

Robustness and ruggedness relation to LC-MS method development and validation

LC-MS parameters

- Large number of LC-MS parameters
 - Changes in some of them result in poor reproducibility
- Complex and multi-step sample preparation procedure

LC parameters

Parameter	Likelihood of uncontrollable change	Recommended extent of variation
pH	Medium	± 0.5 units
Concentration of additives in eluent	Medium	$\pm 10\%$ (relative)
Organic solvent content in the eluent	Low to Medium	$\pm 2\%$
Column temperature	Low	± 5 C
Eluent flow rate	Low	$\pm 20\%$
Column batch and age	Medium	-

Samples and sample preparation

Parameter	Likelihood of uncontrollable change	Recommended extent of variation
Analyte extraction time; solvent amount and composition (in liquid/liquid and solid phase extraction, etc)	High	$\pm 20\%$
Injection solvent composition	Low/High	$\pm 10\%$ (relative)
Matrix effect in broad sense (sample matrix source)	High	6 different

Mass spectrometry

Parameter	Likelihood of uncontrollable change	Recommended extent of variation
Drying gas temp	Low	± 10 C
Nebulizer gas pressure/flow rate	Low	± 5 psi / ± 1 L/min
Ion source configuration (Nebulizer position)	High (if configurations can vary) Not applicable (if fixed source)	According to the ion source design. Should be varied if source is used in different configurations.
Ion source condition (Nebulizer aging, ion source contamination)	High	After analysis of samples versus cleaned system