Appendix E: Laboratory Quality Assurance

For over a century, AOAC INTERNATIONAL has provided the methods of analysis required for the measurement of analytes of interest to those government agencies that regulate products associated with agriculture, public health, and the environment. But during the past several decades, analysts realized that providing measurements based on methods validated and approved through collaborative study was not enough. Analytical results had to be accompanied by concurrent proof that the measurements were correct. That proof could be obtained by the application of the concepts of quality assurance, long used in the industrial world, to analytical measurements.

Scope of Laboratory Quality Assurance

A good analytical method is necessary to obtain valid concentration estimates, but it is not sufficient. The laboratory equipment must be running in accord with specifications. Analysts must be performing their work in a professional manner, and a suitable checking process must be in operation to ensure the quality of analytical results.

The primary reason for performing laboratory analyses is to obtain information that can be used to make informed decisions. Analytical data reported by a laboratory must be fit for its intended purpose and of a sufficient degree of quality, whether the purpose is to enforce standards, determine economic value, or protect the public health. Data must be comparable to those generated in other laboratories. It is no longer sufficient for a laboratory simply to believe or maintain that it is generating quality data. Laboratories must be able to demonstrate that their analyses are correct and in statistical control. Proof of technical competency and comparability is now a requirement in the global marketplace.

AOAC Official Methods are designed for the measurement of specific analytes in defined matrixes. An approved AOAC method has been demonstrated to produce reliable results when applied by a representative sample of laboratories expected to use it in practice. Nevertheless, whenever the method is applied subsequently, each user laboratory must demonstrate that it can produce results comparable to those attained in the original interlaboratory study. This demonstration is necessary when a laboratory analyzes for the same analyte in the same material for which the method was designed, or when it is necessary to extend the method to additional analytes in the same matrix, or to additional matrixes with the same analyte. For some extensions, it may be necessary to conduct further interlaboratory studies.

All analytical results must be traceable to some reference point—either fundamental units or reference materials certified by, or traceable to, a metrological institution. Only some classical gravimetric, titrimetric, and electrometric methods can be traced by any laboratory to fundamental metrological units. Almost all modern methods are based on an instrumental comparison of the response of an analyte with the response of a reference standard when both are stimulated by the same source of energy. This places a great burden on the authenticity of the standard. But even possession of a suitable standard is still not sufficient to produce adequate measurements. All measurements are accompanied by some degree of uncertainty. This uncertainty is of 2 types: a systematic displacement from the true or assumed value and a random scatter of values about a mean or average value. The systematic type affects all measurements in a system equally and is called "bias." If known, it can be corrected for. The random type of uncertainty affects each measurement in an unpredictable manner, but oddly enough, taken as a group their behavior is predictable and is called "random error." The ability to correct for bias and use the predictability of random error of the group is the basis for demonstrating the production of measurements of suitable quality.

The control of bias and random error of analytical measurements is the formal procedure of laboratory quality control. But quality control is only the final stage of a management system of quality assurance, which encompasses all aspects of laboratory operations including housekeeping, supplies, maintenance of records, training personnel, supervision, physical handling of laboratory samples, documentation, and reporting. This chapter reviews only the aspects of quality control as it pertains to the direct production and documentation of analytical measurements. Without the essential organizational infrastructure, however, it is impossible to produce quality measurements. The volumes by Taylor and by Garfield listed in the bibliography are indispensable for supplying this kind of information.

Validation of Methods

The proper use of analytical methods leads to the reliable quantitation of target analytes within the limits of measurement uncertainty. Validation of a method is the planned and documented procedure to establish its performance characteristics. The performance characteristics or the validation parameters of the method determine the suitability for its intended use. They define what the method can do under optimized conditions of matrix solution, analyte isolation, instrumental settings, and other experimental features. The inclusion of particular validation parameters in a validation protocol depends on the application, the test samples, the goal of the method, and domestic or international guidelines or regulations, as applicable. These characteristics are explored and optimized in the laboratory that initially proposes, develops, and refines the analytical procedure. The method is then tested in the interlaboratory study by a group of collaborators. If the test is successful, the method is adopted as an official method. But when used again, at a later time and perhaps in another laboratory, the method must be verified to ensure that the laboratory or analyst can conduct the method of analysis within the specifications developed in method validation.

Analytical measurements are produced by the application of a method of analysis to a test portion taken from a laboratory sample. The method of analysis contains the instructions that must be followed. One of the first principles of analytical work is that the instructions should be followed in exact detail. This point is specifically emphasized in the instructions for the performance of the initial interlaboratory validation of the method, because the performance parameters generated are based on those instructions. If the performance parameters are then later used as the basis of a choice for the use of the method, there is an implied assumption that the same details will be used. To what extent those details may be relaxed is also the subject of testing in the initial validation and is expressed as the ruggedness parameter. Some typical validation parameters to be investigated are listed and explained below.

Calibration.—Calibration relates the response of an instrument to the quantity or concentration of an analyte. In many cases, the re-

sponse bears a linear relationship to the concentration of the analytes. When this response is linear, regression analysis is often used to calculate the relationship. A linear relationship is advantageous because it may permit the use of a single- or double-point calibration, particularly with products of fairly uniform concentration levels such as pesticide formulations or drug dosage forms.

Many analytical methods using modern instrumentation, however, produce curved calibration plots over the range of interest. These instruments often use proprietary, nonlinear algorithms for calculating target analytes. Linear regression analysis is of no value for methods producing curvilinear responses, but modern statistics or graphing packages can be used to generate dose-response curves from nonlinear relationships. Immunoassays produce inverted exponential curves; the blank produces the maximum signal, which decreases with increasing analyte concentration.

The critical aspect of calibration is the standard used for the preparation of the calibration curve. A certified reference material is the best starting point, but these are usually not available for most analytes. Material accompanied by a certificate of analysis from the supplier may be suitable, and often its purity can be checked by dissolving the standard in a suitable solvent and processing a diluted solution by chromatography. The presence of a single peak in the chromatogram is indicative but not conclusive proof of purity.

Many modern analytical methods use instruments that are calibrated at extremely low concentrations. Great care must be exercised in calculating the required dilutions and processing the initial standard solution through multiple dilutions to obtain the final working standard solution. When small volumetric flasks and micropipets are used, their capacities must be checked periodically, particularly those of mechanical pipets.

Accuracy.—Accuracy is defined as the closeness of agreement between the measured value and the accepted, "true," or reference value. Accuracy is indicative of the bias of the measurement process. Accuracy is often evaluated by repetitively spiking the matrix or placebo with known levels of analyte standards at or near target values. The fraction or percentage of added analyte recovered from a blank matrix is often used as the index of accuracy. Added analyte, however, may not always reflect the condition of the natural analyte in the materials submitted for analysis.

When available, a certified reference material, certified by a metrological institution, is analyzed to establish bias. Two classes of materials are recognized by the International Organization for Standardization/Committee for Reference Materials (ISO/REMCO): "certified reference materials" (CRMs) and "reference materials" (RMs). RMs are of a lesser quality than CRMs, which must have "established traceability." The U.S. National Institute of Standards and Technology (NIST) also produces "standard reference materials" (SRMs) that are equivalent to the ISO/REMCO CRMs. "Reference materials" are also available commercially and are usually accompanied by a certificate indicating traceability to standards of a national metrological institution. Microbiological cultures are available from the American Type Culture Collection (ATCC) and others.

Precision.—Precision is a general term for the variability among repeated tests under specified conditions. Two types of precision, repeatability and reproducibility, have been found necessary and, for many practical cases, sufficient for describing the variability of a test method (1). Precision expresses the closeness of agreement (degree of scatter) among a series of measurements obtained from multiple testing of a homogeneous test sample under the method's established conditions. It should be investigated with homogeneous test samples, representative of the matrixes to which the method will be applied and containing the expected range of analyte concentrations within these matrixes. If it is not possible to obtain homogeneous test samples, however, precision may be investigated using test samples artificially prepared in the laboratory to simulate the original test samples.

In practice, precision may be determined at 3 levels: repeatability, intermediate precision, and reproducibility. Repeatability refers to within-laboratory simultaneous replicability; intermediate precision refers to within-laboratory variations that arise in different runs, on different days, with different analysts, and different equipment, etc.; and reproducibility expresses variability among laboratories. System precision may also be established by replicating additions of the analyte solution at various points in the method, and instrument precision is determined by consecutive signal measurement of the same material by the instrument. The instrument precision and the method precision may differ by an order of magnitude. When a precision is given, it is important to understand which precision is being referred to.

Precision is a function of concentration, and it is easier to compare precisions when they are placed on a relative basis by dividing the standard deviation by the concentration to obtain the coefficient of variation (CV), which when expressed on a percentage basis (%) is the relative standard deviation (RSD). Over a relatively small concentration range, 1 or 2 decades, RSD is often a constant. Examination of the precisions of thousands of interlaboratory studies conducted by AOAC INTERNATIONAL over the past century has shown that in general the reproducibility relative standard deviation (RSD_R) in % can be summarized by a simple equation, easily entered into a programmable calculator or computer as:

$$(\text{Predicted})\ RSD_R = 2C^{-0.1505}$$

where C is the concentration expressed as a mass fraction; e.g., for 100%, C = 1; for 1%, C = 0.01; for ppm (mg/kg), $C = 10^{-6}$. RSD_R is more or less independent of analyte, matrix, method, and time. (The precision of instrumental methods is no better than the precision of classical methods at the same concentration.) A preliminary assessment of the acceptability of the precision found in the interlaboratory study can be made by calculating the ratio, designated as HORRAT, of the precision found to that calculated from the equation, as follows:

$$\text{HORRAT} = \frac{(\text{found})\ RSD_R}{(\text{predicted})\ RSD_R}$$

Values falling within the range 0.5–2.0 are generally considered acceptable. Within-laboratory precision (RSD_r) is generally about one-half to two-thirds the among-laboratories precision. Some common values are shown in the following table:

Concentration		RSD_R, %	RSD_r, %
Mass fraction	Common units		
1	100%	2	1
0.01	1%	4	2
0.0001	0.01%	8	5
0.000001	1 ppm	16	10
0.00000001	10 ppb	32	20

These generalizations do not apply to quantitative microbiology, in which colony formation and growth are extremely sensitive to inoculation and incubation conditions, or to enzyme reactions, which utilize a catalytic-type mechanism. They also do not apply to physical properties or to indefinite or mixtures of analytes.

The term "accuracy" is often confused with precision, and it is used by some authors and organizations in the sense of a combination of bias and precision. Methods may be precise without being accurate, or accurate without being precise. The term "accuracy" is used in the sense of "bias." It is also important, when using the term to indicate a difference, to be sure that the subject of the bias is indicated—whether it be a single value, a mean, or a long-term average (accepted true value). Single values and means are properties of the measurement; the long-term average is usually a property of the method of measurement.

Specificity.—Specificity is the ability of a method to respond exclusively to the target analyte and not to any degradant, impurity, or other component of the matrix. Very few methods are absolutely specific, so the term "selectivity" is often used for this property. This parameter shows that the method can be used to quantitate the analyte without interference.

Limit of detection (*LOD*).—The LOD is the smallest quantity of analyte that can be shown to be significantly greater than the measurement (random) error of the blank at a prescribed level of confidence (usually 95%). It is often taken as 3 times the standard deviation of the background noise. When the LOD is calculated, it should be stated what definition and method are used. More rigorous definitions require consideration of false positives as well as false negatives.

Limit of quantitation (*or quantification*) (*LOQ*).—The LOQ is the smallest amount of analyte in a test sample that can be quantitatively determined with suitable precision and accuracy under previously established method conditions. The LOQ is a crucial parameter in assays of low levels of compounds and in the determination of impurities, contaminants, or degradation products. It is often taken as 10 times the standard deviation of the background noise. When the LOQ is calculated, it should be stated what definition and method are used. A multiple, e.g., 2, 3, or 5, of LOQ is often used to establish a level of fortification in residue recovery studies.

The validation of LOD and LOQ is not required when the analyte is within the useful range of the assay. They are important in the determination of low levels of residues and contaminants for exposure estimates required in risk assessments and for surveys of low levels of analytes. Because LOD and LOQ are determined at the lowest useful ranges of the methods, which tend to be regions of poor accuracy and precision, they can be expected to vary considerably.

Ruggedness.—The ruggedness of an analytical procedure is its ability to tolerate small variations in procedural conditions, which may include variation in volumes, temperatures, concentrations, pH, and instrument settings, without affecting the analytical result. It provides an indication of the applicability of the method in a variety of laboratory conditions. Ruggedness is not a quantitative parameter.

Performance Criteria

The advantage of using a standard method of analysis established through the interlaboratory study procedure is that a record exists as to the performance of the method by a group of representative laboratories. This fact does not necessarily imply that any specific laboratory will achieve these characteristics. Every laboratory must determine for itself the performance that it can attain. In comparing performance, a laboratory must be sure that within-laboratory parameters are being compared with within-laboratory parameters and not with among-laboratories parameters. Before using a method with test samples, the laboratory should establish that it can obtain the expected values with formulated materials, previously analyzed products, labeled commercial products, or reference materials. All actual analytical runs should be accompanied by standards, controls, and blanks as appropriate.

In-house method verification does not need to be performed each time a method is used. Rather, it must be completed before a method is put into use. Performance criteria, on the other hand, are parameters that may need to be satisfied for each routine use of a method. They are accomplished through the application of quality control procedures.

Methods should ideally have performance criteria included in the method documentation. These criteria define whether a method, at any given time, in the hands of any given analyst, is performing as it should. Performance criteria are not necessarily the same as those parameters reported in the interlaboratory study. Performance criteria may take the form of such measures as degree of linearity for a series of standards, a maximum level for a blank value, or a relative standard deviation for successive peak heights or areas. These criteria may also specify minimum recovery levels for control materials or acceptable levels of precision for duplicates. In the case of microbiological methods, these criteria may include positive and negative controls. Other applicable criteria may concern the acceptability of the batch of media used or the precision on a single day for a quantitative microbiological method. A means of verifying the adequacy of the entire analytical system at the time the analysis is performed is necessary to ensure that the results meet the requirements of the client.

Performance criteria should be specified in quality assurance documents and should also be a part of the standard operating procedure for the method. These performance criteria act as an ongoing check on quality. If the method fails to perform at the required level, it is necessary to take corrective action to resolve the problem and document this action.

One of the simplest procedures, but of value only when there is a sufficient volume of similar analytical work available to sustain it, is the control chart. It is based on the statistical principle that analytical values distribute themselves according to the normal distribution. A control chart is prepared by plotting the analytical result on the vertical (y) axis against time or the consecutive analysis number on the horizontal (x) axis. The analytical result may be the absolute quantity or concentration of an analyte or the fraction or percent recovery as obtained from a constant control material or from a constant addition. After about 30 values are obtained, the mean ($\bar{x}$) and the standard deviation(s) are calculated. Then horizontal lines are plotted at ($\bar{x} \pm 2s$) and ($\bar{x} \pm 3s$), called warning limits and action limits, respectively. If a subsequent analysis falls above or below the action limits, the cause for the deviation is investigated immediately. If an analysis falls between the 2 limits, no action is taken unless several values fall in this region or if a constant trend up or down is exhibited anywhere on the graph. The action and warning limits can be adjusted as more values are accumulated.

In some analytical procedures, the use of an internal standard is helpful when blanks or standards are not available or when multiple matrixes are analyzed for the same analyte. A known quantity of a noninterfering substance is added to all standards and tests. This procedure, of course, can only give the relative relationships of the analyte in the various test materials. Use of an internal standard or method of addition does not eliminate the necessity for a reference

point. This is the concept of traceability (2). The only time a reference material or a control material is not necessary is with empirical methods, where the method defines the analyte, such as "soluble fiber." For other assays, standard addition is used to prepare a calibration curve for a particular matrix.

Many AOAC methods use blanks as another internal quality control feature to demonstrate absence of contamination. Several types of blanks can be used, depending on their starting point. The reagent blank includes all reagents used in the analysis, including a sample portion known to be free of the analyte. The reagent blank serves as a check on the use of suitable reagents as well as background interference. An instrument blank confirms that no contamination is introduced by the instrument. Other types of blanks include a matrix blank as a check for inherent interference and a field sampling blank as a check for environmental contamination during sampling.

When available, reference materials are useful as a basis for performance assessment. They are usually too expensive to use for routine calibration and control purposes. The occasional use of a reference material certified by a metrological institution assures the laboratory of continued traceability to the internationally recognized measurement system. For local use, however, a homogeneous, stable material monitored by a control chart can be used to demonstrate stability of within-laboratory performance. But local measurements must be aligned with the external components of the measurement system.

Proficiency Testing

Validated methods, statements of measurement uncertainty, calibrations, reference materials, and control charts are all necessary components of a quality assurance program. Analyst proficiency can be demonstrated with reference materials. These components of an internal quality assurance program must be supplemented by interlaboratory comparisons (ISO/IEC Guide 43-1, par. 3.6) to complete the assurance of laboratory quality. In some areas, such as clinical chemistry, participation in periodic exercises is a regulatory requirement.

Proficiency testing is a program external to the laboratory that compares the analytical performance of a group of laboratories. Such external validation gives the laboratory and client assurance that the work performed in the laboratory is at least comparable to the analytical results produced by other laboratories. If formulated, homogeneous matrixes are used, and the program also provides information on the bias of individual laboratories. In proficiency testing, laboratories are not restricted as to what method will be used. Therefore, it does not provide information on method performance unless such information is specifically requested. In very large proficiency programs, sufficient information may often be provided so that conclusions may be reached regarding method performance as well as analyst and laboratory performance.

Proficiency programs are available only for a few analytes in specialized areas, usually those of high commercial volume or of critical importance to public health. Proficiency in the analysis of a given analyte/matrix combination does not necessarily carry over to another. For example, the determination of nitrogen in agricultural commodities is entirely different from its determination in water; analysis of pesticide residues is quite different from analysis of pesticide formulations. General-purpose or research laboratories that perform individual analyses for any analyte in any matrix may not perform a sufficient number of analyses to warrant the expense of participation in proficiency exercises. When asked to perform analyses in a new area, such laboratories may wish to decline the work, contract it out to a more specialized laboratory, or anticipate the necessity for conducting method validation and performance verification as part of the work commitment.

Accreditation

Laboratory accreditation is a procedure by which an authoritative body gives formal recognition that a laboratory is competent to perform specific analyses. It is achieved through external audits against internationally recognized and available standards. ISO Guide 17025 has gained worldwide acceptance as a standard for accrediting testing and calibration laboratories. Accreditation, however, is not a guarantee that a laboratory produces acceptable analytical results. Accreditation ensures competency, not performance; satisfactory participation in proficiency exercises demonstrates the ability to provide acceptable analytical results. Proof that any given analysis is of acceptable quality must be provided with every analysis through the use of accompanying controls, standards, and reference materials.

Documentation

Documentation is the evidence, initially written or printed but now often computer generated, that supplies the proof that statements are correct or that work was performed as stated. The most carefully performed analysis may be invalidated if the analytical work and the associated results are not properly documented. The degree of documentation required depends on the type of work being performed and the customer's needs. Once this has been decided, the documentation must be complete, contemporaneous, and accurate. Lack of documentation may result in a refusal to accept the work or may be the basis for refusal of payment, and in cases in which the end user is the "legal system," lack of documentation may render the data inadmissible in court.

Listed below are examples of the types of information that need to be included in the laboratory record in order to substantiate analytical measurements. This list is not comprehensive; it is an overview of the records to be included in a documentation trail in a specific laboratory. The documentation should be readily available to an auditor.

- An approved master quality document detailing the quality program for the laboratory.
- The current approved written procedure for each essential laboratory activity from the receipt of the laboratory sample to the reporting of analytical results. Procedures cover a range of topics such as analytical methods, instrumentation calibration and maintenance, quality control, safety and health, glassware cleaning, maintenance of microbial cultures, test sample preparation, data reduction, control charting, and analyst training and qualifications.
- Documentation demonstrating the ability to perform satisfactorily each method used in the laboratory. This includes compendial methods such as those in *Official Methods of Analysis of AOAC INTERNATIONAL*, *United States Pharmacopoeia* and *National Formulary*, and the *Food Chemicals Codex*, and the corresponding national official compendia whose use has been authorized by laws or regulations. Noncompendial methods and those developed in-house or acquired from other sources, require a higher level of verification than do compendial methods, particularly with respect to applicability to a

specific analysis. Although all of these methods may have been validated, documentation of the ability of a specific analyst within a specific laboratory to perform the methods is required.

- Documentation demonstrating performance checks, calibration, and routine maintenance of each instrument used in the laboratory.
- Documentation of validation and approval of computer-generated spreadsheets used in calculations of analytical results.
- Documentation that calibration standards are traceable to a recognized source. Traceability is the property of a result of a measurement, or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons, all having stated uncertainties.
- Documentation of receipt, storage, and each transfer of the laboratory sample. "Storage" includes special conditions of temperature, humidity, and time, when these conditions are critical to the stability of the analyte of interest.
- Documentation of any deviation from procedures. Justified deviations from written procedures must be approved.
- An up-to-date signature list that includes the name of each person who is qualified to sign official documents.
- Records of the relevant qualifications, training, skills, and experience of the technical personnel. These records must include internal and external education, and verification of performance of applicable methods and techniques.
- For each analytical run, a record detailing (by unique identification number when appropriate) the equipment, reagents, solutions, calibration standards, critical times/temperatures, test sample numbers, weights, volumes, chromatographic conditions, instrument settings, etc. used in the analysis. Entries must be legible and corrections properly made. All analytical records must be independently reviewed and approved. The record should provide sufficient information to allow satisfactory repetition of the analysis under the original conditions.
- A record of major steps in the analysis, such as weighing, digesting, diluting, data reduction, and data entry, as well as the name of the person who performed them.
- Unique, traceable identification numbers for standard materials. Prepared solutions and standards must be traceable to the original manufacturer's lot number. They must be used before their assigned expiration dates.
- All sets (runs) of replicate analyses and their controls and standards need to be identified and associated with a unique laboratory sample number. This unique number must appear on all documents related to that laboratory sample, including instrument outputs and worksheet attachments.

System Suitability

An important concept designated as "systems suitability" has evolved in chromatographic and instrumental analyses to permit use of columns and instruments that may differ somewhat from each other and from the initial specifications. The desired output is defined in terms of such properties as the relative standard deviation of repeated injections of a standard solution, peak shape or symmetry, resolution from an internal standard or associated analyte, ratio of peak height to peak width at a specified fractional peak height, peak-to-noise ratio, sensitivity (signal intensity per unit concentration), and similar properties. Column and solvent composition or instrument settings may be adjusted to obtain acceptable output within predetermined parameters. In such cases, the system suitability specifications and the settings used to attain the desired output must be documented.

Conclusions

A laboratory quality assurance program ensures that a complete history is created of each laboratory sample from its receipt in the organization to the submission of the final report. The documentation typically contains a statement of the time, location, and processing of the material as well as an inventory and identification of all reagents, supplies, equipment, and instruments used in the procedure. Secondary support operations, such as standardizations, calibrations, and computer programs, must be traceable to their primary documentation. All results must be in statistical control as demonstrated by appropriate charting techniques, and there must be an organizational infrastructure capable of supporting quality and accreditable analytical work.

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