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Future of the Triple Quadrupoles: What is possible and what is practical ?

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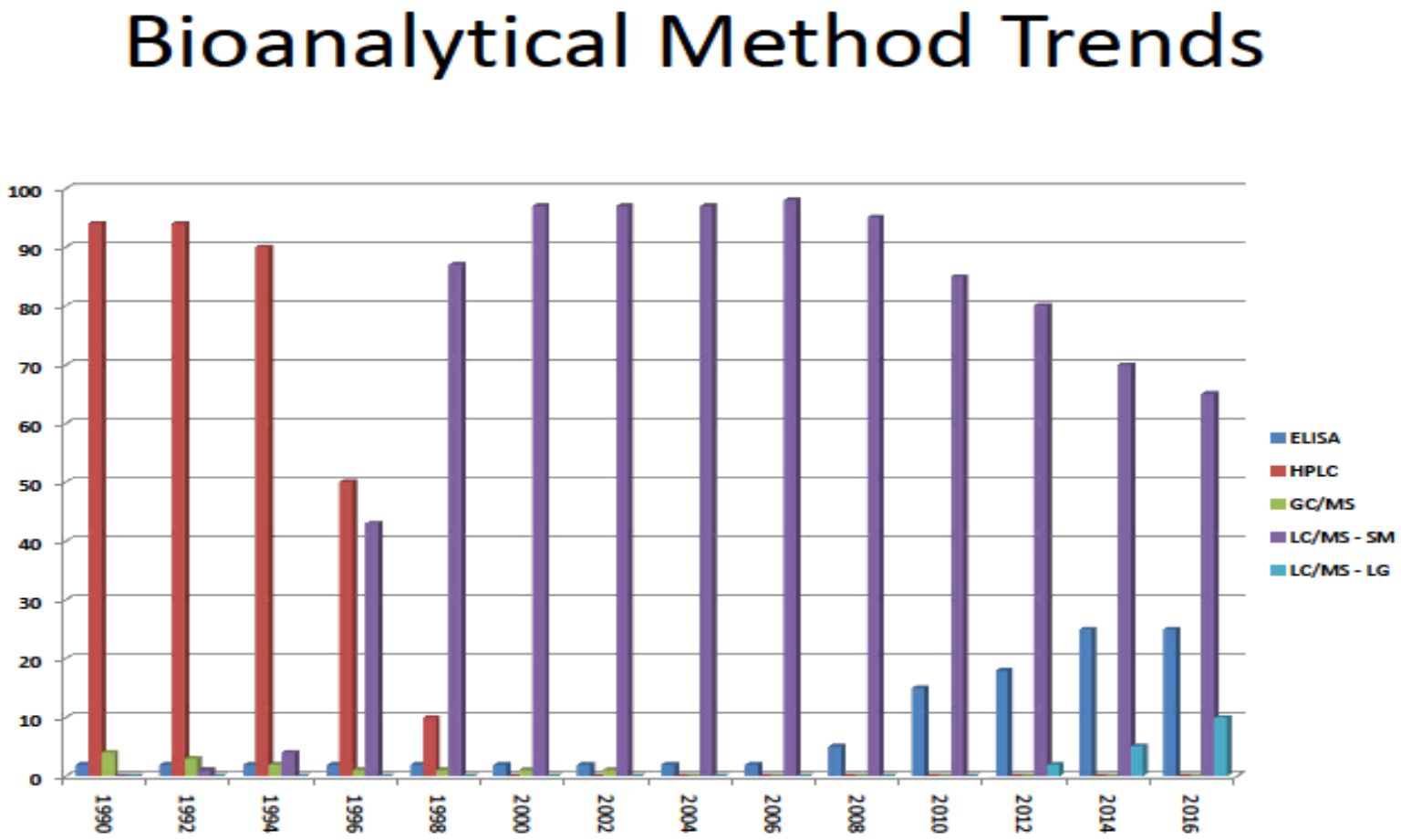
Topics

- Questions
- Feedback
- Possible
- Practical
- Potential

How did we get here?



Questions

- Pharma, Academic, other?
- Triple quadrupole users?
- GLP quantitative users?
- Many requests for small molecule methods requiring more sensitivity?
  - More than you can handle?
  - Occasional requests for small molecule methods requiring more sensitivity?
- Performing mid-large molecule quantitation – e.g., oligonucleotides, peptides, proteins?
  - Expect more requests for above?
- Want greater “ease of use”?
- Want lower cost of ownership?

What is Commonly Requested

- Sensitivity
- Dynamic linear range
- Mass resolution
- Mass range
- Faster acquisition cycle time
- Cost of ownership
  - Ease of use
  - Maintenance
  - Training
  - Consumables
  - Compliance
  - Peripheral compatibility
  - Consistency/Transferability
  - Flexibility - multipurpose

What is Possible and What is Practical

- What are the limitations that make Possible ≠ Practical
  - ROI – for both vendor and user
    - User values influence research dollars
  - Cost of hardware solutions
    - Cost/benefit not always aligned
  - Robustness of cutting edge solutions (API III)
  - More complex operation/not frequently used (APPI, IMS)
  - Upcoming applications
    - on-line DBS/DMS
    - Micro and nanospray

How Will Progress Occur?

- Take advantage of advances for components that can be common between triple-quadrupoles and higher end instruments
  - ionization sources, Q0 lens configurations, electronics, vacuum systems, detectors (share advances between higher end MS and triples)
- Specialization
  - GLP – TSQ Module, TX/LX, Open Accela, nanospray, microspray
  - Discovery – QuickQuan, QuickCalc, TX/LX, LDTD, Open Accela, open access
  - Biopharma – higher mass range, higher resolution, higher sensitivity, protein/peptide focused software, nanospray, microspray
  - QA/QC/CMC – GMP compliance, TX/LX, Open Accela, open access

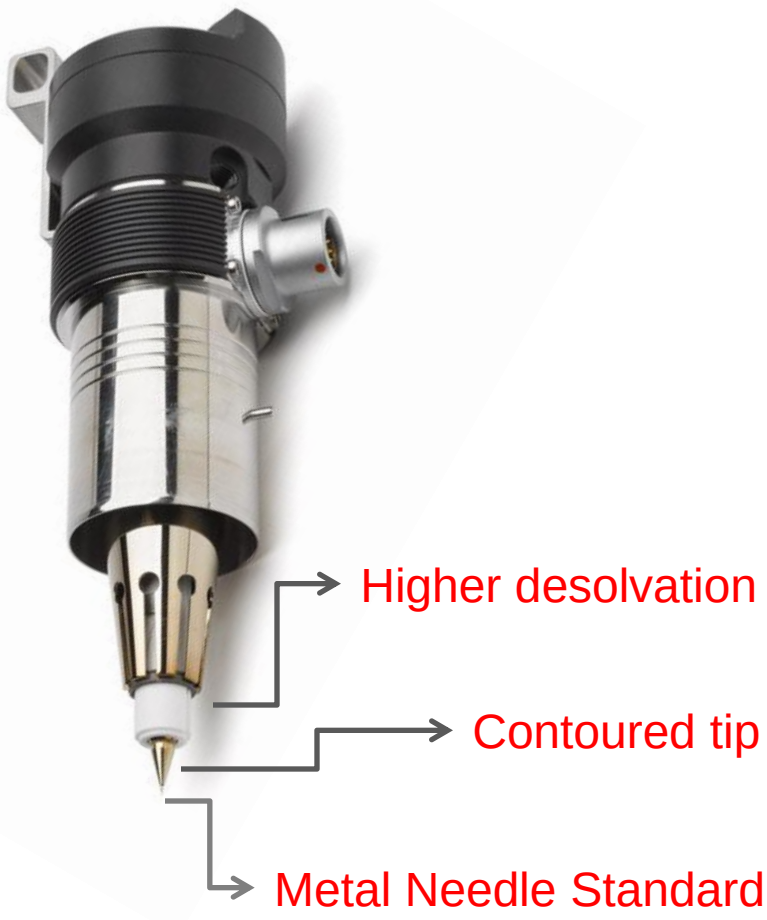
How Will Progress Occur?

- Specialty systems – clinical, GLP, discovery, GMP, etc.
- Multiple levels within each possible – rugged, moderate, superior sensitivity
  - Currently, no vendor differentiates on market and specific need; only price, some performance measures and simplicity/complexity
- DBS/DMS – mandates change in MS interface, simplicity, robustness, carryover and sensitivity challenging
- HRAM/HRMS – what does this mean for triples

RECENT HISTORY OF POSSIBLE TO PRACTICAL

Technology Enhancements: **HESI-II**

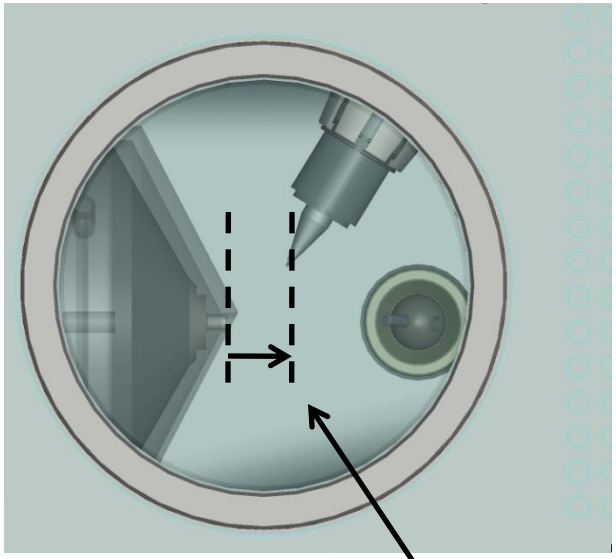
- Benefits**: Sensitivity across a wider range of flow rates**
  - Higher desolvation for >1mL/min flow rates
    - *More heated nitrogen auxiliary gas flow aids desolvation at high flow rates*
  - One piece metal needle allows for easy replacement
    - *Available as low flow and regular (high) flow*
  - Contoured tip for enhanced low flow (micro-spray; 5-25uL) stability
    - *Generates better electrostatic fields enabling spray stability for lower flow rates*



** Backwards compatible*

Technology Enhancements: **Ion Sweep Cap**

- Benefits**: Maximum Robustness in real samples**
  - Fixed Probe Position
    - *Plug & play position ensures spray hits below the "hood"*
    - *Ensure ion transfer tube orifice is never obstructed*
  - Asymmetric Profile Below Orifice Hood
    - *Ensures spray is directed into the drain to reduce re-circulation in the ion source*
    - *Build-up of matrix always occurs below orifice*
  - **Run hundreds of matrix rich samples without compromising sensitivity!**



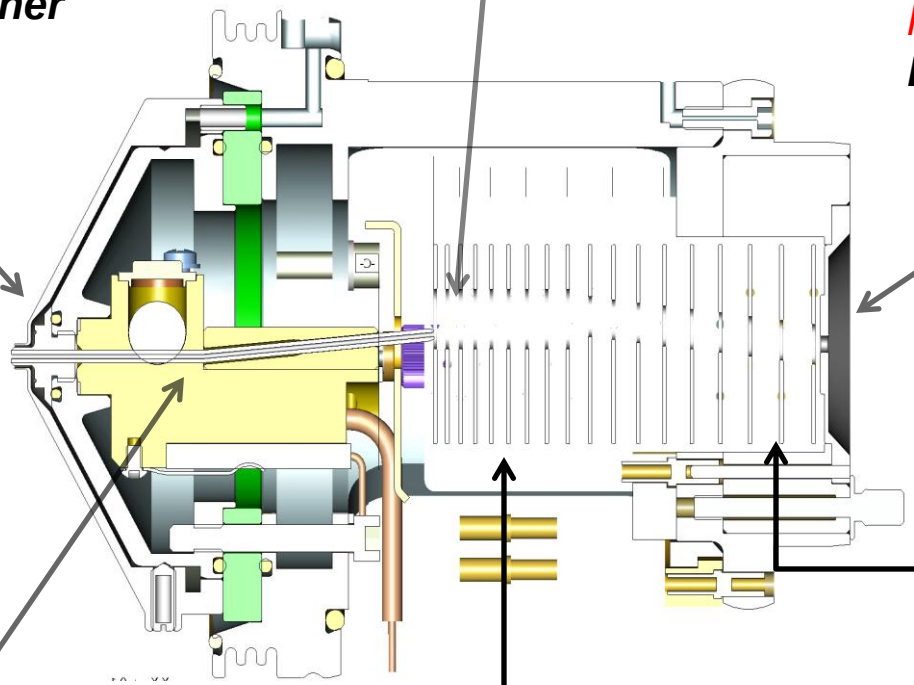
** Backwards compatible*

S-Lens (More Signal, Less Noise)

Improved Ion Sweep Gas Cap (N2 gas limits solvent i.e *less chemical noise*) for ***Higher Robustness***

Off-Axis to instrument axis = ***Less Chemical Noise***

Optimum opening into high vacuum chamber *limits chemical noise* = ***Long-life Turbo Pump***

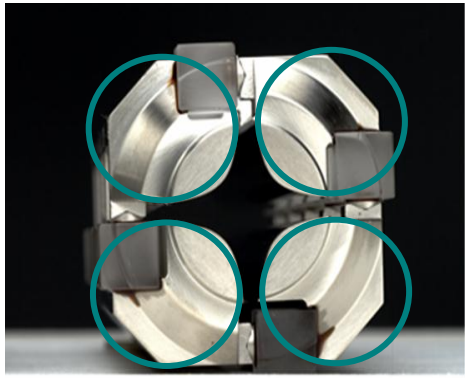


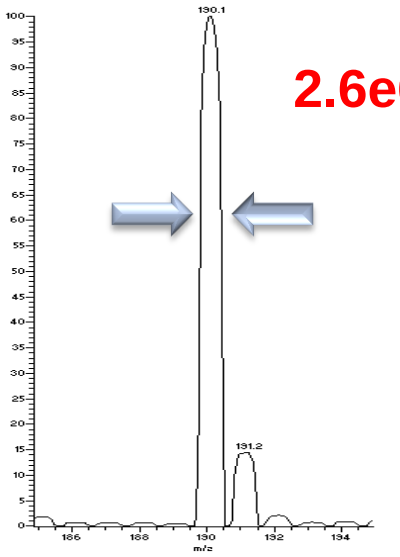
Shorter Ion Transfer Tube = *More gas in (**more ions**)*

Maximum efficiency for pumping gas (removes extraneous solvent laden gas i.e. *less chemical noise*) = ***Better Vacuum*** (note progressive spacing)

H-SRM (HyperQuad Technology)

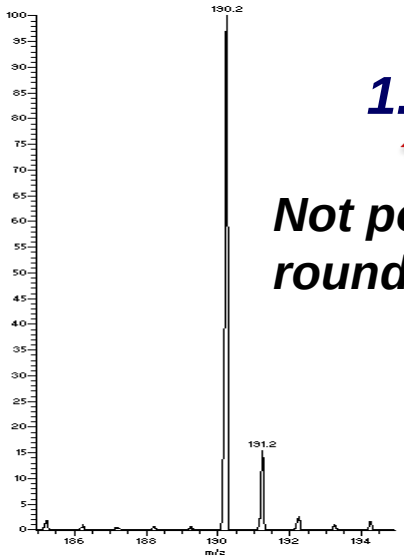
- Improved specificity
- Higher sensitivity of analyses (**Better S/N)**
- Standard on Ultra and Vantage
- **Makes the analytical method more robust**





2.6e6

0.7u FWHM



1.1 e6

Not possible on round rods!

0.1u FWHM

Provides a big advantage in peptide quantitation

HYPER QUADS DRIVEN!

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TSQ Module GLP Bioanalytical Workflow

Watson™
Bioanalytical LIMS

ThermoFisher SCIENTIFIC

What is Practical?

- Sensitivity
- Dynamic linear range
- Mass resolution
- Mass range
- Faster acquisition cycle time
- Cost of ownership
  - Ease of use
  - Maintenance
  - Training
  - Consumables
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Cost of Ownership

- Perspective of both management and operating scientist
- Purchase price
- Routine and non-routine maintenance
- Ease of use – Training, method development, sample analysis, troubleshooting
- Throughput – Ease of use, maintenance, flexibility
- Robustness/transferability – ability to move from one instrument to another
- Upgrade path/Life cycle – including peripherals
- Software ownership
- Compliance – Software validation/compliance
- Data storage and tracking

Potential: Cost of Ownership - Maintenance

- Maintenance software
  - GLP and non-GLP modes
  - Automated calibration and reporting
  - Troubleshooting/diagnostic capabilities
- Remote and/or Routine Diagnostics –
  - Determine issue prior to service visit
  - Auto notification “performance” related parameters – Forepump pressure, spray voltage
- Component/board design – compromise between engineering and serviceability
- Vacuum system – oil free, turbo pump control in “maintenance software”

Potential: Cost of Ownership – Ease of Use

- Paradigm shift in software
  - Remove flexibility to greatly improve cost of ownership
  - Simplify software
    - Tuning
    - Acquisition
    - Processing – TSQ module
    - Reporting – TSQ module
- Simplify GLP System Validation and Qualifications
- Simplify data file maintenance

Potential - Ongoing

- Hardware
  - Alternative Sample Handling
    - Simpler Multiplexing
    - Variety of on-line technologies
    - Rugged and routine nanospray and microspray
  - Next Generation Triple Quads
  - Next Generation Orbi-trap instruments
- Software
  - Further integration with Watson LIMS
  - Application specific – e.g., Biopharma
- Application Specific
  - Dried Blood/Matrix Spots
  - Protein/Peptides

What Really Makes Sense?

- More “Use Specific” configurations
  - Pure GLP Quantitation
    - Triple Quadrupoles
  - Pure Discovery/Non-GLP Screening
    - Exactive (HRAM)
  - Classes of instrumentation (PC Scenario)
    - Full function
    - Specialized function
    - Limited function
    - Extremely robust
    - Extremely sensitive