Development and Validation of LC-MS/MS Methods for the Quantitation of Commonly Co-administered Drugs and in Support of Several Clinical Studies

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Purpose

Develop and validate LC-MS/MS methods for commonly co-administered drugs in support of multiple clinical studies. The drugs validated were cimetidine, itraconazole, paroxetine, valproic acid and moxifloxacin.

Methods

LC-MS/MS was used to validate and analyze the co-admin compounds individually using 5 separate extraction and analysis methods. Multiple Sciex platforms equipped with Shimadzu LC-20AD binary pumps were used as the LC system. Sciex 4000 mass spectrometers were used for the validation and sample analysis of cimetidine and moxifloxacin.

Results

All 5 assays were fully validated following the current FDA guidance and industry standards. The accuracy of the methods were within 15% of the nominal concentrations and the CV was within 15%. Freeze/thaw and 6 hour ambient stability in plasma was confirmed. The recovery of the compounds extracted from plasma passed the acceptance criteria and no significant matrix effect were observed. Hemolyzed and lipemic plasma was also evaluated and had no effect on accurate quantitation of the compounds. Blank plasma in 6 separate lots were analyzed in order to confirm that no interfering peaks were present in the blank matrix. Additionally collection stability was assessed by spiking the compounds into incubated whole blood and at the appropriate time spun down to plasma for analysis. No collection stability problems were observed that would impact the clinical studies.

In accordance with the FDA guidance, the impact of the presence of these co-administered drugs on the sensitivity and selectivity of the measurement of the proprietary drug and its metabolite was assessed. Additionally, the impact of the presence of the co-administered drugs on the freeze/thaw stability, bench top stability and long term storage stability of the proprietary drugs were also assessed. Analytical results demonstrated that these co-administered drugs and the proprietary novel drugs could be measured with acceptable accuracy and precision when analyzed in samples that contained combinations of these analytes. Further, the data indicate that samples containing combinations of the proprietary drugs along with the co-administered drugs were stable when submitted to conditions similar to the conditions that clinical samples would be subjected to.

Conclusion

The accurate/precise validated LC-MS/MS methods were used to support multiple clinical studies. Thousands of samples have been analyzed and reported using these validated methods.