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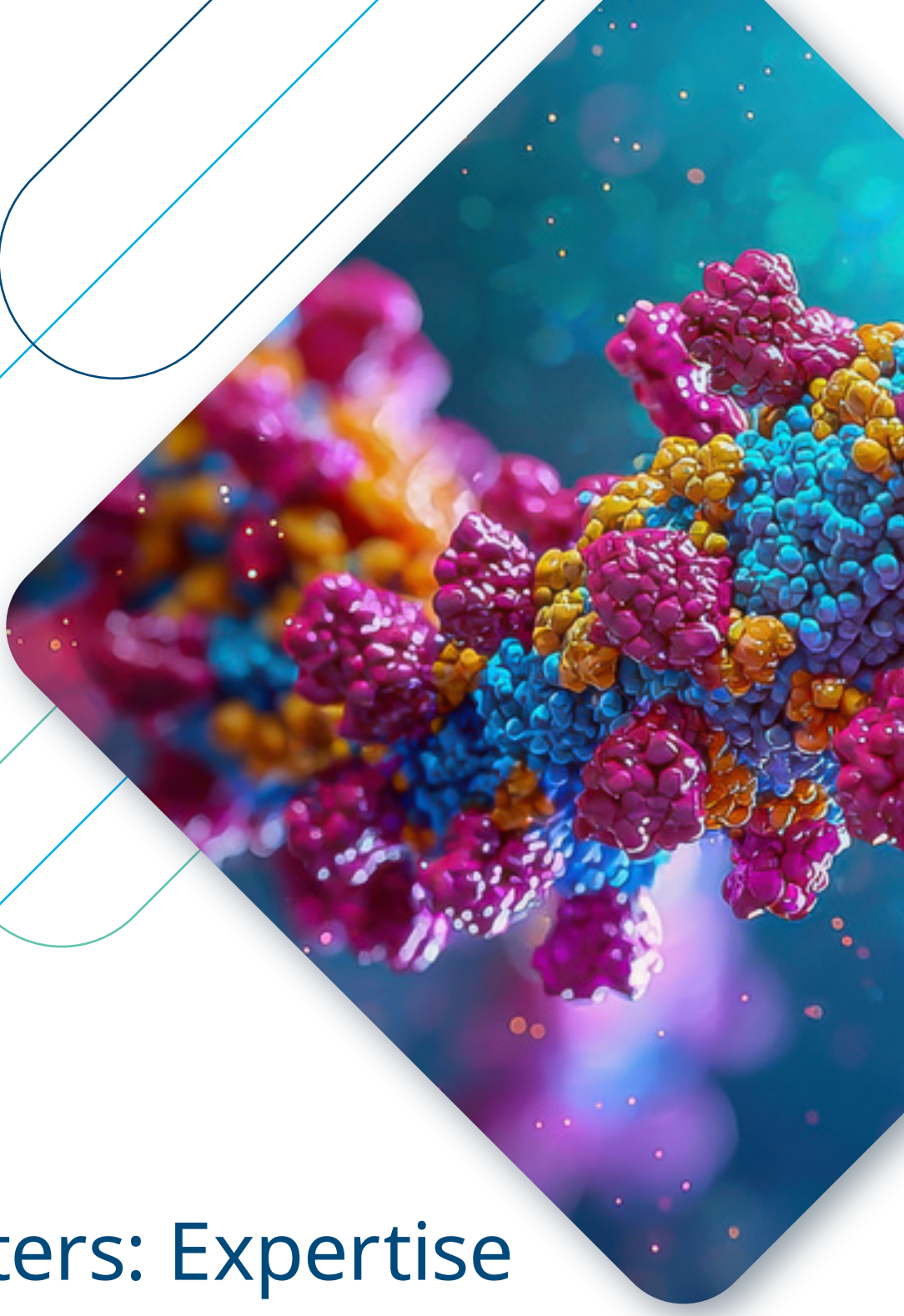

White Paper

Mass Matters: Expertise in Addressing Drug Bioanalysis for T2D and Obesity with LC-MS

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Introduction

The growing prevalence of type 2 diabetes (T2D) and obesity — affecting 37.4 million and 71.3 million[1] individuals in the U.S., respectively — has driven an urgent need for robust bioanalytical strategies across the drug development continuum. From early-stage discovery to clinical sample analysis, the demand for precise and scalable measurement tools has intensified. Currently, there are 173 obesity-related therapies either in development or on the market[2], encompassing a diverse range of structural modalities beyond the dominant GLP-1-based treatments. This expanding therapeutic landscape underscores the critical role of bioanalytical innovation in supporting efficacy, safety, and regulatory success.

Incretin hormone agonists have gained the most attention of late for T2D, obesity and other health problems. In particular, analogs and agonists of glucagon-like peptide-1 (GLP-1), and gastric inhibitory polypeptide (GIP) that enhance insulin secretion have had dramatic impact and feature in many pharmaceutical company pipelines. We also see additional therapies in development for these diseases including dipeptidylpeptidase-4 (DPP-4) inhibitors, dual agonists (i.e., beyond tirzepatide), glucagon signaling receptors, oxyntomodulin analogs, and fasting-induced hormones such as peptide YY (PYY) and amylin analogs. The diversity of compounds and targets aligns well with advances in bioanalytical techniques emerging today, but also emphasizes the fundamentals of bioanalytical method validation and the sample analysis we conduct under global regulatory guidance. Our extensive experience has taught us that obesity and T2D drugs can present some significant bioanalytical challenges associated with their complex structure. In particular, the large peptide moieties, and the required assay sensitivity, demand careful consideration of sample handling, preparation, and analysis.

ADME investigations

Metabolism investigation of the T2D and obesity drugs continue to demonstrate critical importance of candidate selection. As we learn more about these drugs their multifaceted potential is revealing applications not only in advanced management of insulin levels, but a wide range of other health benefits as well. We have successfully applied triple quadrupole (QqQ) liquid chromatography mass spectrometry LC-MS and high-resolution mass spectrometry (HRMS) to understanding drug action through identifying active metabolites and bioactivation and deactivation processes. The identification of metabolites is important to pharmacoKinetic (PK) interpretations helping establish dosing regimens and safety profiles. Drug-drug interactions are also investigated with our LC-MS instruments, which is critically important in the multi-medications field of obesity and T2D treatments.

Evidential metabolism studies have shown significant variation in biotransformation profiles across this therapeutic area. These latest approaches to diabetes treatments and weight management are relatively new, and we are gaining critical insights into drug mechanisms. The peptide GLP-1 drugs for instance can produce several circulating peptides due to proteolytic cleavage with associated long half-lives contributing to important therapeutic profiles[3]. Others such as the DPP-4 inhibitors are primarily excreted unchanged with minor, but active metabolites[4]. These investigations are key to predicting and investigating drug-drug interactions.

Considering the wide adoption of the T2D and obesity drugs in developed nations we can expect significant interest in personalized medical treatment. Here we anticipate the need for advanced biomarker profiling and the use of LC-MS to tailor drug treatment regimens to patient subgroups. This is an exciting area of advancement that we are seeing leverage LC-MS to great effect.

Regulated LC-MS bioanalysis

Pre-clinical animal studies (TK/PK) are conducted under good laboratory practice (GLP) with LC-MS techniques demonstrating excellent utility for these drugs. Analyte stability in blood plasma/serum is of high importance for collection, storage, and analysis. Typically, the peptide drugs employ solid-phase extraction (SPE) where retention mechanisms that offer orthogonality to the subsequent LC separation are preferred. The testing of analyte retention on SPE and LC columns is vital to selective recovery of the analytes from complex blood/plasma matrices. Modern QqQ mass spectrometer instruments when combined with SPE and conventional LC separations have demonstrated sufficient sensitivity at this stage of drug development.

Once these drugs reach clinical phases, sensitivity and selectivity of PK supporting assays become paramount. The increased sensitivity required from human dosing further challenges the bioanalytical methodology. Non-specific binding (NSB) losses of analyte to metal and plastic surfaces requires careful consideration from sample collection to LC-MS detection. Large peptides, as often encountered with the T2D/obesity drugs, are notoriously vulnerable to NSB and instability events-impacting assay sensitivity and reproducibility. The use of LoBind 96-well plates and tubes are important to these assays. Overall, we employ our 30+ years of bioanalytical experience to address stability and NSB impacts with these assays.

Low flow rate chromatography (<100 µL/min) may be used to obtain additional sensitivity over conventional flow LC separations. Specialized LC instrumentation such as the Thermo Vanquish Horizon UHPLC gradient pumping systems have demonstrated excellent utility in this area. Micro-flow chromatography columns, proven during method development and validation to optimize sensitivity, separation power and robustness are another key advance in our bioanalytical approaches.

Finally, HRMS with our quadrupole-orbitrap instruments (Q-Exactive and Exploris) have been used for analyte detection. HRMS provides another dimension of assay selectivity based on mass accuracy and mass resolution. Selectivity of the LC-MS instrument results in sensitivity by differentiating from potentially interfering signal and experimental noise. Depending on the assay, the intact ionized molecule or using MS/MS fragmentation can be used.

Conclusion

The flexibility of modern LC-MS instruments is well suited to the field of T2D and obesity drug bioanalysis when combined with appropriate sample preparation. It is increasingly important to leverage deep bioanalytical experience and to take a holistic approach to assaying this class of drugs. Each assay is developed with consideration of attributes of the chemical structure and the three key aspects of the method: 1) analyte extraction from the biological matrix, 2) LC separation and 3) MS detection. From investigating drug metabolism to in vivo animal studies and ultimately to supporting clinical trials, LC-MS has demonstrated practical utility and highly successful application in the latest T2D and obsity therapeutic advances.

Working with IQVIA Laboratories

IQVIA Laboratories Biosciences leads with science and is an industry leader with experienced bioanalysts who are driving innovation forward with their successful methodologies in obesity and diabetes drug development. While complying with regulatory guidelines, we offer higher confidence in your results for key decision making that will help deliver your project to plan.

References

1. Timeframe of analysis is January 2018 to June 2023 | Patient population sizes include 2022+ data-active patients, or those with Rx or Dx claims in 2022 or 2023 | Source: IQVIA LAAD; US Market Access Strategy Consulting analysis.
2. Citeline Trialtrove, Jan 2025; IQVIA Institute, Jan 2025.
3. Absorption, metabolism, and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species, L. Jensen, H. Helleberg et. al., European Journal of Pharmaseutical Sciences, Vol 104 (2017) 31-41.
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