Sections Included in this Document and Document History

1. Purpose	This procedure describes the process for the estimation of measurement uncertainty.
2. Scope	These procedures apply to chemical, biological, microbiological and physical testing carried out by the FDA and Office or Regulatory Affairs (ORA) laboratories.
3. Responsibilities	FDA and ORA laboratories are responsible for the collection of data and the determination of the estimated uncertainty for analytical methods in use.
4. Background	Every measurement or test has an error of measurement. If repeated, a test or measurement often gives a different result, even though it usually is very similar to the original result. Therefore, a test or measurement gives only an approximation of the true value of the quantity to be measured. A measurement or test is only complete if it includes the measurement uncertainty of the test. This can be thought of as a quantitative indication of the quality of the result.
5. References	National Institute of Standards and Technology (NIST). Technical Note 1297, Guide for Evaluating and Expressing the Uncertainty of NIST Measurement Results. EURACHEM. CITAC Guide, Quantifying Uncertainty in Analytical Measurements. Policy on Estimating Measurement Uncertainty for Testing Laboratories and Annex for Life Sciences Testing Laboratories, American Association for Laboratory Accreditation

6.
Procedure

Identification and documentation of the measurement uncertainty category (listed below) is required by each laboratory. Additionally, each laboratory is required to list all the components of uncertainty and estimate the uncertainty for all methods or technologies on their scope of accreditation.

A. Categories of Tests

The three different categories of tests that have been defined for Life Sciences testing laboratories, as well as the extent of uncertainty estimation are:

I. Qualitative tests and tests reported on a categorical or nominal scale. These do not need a measurement of uncertainty.

II. Well recognized test methods that specify limits to the values of the major sources of uncertainty of measurement and specify the form of presentation of calculated results. In such cases, the laboratory is considered to have satisfied the uncertainty requirements by following the method and reporting instructions.

III. All other test methods, including chemical or biological test methods based on published regulatory or consensus methods, as well as those test methods that need identification of the major components of uncertainty for which the measurement uncertainty is not defined in the method. For these types of tests, uncertainty can be estimated using laboratory control samples or the root sum square (RSS) method. After the application of the required calculation or uncertainty estimation technique given in Section B., other calculations and techniques can be used as supporting evidence.

B. Estimating Uncertainty

The steps for estimating uncertainty are discussed below. Measurement uncertainty does not usually include uncertainty due to sampling or bias.

1. Steps using relative standard deviation of laboratory control samples run through all method steps.

   a. Perform spiked determinations at different concentrations

including tolerance limit.

b. Calculate concentration and percent recovery.

c. Calculate the standard deviation (S) and relative standard deviation (RSD) on results where the process is in statistical control (no outliers or out of control results).

d. Calculate the measurement uncertainty at the 95% confidence level as follows:

$$U = k \times RSD$$

where:

U = uncertainty

k = coverage factor

(for 95% and 50 points, use 2; for less than 50 points, use the appropriate t statistic for 95%)

e. To calculate the measurement uncertainty interval for a measured value, calculate as follows:

$$Interval = U \times c$$

where:

c = concentration

2. Steps using the root sum square (RSS) method.

a. Clearly define what is being measured.

b. Review the method and identify every possible source of uncertainty.

c. Review the sources and determine whether or not the components are included when running laboratory control samples.

d. Quantify all the components. Estimates can come from a variety of sources and do not need to be overly rigorous. Possible sources of quantitative estimates include:

- method validation studies,
- information from published methods or textbooks,

- calibration certification,
- manufacturer's specifications, and
- experience.

e. Consider the components. Assume that the components are independent. Every source may not have to be evaluated if they are deemed insignificant. Components that are less than a fifth of the largest component can be eliminated.

f. Combine the components. The usual method is to square all independent components, add them, and then take the square root of the sum. This is called the *root sum square* method and gives the combined standard uncertainty.

g. Expand the combined standard uncertainty. Multiply the combined uncertainty by a coverage factor based on the level of confidence needed. In most cases a confidence level of 95% is sufficient, so k =2. If 99% confidence is required, then k =3. When estimates are based on limited data, k may vary according to the student t distribution. For example, if the estimate is based on analyses of 20 laboratory control samples, the coverage factor of k = 2.1 for 95% confidence.

3. Reporting Uncertainty Estimates

a. The extent of reporting of the estimates of uncertainty depends on the needs of the client, the specifications for the test, and the intended use of the result. There is no need to report the estimate if it is not desired by the client or not needed for other reasons. Nonetheless, the estimate is to be calculated, along with the means of making the estimate. Documentation is to be sufficient to allow replication of the calculation.

b. If reported, the uncertainty is reported to the same number of significant figures as the result. In most cases, two significant figures suffice. The estimate should also state the level of confidence associated with the coverage factor. Finally, the uncertainty is reported in the same units as the result.

c. The bias is reported in addition to the uncertainty when the method has a known bias and the bias adjustment was not performed.

7. Definitions

Coverage factor – The coverage factor is the number that is multiplied by the standard uncertainty to produce an uncertainty estimate that will contain a large fraction of all values that might be obtained on a test. The coverage factor is commonly noted as *k*, and *k*=2 is used for 95% coverage, and *k*=3 for 99% coverage.

Expanded uncertainty – The expanded uncertainty is the combined standard uncertainty (or standard uncertainty, if there is only one component), multiplied by the coverage factor.

Measurement uncertainty – The measurement of uncertainty is the parameter associated with the result of a measurement that characterized the dispersion of the values that could be reasonably attributed to the measurand.

Measurand - The quantity being measured is the measurand (i.e. the concentration of an analyte).

Repeatability conditions – Identical samples prepared at the same time, by the same analyst, under identical conditions, run on the same instruments are repeatability conditions.

Reproducibility conditions – Reproducibility conditions are identical samples analyzed under different conditions, including any of the following: different times, different equipment, different analysts, or different laboratories.

S_r – This is a standard deviation or relative standard deviation of result produced under repeatability conditions.

S_R – This is a standard deviation of results produced under reproducibility conditions.

Standard uncertainty – The standard deviation for uncertainty is either for the test or for a component of the test. It can be expressed in the units of the measurement, or a percentage, but all components are expressed in the same terms before they can be combined.

8. Records

Measurement uncertainty determinations, calculations and values for laboratory methods in use

9. Supporting Documents

FDA/ORA/Division of Field Science. *ORA laboratory manual*, Section 2, ORA-LAB.5.4.5 Methods, Method Verification and Validation.

10. Attachments

None

Document History					
Version No.	**Status** (I, R, C)	**Date Approved**	**Change History**	**Name & Title**	
				Author	**Approving Official**
1.2	R	03/23/05	Added A2LA Policy and Annex on Measurement Uncertainty to References; Revised 6., 6.A., 6.B.1., 6B.2.; Added 6.B.3.c.	LMEB	LMEB

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