Chapter 3

Metrology

Objectives

This chapter provides an overview of metrology, or the fundamental methods by which objects and phenomena are measured. The chapter will also discuss how metrology relates to biomanufacturing processes.

After completing this chapter the student will be able to:

- explain why traceable standards in a metrology program are important for ensuring regulatory compliance.
- define and contrast the following terms:
  - standardization and calibration
  - accuracy and precision
  - specifications and tolerances
- define the regulatory requirements and guidances for ongoing metrology programs.
- describe measurement traceability.
- outline the elements of a metrology program.
- describe a sample calibration process using a floor scale.

Terms

Accuracy: how close the value of a measurement is to its true value

Device Under Test (DUT): an object that is undergoing testing

Gross Human Error: a type of error caused by a person making a mistake, misusing equipment, blunders, or other similar occurrences.

Precision: the closeness of agreement between repeated measurements of the same quantity under the same conditions; also referred to as **repeatability**

Random Error: a type of error that causes scatter in the results of a sequence of readings; this is a measure of dispersion

Reverse Traceability: the ability to identify and recall, if necessary, all measuring instruments that were calibrated according to a given measurement standard

Specification: an explicit set of requirements to be satisfied by a material, product, or service; in metrology a specification is a documented statement of the expected performance capabilities of a group of identical measuring instruments that include statements of either accuracy or uncertainty

Standardization: the process by which a user adjusts an instrument or measurement system to a defined reading at the beginning of the day/shift or just before use by comparison with one or more certified, traceable calibration standards

Systematic Error: a type of error that causes the average of the readings to be offset from the true value; also referred to as bias

Test Uncertainty Ratio (TUR): the ratio of the stated accuracy of the measurement standard to the stated accuracy of the measuring instrument under test

Tolerance: the maximum allowable deviation or error from a specified value (exemplified by the phrase *plus or minus* used after a given value) to indicate the allowable error

Traceability: a process that demonstrates a chain of unbroken measurements (calibrations or comparisons) from the device being calibrated, to the calibration standard, to national, international, or available intrinsic standards of measurement

Introduction

Every day one must make choices about purchasing consumer products, many of which are related to measurements, such as filling a gas tank, selecting vegetables from a grocery, or choosing a dosage of pain reliever. Measurements help regulate commerce to ensure the product or service is as specified. In manufacturing, inspectors decide to pass or fail a mechanical part coming off the assembly line based on measurements. In biomanufacturing, the Quality department staff can accept or reject a batch of product based on purity measurements. A rejected batch results in significant monetary losses.

Whether it is in daily routine or part of the workplace, decisions are based upon measurements (e.g., a price per gallon of gas or a biopharmaceutical's purity). One neither wants to purchase a gallon of gas and only receive 0.75 gallons nor purchase a medicinal product that is only 50 percent pure. Accurate measurements are needed for a wide variety of situations. And while the ramifications of deciding where to purchase gas versus approving an expensive pharmaceutical differ considerably, the basic principles are the same. This is where metrology plays a role.

Metrology is a science that determines the fundamental methods by which objects and phenomena are measured. Metrology can be used to check that gas pumps are properly dispensing a gallon of gas; it can also be used to help validate a piece of lab equipment that is used to check that biopharmaceutical products meet a pre-determined purity standard.

Metrology also assigns values to measurements. How much is a gallon? *Gallon* has a specific value that was assigned to it many years ago. But how can one be certain of these assigned values? That is why recognized national and international standards are important. A gallon of gasoline purchased is a gallon of liquid as defined by a national standards body. The percentage of a biopharmaceutical's product can be stated with certainty, as the equipment used to check it has been validated using recognized standards. Metrology is also used to link measurements to such standards in a traceable way. This can be compared to a "chain of custody" in an investigation, where evidence is tracked from the crime scene to the court system.

Metrology is vital to biomanufacturing processes. A variety of instruments, equipment, and tools are used during the production of the product and must be inspected to ensure that they meet regulatory requirements and quality standards. For example:

- raw materials must be inspected and weighed to ensure that they meet specifications
- equipment must be validated to ensure that it is functioning properly within established guidelines (see the ***Validation*** chapter)
- noise levels must be verified and chemical fumes analyzed to make sure they each meet government safety standards
- process variable instrumentation (temperature and pressure gauges, flow meters, level indicators, etc.) must be inspected to ensure that it is indicating correct measurements
- air flow and pressure differentials must be monitored in clean rooms
- microbial contaminants must be identified so they can be controlled

- product biochemistry must be verified, including identity, purity, content, potency, etc.
- the sterility of filling processes must be ensured

This chapter will describe how measurements affect biomanufacturing specifically, including processes, materials, product development, and scientific research.

History of metrology

The need to define and standardize various units of measure is almost as old as human civilization. Weights and measures were invented as humans began to gather together in groups, grow crops, raise animals, create goods, and trade with other groups. There were needs to standardize measurements for constructing weapons for hunting and protection; gathering and trading of food and clothing; and establishing territorial divisions.

The units of specific measurements, such as length, were originally defined by using parts of the human body. For weight it was defined as the amount a man could lift or the heft of a stone the size of a hand. Time was defined by the length of a day; and days were between cycles of the moon. Although little detail is known about any of these measurements, artifacts that are 20,000 years old indicate some form of timekeeping.

In one of the earliest civilizations, Babylonian, units were established for length (*Kush*), area and volume (*Sar*), capacity (*Sila*), and weight (*Mana*). The earliest Egyptian calendar was initially based on the moon's cycles. Later the Egyptians realized that the Dog Star in Canis Major (Sirius) rose next to the sun every 365 days at the approximate time the annual flooding of the Nile began. Based on this knowledge they devised a 365-day calendar that began around 4236 BCE. It is recognized as one of the earliest designations in recorded history of a 365-day year.

As civilizations grew they became more sophisticated, trade flourished, more types of goods were produced, and people began to specialize in the work they performed. As a result, better definitions for measurement were required. If one man used the length of his arm as a measurement, it might not match another man's. Around 3000 BCE the first pyramids were being built. Common, well-defined measurements were needed to aid in the construction of these massive structures. The concept of a royal cubit was established to measure length (based on the length of the pharaoh's forearm from the bent elbow to the tip of the extended middle finger plus the width of the palm of the hand). The royal cubit master was carved out of a block of granite to endure for all time. Furthermore, the trading of goods and the levying of taxes became more common. Therefore, measurement definitions for liquid and dry measures became necessary as well. Consequently, traders were assured of getting like value for their products, and appropriate taxes could be collected.

Workers engaged in the building of tombs, temples, pyramids, etc., were supplied with cubits made of wood or granite. The royal architect or foreman of the construction site was responsible for maintaining and transferring the unit of length to the workers' instruments. They were required to bring back their cubit sticks at each full moon to be compared to the royal cubit master. Failure to do so was punishable by death.

Though the punishment prescribed was extremely severe, the Egyptians had anticipated the spirit of the present-day system of legal metrology, standards, traceability, and calibration recall. With this standardization and uniformity of length, the Egyptians achieved surprising accuracy, especially when one considers that thousands of workers were engaged in building the Great Pyramid of Giza. Through the use of cubit sticks, they achieved accuracy of 0.05 percent; for roughly 756 feet (9,069.4 inches) they were within 4.5 inches.

Although the Egyptians achieved good standardization of length, it was only a regional specification. There were multiple standards for the cubit, which varied greatly due to the standard on which they were based. These variations made trade difficult between different regions. As transportation methods and navigation evolved, civilizations traded with those further away. The need grew for an agreement of standards beyond regional ones to support trade.

The progress of measurements

Based on the efforts of early civilizations to standardize measurements, emerging nations (e.g., civilizations of larger populations and geographical regions) around the world made more sophisticated and organized attempts to set a wider range of measurement standards (all of these occur in the Common Era of time, or AD):

1215: King John of England agrees to have national standards of weights and measures incorporated into the Magna Carta.

1585: In his book *The Tenth,* Simon Stevin suggests that a decimal system should be used for weights and measures, coinage, and divisions of the degree of arc.

1670: Gabriel Mouton, a French vicar, is credited for originating the metric system.

1790: Thomas Jefferson proposes a decimal-based measurement system for the United States.

1824: George IV of England establishes the *Imperial System of Weights and Measures*, which is still in use today.

Standards of measurement before the 1700s were local and often arbitrary, making trade between countries difficult. Early standardization and metrology needs were often based on military requirements, especially those of the large maritime powers Great Britain and France.

For reasons of accuracy, efficiency, and economy, the cannons on warships needed to be the same diameter, with corresponding cannonballs of the appropriate size. Requirements to ensure these dimensions were the same led to the early stages of a modern metrology system, with master gages, transfer standards, and regular comparisons. Over time, as measurements became standardized *within* countries, the need arose to standardize measurements *between* countries.

A significant milestone in this effort was the adoption of the Convention of the Metre treaty in 1875. This treaty set the framework for, and still governs, the international system of weights and measures. It is viewed as one of the first voluntary standards with international acceptance and one of the most important in its contributions to science, industry, and commerce.

As the result of a conference in 1958, English-speaking nations agreed to unify their standards of length and mass and define them in terms of metric measures. The American yard was shortened and the Imperial yard was lengthened as a result. The inch was changed to equal 25.4 millimeters.

Scientific progress and technology required more precise measurements, thus new tools/methods were needed. Metrology grew into a science that helped to develop these tools and methods. As measurements were being standardized, efforts to establish quality standards for manufactured products increased.

Quality programs benefit from precise measurements and standards, and metrology, consequently, benefits from the exacting standards that quality programs establish. Advances in fields such as manufacturing, energy, aeronautics, computers/electronics, communications, advanced technology, and pharmaceuticals all benefit from metrology. As technology and manufacturing continue to evolve and quality efforts continue to change, the challenges to measurement and metrology will grow accordingly.

Metrology Fundamentals

The science and body of knowledge dedicated to measurement derives its name from the term *meter* combined with the suffix *-logy* to form metrology. Some confuse the term with meteorology, the study of weather. Though measurements are used in meteorology to monitor weather conditions and provide forecasts, the two are not related.

The field of metrology spans many different disciplines and incorporates knowledge gathered from many diverse fields, such as mathematics, statistics, physics, quality, chemistry, and computer science. Essential to metrology are the fundamental methods by which objects and phenomena are measured; the means for assigning values to measurements; and the certainty of these assigned values. Some of these essentials include:

- establishment and maintenance of units
- measurement methods
- measurement systems
- measurement capability
- measurement data
- measurement equipment specifications
- measurement standards usage
- measurement confidence programs

Common sense is basic to metrology, along with logical and methodical approaches to measurements and standards. A fundamental assertion in metrology is "A chain is only as strong as its weakest link," meaning that metrology essentials are interdependent, as each relies on an assortment of clearly stated definitions and postulations that relate to and build upon each other. Metrology essentials lay the foundation for realization throughout the

world that measurements are accepted and appropriate for their intended purposes. As mathematics is widely considered the universal language, metrology essentials extend that language into daily existence as quantifiable, attributed information.

The basic concepts and principles of metrology were developed from the need to measure and compare a known value or quantity to an unknown, to define the unknown as it relates to the known. What metrology describes is a method for determining the value of an unknown by assigning it a quantity of divisions, commonly referred to as units (e.g., inches, degrees Celsius, minutes, etc.). Every product that consumers buy, sell, use, or produce can be compared, measured, and defined in terms of units of a known.

Without commonly agreed upon units, it would not be possible to accurately quantify the passing of time, the length of an object, or the temperature of an environment. Practically every aspect of the physical world can be related in terms of units. Units allow for counting objects in a building block fashion so they have meaning beyond a simple descriptive comparison. For example, consider relative phrases such as *smaller than*, *brighter than*, and *longer than*. The heart of fundamental metrology concepts and principles involves determining measurement units that are deemed acceptable and repeatable. Units must be maintained as measurement standards.

Units of measurement

Measurement units must be accepted or recognized then agreed upon to conduct most commercial transactions. When this happens, the measurement units are considered standards. The International Vocabulary of Metrology (VIM) defines a unit of measurement as:

> "A particular quantity defined and adapted by convention, with which other quantities of the same kind are compared in order to express their magnitudes relative to that quantity."

The VIM notes that units of measurement have assigned names and symbols, such as *m* for meter and *A* for ampere. Mutually accepted measurement units for parameters, such as weight and length, provide the means for fair exchange of commodities. For example, the value of one ounce of gold can be equated to its equivalent worth in local currency throughout the world. The same cannot be said when using a non-accepted unit, as its equivalent worth cannot be easily determined. For example, a rectangle of gold has no defined equivalent worth because the rectangle is not an accepted unit for mass.

Besides their importance to commerce, consistent and accepted measurement units are required in the science and engineering fields to serve as a common frame of reference that is easily understood by all who utilize it. To facilitate the acceptance of units throughout the world, the General Conference on Weights and Measures (CGPM) adopted the International System of Units (SI) more than fifty years ago to harmonize physical measurements. The SI provides a uniform, comprehensive, and coherent system for the establishment and acceptance of units. The SI system is comprised of three classes of units: base units, supplemental units, and derived units.

Base units

Seven base units were chosen by convention and are regarded as dimensionally independent. Each is defined in terms of a physical phenomenon or constants of nature (except the kilogram). For example, the meter is the length of the path traveled by light during an interval of 1/299,792,458 of a second. The interval is the reciprocal of the speed of light in vacuum. The kilogram is the only base unit that is not defined in the same terms as the other base units. The kilogram is a carefully preserved artifact residing at the International Bureau of Weights and Measures (BIPM). It is also the only unit that includes the prefix *kilo-* as part of its name. All other types of units are derived in terms of the seven base units (and two supplementary units discussed later). Table 3-1 lists the base units. The term *quantity*, used in the heading of this and following tables, refers to the measurable attribute of phenomena or matter. For each quantity in Table 3-1 there is an SI unit name and symbol.

Table 3-1. SI base units

SI Base Units		
Quantity	*Name*	*Symbol*
amount of substance	*mole*	mol
electric current	*ampere*	A
length	*meter*	m
luminous intensity	*candela*	cd
mass	*kilogram*	kg
thermodynamic temperature	*kelvin*	K
time	*second*	s

Supplemental units

CGPM adopted two supplementary units—the SI unit of plain angle and the SI unit of solid angle. Plane angle is generally expressed as the ratio between two lengths, while solid angle is the ratio between an area and the square of length. Both are dimensionless, derived quantities.

Derived units

Derived units are expressed algebraically, in terms of base units, by the mathematical symbols of multiplication and division. Because the system is coherent, the product or quotient of any

two quantities is the unit of the resulting quantity. Table 3-2 gives several examples of derived units expressed exclusively in base units.

Table 3-2. Examples of SI derived units expressed in base units

Quantity	Name	Symbol
area	square meter	m^2
volume	cubic meter	m^3
speed, velocity	meter per second	m/s
acceleration	meter per second squared	m/s^2
density, mass density	kilogram per cubic meter	kg/m^3

Standardization and calibration

Standardization is the process by which a user adjusts an instrument or measurement system to a defined reading at the beginning of the day/shift or just before use by comparison with one or more certified, traceable calibration standards. This can apply to instruments such as balances with check weights, pH meters with pH buffer solutions, dissolved oxygen (DO) probes with DO simulators, etc.

There are many differing definitions for the term *calibration*, but most can be simply stated as "the comparison of a known quantity to an unknown quantity." The known quantity is the standard, while the unknown quantity is the item being tested or calibrated. For example, a calibration may involve the placement of a 20 kilogram mass weight (kg) on a floor scale platform to read and record the corresponding digital display value of 20 kg. The 20 kg mass weight is the known quantity or standard, and the floor scale digital display is the unknown quantity being calibrated or compared to the 20 kg mass weight.

The term *mass weight* in metrology can be a little confusing. Typically, mass weight refers to a single piece certified calibration item (weight) of a certain mass. It is important, however, to understand the difference between the terms *mass* and *weight*. Mass is a measurement that specifies the amount of matter than an object contains. Mass is measured by the object's resistance to a change in motion. Weight is the measurement of the pull of gravity on an object. Mass is measured using a balance, comparing a known amount of matter to an unknown amount of matter (the effect of gravity is negated on a balance), while weight is measured using a scale The mass of an object does not change, despite its location. Weight does change with location. An object on the Earth will have the same mass on the moon but will weigh more because the pull of gravity on Earth is greater than the pull of gravity on the moon.

In addition to mass and weight, a third concept to understand is *density*, or a scientific method to determine the heaviness of an object. Density compares the ratio of an object's mass to its volume. Think of feathers filling the entire area of a small box. If the feathers are compressed

so that they fill only half the box, their mass remains the same but their volume is reduced by half. When this occurs the feathers become more dense.

One definition of calibration states that it is "the comparison of a measurement system of unverified uncertainty to a measurement system of quantified uncertainty to detect or correct any deviation from required performance specifications." Another definition states that calibration "involves a set of operations performed in accordance with a definite, documented procedure that compares the measurements performed by an instrument to those made by a more accurate instrument or standard for the purpose of detecting and reporting, or eliminating by adjustment, errors in the instrument tested."

According to the International Vocabulary of Metrology – Basic and general concepts and associated terms (VIM), 2008, paragraph 2.39:

> Calibration - operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication
>
> NOTE 1 A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases it may consist of an additive or multiplicative correction of the indication with associated measurement uncertainty.
>
> NOTE 2 Calibration should not be confused with either adjustment of a measuring system, often mistakenly called "self-calibration," or with verification of calibration.

Accuracy and uncertainty

As described in the Calibration section of the VIM, accuracy and uncertainty are the primary characteristics that a calibration quantifies. These are terms that define the limits in a calibration process. **Accuracy** is defined as "the closeness of agreement between a measured quantity value and the accepted true value." Closely related, the term **uncertainty** is a property of measurement that defines the range of probable values of the "true quantity."

Another characteristic defined during calibration is precision—"the closeness of agreement between repeated measurements of the same quantity under the same conditions" (repeatability). Precision is not the same as accuracy however (Figure 3-1). An example of accuracy is when calibrating a platform scale, a 20 kg mass weight is placed on the platform and the display reads 20.04 kg; the closeness of agreement, or accuracy, is +0.04 kg. This value can also be stated as the error. Compare this to an example of precision. The 20 kg mass weight is placed on the platform five times and the resultant readings are displayed as follows: 20.08, 20.09, 20.09, 20.08, and 20.09 kg. The results, or closeness of agreement, are within 0.01 kg of each other. This is high precision, but the values are more inaccurate than the previous example because the error is as great as +0.09 kg. This demonstrates that a device can be precisely inaccurate. Accuracy and precision are critical concepts in metrology, but even top scientists and engineers frequently confuse the difference between the two.

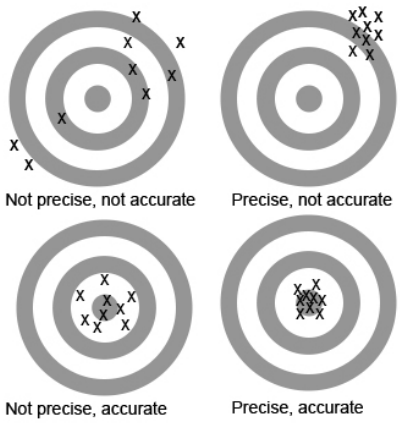


Figure 3-1. Accuracy and Precision

Specifications and tolerances

A **specification** is an explicit set of requirements to be satisfied by a material, product, or service. In metrology a specification is a documented statement of the expected performance capabilities of a group of identical measuring instruments and includes statements of either accuracy or uncertainty. Specifications are used to determine the suitability of a product, such as a measuring instrument, or the measurement standard used to calibrate the measuring instrument.

Tolerance represents the maximum allowable deviation or error from a specified value, exemplified by the phrase *plus or minus* used after a given value to indicate the allowable error. The use of the term *tolerance* is becoming obsolete; it is not included in the VIM.

Classification of Measurement Errors and Their Sources

There are many types of errors in measurement that contribute to the overall uncertainty in a given measurement. Improvements in technology have decreased the impact that these sources of error have had on measurements in the past. Despite these improvements, however, these errors still need to be quantified. The types of errors are referred to as: random, systematic, environmental, observational, and gross human. Figure 3-2 shows examples of random and systematic errors.

Random errors cause scatter in the results of a sequence of readings; this is a measure of dispersion. Random errors cause a lack of precision that may be caused by factors such as drafts, radiation, dirt, noise, and the lack of resolution or readability in the displayed output of a measuring instrument.

Systematic errors cause the average of the readings to be offset from the true value—also referred to as bias. Sources of systematic errors for measuring instruments or equipment sources can include improper leveling, loading, zeroing, excessive wear, and mechanical hysteresis (the lagging of an effect from its cause).

Environmental errors include temperature, pressure, vibration, humidity, and local interference.

Observational errors include parallax and interpolation, but these have been significantly reduced with digital readouts as compared to older analog meters, such as a gauge with a needle.

Gross human errors are those such as mistakes, misuse of equipment, blunders, or other similar occurrences. An example of such an error would be reading a scale display in kilograms but documenting the value in pounds (there are approximately 2.2 pounds per kilogram so such an error could result in a catastrophic manufacturing failure). Another example is when a Mars probe with a cost of over $100 million was lost because NASA was using meters and newtons for its measurements while the project contractor was using yards and pounds.

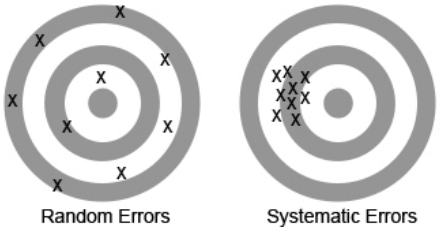


Figure 3-2. Examples of random errors (left) and systematic errors (right)

Measurement Traceability

Measurement traceability is a process that demonstrates a chain of unbroken measurements (calibrations or comparisons) from the device being calibrated, to the calibration standard, to national, international, or available intrinsic standards of measurement. All calibrations within any organization should be designed and operated to ensure that measurements made are metrologically traceable to national, international, or available intrinsic standards of measurement. In the United States the national standards body is the National Institute of Standards and Technology (NIST).

Reverse traceability is the inverse of traceability. It is the ability to identify and recall, if necessary, all measuring instruments that were calibrated by a given measurement standard. This is necessary if it is discovered during the calibration of a measurement standard that it exceeds acceptable specifications.

Test Uncertainty Ratio (TUR)/Test Accuracy Ratio (TAR)

TUR is the ratio of the stated accuracy of the measurement standard to the stated accuracy of the measuring instrument under test. Generally the measurement standard should be more

accurate than the measuring instrument under test. A four to one (4:1) ratio is accepted by most written standards, although 10:1 is most desirable. There are instances where 4:1 is not obtainable, and in some cases a 1:1 ratio is the best that can be achieved.

Standardization

Standardization is similar to calibration, but as discussed previously, it is the process by which a user adjusts an instrument or measurement system to a defined reading at the beginning of the day/shift or just before use by comparison with one or more certified, traceable calibration standards.

Instruments and test equipment

Measurement devices used in metrology are known, recognized, and designated by numerous names, such as:

- instruments
- measuring instruments
- Test Equipment (TE)
- Measuring and Test Equipment (M&TE)
- Test, Measurement, and Diagnostic Equipment (TMDE)
- Device Under Test (DUT)
- Unit Under Test (UUT)

The devices can be found in all metrology programs, whether they are part of governmental, industrial, research, or educational organizations.

Metrology Programs

Metrology programs can be found within any industry and throughout government to support their respective operations. Commercial industries have metrology programs that support their research, development, manufacturing, and maintenance activities to assure the quality of their products and services. Government metrology operations include the United States military, NASA, FAA, and the agency that most impacts the biomanufacturing industry, the FDA.

Organizations that develop and manufacture test equipment have metrology programs to control the quality of their outgoing products; some also provide calibration and repair services to customers. Such services might include field visits to customer sites, as it may not be logistically practical to ship those products back to the manufacturer. There are also third party calibration and repair companies who calibrate, service, and repair test equipment manufactured by other companies.

What all enterprises have in common are written standards and procedures that stipulate the “what” and “how” of the operation of a metrology program. Examples of several universally accepted documented standards and procedures include:

- ANSI/ISO/IEC 17025:2005, General Requirements for the Competence of Testing and Calibration Laboratories
- ANSI/NCSL Z540.3-2006, Requirements for the Calibration of Measuring and Test Equipment
- ISO 10012:2003(E), Measurement Management Systems – Requirements for Measurement Processes and Measuring Equipment

Within the pharmaceutical and biomanufacturing industries, many elements make up an effective metrology program that complies with government regulations. Metrology programs not only make good business sense but also are legally required by the FDA. The FDA is the primary United States regulatory agency responsible for oversight of the biomanufacturing industry. Requirements that prescribe metrology programs are located in the following government documents:

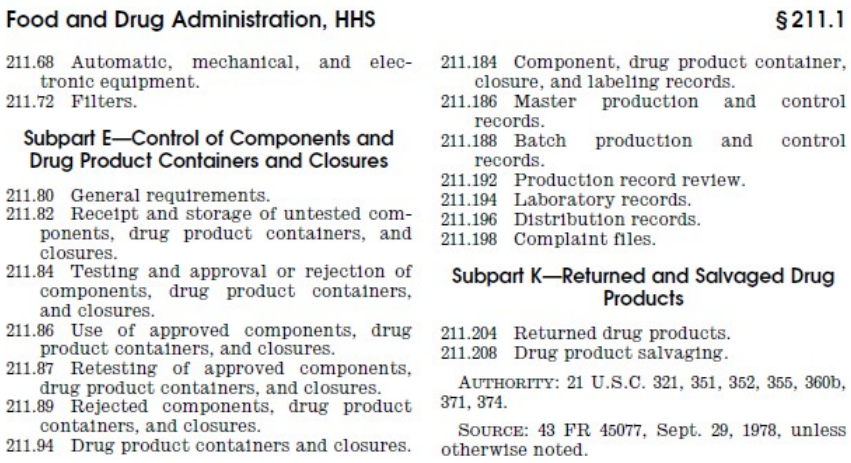
- 21 CFR Part 11 – Electronic Records; Electronic Signatures
- 21 CFR Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
- 21 CFR Part 210 and 211 – cGMP in Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals
- 21 CFR Part 820 – Quality System Regulation (Medical Devices)

For instance, the Code of Federal Regulations (CFR) states the following under 21 CFR, Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart D – Equipment, section 211.68:

(a) Automatic, mechanical, electronic equipment, or other types of equipment, including computers or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

Another section illustrated in Figure 3-3, 21 CFR, Part 211, Subpart I – Laboratory Controls, section 211.160:

(b) Laboratory controls shall include:(4) the calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.



Food and Drug Administration, HHS §211.1

211.68 Automatic, mechanical, and electronic equipment.
211.72 Filters.

Subpart E—Control of Components and Drug Product Containers and Closures

211.80 General requirements.
211.82 Receipt and storage of untested components, drug product containers, and closures.
211.84 Testing and approval or rejection of components, drug product containers, and closures.
211.86 Use of approved components, drug product containers, and closures.
211.87 Retesting of approved components, drug product containers, and closures.
211.89 Rejected components, drug product containers, and closures.
211.94 Drug product containers and closures.
211.184 Component, drug product container, closure, and labeling records.
211.186 Master production and control records.
211.188 Batch production and control records.
211.192 Production record review.
211.194 Laboratory records.
211.196 Distribution records.
211.198 Complaint files.

Subpart K—Returned and Salvaged Drug Products

211.204 Returned drug products.
211.208 Drug product salvaging.

AUTHORITY: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374.

SOURCE: 43 FR 45077, Sept. 29, 1978, unless otherwise noted.

Figure 3-3. Page from FDA Published 21 CFR Part 211

Manufacturers of Active Pharmaceutical Ingredients (API) also adhere to Guidance for Industry, the ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, section V, Paragraph C, Calibration:

- Control, weighing, measuring, monitoring, and testing equipment critical for ensuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.
- Equipment calibrations should be performed using standards traceable to certified standards if they exist.
- Records of these calibrations should be maintained.
- The current calibration status of critical equipment should be known and verifiable.
- Instruments that do not meet calibration criteria should not be used.
- Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an effect on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

These are seemingly short requirement statements that call for many components in a successful metrology and calibration program.

The National Conference of Standards Laboratories International (NCSLI) healthcare committee published a guidance document titled *Calibration Quality Systems for the Healthcare Industries Recommended Practice 6 (RP-6)* as a result of working to meet the needs of business and government oversight. Originally published in 1986 and updated July 2008, RP-6 section 4 (Responsibilities) states:

> The healthcare industry is committed to providing products and services of the highest possible quality and integrity to the world healthcare market. In meeting this commitment, it is the responsibility of each organization to use measuring and test equipment that are

controlled to ensure that any and all measurements made with this equipment are within acceptable limits throughout the equipment's continued use. Thus a calibration quality system should be established.

A calibration quality system should include all elements necessary for the control of measuring and test equipment, as well as the means to provide records of objective evidence of accuracy and conformance. Since each organization functions independently, its methods for implementing a calibration quality system or metrology program could differ from those of another organization. However, within any metrology program, certain basic elements should be addressed:

- adequacy of calibration equipment and standards
- audit requirements
- calibration procedures
- calibration intervals
- calibration quality
- calibration scheduling
- computer software validation
- environmental controls
- labels
- measurement traceability
- personnel requirements
- records
- supplier control

Adequacy of calibration equipment and standards

The metrology program should ensure that the adequacy of calibration equipment is not compromised, and it should contain the following controls:

- Items should be calibrated with measurement systems, standards, and reference materials that have adequate accuracy, stability, and range; this is to completely verify the performance of the calibrated item within its specified tolerance limits.
- Each organization should establish a program that includes measurement uncertainty, uncertainty ratios, accuracy ratios, false accepted risks, false rejected risks, or coverage factors to support the adequacy of its measurement system.
- When the laboratory needs to use equipment not under its physical control, it should ensure that the performance of such equipment is verified before and after use.

- Only authorized personnel should operate equipment. Up-to-date instructions on the use and maintenance of equipment (including any relevant manuals provided by the equipment manufacturer) should be readily available for use by the appropriate laboratory personnel.
- The laboratory should have a defined procedure for the calibration of its reference standards and should be calibrated by a body that can provide traceability to NIST. Such reference standards of measurement held by the laboratory should be used only for calibration and no other purpose.
- Reference materials should be traceable, when possible, to SI units of measurement or to certified reference materials. Internal reference materials should be checked as much as technically and economically practical.

Audit requirements

The metrology program should be subject to periodic audits, conducted at a frequency and to a degree that will ensure compliance with all documented requirements. It is recommended that a procedure describing the audits and audit reporting be created and include:

- The function or group responsible for conducting audits.
- The frequency and extent of audits.
- A description of the auditing methods used to ensure that measurements and calibrations have been performed competently.

Calibration procedures

Documentation such as Standard Operating Procedures (SOPs) or Work Instructions (WIs) should be provided and should contain sufficient information for the calibration of measuring and test equipment.

Calibration intervals

To maintain the capability to produce traceable and reliable measurement results, a metrology program should determine the maximum allowable period between calibrations of reference standards, working standards, and measuring instruments. Calibrations of measuring and test equipment at periodic intervals should be designed to confine the growth of measurement uncertainty to within acceptable limits. Calibration intervals may be specified by the number of days, months, or years. Another term for calibration interval is the frequency of calibration, such as monthly, quarterly, semi-annual, or annual. The use and history of an individual measuring instrument will determine its assigned calibration interval.

There are many recommended methods to determine calibration intervals for reference standards, working standards, and measuring and test equipment. And since these methods are

used to verify the uncertainty of measurement processes, they require periodic calibration to ensure that their verifying attributes are within their respective specified accuracies.

Cost-effective operations dictate that intervals between calibrations must be optimized to achieve a balance between operational support costs and accuracy requirements. The primary purpose of creating a calibration interval assignment is to contain the measurement uncertainty to within acceptable limits that will prevent the use of out-of-tolerance measuring and test equipment. The control of uncertainty to within an acceptable level maintains the corresponding in-tolerance probability.

Calibration interval assignment may be based on a number of factors, such as:

- measuring and testing equipment to manufacturers' recommendations
- published data about the same or similar devices
- influence of environment at the point of use
- required measurement uncertainties
- criticality of a measured quantity value
- periodic adjustment and/or calibration of the individual measuring and test equipment
- expected severity and extent of use
- maximum permissible errors
- measuring and test equipment history

Calibration quality

Calibration reliability

Metrology program controls should be designed to achieve and maintain a specified reliability level. The reliability level of measuring and test equipment can be expressed as the proportion of calibrations that are in tolerance during a specified period, the acceptable quality level, the failure rate, or in any manner that provides a meaningful measure. Reliability levels may be determined by grouping equipment with similar characteristics or by testing individual systems.

When scheduled for calibration, all the measuring and test equipment should be tested to determine whether it is within the required specification limits prior to any adjustment, repair, or cleaning that could affect calibration results. When equipment is found to be out-of-tolerance, corrective action may or may not be necessary depending upon the critical nature of the measurement and the effect upon the process or product. The organization should determine whether corrective action is required.

Deviation from reliability levels

If a reliability level is consistently above or below the specified quality level, action may be

taken to reduce the difference between the specified intended goal and the actual quality level, such as:

- interval adjustment
- procedure change
- specification revision
- limited or special calibration
- removal of measuring and test equipment from service
- measuring and test equipment repair or refurbishment
- replacement and upgrading with new measuring and test equipment
- corrective action and preventive action plan to eliminate recurrence

Nonconformance

A metrology program should provide for timely detection and correction of nonconformance conditions or events. Failures of measuring and test equipment and out-of-tolerance calibration results are considered nonconformance conditions. A nonconformance event that has the ability to directly or indirectly affect process, product, or safety conditions should be investigated to determine the root cause and the contributing factors. The investigation should be objective, thorough, timely, well documented, and scientifically sound.

SOPs should be established for the nonconformance process to identify, record, report, assess, and correct issues and to assist in notifying measuring and test equipment owners. Once identified, the measuring and test equipment should be removed from service. The measuring and test equipment should not be returned to service until the nonconformance condition has been corrected and both the owner and quality assurance representative have authorized the return of the measuring and test equipment to service. The following measuring and test equipment nonconformance information may be documented during the investigation process:

- unique equipment identification number
- date of calibration
- date of last calibration
- calibration interval
- calibration procedure used
- calibration range
- calibration limits
- test points
- measurement error
- location

- AS FOUND and AS LEFT calibration readings
- any adjustments or repairs
- evidence of mishandling, overload, hostile environment, lack of maintenance or cleaning
- review and evaluation of past calibration and service records for calibration interval adjustment
- unique reference measurement standard identification number
- due date of calibration for the reference measurement standards used

The metrology program should establish criteria for out-of-tolerance parameters that result in a nonconformance condition. Operation parameters, process variables, and process limits should also be documented. Changes to either the process or the measuring and test equipment specifications should also be documented.

Tolerances are established and used to determine out-of-tolerance conditions where the AS FOUND error during calibration has exceeded the stated calibration tolerance. Process tolerances are set to ensure proper process control and conformance to defined specifications. Calibration tolerances are set to ensure that the measuring and test equipment accuracy and precision are maintained and set tighter than the process tolerance and must take into account the measurement system's built-in variability, such as drift, hysteresis, non-linearity, temperature effects, etc. Calibration tolerances should be determined after the process requirements and tolerances are evaluated.

Measurement uncertainty

The uncertainty of calibration applies only to measurements conducted during the calibration. When measuring and test equipment are used in a manufacturing or testing environment, additional uncertainty components must often be added to obtain the actual uncertainty in use. Examples of additional measuring and test equipment uncertainty include:

- readout uncertainties
- exposure to different environmental conditions
- drift
- sampling errors
- electromagnetic interference

Measurement uncertainties should be calculated when:

- required by the customer
- the uncertainty is relevant to either the application or validity of the calibration result (i.e., where the uncertainty affects compliance to a specification or stated limit that directly or indirectly influences the release of product) or the control of measurement risk

- a calibration and/or testing laboratory performs internal calibrations in support of its accredited activities that require the declaration of estimates of uncertainty for its calibrations and/or testing

A national or international accepted procedure for expressing measurement uncertainty should be used for guidance.

Measurement assurance

A measurement assurance program provides confidence that measuring systems maintain the capability of achieving intended uncertainties, thereby ensuring continued measurement traceability. Where possible, measurement assurance activities should be chosen so that failure in any one major component of the measuring system would likely be revealed. Measurement assurance activities should provide a level of scrutiny corresponding with either the reported measurement uncertainty or the stated measuring and test equipment tolerance.

Measurement assurance methods may include:

- use of check standards in conjunction with statistical process control
- independent tests of measuring system performance
- calibration of measuring system by multiple independent methods
- prompt investigation of the root cause of abnormal behavior of a measuring system
- statistical analysis of calibration data for self-consistency or correlation between different measurements
- statistical analysis of repeat calibrations over time to identify abnormal trends
- participation in proficiency testing or comparisons

It is recommended that standard operating procedures be used to control the Measurement Assurance Program (MAP). Risk analysis of the probable likelihood and magnitude of calibration failures, as well as the possible risk of an erroneous calibration to the intended application, may provide useful guidance on the creation of a robust measurement assurance program. When calibration failures are observed, the performance of the measurement assurance program in identifying these failures should be assessed. If necessary, refinements should be made to the measurement assurance program, measuring system, or calibration procedures.

Risk assessment

Risk assessment is the systematic evaluation of an analysis of facts and the deduction of possible consequences concerning either a process or function. This process identifies the potential risks and assesses means to reduce the risk to acceptable levels. This acceptable level of risk is also referred to as the Reliability Target. Risk assessment is a useful tool for all measurement assurance activities to determine risk target levels used for measurement uncertainty limits and calibration interval assignment and adjustment.

Risk assessment methods may include:

- identifying the appropriate risks associated with a process or function
- assessing risks such as Failure Modes and Effects Analysis (FMEA) or Fault Tree Analysis for each identified risk
- assigning Risk Targets (Reliability Target) for each assessed process

Calibration scheduling

To effectively manage the periodic calibration of measuring and test equipment, a validated system is required. Depending upon the size of the equipment inventory and the resources available, the scheduling system may consist of manual or computerized scheduling. Regardless of the type of system implemented, it should accomplish the following objectives:

- identification of calibration due dates of measuring and test equipment on or before a specific due date or within a specific date window (range) established in the organization's calibration quality system
- flexibility to allow, if appropriate, calibration of measuring and test equipment before each use rather than on a periodic schedule
- notification mechanism for pending calibrations to assist equipment users in resolving any equipment scheduling conflicts, as well as for the appropriate individual when the calibration date has been exceeded
- identification of equipment status

When either measuring and test equipment are transferred from one location to another or new equipment is received, an equipment record should be updated/entered in the metrology program before the equipment is put into service.

Computer software validation

Calibration-related computer software must be managed and controlled related to its development, validation, maintenance, and use. Some examples of calibration-related software include:

- calibration-management software
- measuring and test equipment control software and data-collection software

- statistical software
- test-procedure software

Validation to an established protocol is necessary to demonstrate compliant software. Software validation is as important as hardware calibration, as it ensures the quality of measurements that are controlled or assisted by computer. Software changes should be controlled using documented processes.

A validated software package adhering to FDA 21 CFR Part 11, Electronic Records; Electronic Signatures can dramatically streamline efficiency and enhance the compliance of a calibration quality system. The software should be operated and maintained per approved Standard Operating Procedures detailing the following:

- use and operation:
  - how, when, and where data are entered into the software
  - specific instructions on how to navigate the software
  - instructions detailing the extrapolation of information to make measurement or business decisions
  - detailed explanation of how specific functionality in the software implementation relates to the measurement or business process
- administration:
  - specific details on the administrative roles (administrator, user, etc.) pertaining to the software and the corresponding business roles assigned to them
- software configuration control (the steps necessary to ensure that adequate control is maintained over the baseline software configuration):
  - configuration should be specifically approved and detailed, and subsequent changes should be documented and assessed through the organization's approved change-control policies
  - explanation of rights within each defined administrative and operative role
  - details on what rights/roles are designated within the process
  - verification/documentation of identities of individuals using electronic signatures
  - both back-up and restore procedures and disaster recovery procedures
- training:
  - specific training procedures should be detailed for applicable personnel roles within the software with specific provisions for the documentation of such training

Commercial, off-the-shelf, or custom-designed Computerized Calibration Management Software (CCMS) packages may provide the functionality necessary to replace a paper-based calibration management program. Where the necessary criteria are met and documented in a CCMS implementation, the software's electronic (paperless) functionality incorporated into a

calibration quality system is acceptable as the equivalent to a paper-based calibration management program.

The lack of a validated CCMS may fail to demonstrate a compliant process for scheduling and tracking of measuring and test equipment in a calibration quality system. In addition to a CCMS's ability to meet applicable regulatory requirements, an organization may consider the overall system compatibility of a CCMS through the use of a formal investigation through stated system design policies prior to purchase and implementation.

Prior to implementation of a CCMS, the network infrastructure hosting the software should be validated according to the organization's policies on network security. Network infrastructure susceptible to security breaches or lacking recommended specifications to host a CCMS could compromise the integrity of the CCMS despite any validation performed on the software. The CCMS should be validated as installed on the network infrastructure following established validation policies in the organization. This validation can reference:

- user requirement specifications
- functional requirement specifications
- manufacturer's specifications

Environmental controls

The calibration environment should be controlled, when possible, to the extent necessary to ensure measurement quality. Conditions affecting measurement quality should be corrected as appropriate. Environmental parameters to be considered for control include:

- temperature
- relative humidity
- barometric pressure
- vibration
- electromagnetic interference
- voltage regulation of electrical power

Variation in these parameters is generally limited and maintained through proper laboratory design and construction. However, laboratory ambient temperature and relative humidity are parameters that should be monitored on a daily basis. The calibration environment should be controlled only to the extent required by the most environmentally-sensitive measurement performed in the area. The environmental conditions that might adversely affect test and calibration results should be documented. To comply with environmental requirements, pertinent environmental conditions should be monitored and recorded.

Cleanliness should be maintained to the proper degree in all calibration laboratory areas and should be consistent with "good housekeeping" practices. If environmental control is lost and the ambient operating conditions exceed the established limits, all calibrations within the affected areas should cease until either environmental control is returned and an appropriate

stabilization period has been achieved or the conditions are determined not to adversely affect the calibrations being performed. Regarding field conditions, pertinent environmental conditions should be recorded together with the calibration data. Correction factors due to the environment should be addressed when necessary.

Labels

All measuring and test equipment included in the calibration quality system must be clearly identified to alert the user of its calibration status. The calibration status should be indicated by a label or tag applied prominently on the equipment or by some other means clearly evident to the user. Requirements for calibration labels can include:

- unique identification of measuring and test equipment
- date of calibration
- due date for next calibration
- conformance to specifications or limitations of use
- individual performing calibration or affixing the label

Calibration labels can be characterized based on the intended use of the measuring and test equipment. Some examples are:

- Calibrated Standards: label applied to metrology standards only
- Calibration: label placed on equipment calibrated on a periodic basis
- Limited Calibration: label placed on equipment calibrated on a periodic basis that notifies the user that the equipment does not meet all procedural specifications but is adequate for the intended application
- Calibrated by User: label indicates that the equipment requires frequent calibration and therefore is calibrated by the user

Additional informative labels should be used when appropriate. Examples are:

- Calibration Void If Broken: label placed in such a manner as to ensure that unauthorized personnel cannot make any calibration adjustments.
- Out of Service/Failed Calibration/Do Not Use: label to be placed on equipment that failed calibration, requires repair, or has exceeded its calibration due date

Regardless of the label method utilized, each organization must decide which methods are most appropriate for its calibration quality system.

Measurement traceability

The calibration quality system should be designed and operated to ensure that measurements made by the organization are metrologically traceable to national, international, or available intrinsic standards of measurement; calibration certificates and reports should state this traceability and provide the following: the measurement results and associated uncertainty of measurement and/or the statement of compliance with an identified metrological specification.

When intrinsic standards are used, the organization should demonstrate (via measurement assurance techniques, interlaboratory comparisons, or other suitable means) that within stated uncertainties its intrinsic standard measurement results are equivalent to those of national or international standards.

Reference standards of measurement should be calibrated by a competent body that can provide metrological traceability. When feasible, reference materials should be metrologically traceable to either national or international standards of measurement or to national or international standard reference material. When traceability of this level is not available, requirements may be satisfied by:

- participation in a suitable program of interlaboratory comparison or proficiency testing
- use of international or national accepted standards
- use of ratio or reciprocity-type measurements
- use of certified reference materials
- use of consent standards that are mutually agreed upon by all parties concerned

A system of periodic checks should be implemented to assure the continued validity of standards, reference materials, and related measurement systems used in making traceable measurements.

Personnel requirements

Competent personnel are an important component of a properly-managed metrology program. Personnel include all persons whose activities influence or affect the quality and validity of the calibrations performed. Calibration personnel should possess and exhibit characteristics of professionalism, integrity, and quality.

Qualifications

Candidates should possess adequate qualifications relevant to their proposed job assignment. Qualifications to perform their assigned tasks are established through an individual's education, training, experience, or any combination thereof.

The qualifications of internal or contracted calibration personnel and supervision should be documented and evaluated to ensure that personnel are qualified to perform assigned work tasks. Personnel that do not possess the appropriate qualifications for a specific task should not perform the task until qualified.

Selection

The selection of both internal or contract calibration personnel and supervisory personnel is important in establishing and maintaining an effective calibration quality system. Candidates should be evaluated to determine their competence to perform the requirements of the job assignment. Candidates should possess:

- the ability to follow detailed instructions, processes, and procedures

- knowledge regarding the use of measuring and test equipment and standards
- discipline to comply with guidelines, practices, rules, and regulations
- attention to detail and commitment to quality to consistently perform calibration activities
- ambition to continue the learning process and continuously improve technical abilities
- relevant technical education, training, and experience in the area of the job assignment
- knowledge of metrology practices, calibration concepts, and troubleshooting techniques commensurate with their job assignment level

Training

Documented job descriptions for each employee should define job functions and required competencies. Training should be related to the particular job functions and operations that the employee performs and should be properly documented and readily available for review or audit.

Training should occur on a regular basis to ensure competence. An effective program for identifying the need for training, scheduling training sessions, and tracking the results of training programs needs to be in place to ensure that all personnel (including managers) are appropriately qualified and adequately trained. Only qualified individuals should conduct or provide training, and the effectiveness of the program should be evaluated on a consistent basis.

Records

Records should be maintained for all measuring and test equipment that are included in the metrology program. These records may be individual equipment records or records for a system involving several pieces of measuring and test equipment.

The laboratory should establish and maintain procedures for identification, collection, indexing, access, filing, storage, maintenance, and disposal of quality and technical records. Records should be retained for a period of time sufficient to satisfy all regulatory, operating policy, and contractual requirements. The National Institute of Standards & Technology (NIST) recommends that records be retained for five years.

Safeguarding

Measures should be taken to safeguard records to the level required to meet regulatory and contractual requirements. The laboratory should have procedures in place not only to back-up records stored electronically but also to prevent both unauthorized access to and amendment of these records.

Content

Content of the records should include:

- identification: a unique identification should be assigned to each item of measuring and test equipment in the metrology program. A unique identification number is important to meeting measurement traceability. Examples of equipment identifications are:

- manufacturer's name and the model/serial number of the equipment
- inventory property number
- company identification number
- code marking

- location: records should provide the information necessary to locate the measuring and test equipment due for calibration.
- calibration history: a retrievable record system should be maintained on all measuring and test equipment that requires calibration so as to provide the information necessary for the control, audit, and history of the calibration quality system. The record system should include:
  - the date of each calibration and the due date for the next calibration
  - identification of the individual who performed the calibration and any other signatures required by regulatory requirements
  - test or calibration results and, where appropriate, the units of measurement
  - records of out-of-tolerance conditions and supporting data
  - information, or the location of such, necessary to duplicate all graphs, tables, reports, or certificates issued with the measuring and test equipment
  - the uncertainty of measurement and/or a statement of compliance with an identified metrological specification
  - reports, or the location of such, received from outside laboratories indicating instrument accuracy and traceability
  - identification of the standards used to perform the calibration
  - identification of the procedure employed to perform the calibration
  - environmental conditions at the time of the calibration that were included in establishing the equipment's accuracy and traceability
  - changes in location of equipment during their period of use
  - data required by the procedure

- traceability documentation: records should provide all documentation that substantiates and identifies the means of achieving direct or indirect metrological traceability. This should be stated in terms of internationally recognized standards, national standards, intrinsic standards, mutual-consent standards, ratio or reciprocity-type measurements, or program of inter-laboratory comparison. Measurement uncertainty statements should support metrological traceability. To determine a period of liability through the investigation of the impact-to-product of an out-of-tolerance

standard, a procedure should be established for determining reverse traceability within specified dates.

- calibration specifications: records should detail specific information pertaining to the current user requirements for measuring and test equipment to ensure that the calibration activities support the intended use. This information should be updated as necessary. The following should be considered:
  - process parameters, range, limits, and tolerances
  - calibration parameters, range, limits, and tolerances
  - calibration procedures
  - calibration interval
  - rationale for ranges and tolerances, such as regulations and process requirements
  - criticality categorization
- recording of calibration results: regulatory documents require the recording of calibration results. Individual measurement results, or data, may be used to determine the overall calibration result.
- measurement result: the values of individual measurements to test specifications or requirements are measurement results. These may be recorded on Calibration Certificates, Calibration Test Results, or Equipment Records and are recorded as stated values with attributes of time. Depending on when the measurement is made, the measurement result has one of the following two names:
  - AS FOUND: the measurement results obtained prior to cleaning, adjusting, or repair of the unit under test; for some disciplines, the cleaning step is to be performed prior to taking the AS FOUND result (i.e., dimensional measuring and test equipment).
  - AS LEFT: the measurement results after the AS FOUND measurements are obtained; these results can reflect measurements of a unit in test that may or may not have been cleaned, adjusted, or repaired prior to the measurements. These would be the final test readings obtained whether the unit was within tolerance or out-of-tolerance. Measurement results are useful in determining in-tolerance and out-of-tolerance status for measuring and test equipment and can be used collectively to determine the calibration result.
- calibration result: indicates the status for the measuring and test equipment as a whole. It may also be referred to as a verification result or a confirmation. The calibration result may be recorded on Calibration Certificates, Calibration Test Results, or Equipment Records and is typically documented in two ways:
  - Pass/Fail
  - In-Tolerance/Out-Of-Tolerance/Adjusted/Limited

A calibration result can be used to determine the type of calibration label that will be applied to measuring and test equipment, as well as to calculate adjustments to calibration intervals.

Supplier control

Biomanufacturing organizations that utilize outside supplier maintenance and calibration services should ensure that the supplier's calibration quality system complies with all the organization's requirements. To this end, the organization is advised to establish an agreement with outside supplier service organizations to:

- use approved procedures outlining methodology used in maintaining and calibrating the client's measuring and test equipment
- provide a certified report of calibration, complete with all necessary supporting documentation
- perform the maintenance and calibration activities that meet the organization's specific requirements
- provide a copy of a quality manual or relevant documentation of their quality system
- provide objective evidence of quality records, environmental control, equipment history files, and any other relevant quality materials

Supplier specifications

The organization should provide the supplier with a specification document that can be used to ensure that calibration activities and desired results match the organization's requirements. This document may include, but is not limited to:

- type of calibration service
- applicable documents, technical reference, or standard
- equipment specification
- service performance requirements
- physical, environmental, and data-format requirements
- safety and biohazard requirements
- confidentiality and security requirements
- certificate of calibration requirements
- notification of nonconformance

Supplier audits
Each organization is responsible for periodically conducting a documented audit of all suppliers that attests to the capabilities of the supplier and the competencies of all supplier personnel. Periodic evaluation of accredited suppliers may be used in lieu of audits when the contracting organization's regulatory requirements are met by the accreditation process.

Metrology program summary

The fundamental components of a solid metrology program require all the elements previously described. The program can also include other enhancements, such as round-robin calibrations of artifact-measuring instruments with other external calibration laboratories, to confirm the validity of internal methods and practices.

Metrology programs can vary in size and shape from one site to another, with the only differences due to the local organization's needs. Regardless of size, however, the essentials remain the same throughout the world of metrology.

Calibration in a Biomanufacturing Environment

This section describes a representative instrument calibration process using a mass-measuring instrument such as a floor scale. The floor scale can be used in the biomanufacturing to measure the gross weight of raw materials or perhaps the weight of a portable tank from an empty state to a predetermined measured value as ingredients are added to the tank.

In this example a portable floor scale will be used with the local display set to read in the kilograms (kg) unit of measure and set to a display resolution of 0.1 kg. Prior to starting the calibration there are several steps to take. The metrology technician will first review the applicable calibration SOP, then review the calibration parameters as stated in either the SOP or the instrument database. The instrument calibration data sheet is then prepared (Figure 3-4). Finally, the calibration standards and tools are gathered and taken to the scale location.

Work Order No:			Instrument ID No.:		
Unit Description:			Serial No.:		
Bldg/Rm. No.:			Process Tolerance:		
Range & Units:			Process Range:		
Calibration SOP:			Calibration Tolerance:		
GXP Classification	GMP ☐ GCP ☐ GLP ☐ Non GXP ☐		Criticality:	Critical ☐ Non-Critical ☐	
Metrology Standard ID Numbers:			Calibration Date:		
			Due Date/Interval:		
			Technician(s):		

DATA SOURCE	AS-FOUND			AS-LEFT		
	Standard	Instrument	Error	Standard	Instrument	Error

CALIBRATION SUMMARY	
AS-FOUND CONDITION (Check One)	AS-LEFT CONDITION (Check One)
☐ Initial Calibration	☐ ≤ Calibration Tolerance- No adjustment performed
☐ ≤ Calibration Tolerance- No adjustment required	☐ ≤ Calibration Tolerance- Adjusted
☐ > Calibration Tolerance and ≤ Process Tolerance	☐ > Calibration Tolerance and ≤ Process Tolerance
☐ > Process Tolerance - Out of tolerance report required.	☐ Failed Calibration
☐ Damaged or No As Found Data	☐ Other- Describe in Comments

Comments:

APPROVALS			
Calibrated By:	Date:	Reviewed By:	Date

Figure 3-4. Sample instrument calibration data sheet

The calibration SOP or Work Instruction (WI) will include various components as dictated by the local quality function, but this example will focus on the steps to perform the calibration itself. Listed below are the representative steps the technician will perform during the calibration:

1. Perform a visual inspection of the unit. Verify that the weighing surface and associated instrumentation is in good repair and clean and free of defects that would impair its operation. Record any findings on the instrument calibration data sheet comments section.
2. If instrument calibration parameters are protected from adjustment with passwords or other protective means, obtain the necessary information or materials in case adjustment becomes necessary during calibration.
3. If the unit is portable, position it in the exact location where the calibration will be performed. Verify that the instrument is located where it will be subjected to environmental conditions (temperature, relative humidity, airflow, and vibration) similar to those that it will be subjected to during its use.
4. If equipped with one or more leveling indicators, verify that the unit is level. If not, adjust the levelers (if applicable).
5. Verify that the unit has been energized for at least 30 minutes. If not, turn the power switch to the “on” position and allow a minimum warm-up time of 30 minutes.

6. Zero the instrument reading by pressing the appropriate key. Consult the manufacturer's operation and maintenance manual for guidance if required.
7. Perform the required tests in an increasing direction (e.g., 0 kg, 200 kg, etc.) while recording the calibration standard mass weight values and the unit displayed values on the instrument calibration data sheet. Following the placement of each mass weight onto the weighing surface, allow adequate time for the display to stabilize.
8. Record the calibration standard mass weight values and the unit displayed values in the appropriate As-Found section of the instrument calibration data sheet.
9. Compare the calibration standard mass values to the unit display readings to determine the error of each weighment.
10. Unit errors less than or equal to the Calibration Tolerance do not require adjustment. If this applies, and adjustments are not to be performed, proceed to step 13.
11. Unit errors that are found to be greater than the Calibration Tolerance require adjustment. If the unit is equipped with internal calibration capabilities, or if the unit is equipped for calibration using external masses, perform the applicable calibration exercise. Consult the manufacturer's operation and maintenance manual for the calibration procedure if required. If adjustments are made to calibration coefficients, record the As-Found and As-Left coefficient values, if available, in the comments section of the instrument calibration data sheet.
12. If adjusted, repeat steps 6 through 9 while recording the values in the appropriate As-Left section of the instrument calibration data sheet.
13. Verify completion of the instrument calibration data sheet and review for accuracy.
14. Sign and date the instrument calibration data sheet.
15. Place a completed CALIBRATION label in a visible location on the unit.

Calibration of the floor scale using the calibration SOP and instrument calibration data sheet can now be performed.

Check Your Knowledge

1. Essential to metrology are the fundamental methods by which and phenomena are measured; the means for assigning values to measurements; and the certainty of these assigned values.
2. Which famous historical document includes national standards of weights and measures?

   a. The United States Constitution
   b. The Treaty of Ghent
   c. The Bill of Rights
   d. The Magna Carta

3. Which of the following is NOT an SI base unit?

   a. mole
   b. yard
   c. kilogram
   d. degree Kelvin

4. What is the term that describes the closeness of agreement between a measured quantity value and accepted true quantity value?

   a. accuracy
   b. precision
   c. calibration
   d. certainty

5. A zeroing error of a scale is an example of what type of error?

   a. random
   b. environmental
   c. human
   d. systematic

6. The metrology program should be subject to periodic_____, conducted at a frequency and to a degree that will ensure compliance with all documented requirements.

Activities

1. Using a balance and a set of weights, ensure that the balance is properly calibrated; repeat the calibration five times and record your findings.
2. Research FDA requirements related to metrology and write a two-page report on how these requirements can impact product quality.
3. Consider the challenges and benefits of working as a metrology technician. Discuss your thoughts with your fellow students.