Laboratory Quality Control, Statistics, and Measurement Uncertainty

Student/Instructor Guide

January 18, 2017

Table of Contents

Instructional Preparation Guidelines

Items contained in blue text are instructor notes and can be "hidden" for a cleaner look for the students.

Presentation Methods

Classroom

Evaluation Methods

Pre-Course Assessment

Post-Course Assessment

Homework and Quizzes: Because of the short duration, homework may not be applicable to this course.

Optional – Instructor should provide additional data sets from a local laboratory for student classroom work beyond what is included in the course.

Training Aids

None identified

Associated Training Materials

Whiteboard

Calculators or access to a computer with Excel

Notes to Instructor

Make copies of references available to students to use as additional materials for study.

References

US. Department of Energy. DOE Quality Systems For Analytical Services. Vol. 2.9. May 2013. Web. Jan. 2017.

Cooper, Greg. "Basic Lessons in Laboratory Quality Control." Quality Control. Bio-Rad Laboratories, Inc., Apr. 2008. Web. Dec. 2016.

Title - Slide 1

Introduction

1. **Introduce Self**

   Introduce self and Break Ice

2. **Learning Objectives**

   Hand out and review Learning Objectives

3. **Overview**

   Describe to the students how the course is to be taught and evaluated.

4. **Motivator** – What's In It for Me? Laboratory technicians must have a firm understanding of the quality control and statistics that are used to ensure quality data is released from the lab. Their role in the process cannot by under-estimated.

5. **Questions**

   Student Background

   Inquire to find out what kind of background the students may have to help tailor the discussions.

   Student Questions

   Convey to the students the ability to feel free to ask questions at any time.

Course Objectives

Objective Review – Slides 2 through 5

Discuss the course objectives

TO 1 – Discuss a laboratory quality assurance plan

EO 1.1 – Define quality assurance

EO 1.2 – Describe the elements of a laboratory quality assurance plan

EO 1.3 – Discuss the importance of a laboratory mission statement

EO 1.4 – Explain how laboratory safety is incorporated in a quality assurance plan

TO 2 – Discuss and use the basic elements of a laboratory quality control program including basic statistics and tools.

EO 2.1 Explain what a quality control program is and why it is important.

EO 2.2 Define and apply the following terms associated with a laboratory quality control program:

- Quality Control Samples
- Mean
- Standard deviation
- Control Charts
- Method Blanks
- Relative Percent Deviation
- Matrix Spike and Percent Recovery

EO 2.3 Given a data set, calculate the mean and standard deviation.

EO 2.4 State how confidence levels are used to produce a quality control chart.

EO 2.5 Given a data set, create a quality control chart showing the 2 and 3 sigma data lines.

EO 2.6 Given a quality control chart, identify out of limit data.

EO 2.7 Identify and differentiate random error and systematic error.

EO 2.8 Given a quality control chart, identify and differentiate shift and trend in a data plot.

EO 2.9 Describe the ways in which a laboratory technician is involved in a laboratory control program.

TO 3 – Discuss radiochemistry laboratory measurement uncertainty

EO 3.1 State why radiochemistry measurement uncertainty is calculated differently.

EO 3.2 Describe what factors may be included in a radiochemistry uncertainty calculation.

EO 3.3 Describe how radioactive measurement uncertainty can be improved.

Quality Assurance

Quality Assurance – Slide 6

Every laboratory is required to have a quality assurance plan. Quality Assurance (QA) is defined as an integrated system of activities involving planning, quality control, quality assessment, reporting and quality improvement to ensure that a product or service meets defined standards of quality with a stated level of confidence.

A formal QA plan can be a useful foundation document from which to derive quality control and assessment guidelines for all methods run within a lab operation. In addition to QC guidelines, a QA plan should contain a laboratory mission statement, overall QA objectives, an organizational chart, a code of ethics, training and safety practices and procedures. This course provides detailed lessons in the objectives and training aspects of a QA plan general understanding of the other elements listed.

Laboratory Mission Statement

Mission Statement – Slide 7

A mission statement defines a lab as what it does and established the baseline for the culture. It can also be viewed as a declaration of the core purpose and focus and communicate a sense of direction for the entire organization. The mission statement defines the purpose and place for the laboratory as well as setting the culture.

Organizational Chart

Typical Organizational Chart – Slide 8

A lab is led by individuals who themselves have demonstrated that they understand what it takes to succeed. It is important for the individual workers to be able to place a face with a name and can ask questions of the correct personnel. By having an organizational chart, the workforce understands where they fit in the organization and see where they can go if they too have the energy and commitment to lead the group. The top down approach to an organizational chart allows everyone to visually understand where the responsibility lies and where the decisions come from.

Safety Practices

Lab Safety – Slide 9

Typically, laboratories will have a safety program and chemical hygiene plan that spells out the procedures and guidelines for safe work. The quality assurance plan will refer to these documents and make an overall statement of the laboratory's safety objectives.

Quality Assessments

Assessments – Slide 10

Assessments serve to review the laboratory data and processes to identify errors, recommend corrections, and ensure the quality assurance plan elements are followed. Many laboratories use these assessments to adjust and ensure the data quality objectives are still aligned with the customer requests. Both internal and external assessment are used for this purpose.

Internal assessments are more common because they involve members of the organization that already understand the operations and can more quickly identify areas of improvement and can most efficiently affect the change. Internal assessments are also typically less costly.

External assessments will involve outside entities, usually in the same industry and will compare the data and quality to similar laboratories or against a known set of objectives. Some customers will require external assessments as part of the laboratory's quality assurance plan. External assessments tend to be more of an impact on a budget and require considerable coordination and time. The external team will need a space, time to review procedures and processes, and facility support to produce the reports as part of the assessment.

Laboratory staff must understand that assessments are a part of the laboratory quality and work with the teams to ensure accuracy and truth are used as the input to the process.

Quality Control Program

QC Program - Slide 11

For a lab to be consistent and trustworthy, a good QC program must be followed and adhered to for every aspect of the facility. Stress to the students the need to ensure that policies and procedures must be followed.

A QC program is a set of procedures and processes that intends to ensure that the results or products adhere to a defined set of quality criteria or meets the requirements of the client or customer. The QC program is a part of the Quality Assurance Plan. Laboratories can use several methods to meet the quality objectives established in the plan.

One of the most important ways to establish sound laboratory QC is using well-trained personnel and tested procedures. Personnel are qualified to perform the work through multiple runs of analysis and the procedures are verified and validated against known sources to ensure the results are reproducible.

Certified standards are analyzed along with samples that are submitted to the lab. These standards are provided a Certificate of Analysis from the manufacturer that provides information regarding the quality of analytes (or isotopes) in the standard. Once the results are produced, the data for the standard is processed through data confidence checks. The standard data is compared to test results to ensure it is within specified limits. This data is plotted on control charts. Other analysis data such as that from replication or duplication of samples and adding known quantities of material to samples (spiking or tracing) are also ways to check the quality of the results of sample analysis.

Laboratory instruments also have rules governing calibration limits and testing to ensure the data is accurate. Many labs check instrument calibrations on a specified cycle and require recalibration when results are not within limits.

Laboratories may hire outside entities to duplicate their results and ensure limits are applied to the duplicate results. These programs are referred to as intra- or inter-laboratory analysis and can help prevent a single laboratory from becoming a statistical island. If the data produced by the two laboratories is not reproducible within acceptable limits, results can be considered invalid and require repeat work. This type of program should be used in addition to the internal program, not as the only source of QC.

Using trained personnel, tested procedures, data confidence, and external data assessments, laboratories ensure their customers that the data is accurate, consistent, and reliable.

Quality Control Program Terms and Definitions

Quality Control Samples

QC Samples – Slide 12

To assure that a test run is valid and results are reliable, quality control samples should be used in the performance of each analysis. The quality control samples should be treated in the exact same manner as the test samples and are used to validate the test run. Quality control samples are usually required to be run as part of a batch of samples.

Mean

Mean - Slide 13

Some data provided but instructor can create multiple sets of data for use by the student. This data should be used in a Lab setting and used to calculate mean, standard deviation, and confidence levels. Also, these charts can be used to help the student identify out of control values, trends, and shifts in the data in later objectives.

What is the mean of the following data sets? – Slide 14

Have the students calculate the mean using the data provided.

Set 1 –145

Set 2 – 4.3

Set 3 – 11.38

The mean (or average) is the laboratory's best estimate of the analyte's true value for a specific level of control. The mean is simple calculation where the sum of the sample results is divided by the total number of samples. A QC sample mean is used to compare QC samples analyzed with a set (batch) of sample using a control chart. The calculation for determining mean is shown below:

$$\overline{X} = \frac{\sum X}{N}$$

Where:

N represents the total number of data points.

ΣX represents the sum of all data points.

Standard Deviation

Standard Deviation - Slide 15

What is the standard deviation of the following data sets? – Slide 16

Have the students calculate the standard deviation using the data provided.

Set 1 –11.8

Set 2 – .47

Set 3 – .443

Standard deviation (precision) represents how close numerical values (i.e., QC values) are in relation to each other. The standard deviation is used to determine the amount of consistency that is expected from future testing of QC samples.

Standard deviation is calculated for QC samples from the same data used to calculate the mean. It provides the laboratory an estimate of the test consistency. The reproducibility of a test may be consistent (have a low standard deviation) or inconsistent (high standard deviation). Results that are not consistent may be due to human error, procedure issues, instrument malfunctions, or sample inconsistencies. It is desirable to get repeated measurements of the same specimen as close as possible. The calculation for standard deviation is shown below:

$$S = \sqrt{\frac{\Sigma(X - \overline{X})^2}{N}}$$

where S = the standard deviation of a sample,
Σ means "sum of,"
X = each value in the data set,
$\overline{X}$ = mean of all values in the data set,
N = number of values in the data set.

Confidence Levels

Confidence Levels - Slide 17

What are the 2σ and 3σ confidence levels for the following data sets? – Slide 18

Have the students calculate the 2σ and 3σ confidence levels using the data provided.

Set 1 –23.6, 35.5

Set 2 – 0.93, 1.4

Set 3 – 0.886, 1.33

Have students save all data for use with the control charts.

The confidence levels (sigma or σ) used for a data set are directly associated with the standard deviation. The 1σ confidence level is equal to the standard deviation and identifies that 68% of data will fall within this range. In a typical lab, the QC sample control chart limits are set at 2σ and 3σ of the data used to create the chart. In a normal distribution, 95% of all data should fall within ±2σ and 99.7% should fall within ±3σ. As only 0.3%, or 3 out of 1000 points, should fall outside the ±3σ limits, any value outside of ±3σ is assumed to be associated with a significant error condition. Results for that sample or batch of samples should not be reported. Laboratory rules governing rejection of results are based on these limits and other properties of the analysis that are determined by the lab.

Method Blank

Sample Batching – Slide 19

Briefly review sample batches and what makes them up.

Method Blank – Slide 20

Discuss the importance of blank analysis and how a contaminated sample batch can alter the results (counts not included or falsely included in a sample result).

Method blanks are often used in analysis, especially radiochemistry analysis, to check for cross-contamination of samples during processing. The method blank is used to evaluate contamination resulting from the entire preparation and analytical procedure. Typically, a sample of water (or other matrix acceptable solution) known to contain no traces of the results in question is included in a sample batch. It is analyzed in the same manner as the samples. The minimum requirement is usually one per batch. The results of the blank are expected to show no detectable amounts the analyte(s) of interest. Rules governing detectable amounts on method blanks are set by each laboratory but, a value of 10% of the highest activity sample is typical. A contaminated blank is indicative of a loss of sample and can cause sample analysis to be unexpectedly low.

Relative Percent Deviation

Duplicate – Slide 21

Instructor should provide several examples of how % RPD can be used to validate a set of data.

The relative percent deviation (% RPD) is a standard QC procedure and defined as the demonstration of precision or the reproducibility of two independent samples. This is also referred to as a sample duplicate. If precision is acceptable, the two levels obtained should be quite close, usually within 15% of each other. The duplicate analysis is usually a sample being checked. But it can also be a QC sample or a sample where a known amount of chemical was added, called a Matrix Spike (MS) and Matrix Spike Duplicate (MSD). If a duplicated sample is homogenous (same throughout), the two analytical results should agree. The % RPD checks the homogeneity of the sample and the ability of the analyst to be precise.

There are several factors that can adversely affect precision. The most common is if the analyte concentration is low or close to the detection level. At this point a small difference in levels will lead to an elevated % RPD. For example, if two results were found to be 0.01 and 0.02 ppm, the % RPD would be 66.7%. However, if two results were 5.01 and 5.02 (same absolute difference of 0.01 ppm), the % RPD would be 0.020%. The duplicate (precision) sample is usually carried out with each batch of ten samples. % RPD is simply the difference between two measurements divided by the average of the two measurements.

Duplicate Calculation – Slide 22

Result of calculation = 0.04

The calculation for % RPD is shown below:

$$\%\,RPD = \left(\frac{|X1 - X2|}{\overline{X}} \right) \times 100\%$$

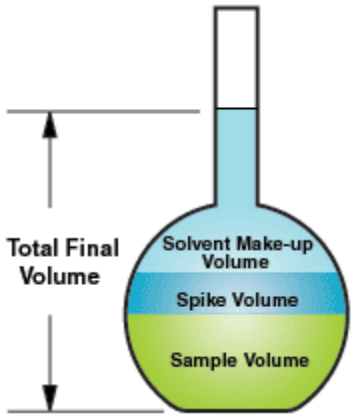
where:

X1 = assayed value of a given nuclide from the first measurement
X2 = assayed value of a given nuclide from the duplicate measurement
$\overline{X}$ = mean value of X1 and X2.

Matrix Spike and Percent Recovery

Matrix Spike – Slide 23

Unlike the QC sample which uses an uncontaminated sample matrix with a known value, the matrix spike (MS) sample consists of the original sample matrix to which a known amount of analyte is added. The sample is "spiked" and results can be compared to the known value, reported in percent recovery of the spiked amount. This technique can provide valuable data for the analysis process. Analytes of interest may be lost as a part of the chemistry or techniques used. A typical range of 75% to 125% is expected, but individual methods may adjust the limits.



Matrix Spike Calculation – Slide 24

Result of calculation = 0.84

The calculation for matric spike recovery is shown below:

% Spike Recovery =

[(Spiked Sample Result - Unspiked Sample Result) * 100%] / [Amount of Spike Added]

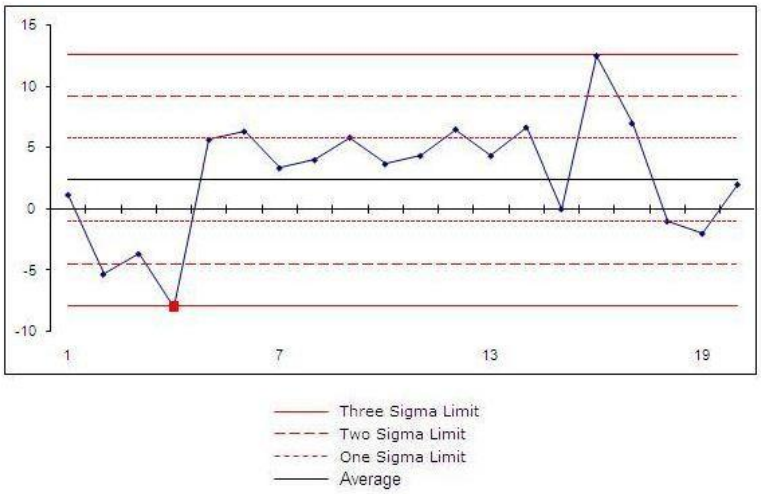
Quality Control Charts

Typical Control Chart - Slide 25

Have the students use the previously calculated data to establish a control chart. Excel or graph paper can be used for this evolution.

Quality control charts provide a visual reference of data trends. Data from QC samples, % RPD calculations, and % spike recoveries are plotted and tracked on a chart and provide an image. This provides a visual representation as to where they stand as compared to the expected results and past results.

Laboratories use the charts to determine if an individual data point confirms or denies the result as acceptable. QC samples, duplicate results, and matrix spike recoveries can be depicted on QC charts.



Types of Error

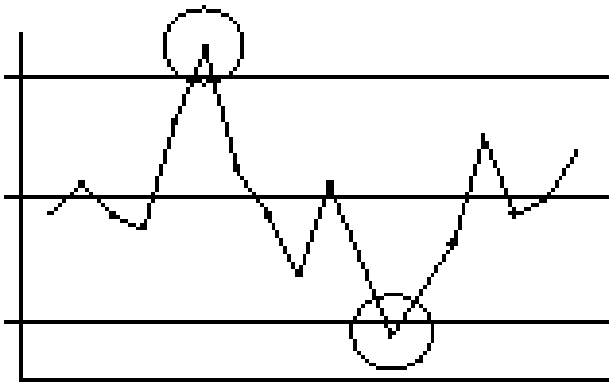
Measurement errors can be divided into two components: random error and systematic error.

Random Error

Analysis Error: Random – Slide 26

Use the whiteboard or other means to show a normal distribution bell curve as it relates to this topic.

Technically, error is any deviation away from an expected result. Random error is always present in a measurement, unpredictable, and it cannot be eliminated. It may be caused by instrument response, human errors, weather, etc. For QC **r**esults, any positive or negative deviation away from the calculated mean is error. Acceptable (or expected) random error is error that is less than 3σ. Unacceptable (unexpected) random error that is any data point outside the expected population of data (e.g., a data point outside the $\pm 3\sigma$ limits).



For most laboratories, any result outside the 3σ boundary will place an analysis "out of control" and will render the results of that sample or batch of samples unacceptable. Two consecutive points between 2σ and 3σ on the same side of the mean also identifies unacceptable results. In either case, laboratories may require the sample or batch of samples to be repeated. To bring an analysis back under control, some number of data points within the control limits are required. Typically, two consecutive QC points within the control band are required to return the analysis to normal.

Systematic Error

Analysis Error: Systematic – Slide 27

Systematic error is predictable and typically constant or proportional to the true value. If the cause of the systematic error can be identified, then it usually can be eliminated. Systematic errors are caused by faulty calibration of measurement instruments, inferior methods of observation, or environmental interferences during the measurement process, and always affect the results of an experiment in a predictable direction. Incorrect zeroing of an instrument leading to a zero error is one example of the introduction if systematic error in instrumentation.

Trend

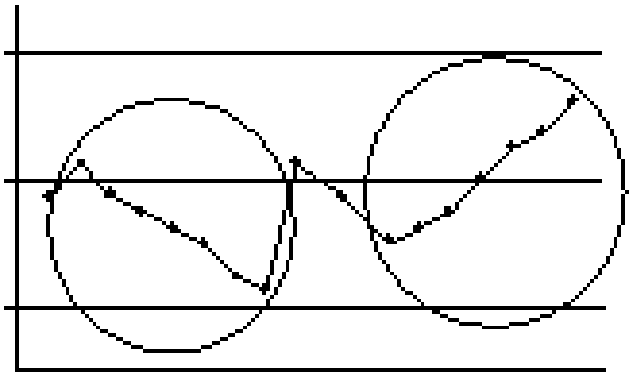
Trend – Slide 28

A trend indicates a gradual loss of reliability in the test system. Trends are usually subtle and most noticeable by reviewing sample data over an extended period. Typically, any data that moves in the same direction for 7 or more points (above, below, or across the control limit line) is considered a trend.

Causes of trending may include, but not limited to:

- Deterioration of the instrument (e.g. light source)
- Accumulation of debris (e.g. in sample/reagent tubing, on electrode surfaces)
- Aging of reagents
- Deterioration of control materials
- Deterioration of calibration

An example of a downward and an upward trend in data is show below:



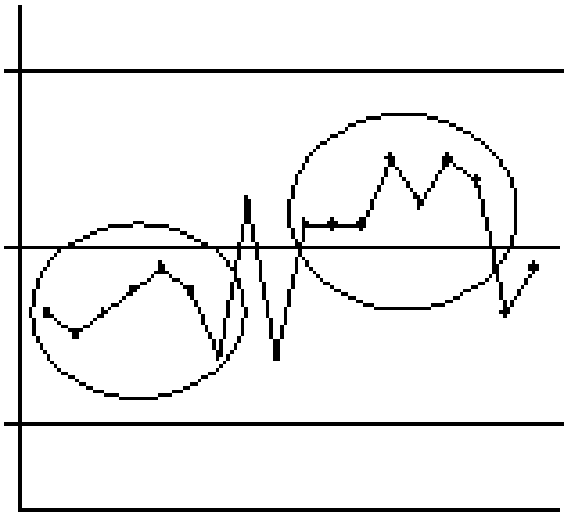
Shift

Shift – Slide 29

Abrupt changes in the control mean are defined as shifts or bias. Shifts in QC data represent a sudden and dramatic positive or negative change in performance. Usually, seven or more consecutive points above or below the calculated mean is considered a shift. Shifts may be caused by:

- Change in reagent formulation
- Change of reagent lot
- Major instrument maintenance or recalibration
- Change in room temperature or humidity
- Failure in the sampling system
- Failure in reagent dispensing system
- Inaccurate calibration/recalibration

An example of a shift in data is represented below:



Laboratory Technicians

Laboratory Technicians – Slide 30

Discuss with the students Conduct of Operations (Con Ops) expectations and how that plays a role in the QC program.

Lessons learned should be applied here.

Laboratory technicians play an important role in a quality control program. From following procedures to proper use of tools and techniques, the laboratory technician can have an impact on the data that is produced. In addition, laboratory technicians are the first line of defense when troubleshooting is required. The laboratory technician may see or hear something during the process of the analysis that will help the chemists, scientists, or management team identify or correct problems. For example, if a technician is required to think outside the box during performance of a procedure to produce acceptable results, that information should be relayed to the procedure author to ensure the change is instituted for all involved. Consistency is expected in the performance of an analytical procedure. In addition, all technicians performing a procedure should be expected to perform it the same way.

Laboratories must have a well-trained workforce. Using classroom and on-the-job training (OJT), technicians learn the techniques and the equipment to produce consistent results. A good OJT program will have technicians watch experienced workers perform the analysis, then be guided through the steps, and finally perform it successfully multiple times with consistent results independently.

Laboratory technicians are required to follow procedures. By doing so, the results from one technician to another can be compared to identify weaknesses. Several laboratories institute proficiency assessments to ensure that a technician’s skills and abilities remain high enough for consistent results.

When laboratory procedures are developed, technicians are used to validate the data. Having several individuals perform the same test is a good way for the scientists and chemists to determine if the procedure has the rigor and flexibility needed perform consistently. Procedure validation also establishes the control limits for the procedure.

Radiochemistry Laboratory Measurement Uncertainty

Measurement Uncertainty – Slide 31

Laboratory measurements, even under the closest scrutiny, provide normal (expected) error. This was discussed in the standard deviation section. Radiochemistry laboratories cannot assume that these errors are consistent, especially when regulatory limits and expectations are involved in the reporting of data.

Instead of focusing on the normal distribution of random error, laboratories will calculate the expected error based on all the inputs, using what is called total propagated error. These inputs include:

- Instrument error
- Measurement errors (from multiple dilutions or non-calibrated devices)
- Counting error
- Radioactive half-life

When all errors are calculated individually, much larger ranges of uncertainty can be seen, but still in the 95% confidence level. This is typically used when multiple measurements are not possible as they are for quality control standards. Several variables are considered when calculating the uncertainty of a radiochemistry measurement.

In radiochemistry counting, short count times can significantly contribute to error. This must be taken into consideration when determining the total uncertainty for an analysis. Doubling the count time can reduce the uncertainty of a measurement by more than one-half when the number of counts and the time are used in the uncertainty calculation.

In many cases, a sample must be diluted multiple times, either for handling considerations (dose concerns) or to properly separate an isotope of interest. Human performance errors and measuring device errors are introduced each time, and by considering this, a more accurate range of data can be assumed.

Radioactivity counting theories and instrumentation is inherent to errors from voltage changes, light emission, radioactive decay uncertainties, etc. Radiochemistry calculations for uncertainty take these factors into account.

Total Propagated Error – Slide 32

Use this slide to demonstrate the complexity of total propagated error. This example considers only two measurements. A typical radiochemistry calculation may have 6 or more individual measurement errors to account for. Stress that this is NOT testable.

Radiochemistry laboratories use total propagated error to more accurately reflect the conditions at the time the data is produced.

To improve the uncertainty values, laboratories can extend count times, use calibrated or certified measuring equipment, and ensure procedures address areas of human error. Because some radioactive counting errors cannot be reduced, areas where the laboratory can have an effect is typically where errors are addressed. The use of tight tolerances on control charts can be used in cases where uncertainties may exceed levels prescribed by customers and allow the laboratory to provide the quality data that is expected.

Course Review

Questions – Slide 33

Objective Review - Slide 34

The summary should provide a recap of what was covered.

A. Restate the Motivator
B. Restate the Terminal Objective
C. Review Enabling Objectives
D. Add Other Summary Items as Necessary

Include these elements in the order that best promotes learning:

Review Objectives and Major Learning Points - Tell them what you told them. Don't re-teach the lesson.

Elicit Questions - Ask for all unanswered questions related to the topic.

Connect to the Job - Explain how the transfer of the knowledge and skills back to the job supports performance.

Answer All Questions - Always.

Punctuate the Finish! – Revisit the motivator, "What's In It For Me?"