Manual Integration Policy and Technical Assistance Document (NC WW/GW LC Policy 04/09/2010)

The emphasis of this policy is on gas chromatographic (using many detectors including mass spectrometers) data reduction, but the principles apply to all analytical procedures, which employ an instrument response measurement that can be manipulated by the analyst (e.g., ion chromatography, ICP, ICP/MS, autoanalyzers).

When manual integration may be employed

Manual integration is used to provide accurate quantitation of peak area where the original integration or identification provided by the data system is in error. This integration must only include the area attributable to the specific target compound. The area integrated must not include baseline background noise. Manual integration may only be used when peaks are distinct with a valley between the peaks. The area integrated must not extend past the point where the sides of the peak intersect with the baseline noise. Manual integration relies solely upon the experience of the analyst to determine proper integration for each peak and must be employed only by experienced analysts thoroughly trained in the chromatographic software. Integration parameters (both automated and manual) must adhere to valid scientific chromatographic principles. All data must be integrated consistently and appropriately in standards, samples and quality control samples.

It must be a laboratory's routine operating procedure to report automated peak integration results. Exceptions include situations where an obvious error in the determination of the peak area has been made, when the analytical method has specific integration requirements or when a regulatory program has specific integration requirements. When the data system integration is not technically sound, the analyst is obligated to employ manual integration. Integration over a range of compounds (e.g., hydrocarbons) may routinely require manual intervention, depending upon the capabilities of the chromatographic software. The analyst should seek to minimize manual integrations by properly maintaining the instrument, updating retention times, and optimizing peak integration parameters (e.g., area reject, peak width, threshold, etc.).

All computerized data reduction must be reviewed carefully by the analyst to determine the accuracy and appropriateness of the quantitation performed by the data system. Any errors must be corrected using this document as a guideline to define appropriate integration. The document must describe procedures for completing and documenting corrections to analytical results.

The failure of the software to appropriately integrate a peak is usually obvious from visual inspection of the chromatogram (i.e., at an appropriate scale - enlarged chromatograms must be used to discern baseline noise). Errors may include; but are not limited to, the following:

- Peak splitting by the chromatography software,
- Adding area due to a co-eluting interferant,
- Failure to detect a peak or the wrong peak is identified by the chromatographic software,
- Baseline noise (the signal-to-noise ratio is less than 3:1),
- Matrix interference,
- Well-defined peaks on the shoulders of other peaks,
- Negative spikes in the baseline,
- Excessive peak tailing due to failure of the instrument response to return to baseline or a rise in the baseline, and
- Failure to separate peaks.

Documentation requirements

When manual integration is employed, the laboratory must clearly identify manually integrated compounds, document the reason the manual integration was performed, the date performed and who completed the work. A flag or qualifier code may suffice for simple manual integrations. In addition, a hardcopy printout of the data displaying the manual integration shall be included in the raw data package (i.e., both the original and manually integrated chromatograms, of similar scale, must be present in the data package). All information necessary for the historical reconstruction of data must be maintained by the lab. Additionally, the laboratory must employ a

systematic data validation procedure to check manual integrations to assure integrations are technically sound and representative of the response.

When manual integration is inappropriate

Under no circumstances will manual integration be performed solely for the purpose of meeting quality control criteria, nor is it to be used as a substitute for proper sample preparation (e.g., cleanup), proper instrument optimization or maintenance on the chromatographic system. Corrective actions, with regard to the instrumentation for computer software, must be taken if manual integrations become common for an analysis or an instrument that normally uses automated peak integration. Examples of inappropriate manual integration may include the following:

- Peak trimming, shaving or clipping
- Peak enhancement
- Baseline elevated above the signal
- Baseline dropped below the signal
- Improper peak identification
- Selectively adjusting integration events
- Insufficient sensitivity

Problematic compounds must be specifically addressed in the method Standard Operating Procedure (SOP) and have detailed quantitation instructions. Supporting data (i.e., duplicates, dilutions, second column confirmation or second method confirmation) may be required to settle borderline cases. In some instances, the affected data may have to be reported as estimated.

Elements of an effective manual integration SOP

Each laboratory must develop a Standard Operating Procedure (SOP), describing manual integration procedures. Alternatively, the laboratory may include manual integration procedures in all applicable method SOPs. An effective manual integration SOP may contain the following:

- Ethics/accountability
- Definitions of integration and manual integration
- Definitions of integration events (e.g., area reject, peak width, threshold, etc.)
- Procedures for instrument optimization
- What constitutes acceptable integration
- Consistency with standards and quality control samples
- Representative of response
- When appropriate (including problematic compounds and regulatory program-specific requirements)
- When not appropriate
- Review/validation procedures
- Documentation requirements
- Minimum S/N ratio