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A. PURPOSE

Determination of uncertainty is a way of defining and quantifying the magnitude of the parameters associated with a process that may contribute to the error (or uncertainty) that's inherent within certain processes. Since all measurement has a potential for variability, determination of the uncertainty associated with a process allows users of such measurements to understand the reliability, and hence suitability, of the measured values for its intended use.

Within controlled substance analyses, weight measurements of drug materials often need to be reported. Additionally, when applicable, reports involving purity or concentration may also need to be reported. When reporting measured values (e.g., weights, purity, concentration), uncertainty of measurement(s) will be listed so that readers of such reports will have an understanding of the confidence limits, or uncertainty, of such values. For information on criteria weights see SOP CS-5.1 Uncertainty Action Levels. This procedure describes how uncertainty values are calculated for use within controlled substance evidence examinations

Uncertainty values will be reported when exact weights, volumes, or other quantitative values are listed within a report. Approximate values of measurements will not have an accompanying uncertainty value within reports.

B. RESPONSIBILITY

All individuals assigned to developing uncertainty budgets will follow the guidelines set forth in this procedure. Surrogate weights shall be weighed on all balances as an ongoing component of measurement assurance. Occasional lapses in weekly measurements for personal balances (e.g., due to absences from the laboratory) are anticipated and do not require compensatory measurements. Uncertainty measurements within this procedure shall be evaluated and/or updated annually within the month of May.

C. DEFINITIONS

1. Uncertainty of Measure [4]: is a parameter associated with the result of a measurement that characterizes the dispersion of values that could reasonably be attributed to the measurand.
2. Measurement that Matters [4]: A determined value that is used, or may reasonably be used, by an immediate or extended customer (anyone in the judicial process) to determine, prosecute, or defend the type or level of criminal charge(s).

3. Type B Evaluation [2]: method of evaluation of uncertainty by means other than the statistical analysis of a series of observations.
4. Readability: the smallest increment which the balance displays (i.e., 0.01g or 0.001g).
5. Repeatability: closeness of the agreement between the results of successive measurements of the same item carried out under the same conditions (ex: a balance's ability to consistently deliver the same weight for a given mass).
6. Linearity: the quality of delivering a significantly identical sensitivity throughout the weighing capacity of a balance.
7. Standard Uncertainty [2] (u_i): a component of uncertainty, represented by an estimated standard deviation equal to the positive square root of the estimated variance.
8. Distribution:
   a. Normal [2]: A pattern of frequency of values arrayed around a central mean value, such that the pattern is consistent with a Gaussian distribution
   b. Rectangular [2]: A distribution of values that that there is equal probability that a value lies anywhere within the interval.
9. Combined Standard Uncertainty [2]: (u_c) square root of the sum of the squares of the uncertainty factors, used to express the uncertainty of many measurement results.
10. Coverage Factor (k): when applied to the combined uncertainty allows for the definition of the confidence interval; (k = 2 allows for a 95% confidence interval, k = 3 allows for a 99% confidence interval).
11. Expanded Uncertainty [1] (U): the interval in which a value (y) can be confidently asserted to lie.
12. Index: demonstrates the individual factor's contribution to the event uncertainty.
13. Standard Deviation: A value associated with a normal, or Gaussian distribution describing an average departure from the mean value.

D. PROCEDURE

When uncertainty values will be calculated the resources used to ensure proper measurement calculation include:

1. Use of ISO 17025 vendors for calibration services.

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2. Review of the scope of accreditation for calibration services to ensure their scope includes the needs of the laboratory.
3. Use of ISO accredited vendors as the source of Certified Reference Materials (CRM). Review of the Certificate of Analysis (COA) to determine the "true" concentration with reported uncertainty range.
4. Assessment of the capability of the vendor to provide the supply or calibration service needed when an ISO accredited vendor cannot be used. Documentation of this review will be maintained within the Quality Section.
5. Equipment having significant effect on results where uncertainty will be reported will be calibrated by a calibration laboratory according to the following schedule:
    a. Masses: according to GL policy
    b. Balance: according to GL policy
    c. Pipettes: according to GL policy
    d. Class A glassware: none (glassware will be replaced when necessary (e.g., when significant visual defects are observed)).

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Developing an Uncertainty Budget Associated for Weighing

For an example of an uncertainty budget spreadsheet see below. An Excel spreadsheet may be used to perform all the needed calculations.

1. Specify the measurement process (i.e., identify the measurand)
2. The following aspects of the procedure can influence the uncertainty:
    a. Instrument Readability –obtained from manufacturer's instrument manual, most balances will have two ranges and the Uncertainty should be calculated for both ranges.
    b. Instrument Linearity - obtained from manufacturers instrument manual
    c. Instrument Repeatability – this may be given in the manufactures specifications for the instrument however for the purposes of these budgets repeatability will be determined in the laboratory by one of the following methods:
        i. Use data obtained during the daily use of the instrument. Use the values obtained from the daily instrument check to determine the standard deviation. These values are acceptable to use when there are sufficient data points for masses over the working range of the instrument (a minimum of ten data points at the low region, middle region, and high

region of the range is desired). Use worksheet SOP CS-2.1 to compile the data and calculate the standard deviation.

ii. Weigh a certified mass multiple times (minimum twenty) then calculate the standard deviation for the readings. It is preferred to use masses throughout the range of the instrument and use the largest standard deviation in the calculation.

Example: For a balance that has a range of 0.001g to 300g, weigh masses at 0.200g, 100g, and 300g, if available. See applicable worksheet (e.g., CS-2.1)

iii. It is acceptable to use a combination of historical data and data obtained specifically for the purpose of determining the uncertainty budget in order to calculate the standard deviations.

d. Environmental conditions – although it is important to understand that environmental factors may have some influence on uncertainty, these generally will not significantly affect the work performed. However, these environmental factors will be incorporated during normal weighing events that are encountered within the previous steps.

i. Temperature

ii. Humidity

iii. Air flow

e. Sample loss during weighing – these will not significantly affect the work performed and should be minimal because all analysts abide by good laboratory practices. Since there is no possibility in sample loss when using solid weights, this factor will not be incorporated during normal weighing events that are encountered within previous steps.

3. Determine to what extent the factor affects the overall uncertainty budget. An item that contributes less than 1% to the budget can be eliminated from the budget.

4. Calculate the standard uncertainty based on the type of distribution the data represents ($\sum(u_i)^2$)

   Calculate the Index: If the item represents 1% or more of the total uncertainty then it won't be included in the budget.

5. Calculate the Combined Standard Uncertainty: **Uc** = square root of ($\sum(u_i)^2$)

6. Calculate the Expanded Combined Uncertainty using a coverage factor of 2.

   Coverage Factors: Two factors will give a 95% Confidence Level, three factors will provide a 99% Confidence Level.

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7. Evaluate the expanded uncertainty.
    a. Review calculations for accuracy
    b. Ensure that the expanded uncertainty value(s) makes logical sense. Evaluate the value(s) to determine if it meets the needs of the customer. An expanded uncertainty value that is overly large may not provide helpful information to the customer. For example, an expanded uncertainty of +/-50% would not give practical information to a customer and should not be used.
8. The calculated expanded uncertainty value will be used and reported as a Confidence Level.

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Example of budget chart for weights:

Low Range: (<110g)				
Factor	Value (x), g	Uncertainty of the individual factors (u_i), g	Distribution	Index (Relative contribution to u_i in %)
Readability	From manufacture	x/distribution value	**Rectangular** (use the square root of 3 as the distribution value)	The uncertainty for the factor divided by the subtotal of the standard uncertainties **$(u_i)^2 / (\sum(u_i)^2)$**
Repeatability	Determined in house this is the SD determined as listed above	Since this is a normal distribution the value is the SD obtained from the calculations	**Normal –** (normal distributions needs no estimation of the value since it has been calculated)	The standard uncertainty for the factor divided by the subtotal of the standard uncertainties **$(u_i)^2 / (\sum(u_i)^2$**
Linearity	From manufacture	x/distribution value	**Rectangular** (use the square root of 3 as the distribution value)	The standard uncertainty for the factor divided by the subtotal of the standard uncertainties **$(u_i)^2 / (\sum(u_i)^2$**
Subtotal of the uncertainty $(\sum(u_i)^2)$		Sum of the square of each of the uncertainty factors		
Uc = square root of $(\sum(u_i)^2)$	Square root of the sum of the squared uncertainty components	grams		
Expanded Uncertainty (U); where (k) = 2	Uc*the coverage factor U =(u_cx2)	**gram/weighing event**		

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E. DOCUMENTATION

Documentation for the calculation of uncertainty budgets will be maintained within the Section. The uncertainty budgets will be evaluated by the Deputy Director and will be reviewed by either the Quality Section or the Director. If the budgets are distributed electronically for common use (e.g., shared drive), appropriate measures will be in place to ensure that calculated values can't be changed (e.g., locked cells within Excel files)

F. SOURCES OF ERROR

1. Not considering all substantial contributors within the uncertainty budget.
2. Based on the data, applying the wrong type of distribution.

G. REFERENCES

[1]SWGDRUG Supplemental Document SD-3 "Quality Assurance/Uncertainty
www.swgdrug.org

[2]"NIST Reference on Constants, Units and Uncertainty"
http://physics.gov/cuc/uncertainty

[3]General Metrological Terms: http://iso.org

[4]ASCLD/LAB International "Estimating Uncertainty of Measurement Policy'

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Example of Uncertainty Budget and Calculations

Mettler top loading XS203S (#14) (Serial No.: B428788469)	
Specificiations per manufacturer documentation (pg. 2)	
Weighing Range:	210g

Items that influence balance uncertainty (considered in determining uncertainty)

Readability	0.001g	From Model Specification and Certificate of Traceability sheets - whichever value is larger will be listed.
Repeatability	0.001262g	Largest empirical std. deviation value selected from daily certified weight values and any additional weighings (see attached table)
Linearity	0.002g	From Model Specification and Certificate of Traceability sheets - whichever value is larger will be listed.
Measurement Unc (formerly "Accuracy")	0.0014g	Reported from Certificate of Traceability (listed at 95% Conf Level) High & Low Range values are assumed to be the same
Environmental Factors	Insignificant - This is demonstrated by daily instrument check and repeatability	
Number of weighing events	Varies	
Sample loss during transfer	Not applicable with reference weights. Can be significant but is dependent on sample type. Minimized by users following good laboratory practice.	

Sources of Uncertainty	Value	Distribution	Divisor based on distribution	Standard Uncertainty (u_i) (value/distribution)	Relative Index (% factor contributes to the std uncertainty) ($u_i/(\sum u_i)$)*100
Readability	0.001g	rectangular	√3	0.00057735	16.99
Repeatability	0.001262g	normal	1	0.001262273	37.14
Linearity	0.002g	rectangular	√3	0.001154701	33.98
Measurement Unc (formerly "Accuracy")	0.0014g	rectangular	2*√3 ("2" needed for k=2 to be k=1)	0.000404145	11.89
Subtotal of Standard Uncertainty factors ($\sum u_i$)				0.003398469	100.00
Subtotal of the Sum of the Squares of the Uncertainty Factors ($\sum (u_i)^2$)				0.00	
Combined Uncertainty U_c = square root of ($\sum (u_i)^2$)				0.001850 g	
Expanded Combined Uncertainty U (95% Confid. Level ; k=2) ; U = (U_c * k)				**0.004 grams/weighing event**	

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Revision #	Revision History
3	Word changes were made within the 'Purpose' and 'Responsibility' sections. Font colors were changed – everything black and removed strikeouts for clarity. Part F: Uncertainty budget is maintained in Section (changed from notebook in CSA Laboratory). Part H: Added evaluation criteria of Deputy Director, Quality Section, Director. Also added statement about adding security to prevent unauthorized change to electronic budgets. General formatting corrections made throughout document. Additional changes can be seen in the document from QualTrax.
4	Issue date heading removed from the History section. Schedule of calibrations were changed from annually to now referring to the GL policy (GL 21).
5	General formatting changes. Schedule of calibrations were changed from annually to now referring to the GL policy (GL-21). Elaborated on sample loss. Removed section on 'Developing Uncertainty Budget for Drug Purity/Quantitation Determination.' Added schedule for uncertainty evaluation.

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