A PRIMER *on* QUALITY *in the* ANALYTICAL LABORATORY

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Preface

This work is intended to be, as the title implies, a brief introduction to the principles of quality that are important for workers in a modern industrial analytical chemistry laboratory. It is intended to be a textbook for students preparing to become technicians or chemists in the chemical process industry. It is intended to be a quick reference for new employees in an industrial laboratory as they begin to learn the intricacies of regulations and company policies relating to quality and quality assurance. It is also intended for experienced laboratory analysts who need a readable and digestible introductory guide to issues of quality, statistics, quality assurance, and regulations.

Traditionally, the education that chemists and chemistry laboratory technicians receive in colleges and universities does not prepare them adequately for some important aspects of the real world of work in their chosen field. Today's industrial laboratory analyst is deeply involved with such job issues as quality control, quality assurance, ISO 9000, standard operating procedures, calibration, standard reference materials, statistical control, control charts, proficiency testing, validation, system suitability, chain of custody, good laboratory practices, protocol, and audits. Yet, most of these terms are foreign to the college graduate and the new employee.

This book fills the void that currently exists for these individuals. It is intended to be a textbook for courses that exist or will exist in colleges and universities as teachers begin to address this gap between education and practice. But it will also be a valuable resource as new laboratory workers begin their jobs and become overwhelmed by the myriad of laboratory practices that they never learned about in school but are extremely important to their new employer.

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Dedication

First, I dedicate this effort to my wife of 25 years, Lois, who has given me so much love for such a long time, providing such genuine happiness that it is simply overwhelming. Second, I dedicate this book to my three daughters, Angie, now known as Sister Mary Emily, and Jeanie, and Laura. In all their extraordinary goodness, I want to shout to the world what a huge blessing they are — more than any father could ever hope for. Finally, I thank my almighty Father from the bottom of my heart for giving me my faith, my family, and my talents. All good things come from Him.

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1 *Introduction to quality*

As citizens of the modern world and as consumers in a comfortable society, we have come to expect the highest standards of quality in all aspects of our lives. When we buy a new car, we expect that we can drive it for tens of thousands of miles free from defects in workmanship. When we elect our government officials and pay our taxes, we expect a responsive government, schools with high academic standards, air and water free of pollution, and an infrastructure that is solid and in good repair. When we pay our utility bills, we expect to always have electricity, heat, water, and a working sewer system for our homes. A quality lifestyle means excellence in consumer products, environment, health and safety, government services, and so on.

Each individual government agency and each individual private company define the terms by which the demands fro quality are met within their own enterprise. A construction company will specify a particular grade of lumber in the homes it builds. A department store will stock and sell consumer products that relfect the reputation it wihses to sustain with the public relative to quality and price. A government health agency seeks to provide the health care policies and services its citizens have come to demand. A pharmaceutical company purchases raw materials, maintains a manufacturing area, hires employees, and assures the quality of its products so that it will continue to function indefinitely as a producer of drugs and medicines that the public will want to buy.

Some of these government agencies and private companies, because of the nature of their business, will utilize the services of an analytical chemistry laboratory as part of their overall need to assure the required quality operation. For example, municipal governments will employ the use of an analytical chemistry laboratory to test their water supply on a regular basis to make sure it is free of toxic chemicals. The pharmaceutical company will house an analytical chemistry laboratory within its facility to routinely test the products it produces and the raw materials that go into these products to make certain that they meet the required specifications. A fertilizer plant will utilize an analytical chemistry laboratory to confirm that the composition of its product meets the specifications indicated on the individual bags of fertilizer. Companies that produce a food product, such as snack chips, cheese, cereal, or meat products, will have an analytical chemistry laboratory as part of their operation because they want to have the assurance that the

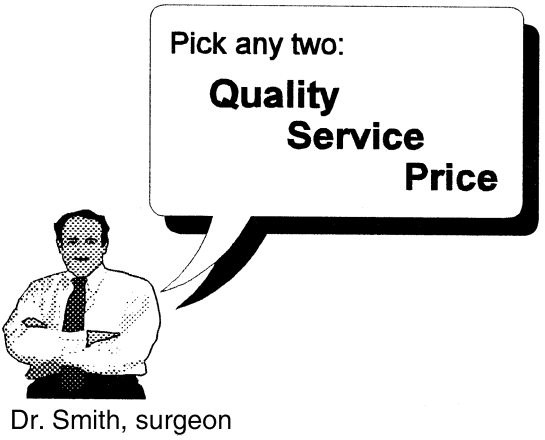

Figure 1.1 Given a choice, people will almost always pick quality.

products they are producing meet their own specifications for quality, consistency, and safety, as well as those of government agencies, such as the Food and Drug Administration.

In these cases, the analytical laboratory is one component of many that plays a part in a total quality scheme, or **Total Quality Management, TQM**. TQM is a concept wherein all workers within an enterprise, from upper management to custodians, are managing their own particular piece of the puzzle with utmost concern and care for quality — quality in design, quality in development, quality in production, quality in installation, and quality in servicing. Besides the laboratory, components may include manufacturing, production, research, accounting, personnel and physical plant — virtually all aspects of an operation as depicted in Figure 1.2. The implementation of TQM emphasizes such things as (1) major paradigm shifts, if necessary, possibly meaning major cultural changes in what are routine practices and thought processes, (2) a focus on the customer, (3) a focus on improving efficiency and reducing waste, (4) a process of incorporating quality ideals in all products and processes and establishing quality criteria for all components of the enterprise, (5) a focus on training and lifelong learning, 6) a progressive management style suggesting a "team approach," (7) policies that work to identify and solve problems and constantly evaluate outcomes, 8) policies that encourage and reward employees, (9) a structure and climate conducive to quality improvement, and (10) the constructive analysis of failure. The system in place to implement TQM is often termed a **Quality System**, which consists of an organization's structure, responsibilities, procedures, and resources required for this implementation. The key lies with

upper management and instillation of a positive attitude toward quality on the part of each individual employee. It then becomes a personal responsibility of each member of the team, including the laboratory personnel.

Figure 1.2 In a Total Quality Management system, all aspects of an enterprise, including managers, accountants, lab analysts, custodians, manufacturing personnel, researchers, production workers, and support stafff are focused on quality.

Laboratory personnel are as intimately involved in TQM as any other employee and aspects of their work touch on all of these ten points. The manner in which TQM principles specifically apply to laboratory personnel, however, is unique to them. They are concerned about analysis methods, choice of laboratory equipment, error analysis, statistics, acquisition of laboratory samples, etc.

How, specifically, does an analytical chemistry laboratory assure the quality of its work? The purpose of this monograph is to discuss the processes utilized by analytical chemistry laboratories through which the results reported to their customers and clients, whether internal to their company or external, are assured to be of the highest quality and greatest accuracy possible. The methods, procedures, and techniques employed by these laboratories for the individual analyses that they perform are what are called into question and tested. In most cases, methods of statistics must be applied because the measurement techniques are subject to errors that often cannot be identified or compensated.

2 *Quality standards and regulations*

In today's world, the economies of nations are intertwined. Raw materials mined or manufactured in one country are sold in another. Industrial, agricultural, and other products manufactured in one country are sold in another. In the U.S., foreign products from automobiles to toys are commonplace. The American farmer sells grain to other countries. Middle Eastern countries sell crude oil to the U.S. and other countries. The list is long, and thus the demand for quality is global.

For this reason, an international standards organization governing global quality has been created. It is called the **International Organization for Standardization** or **ISO**, and is a worldwide federation of national standards bodies. The purpose of the organization is to promote common standards developed by its technical committiees. Each member body has a right to be represented on a committee. The U.S. member body is called the **American National Standards Institute**, or **ANSI**. In turn, the **American Society for Quality**, or **ASQ**, is the U.S. member of ANSI responsible for quality management and related standards. The ISO standards are generic and apply to any industry (Figure 2.1).

The current set of quality standards endorsed by the ISO is the **ISO 9000** series. This series is a set of documents drafted by the member delegates and is intended primarily to ensure that the exchange of goods between companies is of high and internationally acceptable quality. ANSI and ASQ have adopted ISO 9000 word-for-word for use in the U.S. The original documents, published in 1994, are designated ISO 9000, ISO 9001, ISO 9002, ISO 9003, and ISO 9004. The corresponding ANSI/ASQ designations are ANSI/ASQ Q9001-1994 through ANSI/ASQ Q9004-1994. While the ISO standards address quality management and quality assurance, they do not provide test methods or quality control procedures for laboratories. However, ISO, in conjunction with the International Electrotechnical Commission (IEC), has published ISO/IEC Guide 25, which lists the general requirements for the competence of calibration and testing laboratories. The ISO series is important because it can be the basis by which laboratories, indeed entire

Figure 2.1 Official logos for ISO and ANSI, the two organizations that impact quality in the U.S.

companies, become internationally registered, accredited, and/or certified. ISO 9000 certification will be discussed in Section 9.

The ISO has also produced a set of quality standards specifically for environmental management. This is the ISO 14000 series. The areas addressed by ISO 14000 are Environmental Management Systems, Environmental Performance Evaluations, Environmental Auditing, Life Cycle Assessment, and Environmental Labeling.

Besides ISO standards, pharmaceutical companies in the U.S. are governed under certain circumstances by separate federal regulations adopted by the Food and Drug Administration (FDA). These regulations are known as **Current Good Manufacturing Practices**, or **cGMP**. The cGMP were developed to ensure that pharmaceutical products are produced and controlled according to the quality standards pertinent to their intended use. The cGMP are found in Parts 210 and 211 of Chapter 21 of the Code of Federal Regulations (21 CFR 210 and 21 CFR 211). Also, U.S. environmental laboratories, pharmaceutical laboratories, and laboratories found within chemical companies in the U.S. are governed by separate federal regulations adopted by the Environmental Protection Agency (EPA) as well as the FDA. These regulations are known as **Good Laboratory Practices**, or **GLP**. The EPA GLPs are found in Part 160 of Chapter 40 of the CFR (40 CFR 160) and the FDA GLPs are found in Part 58 of Chapter 21 of the CFR (21 CFR 58). GLP will also be addressed in detail in Section 7.

3 *Principles and terminology of quality assurance*

First, one should distinguish between quality assurance and quality control. **Quality control** can be defined as the overall system of operations designed to control a process so that a product or service adequately meets the needs of the consumer. **Quality assurance** is the system of operations that tests the product or service to ensure compliance with defined specifications. In a candy factory, quality control would consist of the company procedures to ensure that the candy-making process is set up to be free of potential contamination sources, such as insects, hair strands, etc., while the quality assurance operations might simply consist of a random tasting of the product. For a company that manufactures basketball hoop and backboard units, the quality control operation might consist of regular inspection of the manufacturing operation and its components and processes, such as the welding process, to see that it is being carried out according to specification. Quality assurance would consist of a random testing of the finished products for strength, proper dimensions, etc. In an analytical chemistry laboratory, a quality control program would consist of the system in place to monitor the overall performance. Are the lab workers properly trained? Are the instruments properly calibrated? Are the key elements of the program being properly documented? A quality assurance operation consists of the laboratory testing of the company products, or an agency's samples, etc., to determine if they are within specification.

Consider what is termed the **sample**. A sample is a small portion of a large bulk system that is acquired and taken into the analytical laboratory in lieu of the entire system. For example, it is not practical to bring the entire contents of a 5000-gallon tank of liquid sugar solution used in a pharmaceutical preparation into the analytical laboratory for analysis. The small portion of the solution, perhaps a small vial, that is obtained for the analysis is called the sample, and that is what is taken into the laboratory for analysis. How well a sample represents the entire bulk system, and what fundamental issues of quality are involved when obtaining the sample are important questions and will be dealt with in Section 6. The process of obtaining the sample is referred

to as **sampling**. The component of the sample that is under investigation, and for which a concentration level is sought, is call the **analyte**.

The measurements made and results reported on the sample must be **valid**. This means that the sampling and measurement systems must be perfectly applicable to the system under investigation, the instruments and measuring devices used must be **calibrated**, and the data must be handled and the results must be calculated and/or reported according to nominally acceptable norms that are well grounded in scientific principles and facts. Accordingly, all sampling, measurement, and reporting schemes proposed or used for a given analysis must be **validated**, and it is often the full-time job of one or more experienced laboratory analysts to perform this **validation study**. To a certain extent, this work is a research project. After a new method is proposed for a given work, the analyst must execute the procedure repeatedly using a sample with an expected outcome in order to gather information relating to precision, accuracy, and bias. These latter terms are defined below.

The **measurement system** mentioned above consists of all the physical equipment, facilities, logistics, and processes that need to be configured in order to make the measurement that is needed. These can include sampling locations (from what parts of the whole bulk system does one take a sample), the actual taking of the sample (equipment and technique), the laboratory preparation of the sample, the instruments and equipment needed in the laboratory, and **calibration** and data handling methods. **Accuracy** is the degree to which the result obtained agrees with the correct answer. (Usually, the correct answer is not known.) **Precision** is the degree to which a series of measurements made on the same sample with the same measurement system agree with each other. **Bias** is an error that occurs over and over again (systematic) due to some fault of the measurement system. Precision, accuracy, and bias are illustrated in Figure 3.1.

Calibration is a procedure by which an instrument or measuring device is tested in order to determine what its response is for an analyte in a test sample for which the true response is either already known or needs to be established. One then either makes an adjustment so that the known response is, in fact, produced, correlates the response of unknowns with that of the known quantity, or, if the device or instrument is deemed defective, either removes the device from service permanently or effects repairs. For example, when calibrating a pH meter, one immerses the pH probe into a test solution whose pH is known (buffer solution) and then tweaks the electronics so that it gives that pH on the display. When calibrating a balance, one places an object of known weight on the pan. If the correct weight is displayed, the balance is calibrated for that weight of sample. If the correct weight is not displayed, one concludes that the balance is out-of-calibration and it is taken out of service. When calibrating a spectrophotometer, one measures the instrument's response for a series of known test samples, all of a different concentration, and plots the response vs. concentration (a so-

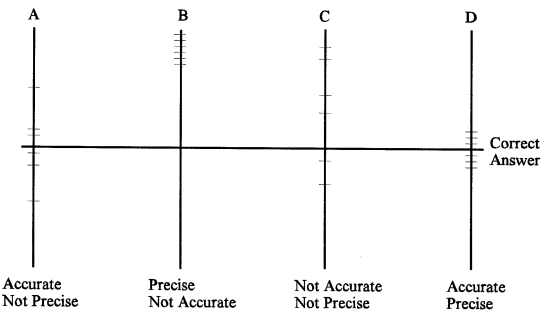

Figure 3.1 An illustration of precision, accuracy, and bias. When accurate but not precise, the measurements are bunched loosely around the correct answer (A). When measurements are bunched, but not around the correct answer, they are precise but not accurate, and a bias is indicated (B). When there is a large spread in the measurements and the mean is not near the correct answer, they are neither precise nor accurate (C). When accurate and precise, the measurements are bunched tightly around the correct answer (D).

called **calibration curve** or **standard curve**; see Figure 3.2.). If it is linear, the instrument is said to be calibrated and unknown samples can be correlated with their responses to give the results.

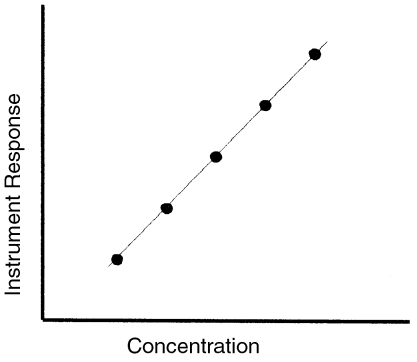

Figure 3.2 A calibration curve or standard curve.

At the end of Section 1, it was mentioned that measurement techniques are subject to errors, and bias was also mentioned. In general, errors are of three types: (1) those that are **systematic errors** and produce a known bias in the data, (2) those that are avoidable blunders that are known to have occurred, or were found later to have occurred, the so-called **determinate errors**, and (3) those called **random errors**, or also **indeterminate errors**, which are errors that occur, but can neither be identified nor directly compensated. Correction

factors can be applied to data resulting from systematic errors. Measurements resulting from determinate errors can be discarded. Random errors are dealt with by applying concepts of statistics to the data. Section 4 will deal with this very important aspect of quality assurance in an analytical laboratory.

4 Elementary statistics

4.1 Introduction

Accuracy in the laboratory is obviously an important issue. If the analysis results reported by a laboratory are not accurate, everything a company or government agency strives for, the entire TQM system, may be in jeopardy. If the customer discovers the error, especially through painful means, the trust the public has placed in the entire enterprise is lost. For example, if a baby dies due to nitrate contamination in drinking water that a city's health department had determined to be safe, that department, indeed the entire city government, is liable. In this "worst-case scenario," some employees would likely lose their jobs and perhaps even be brought to justice in a court of law.

As noted in the last section, the correct answer to an analysis is usually not known in advance. So the key question becomes: **How can a laboratory be absolutely sure that the result it is reporting is accurate?** First, the bias, if any, of a method must be determined and the method must be validated as mentioned in the last section (see also Section 5.6). Besides periodically checking to be sure that all instruments and measuring devices are calibrated and functioning properly, and besides assuring that the sample on which the work was performed truly represents the entire bulk system (in other words, besides making certain the work performed is free of avoidable error), the analyst relies on the precision of a series of measurements or analysis results to be the indicator of accuracy. If a series of tests all provide the same or nearly the same result, and that result is free of bias or compensated for bias, it is taken to be an accurate answer. Obviously, what degree of precision is required and how to deal with the data in order to have the confidence that is needed or wanted are important questions. The answer lies in the use of **statistics**. Statistical methods take a look at the series of measurements that are the data, provide some mathematical indication of the precision, and reject or retain **outliers**, or suspect data values, based on predetermined limits.

4.2 Definitions

Some definitions that are fundamental to statistical analysis include the following.

Mean: In the case in which a given measurement on a sample is repeated a number of times, the average of all measurements is an important number and is called the *mean*. It is calculated by adding together the numerical values of all measurements and dividing this sum by the number of measurements.

Median: For this same series of identical measurements on a sample, the "middle" value is sometimes important and is called the *median*. If the total number of measurements is an even number, there is no single "middle" value. In this case, the median is the average of two "middle" values. For a large number of measurements, the mean and the median should be the same number.

Mode: The value that occurs most frequently in the series is called the *mode*. Ideally, for a large number of identical measurements, the mean, median, and mode should be the same. However, this rarely occurs in practice. If there is no value that occurs more than once, or if there are two values that equally occur most frequently, then there is no mode.

Deviation: How much each measurement differs from the mean is an important number and is called the *deviation*. A deviation is associated with each measurement, and if a given deviation is large compared to others in a series of identical measurements, this may signal a potentially rejectable measurement (outlier) which will be tested by the statistical methods. Mathematically, the deviation is calculated as follows:

$$d = |m - e| \tag{4.1}$$

in which d is the deviation, m is the mean, and e represents the individual experimental measurement. (The bars (| |) refer to "absolute value," which means the value of d is calculated without regard to sign; i.e., it is always a positive value.)

Sample Standard Deviation: The most common measure of the dispersion of data around the mean for a limited number of samples (<20) is the sample standard deviation:

$$s = \sqrt{\frac{d_1^2 + d_2^2 + d_3^2 + \ldots}{n - 1}} \tag{4.2}$$

The term $(n - 1)$ is referred to as the number of **degrees of freedom**, and s represents the standard deviation.

Example 4.1

The percent moisture in a powdered pharmaceutical sample is determined by six repetitions of the Karl