Issues to address when isotopically labeled analogues of analytes are used as internal standards.

The detection of drugs and their metabolites (collectively referred to as drugs in this article) in biological tissues and fluids (media) has always been an important component of clinical diagnosis, forensic testing, pharmacological research, and drug discovery. Thanks to advances in analytical instrumentation and a greater understanding of metabolism, we can now detect drugs at concentrations that were once undetectable (*1, 2*). At the same time, a growing emphasis on monitoring illegal drug use in the workplace has required massive testing of urine specimens, which has stimulated significant advances in specimen pretreatment technologies.

New GC/MS/MS and LC/MS/MS instruments are capable of achieving higher specificity and S/N, which is advantageous for identifying unknown metabolites at very low concentrations. However, robust GC/MS methods still play a major role in identifying higher levels of well-characterized drugs in therapeutic monitoring, emergency room screening, and workplace testing. In most situations, the newer instruments do not generate better quantitative results than GC/MS.

If analytical instrumentation and specimen pretreatment technologies are the "hardware" aspects of the analytical sciences, then isotopically labeled analogues (ILAs) may be considered the complementary "software" component that is needed for advanced hardware to reach its full potential in quantitation. In this article, we look at how to overcome problems associated with using ILAs as internal standards (ISs) for the quantitation of drugs in media (*3–5*). All of the data and discussion are drawn from GC/MS studies for two reasons: The use of ILAs as ISs was originally developed for GC/MS, although the approach is readily adaptable to GC/MS/MS, LC/MS, and LC/MS/MS applications; and, despite many GC/MS/MS, LC/MS, and LC/MS/MS studies using ILAs as ISs, we know of none that try to better understand the standards themselves.

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