MS IS READY FOR QC. ARE YOU?

ROLE AND POSSIBILITIES OF MASS SPECTROMETRY IN QC LABS

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Dr. Corné J.M. Stroop
Director Biologics & Vaccines Analytics
MSD

Disclaimer

In this presentation, the speaker presents his personal view and his experience obtained in industry including inputs from experts in this field. The given examples may, but do not necessarily reflect Merck/MSD strategies. No reference is made to any of MSD's products.

FOR MORE THAN A CENTURY, MSD HAS BEEN INVENTING

TO SOLVE SOME OF THE GREATEST CHALLENGES TO PEOPLE'S HEALTH AND WELL-BEING AROUND THE WORLD.

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operating in more than 140 countries

MRK

Merck & Co., Inc.
is our legal name and is listed on the New York Stock Exchange under the symbol "MRK."

69,000

EMPLOYEES
approximately 69,000 worldwide (as of 12/31/17)

BUSINESSES
Prescription medicines, Vaccines, Biologic therapies, Animal Health products

2017 REVENUES
$40.1 billion, 57% of sales come from outside the United States

2017 R&D EXPENSE
$9.98 billion; 20+ product pipeline programs in late-stage development

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Questions and Requirements to Consider (I)

- Are there alternative methods?
  - What *critical quality attribute (CQA)* needs mass spectrometry?
  - Specificity is driver (*e.g. focused LC-MS for IgG oxidation or deamidation*)
  - Easy in R&D ≠ easy in QC!
  - Qualitative vs. Quantitative?
  - Examples: N-terminal sequencing, peptide mapping LC-UV, bioassay
- Which MS methods?
  - Identification testing (*e.g. mass fingerprint (m/z)*)
  - LC with mass detection (*e.g. Waters' QDa*)
  - Peptide mapping LC-MS (*e.g. multiple attribute method (MAM) or focused method for specific PTM)*
  - Glycoforms, or glycoprofile on MALDI-TOF

Questions and Requirements to Consider (II)

- Which MS instrumentation?
  - A wide range from Waters' QDa to Brukers' FT-ICR-MS
  - The more settings, the less QC worthy
  - Locked settings & operator mode
  - Same settings on same system in different labs > same results?
  - Instrument robustness
  - Data integrity

Questions and Requirements to Consider (III)

Other aspects to consider:

- Instrument qualification (~6 months post-purchase)
- Available expertise, and training:
  - New developments too fast for a typical QC expert
  - Non-QC MS expertise needs to be readily available
  - Sufficient sample/work load
  - Troubleshooting might require an high-end MS instrument
- Method transferability
- Pricing:
  - Several QC labs, same configuration
  - Testing on Import labs
  - Tough, but not impossible (business case!)
- Software applications

Requirements - Software

Software applications:

- Chromatography Data System (CDS)
  - *Chromeleon* (Thermo), data acquisition for both LC and MS
  - *Empower* (Waters), data acquisition for LC and QDa (EIC only)
  - *UNIFI* (Waters), specific and 21 CFR part 11 compliant for LC-MS
- Data processing can be either vendor-specific (*MassLynx*, *HyStar*, *Analyst*), or vendor-agnostic (*Expressionist*)
- Vendor-specific software is increasingly 21 CFR part 11 compliant, with special packages for GMP and Data Integrity
- Industry Guidance: Data Integrity and Compliance with Drug cGMP (www.fda.gov)
- Applications for specific *biologics* applications (most are actually R&D oriented)

MS Use in QC Labs

It is worthwhile to realize that MS use in QC labs is not limited to release testing.

- Release of drug substance & drug product (*MS use possible*)
- Stability testing (*less likely*)
- Critical reagent qualification (*more likely*)
- First-line troubleshooting:
  - QC MS method (*very likely*)
  - QC non-MS method (*less likely*)
- Analytical method transfer (*No MS, unless MS release method*)

Examples

Remember, even NMR has made it into QC release testing:

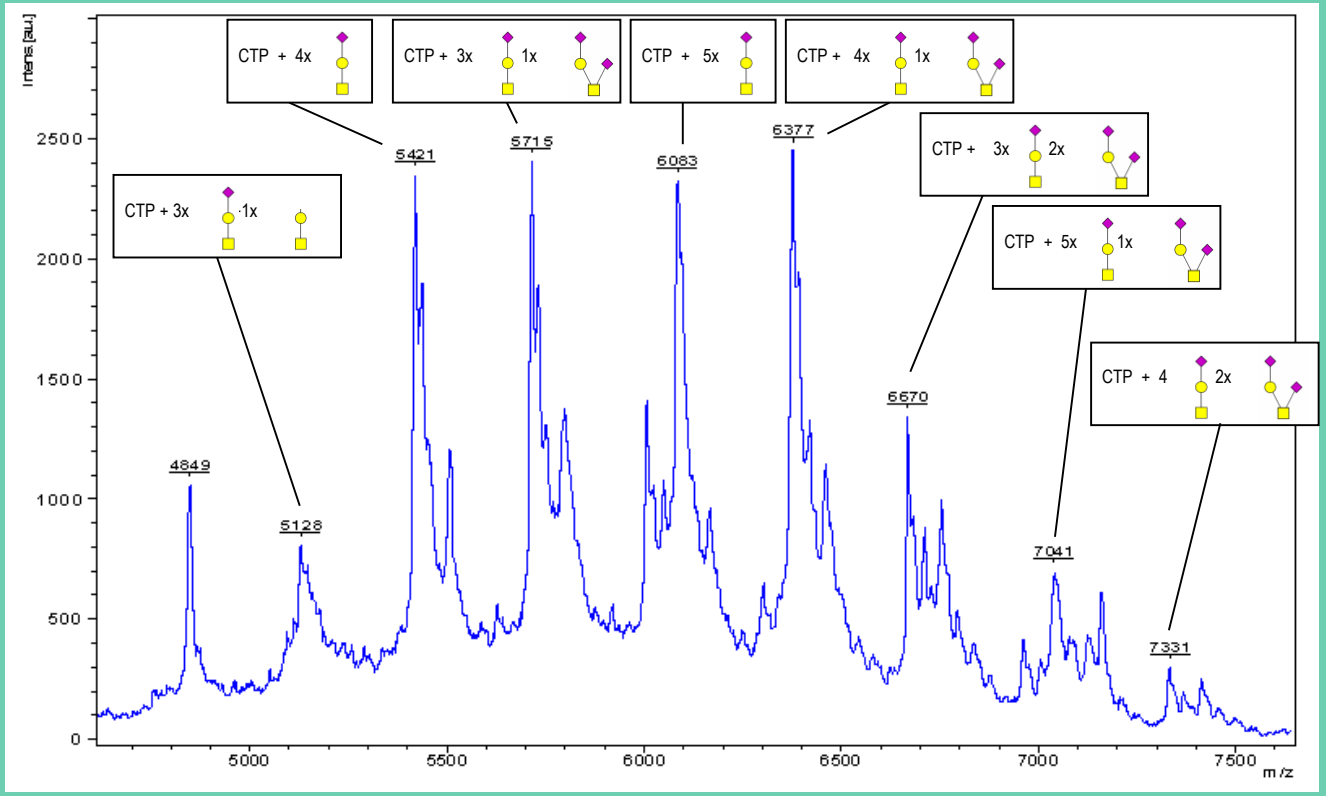
- Following the 2007-2008 heparin crisis, heparin sodium drug substance is being released using ^{1}H-NMR to monitor for oversulfated chondroitin sulfate (OSCS) contaminant

Known issues:

- Accuracy impacted MS settings & sample load
- Linearity can be tough to validate
  - Solved by isotopically labeled internal standard (commercially available)
- Same LC-MS system in 3 different labs (US and Germany) > not equivalent at method transfer

Example – O-Glycosylation Sites

- MALDI-TOF-MS (Bruker *microflex*) of a C-terminal peptide
  - C-terminal peptide in 50% ACN/2% TFA; DHAP matrix



MAM via Peptide Mapping

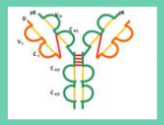
Direct measurement of CQAs at molecular level

Quality Attribute	Current Method
Identity	Immunoassay
Glycosylation	HILIC-Fluor
Charge Variants	HP-IEX
Oxidation	HIC
Clips	red. CE-SDS
Process Impurities	HCP/ProA ELISA

MAM
Peptide Mapping

Thermo Q-Exactive LC-MS

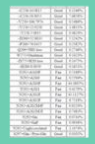
Characterization



30 minute
Digest

LC-MS/MS

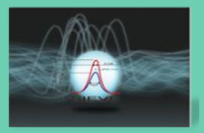
Search
Algorithm



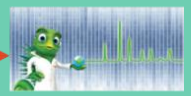
Results

LC-MS1 only

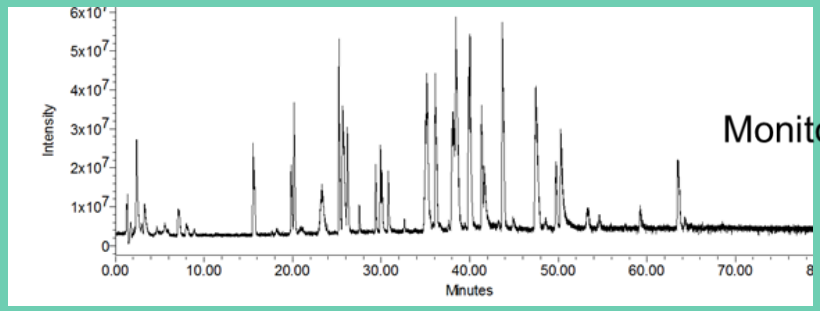
Targeted and
untargeted peak
detection



Compliant method



LC-MS TIC



Monitoring

30 min Tryptic digest—Ren, D. et. al. Anal Biochem. 2009 Sep 1;392(1):12-21

MAM—Rogers, R. S. et. al. mAbs 2015 Sep 3;7(5):881-90

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Contributors:

Merck Research Laboratories (NJ, US):

Douglas Richardson

Merck Manufacturing Division (Oss, NL):

QC:

Alex Tax, Bülent Üstün, Hugo van Helden, Sander Vink, Johan Nijenhuis

BVA:

Joop Waterval, Michiel van de Waterbeemd

THANK YOU!