazine** S/N = 28

**6490 Triple Quad** with on-line enrichment
Peptide MRM on 6460 vs new 6490 Triple Quad

1 femtomole on 6460

LVNEVTEFAK
575.5 → 937.5

100 attomole on 6490
Triggered MRM – What Problem Does tMRM Solve?

Data dependent product ion scans leaves gaps in MRM
- mix of raw and synthetic points
- higher RSDs and higher LOQs

Gap in MRM trace, numerically filled in. Typically > 100 msec

Targeted Quant + Compound Identification
tMRM for up to 8 Confirmatory Ion Transitions
- when primary compound MRM triggers confirmatory MRM

Faster compound ID at higher sensitivity with tMRM

Plot counts versus m/z for product ions
“Composite MS/MS spectra for compound b”

<table>
<thead>
<tr>
<th>Product</th>
<th>Ion Scan Time</th>
<th>%MRM Sensitivity</th>
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</thead>
<tbody>
<tr>
<td>QTRAP 5500</td>
<td>~ 100 msec</td>
<td>~ 10%</td>
</tr>
<tr>
<td>Vantage</td>
<td>~ 150 msec</td>
<td>~ 2%</td>
</tr>
<tr>
<td>Xevo</td>
<td>~ 150 msec</td>
<td>~ 2%</td>
</tr>
<tr>
<td>6490</td>
<td>~ 30 msec</td>
<td>100%</td>
</tr>
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</table>
The 6490 has Zeptomole Capability

**what is a zeptomole?**

Photo of new 6490 taken from 1 meter distance
How far away is $10^{21}$ meters?
The Milky Way Galaxy as seen from Hubble

$10^{21}$ meters from the earth is at the edge of the known universe
The New 6490 Triple Quad System

- New era in sensitivity – Zeptomole
- New era in linearity – Six decades of linearity
- New iFunnel Technology
- Improving compound identity - tMRMs

“Delivers Unprecedented Quantitative Excellence”