

Overview of LC-MS Quantitative Solutions for Biotherapeutic Analysis

Featuring *SCIEX Instrumentation and Technologies*

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LC-MS Solutions		LC-MRM for ultra-sensitive quantification	MicroLC for enhanced sensitivity	Quantitative Ion Mobility	MRM3	HRAMS	MRMhr	SWATH
SCIEX Products		6500+ QQQ & QTRAP® 	M5 MicoLC, OptiFlow™ source, 6500+ 	DMS technology 	QTRAP® 	TripleTOF® & X500B 		
Quantitative Challenges	Endogenous interference from matrices							
	Sensitivity, accuracy, precision							
	Analyte fragmentation							
	Linear dynamic range							
	Analysis throughput							
	Quantification of large number of analyte							
	Quantification of non-digested proteins							

Figure 1. Summary of SCIEX Quantitative Solutions and Instrumentations to Solve Analytical Challenges in Biotherapeutic Industry. Darkest green color indicates the most applicable technology.

Introduction

The therapeutic potential of biologic moieties has driven an increased need for the development of quantitative analysis across multiple stages of development. This advancement is paralleled with development of improved LC-MS quantitative technologies. Herein, an overview of SCIEX LC-MS solutions for quantitative biotherapeutic analysis are presented (Figure 1). These techniques can aid scientists in overcoming current analytical challenges to deliver superior quantification results with high sensitivity, accuracy, reproducibility, throughput and robustness across various biotherapeutic molecule classes.

SCIEX Technologies and Workflows

LC-MRM Analysis

Featuring **SCIEX Triple Quad™, QTRAP® Mass Spectrometers and Immunoaffinity Workflow**

Multiple reaction monitoring (MRM) analysis offered by the triple quadrupole and QTRAP systems is the leading technology for large molecule quantification. Its sensitivity, specificity and speed allow scientists to quantify multiple target analytes at low levels in complex matrices with a single injection. When coupling with

analytical flow or micro-flow HPLC, the analysis throughput is maintained by as high as over 200 samples per day. As with most analytes of interests present in biological fluids, one major challenge in large molecule bioanalysis is the extremely low levels of targeted biotherapeutics present in matrices with the existence of high abundant interference. This makes the need for appropriate sample preparation paramount. Immunoaffinity capture has been introduced as common sample preparation procedure for biotherapeutics bioanalysis, as it can specifically enrich the target analyte based on antibody-antigen interaction and thus reduce matrix interference.

SCIEX developed an immunoaffinity-LC-MRM workflow to quantify proteins and peptides in biological matrices. The optimized procedure nearly eliminates interference from the matrix and allows the entire sample preparation (bead preparation, immunocapture and digestion) to be completed in 5 hours (Figure 2). The QTRAP 6500+ or Triple Quad 6500+ mass spectrometer provides high sensitivity, robust performance and broad dynamic range for MRM quantification of the signature peptides from target analyte. This workflow has been successfully applied to quantify various types of biotherapeutics^{1,2,3,4,5}. Figure 3 and 4 show an example of trastuzumab quantification in rat plasma. The assay LLOQ reaches 5 ng/mL; the calibration curve is linear over 4 orders of

magnitude and displays a regression coefficient (r^2) of 0.99502 using a weighting of $1/x^2$.

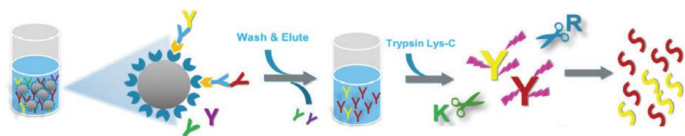


Figure 2. Immunoaffinity Sample Preparation Workflow.

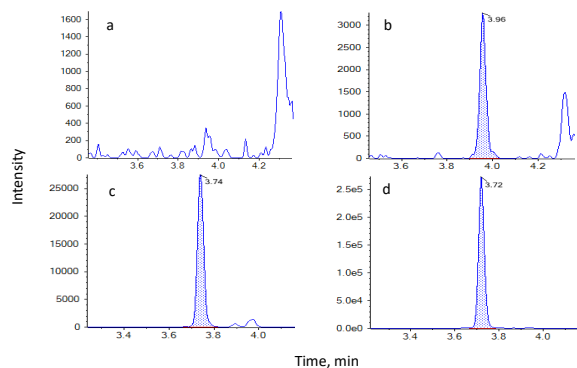


Figure 3. Extracted Ion Chromatograms of Trastuzumab Quantification in Rat Plasma. a) blank; b) 5 ng/mL; c) 50 ng/mL; d) 500 ng/mL.

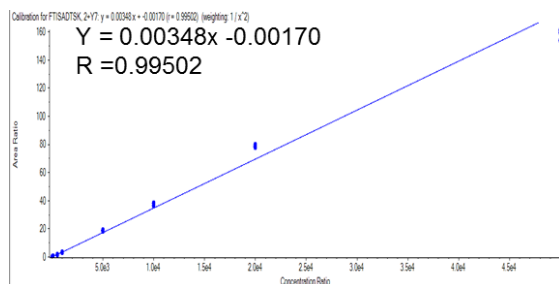


Figure 4. Calibration curve for quantitation of trastuzumab in rat plasma (5 ng/mL to 50 000 ng/mL).

MicroLC for Enhanced Sensitivity

Featuring SCIEX Triple Quad and QTRAP Mass Spectrometers with OptiFlow™ Turbo V source and M5 MicroLC system

Small mammals are commonly selected for preclinical bioanalysis studies. As the amount of biological sample that can be collected from a small animal is limited, studies requiring ultra-low-level detection due to the small sample volume has driven the need for sensitivity improvement for LC-MS assays. The implementation of microflow chromatography to MRM based sample analysis can be an efficient solution to meet this need.

The integration of M5 microLC into immunoaffinity-MRM workflow, demonstrates a number of important observations^{4,5,6,7}. The assay sensitivity is significantly improved by applying low micro liter per minute flow rate for LC separation. Meanwhile, by utilizing trap-elute function and relative high flow rate for sample loading (Figure 5), the high analysis throughput is achieved. The OptiFlow Turbo V Source provides stable spray at nL to low $\mu\text{L}/\text{min}$, requiring no probe or electrode position optimization. As an example, we were able to achieve a LLOQ of 1 ng/mL for trastuzumab emtansine quantification in 25 μL mouse plasma (Figure 6). The assay accuracy is 87-109% and CV%*s* are below 15% for all tested samples. The calibration curve covered 4.5 orders of magnitude (1-20000 ng/mL) (Figure 7) and displayed a regression coefficient (r) of 0.996 using a weighting of $1/x^2$. A >5 fold increase on peak area and 3 fold increase on S/N were observed between micro flow and analytical flow analysis (Figure 8).

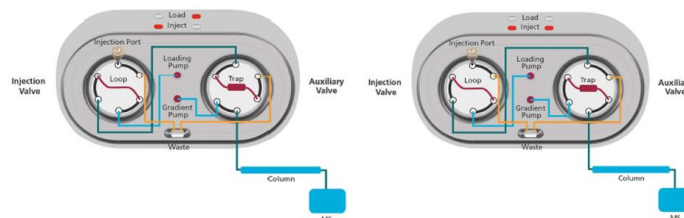


Figure 5. Valve configurations for "load" position (left) and "inject" position (right).

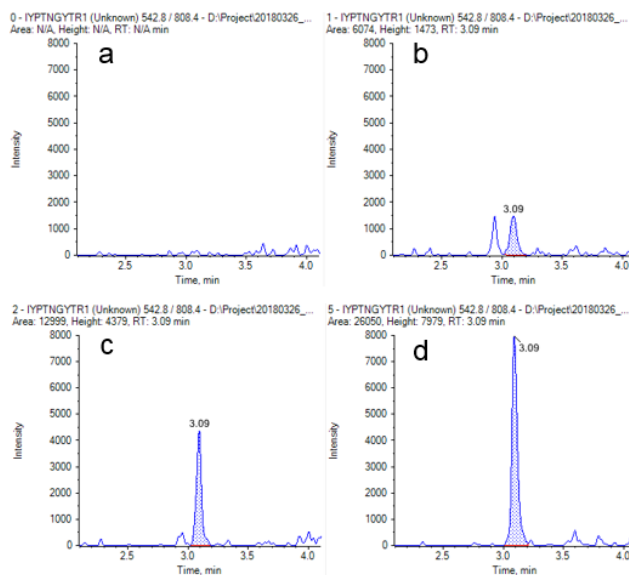


Figure 6. Extracted Ion Chromatograms (XICs) of Selected MRM for Trastuzumab emtansine Quantification in Mouse Plasma. a) blank; b) 1 ng/mL; c) 2 ng/mL; d) 5 ng/mL.

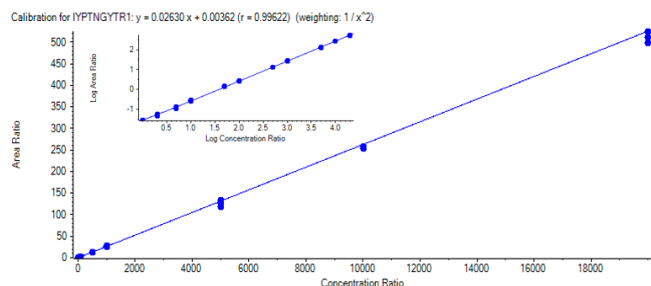


Figure 7. Calibration Curve for Quantitation of Trastuzumab emtansine in Mouse Plasma (1 ng/mL to 20000 ng/mL).

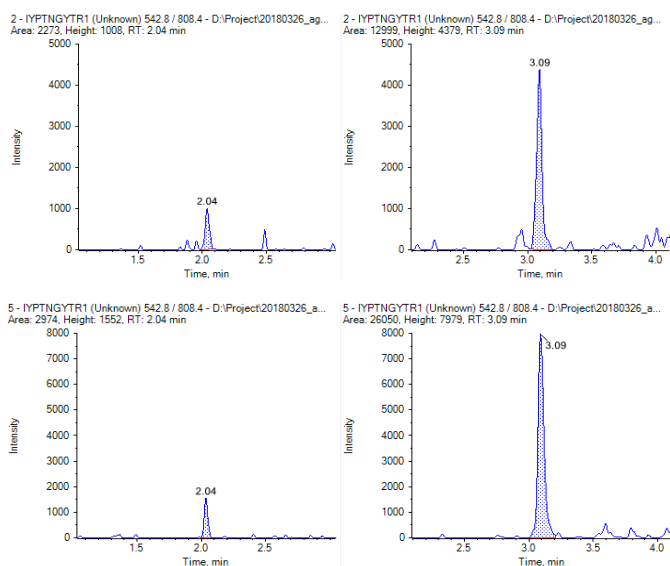


Figure 8. Extracted Ion Chromatograms (XICs) of Selected MRM for Trastuzumab emtansine at 2 ng/mL (top) and 5 ng/mL (bottom). The left are XICs generated with analytical LC flow rate, the right are XICs generated with microLC flow rate.

Differential Mobility Separation Mass Spectrometry

Featuring SCIEX SelexION® Differential Mobility Separation Technology

Although MRM is the dominant MS technology for large molecule bioanalysis, it has its own limitation when dealing with 1) complex matrix samples with significant isobaric interferences at the MSMS level; 2) analytes with low fragmentation efficiency or lack of abundant fragment ions (spreading ion current across many product ions). In these scenarios, relying on MRM alone may be insufficient to provide desired sensitivity and/or selectivity. An orthogonal separation technology is required to improve quantification performance.

Differential Mobility Separation (DMS) using SelexION Technology adds an additional level of selectivity providing gas phase separation of isobaric species based on their chemical properties and ion mobility (Figure 9). DMS applies high and low

energy fields from an asymmetric waveform between two planes; ions from the peptide sample travel through the fields based on their size, shape and charge and differentiate based on their migration time (Figure 10). In addition to adding an additional level of ion separation prior to the instrument orifice, SelexION Technology is also compatible with fast cycle times required for quantification workflows, including MRM or selective ion monitoring (SIM). One example is MRM quantification of exenatide in plasma⁸. Exenatide is a therapeutic cyclic peptide with low CID fragmentation efficiency. As shown in Figure 11, a dramatical improvement of S/N for 5 pg/mL exenatide sample was observed while DMS was used. Another example is quantifying a large therapeutic peptide (PN1944) with SIM mode⁹. Similarly, DMS significantly reduced the background signal for PN1944 thereby improving the S/N (Figure 12).

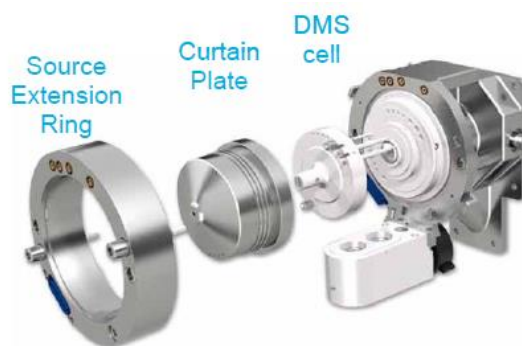


Figure 9. High Selectivity Quantitation using SelexION Technology on the QTRAP System. The SelexION Technology is an easy to install differential mobility device used to provide additional selectivity to any quantitative experiment.

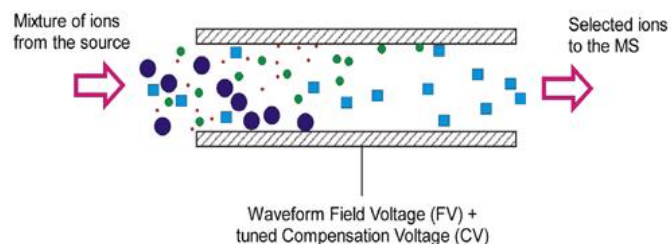


Figure 10. Principle of Differential Ion Mobility Spectroscopy (DMS). As the mixture of ions enters the drift tube, they are separated according to differences in each individual molecule's size, shape, and charge. An optimized combination of separation voltage (SV or waveform field voltage, FV) and compensation voltage (CV or COV) separates the analyte from background ions.

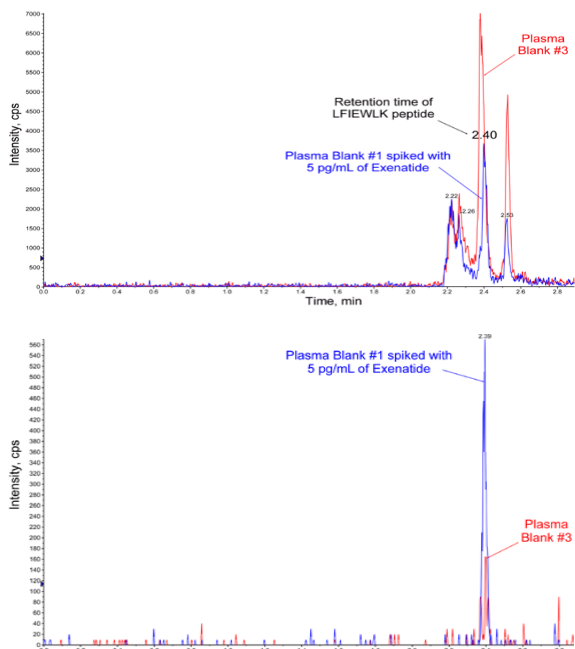


Figure 11. Improved signal/noise using DMS for exenatide. Plasma samples spiked with exenatide (5 pg/mL) and blank plasma samples were analyzed for the presence of the exenatide signature peptide *without* the SeleXION Ion Mobility device (*top panel*) or *with* the SeleXION device (*bottom panel*). Traces in *blue* indicate peaks due to exenatide-spiked plasma, and traces in *red* indicated peaks due to blank plasma samples.

MRM³ Technology

Featuring SCIEX QTRAP® Mass Spectrometers

Quantitation of proteins by Multiple Reaction Monitoring (MRM) requires selection of peptides which are unique to the sequence of the protein of interest. When a protein therapeutic is part of a protein family with very high sequence homology, this can often restrict the choice of unique peptide selection for quantification of that specific protein. Therefore, having an additional level of selectivity in the MS quantification methods is crucial for the analysis of protein isoforms of high sequence homology in complex biological matrices.

SCIEX QTRAP mass spectrometers offer a unique MRM³ workflow that provides additional specificity by monitoring the secondary product ions of a peptide of interest, rather than just the product ions (Figure 13). This additional level of selectivity, combined with the high sensitivity and speed of QTRAP systems, make MRM³ analysis an effective quantitative strategy for peptides and proteins in matrices with significant background interferences.

Q3 with no collision energy for higher sensitivity) can yield **poor**

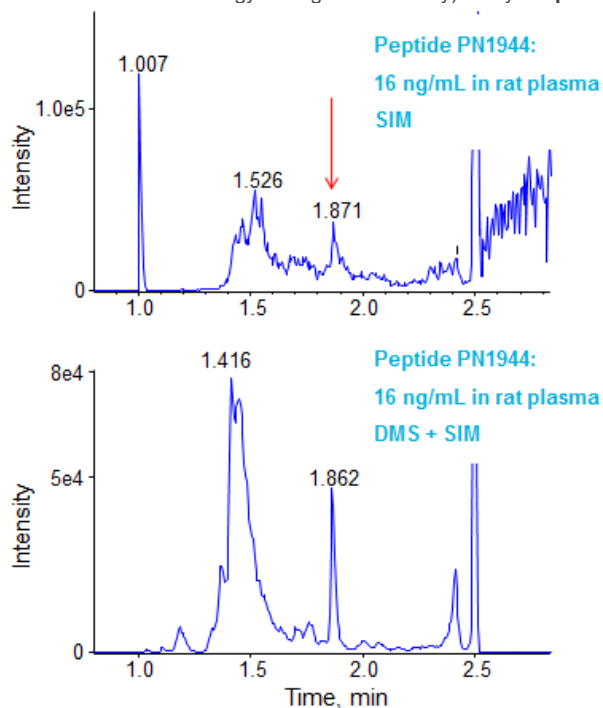


Figure 12. Improved Signal/Noise using DMS for peptide PN1944. Analysis of the peptide in SIM mode (monitoring precursor m/z in Q1 and Q3 with no collision energy for higher sensitivity) can yield poor selectivity. This is evident in the first sample (*top panel*) where the peptide signal at 16 ng/mL is largely obscured by background noise. Analysis of the same sample with DMS (*bottom trace*) shows greatly improved signal-to-noise for the target peptide.

CYP450 3A5 protein (which shares ~80% amino acid sequence identity with isoform 3A4) is selected as an example analyte undergoing both MRM and MRM³ analysis¹⁰. Three MRM transitions for the peptide DTINFLSK are shown at 4.8 fmol on column in Figure 14; 2 of the 3 transitions showed significant interferences. The MRM³ data demonstrated improved specificity (Figure 14). A similar observation was made for the SLGPVGFMK peptide, where two of the three monitored MRM transitions showed some interference, but the MRM³ data had improved specificity and ultimately accuracy. Concentration curves for two peptides to the CYP 3A5 protein were generated in digested liver microsomes. For both peptides, the MRM³ assay provided lower limits of quantitation than the MRM assay. Quantitation limits of 1.2 fmol were obtained for MRM³ (Figure 15). Good linearity was obtained across the concentration range defined – from LLOQ of 1.2 fmol to 805fmol on column in 1 µg of digested protein (Figure 15).

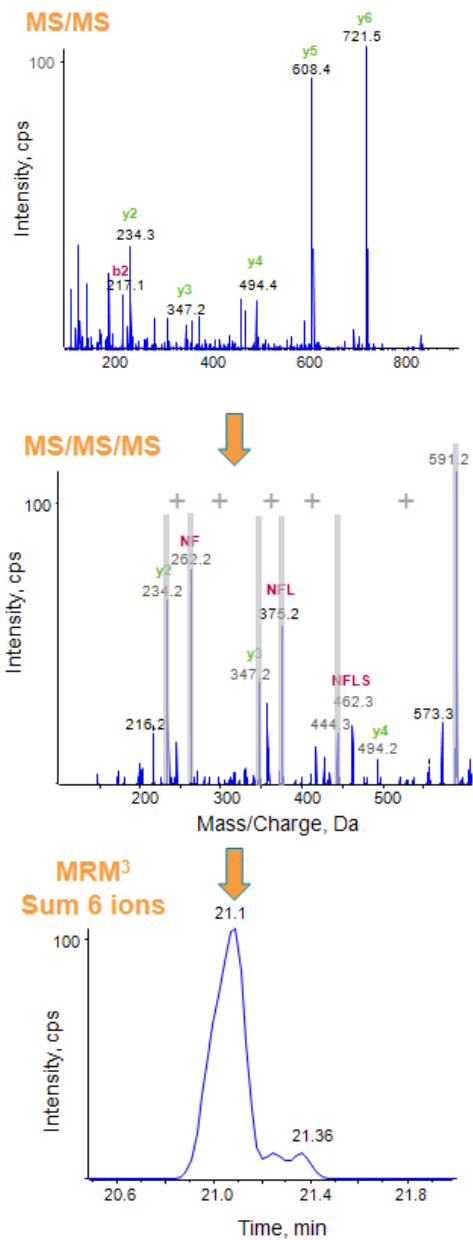


Figure 13. MRM³ Assay Design. A dominant product ion from the MS/MS spectrum (top) is selected for MS/MS/MS analysis (middle). Multiple product ions can be assessed to find which produces the best secondary product ion spectrum. Analysis of the MS³ fragmentation is used to optimize the excitation energy and select the best second-generation fragments to extract and use in quantitation. Multiple second-generation fragments can be used to generate MRM³ XICs (bottom). Data shown here is for the CYP450 peptide DTINFLSK, at 4.9 fmol on column.

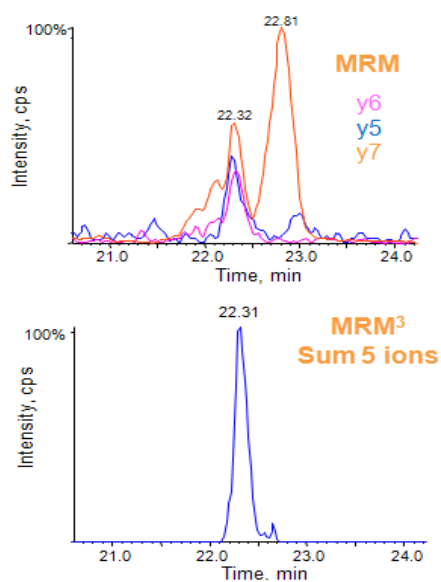


Figure 14. Comparing MRM and MRM³ Specificity. MRM³ workflow provides high specificity by quantifying secondary product ions generated from a peptide of interest. Two of three MRM transitions detected for the SLGPVGFMK peptide of CYP450 3A5 (top) show significant interferences, where MRM³ detection of secondary product ions from the peptide (bottom) provides a more selective detection.

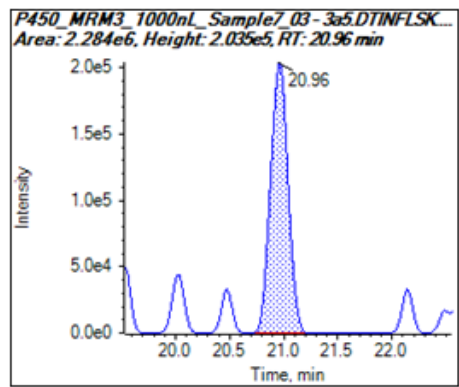
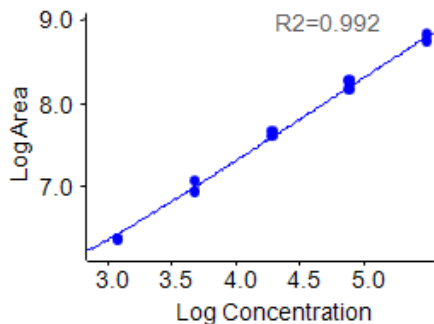


Figure 15. Standard concentration curve for peptide DTINFLSK using MRM³ Workflow. A linear concentration curve was obtained for the concentration range interrogated (top). A coefficient of variance of 2.7% and an accuracy of 116% was obtained at the LLOQ of 1.2 fmol on column, with the MRM³ signal at the LLOQ shown in the bottom pane.

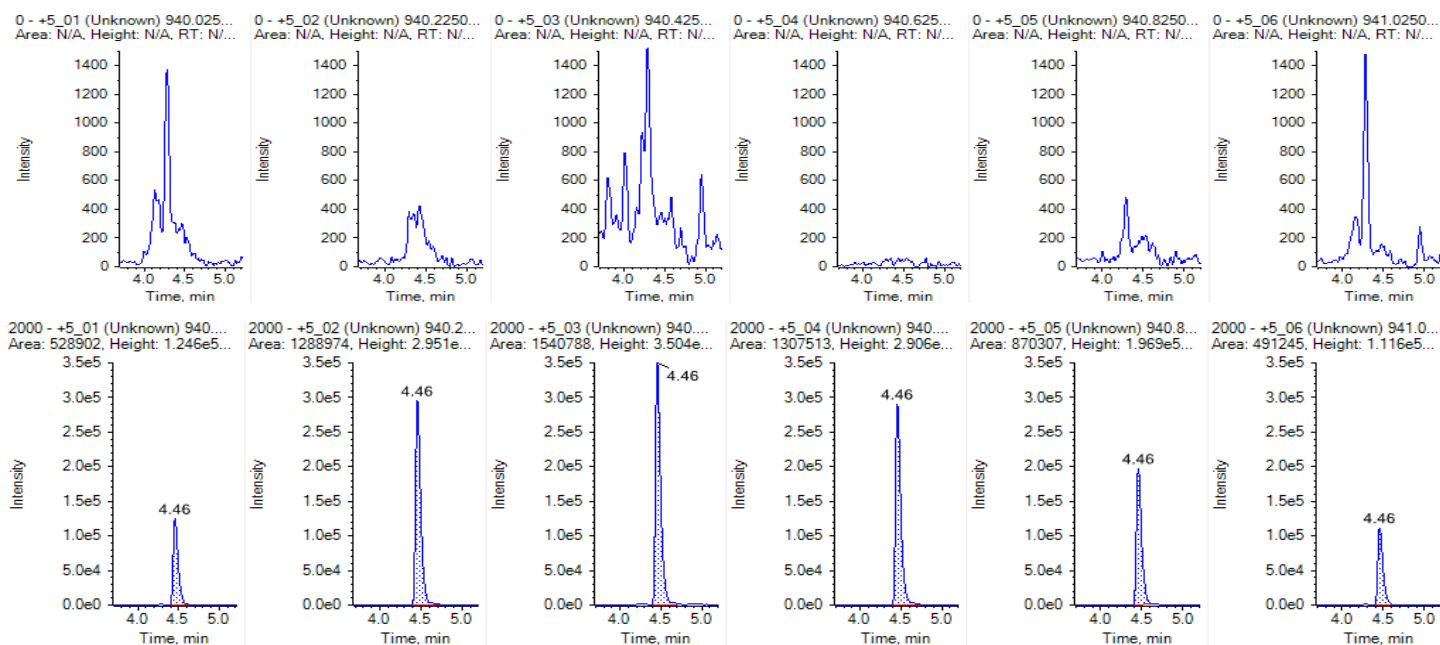


Figure 16. XICs of RTP004 in matrix blank sample (top panel) and at 2000 ng/mL (bottom panel) in rat serum with different extraction windows for different isotopic ions. From left to right are: 940.05, 940.25, 940.45, 940.65, 940.85, 941.05 ± 0.025 Da.

High Resolution Accurate MS (HRAMS) Workflow

Featuring SCIEX X500B QTOF and TripleTOF® Mass Spectrometers

High resolution accurate mass spectrometry (HRAMS) has become more applicable and important for bioanalytical quantitation. The high resolving power and mass accuracy allows quantitation based on the precursor ion of the target analyte, thereby significantly improving the assay sensitivity for the large peptides with low fragmentation efficiency and minimizes the background interference from matrix. At the same time, HRAMS requires no MS/MS parameter optimization compared with MRM based methodologies.

HRAMS workflow has been widely applied on SCIEX X500B QTOF and TripleTOF Mass Spectrometers. One example is the quantification of RTP004¹¹. RTP004 is a 35-mer peptide predominantly containing arginine and lysine amino acid residues. It serves as an excipient in DaxibotulinumtoxinA for injection. The high resolving power of TOF analyzer minimizes the background interference from rat serum and allows quantification based on a single isotopic ion. As shown in Figure 16, the dominant isotopic ion at m/z 940.6541 was selected for TOF quantification, because the baseline noise level observed in the matrix blank was minimal. With this workflow, the assay LLOQ (S/N = 10) for RTP004 quantification reached 15.625

ng/mL (Figure 17). The assay linear dynamic range achieved was three orders of magnitude (from 15.625 ng/mL to 8000 ng/mL), with a regression coefficient (r) of 0.99771 (Figure 18) and a coefficient of variation (CV) from triplicate analysis < 8.0 %.

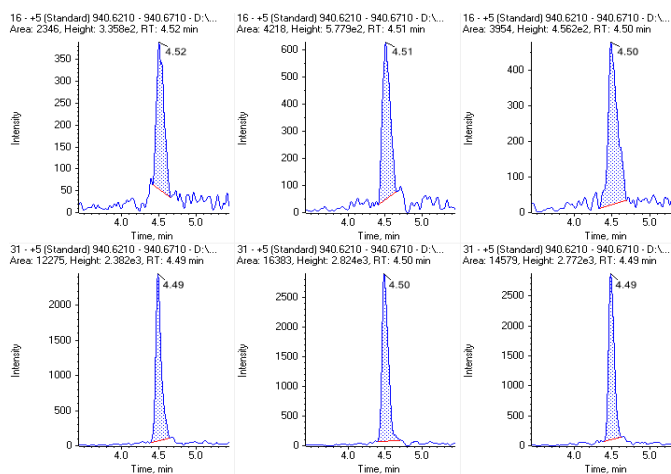


Figure 17. XICs of RTP004 at 15.635 ng/mL (top panel) and 31.25 ng/mL (bottom panel) in rat serum.

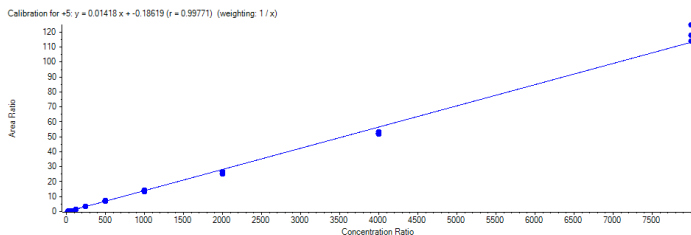


Figure 18. Calibration curve for quantifying RTP004 in rat serum from 15.625 to 8000 ng/mL prepared as three independent triplicates.

MRM^{HR} Workflow

Featuring SCIEX TripleTOF[®] and X500B QTOF Mass Spectrometers

For the analyte with complex fragmentation pathways coupled with the variability of matrix effect, unit resolution quantitation methods are not ideal options, because of the lack of resolving power and the length method optimization process. To overcome these limitations, a unique high resolution-based quantification method, MRMHR can be employed.

The mechanism of a MRMHR workflow for quantitation is to acquire full scan TOF MS/MS spectra for each species of interest. The high resolution extracted ion chromatograms (XICs) of specific product ions or a sum of ions can then be used post-acquisition for quantitation to achieve optimum sensitivity and selectivity (Figure 19). MRM^{HR} is an ideal workflow for quantifying various biotherapeutics in biological matrix, especially oligonucleotides, for two core experimental attributes. Selectivity of signature fragment ions in matrix cannot necessarily be predicted prior to data acquisition, oligonucleotides analysis takes advantage of the post-acquisition fragments selection offered by MRM^{HR}. For example, the three most intense fragment ions of oligonucleotide 1 in the MS/MS spectrum showed poor S/N in matrix samples, therefore could not be used for quantitation. In contrast, other less intense transitions showed excellent selectivity, and were subsequently included in the assay (Figure 20)¹². Also, biological samples are typically extremely complex due to the lack of efficient sample cleanup for oligonucleotides. Therefore, MRM^{HR} workflows offer significant advantages over a full scan TOF MS approach, because of the added selectivity. Figure 21 shows a comparison of the TOF-MS and MRM^{HR} workflows for oligonucleotide 1. The XICs from the TOF-MS approach show matrix interference, while the specificity of the MRM^{HR} workflow produced significantly lower limits of detection and quantification by reducing the matrix effect. Figure 22 shows the calibration plot of oligonucleotide 1. The lower limit of quantification (LLOQ) using the MRM^{HR}

workflow was 0.05 nM, while the LLOQ was 10-fold higher with full scan TOF-MS workflow.

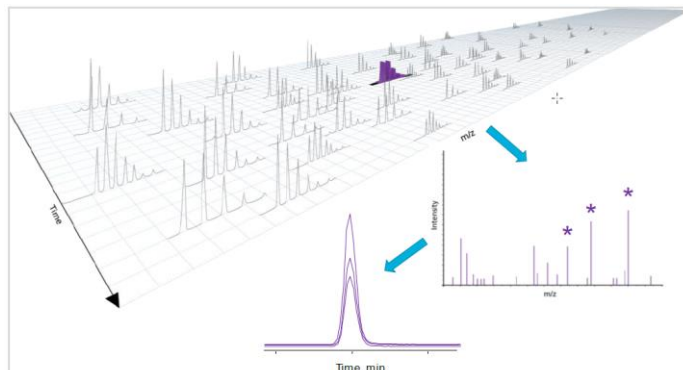


Figure 19. MRM^{HR} workflow using the TripleTOF Systems. In the MRM^{HR} workflow, a fixed number of analytes are targeted, and high-resolution MS/MS spectra are collected across an LC run. Precursor masses are selected at narrow resolution such that mainly the target compound is passed into the collision cell (top). This produces a full scan MS/MS spectrum enriched for the analyte of interest (right). Then, any number of fragment ions can be extracted at high resolution post-acquisition to generate MRM-like data (bottom).

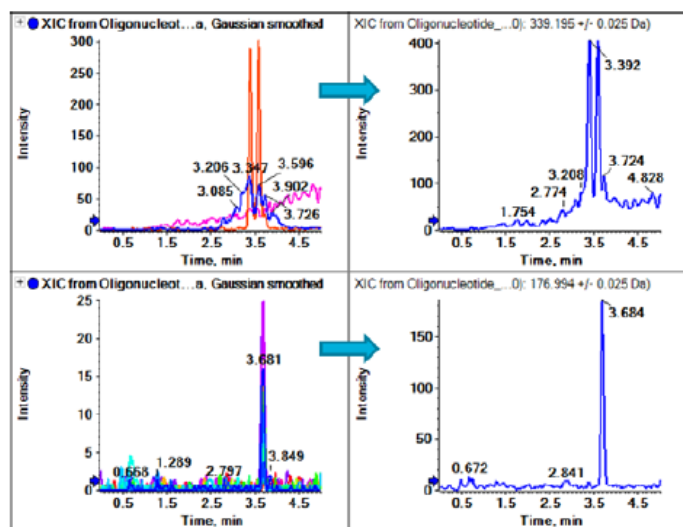


Figure 20. Post-Acquisition Extraction of Structurally Specific Ions. In the case of Oligonucleotide 1, the three most intense fragment ions (top left) are non-selective in plasma at low concentrations and therefore summing of these XICs does not provide a good assay (top right). Because the full scan MS/MS spectrum is acquired in the MRMHR workflow, this allows different fragment ions to be selected and extracted for quantitation (bottom left, summed bottom right), and therefore requires significantly less method development than traditional MRM approaches.

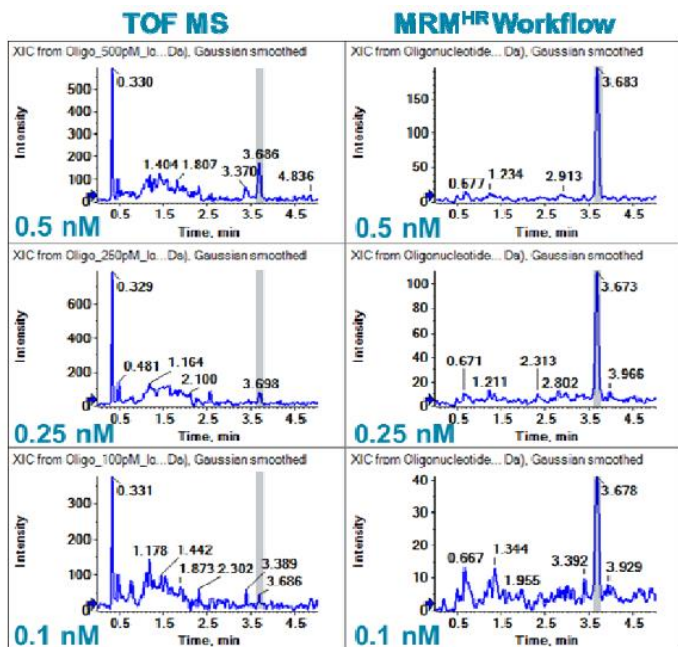


Figure 21. Selectivity of MRM^{HR} Workflow in Complex Matrices Allows Better LLOQs to be Obtained. In the case of Oligonucleotide 2, background interferences in full scan TOF MS result in higher limits of detection and quantitation (0.5 nM), while the selectivity of the MRM^{HR} workflow allows quantitation of concentrations less than 0.1 nM.

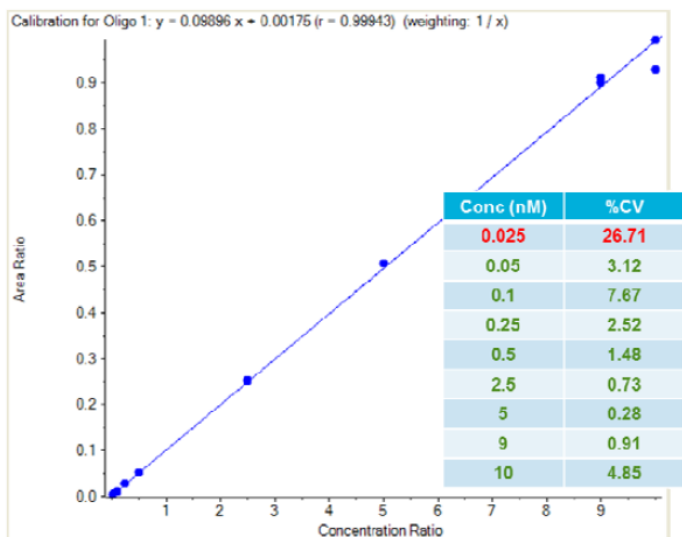


Figure 22: Standard Concentration Curve for Oligonucleotide 2 in Matrix using MRM^{HR} Workflow. Concentration curve for Oligonucleotide 2 in plasma, using Oligonucleotide 2 as an internal standard. Using MRM^{HR}, excellent linearity was observed, with a lower limit of quantitation of 0.05 nM.

Intact Protein Quantification

Featuring SCIEX TripleTOF and X500B QTOF Mass Spectrometers

While traditional LC-MS workflows for protein quantitation are mostly based on enzymatic digestion of the target protein followed by quantitation of signature peptides, LC/MS based quantitation of intact therapeutic proteins using high resolution accurate mass spectrometry (HRAMS) provides an innovative new solution for intact protein quantification. As it offers a high throughput platform allowing accurate quantitation and differentiation of major modifications at the intact protein level.

Challenges still exist in quantifying intact therapeutic proteins, especially monoclonal antibodies in complex biological matrix, mainly due to 1) distribution of protein signal over multiple charge states of multiple glycoforms; 2) interference from matrix proteins; 3) limited guidance on data analysis. To overcome these challenges, SCIEX developed a comprehensive workflow for intact protein quantification in biological matrices. As shown in Figure 23, the biological samples are processed through immunoaffinity cleanup and injected to HRAMS analysis. The raw MS spectra corresponding to the LC peak were processed by either deconvolution or XIC for quantitation.

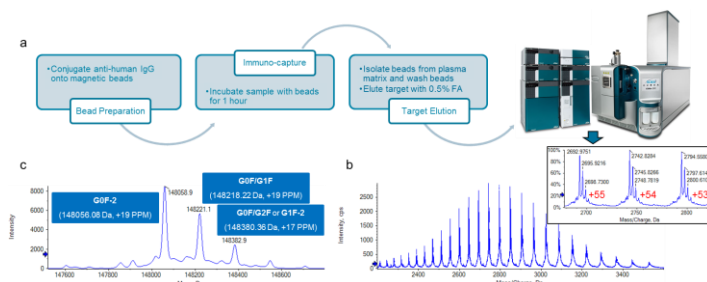


Figure 23. Immucapture Workflow. a) Immuno-capture workflow for target enrichment/purification; b) raw spectrum of enriched/purified trastuzumab from rat plasma, generated in SCIEX X500B QTOF system; c) deconvoluted data of raw spectrum in fig.1b (Input m/z range: 2200-3600. Resolution: 5000. Output mass range: 130-170 kDa).

SCIEX offers three data processing strategies for intact protein quantification. The first approach is to extract ion chromatograms from specific charge states. The ions from a few most intense charge states can be selected for the construction of XIC. Summing of more charge states can reduce variability in the assay by compensating for changes in charge distribution between different samples. The second approach is based on deconvoluted mass spectra which can be directly processed by MultiQuantTM software. The peak height rather than peak area of the deconvoluted spectra was used for quantitation^{13, 14}. The third approach is an automated data reconstruction workflow in

Research PeakView® software¹⁵: Every raw mass spectrum is deconvoluted, then the original raw mass spectrum is replaced by the corresponding deconvoluted data, to generate a reconstructed data file. After data reconstruction, by generating XICs of major glycoforms of mabs, interference from matrix proteins are filtered out thoroughly and much cleaner XIC peaks can be observed (Figure 24). With this approach, glycoforms of G0F-2 and G0F/G1F were detected in 50 ng/mL of trastuzumab in rat plasma (Figure 25). Quantitation was achieved with a linear dynamic range of 100 to 50 000 ng/mL.

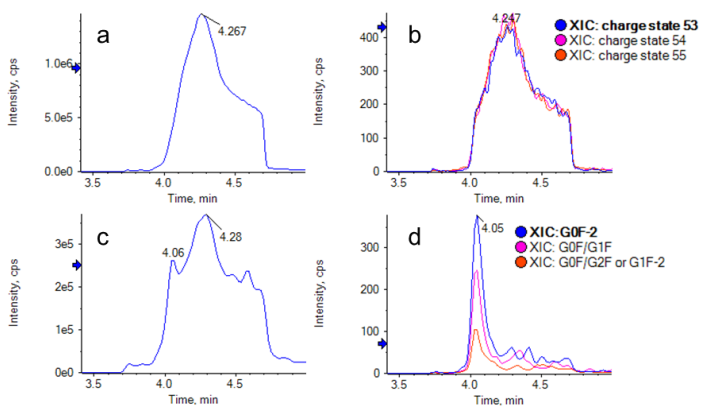


Figure 24. Chromatograms of 200 ng/mL trastuzumab in rat plasma. a) TIC, non-deconvoluted; b) XICs of the most abundant charge states from non-deconvoluted data, isolation window ± 0.1 Da; c) TIC after data reconstruction; d) XICs of major glycoforms in deconvoluted data after data reconstruction, isolation window ± 2 Da.

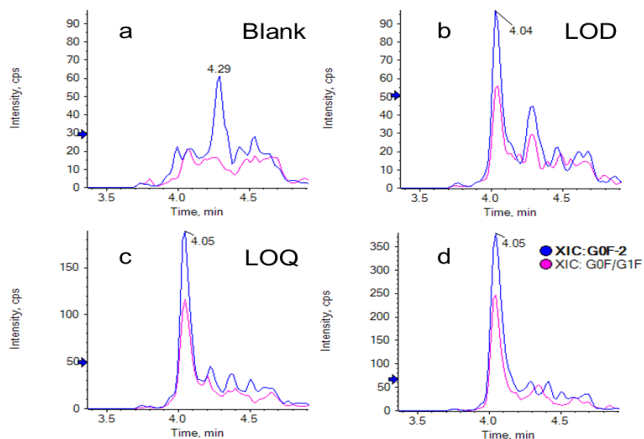


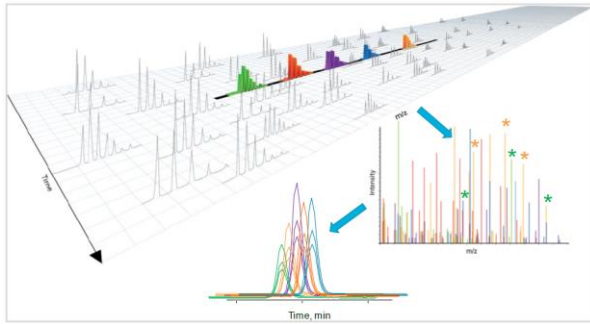
Figure 25. XICs of glycoforms G0F-2 and G0F/G1F: a) blank; b) 50 ng/mL, LOD; c) 100 ng/mL, LOQ; d) 200 ng/mL.

SWATH® Acquisition

Featuring SCIEX TripleTOF and X500B QTOF Mass Spectrometers

During biopharmaceuticals manufacturing, process-related impurities and other trace contaminants are accompanied with the recombinant biopharmaceutical products. Among them, host cell proteins (HCPs) are a major type of protein impurity derived from the host organism. The detection and quantification of HCPs is an area of particular concern, as these contaminants can elicit an adverse response in patients. The high complexity and the wide dynamic range of protein concentrations in the multiple purification stages of biopharmaceutical production poses challenges for the traditional data dependent workflows for HCP quantification. While data dependent acquisition only generates MS/MS spectra of precursor ions with high intensity, data independent acquisition strategies is more suitable workflow for HCP analysis by providing increased reproducibility and comprehensiveness of data collection.

SWATH® acquisition brings together data independent acquisition for comprehensive information collection and targeted data processing for HCP quantification (Figure 26). The Q1 window can be stepped across the mass range with flexible m/z isolation windows, collecting full scan composite MS/MS spectra at each step, with an LC compatible cycle time. SCIEX developed a SWATH acquisition-based workflow as a generic setup to estimate protein level of all identified HCPs (Figure 27)¹⁶. In this workflow, both data dependent (DDA) and data independent SWATH® acquisitions are performed for generating protein ID and quantification. HCP protein identification and ion library generation are accomplished by using ProteinPilot™ database search engine. SWATH acquisition data processing is performed by PeakView software, in which XICs are automatically generated and the peak areas of abundant fragment ions from signature peptides are exported for downstream statistical analysis and quantitation. For targeted quantification, MultiQuant™ software can automatically integrate peaks of signature fragment ions for the targeted protein, thereby providing accurate HCP quantification for monitoring this protein across the different purification stages.



Conclusions

Presented in this technical notes are quantitation workflows using SCIEX instrumentation and technologies, providing comprehensive workflow solutions to cover a wide variety of biomolecule types, from monoclonal antibodies, ADCs, peptides to oligonucleotides. SCIEX provides analytical tools to address needs and challenges faced during biopharmaceuticals development for a wide variety of applications.

Figure 26. SWATH Acquisition. In this workflow, instead of the Q1 quadrupole transmitting a narrow mass range through to the collision cell, a wider window containing more analytes is passed. This produces a more complex MS/MS spectrum which is a composite of all the analytes within that Q1 m/z window. Because the fragment ions are high resolution, high quality XICs can be generated post-acquisition to produce the MRM-like data. This Q1 window can be stepped across the mass range, collecting full scan composite MS/MS spectra at each step, with an LC compatible cycle time. This enables a data-independent LC workflow. After data acquisition, the data is interrogated by generating XICs from the high-resolution MS/MS for specific peptide fragment ions to generate MRM-like data to integrate for quantitation. MS/MS for specific peptide fragment ions to generate MRM-like data to integrate for quantitation.

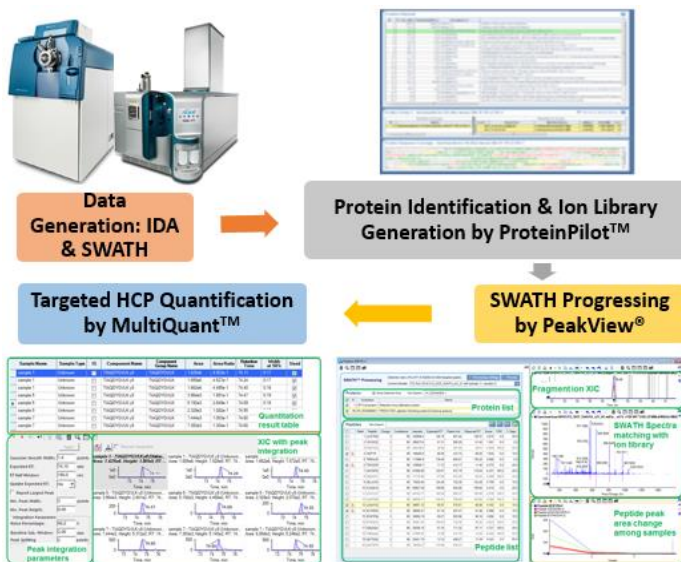


Figure 27. The general workflow to estimate protein level of all identified HCPs.

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