# Rapid LC-MS/MS compound method development and sample analysis for DMPK workflows

Bianca Silva[1], Mike Knierman[1], Steve Ainley[2], Jeremy Lawton[2], Wayne Lootsma[2]

[1]Agilent Technologies

[2]Sound Analytics LLC

ASMS 2026
WP 221

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## Introduction

### Bioanalysis – DMPK – studies

Drug metabolism and pharmacokinetics (DMPK) studies are essential to understanding the absorption, distribution, metabolism, and excretion (ADME) of drug candidates and play a critical role in drug discovery and development. The characterization of DMPK properties for modern therapeutics increasingly requires advanced analytical techniques due to long half-lives and low systemic concentrations. DMPK labs need a workflow that includes robust and easy to maintain instrumentation, easy to use and efficient software to enable the analysis of hundreds of compound studies a week. Rapid review of the results is necessary to deliver high quality results in a timely fashion. Training requirements of new lab personnel needs to be minimized on the operation of this workflow to keep lab operations running well.

### Bioanalysis - Workflow

Bioanalysis are based on synthetic molecule testing *in vivo* and *in vitro* assays. Depending on the assay, more than 1000 of injections including ~ 700 compounds screening are performed on weekly basis. Liquid chromatography–tandem mass spectrometry (LC-MS/MS) has become a cornerstone of DMPK research, offering high sensitivity, selectivity, and throughput for the quantitative analysis of diverse compound classes. A simplified workflow is showed below.

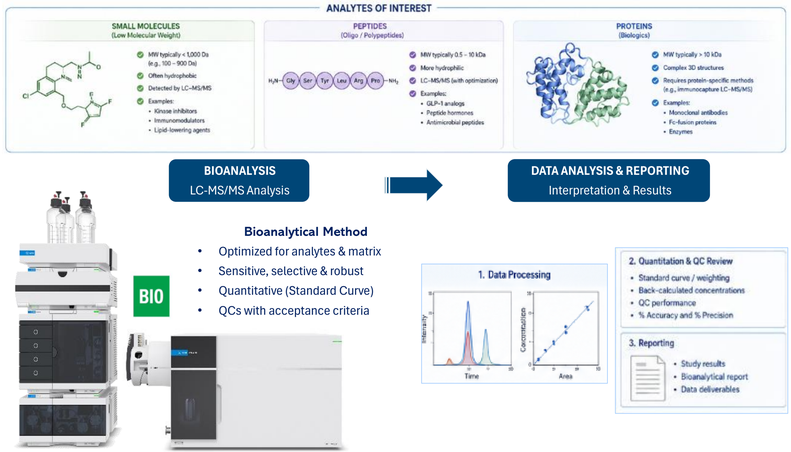


Figure 1. General workflow for Molecules in Bioanalysis studies.

### The Agilent solution for DMPK/Bioanalysis analysis

Agilent 6495D triple quadrupole LC/MS systems, combined with the *Sound Analytics LeadScape* solution, are designed to streamline method development and support robust, high-quality bioanalytical assays across multiple modality types. These capabilities enable efficient evaluation of DMPK properties and facilitate the optimization of drug candidates during early discovery. *LeadScape for Agilent* software delivers the speed of developing compound specified methods, rapid sample analysis and review, and enterprise method management in an easy – user friendly interface. Additionally, the 6495D LC/TQ does not require any special settings to switch between peptide and small molecules methods.

## Experimental

### Methods

An Agilent Infinity II Bio UHPLC coupled to an Agilent 6495D triple quadrupole LC/MS (LC/TQ) running MassHunter and LeadScape software was used for the analysis of five compounds and one internal standard. Compound specific methods were rapidly developed using LeadScape. Samples were prepared using eight calibration levels in extracted commercial biological matrix samples along with several spiked with a blinded concentration.

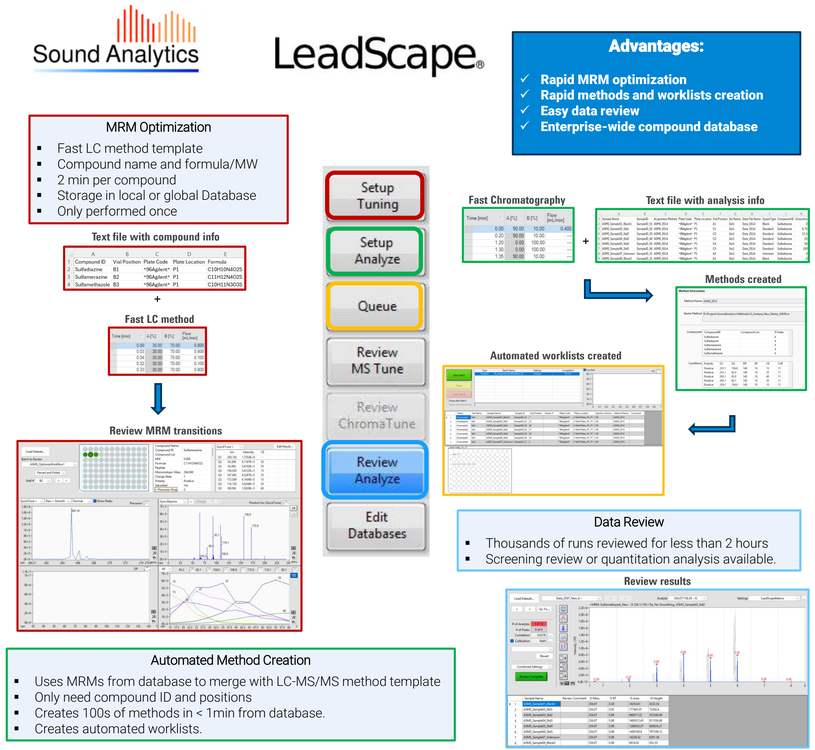


Figure 2. LeadScape for Agilent workflow.

## Results and Discussion

### From Methods creation to Review data – Few steps: multiple runs

The combination of automated method generation and the high sensitivity of the 6495D LC/TQ instrument resulted in accurate and precise quantitative data at low concentration levels commonly encountered in DMPK studies. Sample acquisition and processing were completed quickly, demonstrating the efficiency of the software-driven workflow. Overall, these results highlight the advantages of combining advanced mass spectrometry instrumentation with intelligent software solutions to support fast, reliable, and high-quality data generation for DMPK applications.

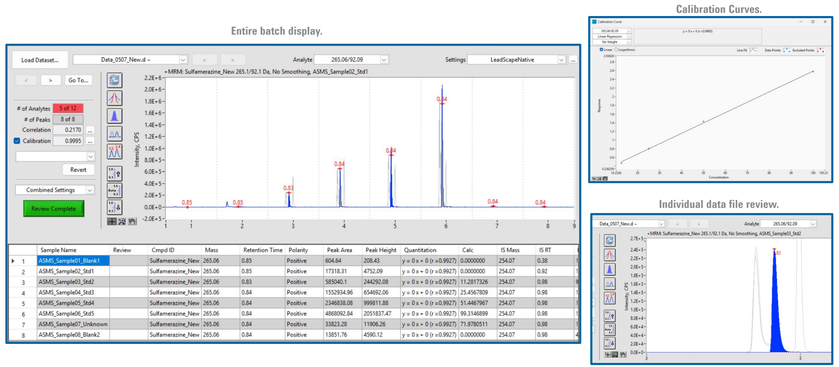


Figure 3. Easy to review individual chromatograms vs entire batch and calibration curves.

## Conclusions

- **User-friendly workflow:** A fast, reliable, and efficient bioanalysis workflow generated high-quality data using LeadScape for Agilent.
- **Excellent performance:** The 6495D LC/TQ demonstrated the sensitivity and the speed necessary for DMPK laboratories.
- **High Throughput:** The integration of LeadScape software with the Agilent LC/MS 6495D LC/TQ system enabled rapid optimization and acquisition of MRM transitions, significantly reducing method development time. Compound specific acquisition methods were generated quickly and applied to the study set efficiently, allowing multiple compounds to be analyzed within a single system setup. This approach eliminated time-consuming manual steps typically associated with method setup and sample organization.

DE-014949