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COMMENTARY

Measurement Science for Food and Drug Monographs: Toward a Global System

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ABSTRACT This article continues USP's public dialogs about applications of modern measurement science (metrology) to public or private specifications (monographs) of food and drug articles. An objective of the discussion is to promote understanding of traceability and uncertainty of measurement results. Adoption of modern metrologic principles helps ensure that a measurement of one or more property values (attributes) of a food or drug article are acceptable without regard to when (time), where (space), or how (technology) the measurement was conducted. The approach is applicable to both in-process and end-product measurements and facilitates and supports understanding of manufacturing and measurement variability relative to acceptance criteria. Application of modern metrologic principles to measurement of food and drug articles expands opportunities to ensure availability of good quality food and drugs in national and international markets.

KEY WORDS measurement · regulatory science · specifications · traceability · uncertainty

INTRODUCTION

Metrology is the science of measurement and embraces legal, fundamental, and applied concepts. Metrology is an old science that originally was driven by needs of commerce. Ancient Phoenicians invented a primitive balance made from wood and cloth to ensure equity in trade. Commerce still is the major motivation for a branch of metrology—*legal metrology*—that includes regulatory requirements in many sectors of manufacturing, including food and drugs. Another branch of metrology—*scientific* or *fundamental metrology*—of academic interest and involves the establishment and realization of measurement units (such as the International System of Units, SI), research into new measurement methods, development of measurement standards, and transfer of metrological traceability throughout a measurement system. Fundamental metrology is usually confined to national entities legally responsible for a nation's primary standards, i.e., national metrology institutes (1). The interface of legal metrology and fundamental metrology is often called *applied metrology*, which concerns the application of measurement science to manufacturing, ensuring the suitability of measurement instruments, their calibration, and quality control of measurements. The United States Pharmacopeial Convention (USP) is involved in all three aspects of metrology as it evolves its compendia—the United States Pharmacopeia (USP), the National Formulary (NF), the USP Dietary Supplement Compendium, the Food Chemicals Codex (FCC), and the USP Pharmacists' Pharmacopeia. These compendia provide monographs that document food and drug quality and are allied with physical reference materials, where feasible.

During the past five years and more, USP has worked to advance measurement science for its food and drug monographs (2–4). In part, the way has been made easier by a general movement on the part of national drug control laboratories (official medicines control laboratories) towards ISO 17025 and other approaches (5) that encourage traceability and comparability of results. In part, it has been resisted because many either do not understand measurement science or do not see its value. This article articulates the argument for sound measurement science approaches in all food and drug quality measurements.

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Adoption of this science allows one or more measurement procedures in a monograph for a compendial article to yield traceable results that can be accepted everywhere. Although this article focuses on compendial control of drugs after market access, the general approach is applicable during all phases in the life cycle of food and drug and is pertinent to both in-process and end-product testing.

Metrology

Just as a food or drug should be consistent and fit for purpose, the motivations for metrology are consistency and fitness of measurements. Thus, metrology is a core science that helps ensure that a material is fit for its intended use, which, for the purposes of this article, refers to food and drugs. Several concepts undergird modern measurement science and its applications to measurement of food and drug articles. Trade in food and drugs undergirded by sound process and product measurements is critical given their centrality to our daily lives.

Comparisons

All measurements are based on comparisons—the comparison of a property (attribute) of one item (the food or drug article) with that of another item, preferably an agreed-upon reference material. All quantitative measurements have three components: 1) the measurement procedure with its method (the specific application of a method is a procedure) that is used to make the comparison between the article and its reference material, 2) the article itself and the corresponding reference material, and 3) the results of the measurement. Measurements may compare a known and an unknown (to assign a value to the unknown) or two knowns (to evaluate their similarity). In food and drug measurements, the former is applied relative to a known (the reference material) to verify that the article of food and drug commerce meets acceptable standards of quality during its availability in the marketplace.

Traceability

The *International Vocabulary of Metrology—Basic and General Concepts and Associated Terms* (6) is available and defines traceability as the property of a measurement result whereby the result can be related to a reference by a documented unbroken chain of measurements, each contributing to the measurement uncertainty. Metrological traceability to a common reference material (preferably associated with SI units) ensures consistency and comparability of measurements across time, space, and technology. To ensure metrological traceability, measurements require a reference material associated with a property value of stated uncertainty.

Uncertainty

Uncertainty is a necessary and inherent consequence of any measurement/comparison and is defined as a nonnegative parameter characterizing the dispersion of the quantity values attributed to a measurand. The measurand itself is defined as the property attribute of the matrix (e.g., the natural-source or processed food or drug product) or material (food ingredient, drug substance, or excipient) under test. Individual measurement values or even the mean values of a set of measurements cannot be compared without consideration of the uncertainty associated with the values. For drugs (the drug product and its ingredients), terminology has arisen to describe how critical quality attributes are understood and then developed through careful attention to characterization studies (7). From these studies arise control tests, procedures, and acceptance criteria that form the basis for either the private (regulatory) or public compendial specification. The tests in the specification allude to measurands of the article with documentation of compliance via a conformity assessment by first, second, or third parties.

Comparison of Results

A key and critical concept in metrology is that only the *results* of a measurement can be compared between known and unknown matrices and materials—but not the measurement procedures/methods or the materials being measured. As noted above, these results include the mean value and its associated uncertainty. The results of measurements are subjected to further assessment. The properly assessed results then may lead to decisions and/or conclusions regarding the methods or materials—for USP, the food and drug articles and/or the ingredients in their packaging. USP has recently published articles addressing when a procedure is acceptable and when results from two procedures can be deemed equivalent or better (8,9). When one invokes the phrase "equivalent or better," one is necessarily speaking about results (and subsequent decisions based on these results). In metrology applied to chemical measurement (or chemical metrology), neither the method/technique nor the procedure/protocol can be declared equivalent or better (but note that ISO and VIM no longer use the terms *technique* or *protocol*). Rather, results are equivalent or better when two procedures are compared via a common reference material.

The science of metrology systematically involves a series of measurements (comparisons) tracing back through

increasingly accurate methods and well-characterized materials, leading ultimately and ideally through an unbroken chain to the definition of the measuring unit itself (Fig. 1). The definition of the unit and the realization of the unit via measurement are distinctly different. The definition of the unit is without uncertainty and is based on the metrological concept of trueness (absence of bias) (10). The unit often is arbitrary but historically significant and may include assumptions and conventions. For instance, the SI unit of mass is defined by the mass of a cylindrical artifact (prototype) made of a Pt–Ir alloy and safeguarded at the International Bureau of Weights and Measures (BIPM) near Paris. These concepts are critically important to measurements of attributes of food and drugs, where results are typically expressed in terms of mass.

This international artifact, $\mathcal{K}$ is exactly 1 kilogram with no uncertainty. It is compared to national prototypes of similar construction and composition for each country that has signed the Treaty of the Meter, which dates to 1875 (11). However, during the course of comparisons with other kilograms, metrologists soon observed that the surface of the prototype accumulated contaminants that affected its mass and thus the uncertainty in making comparisons. Therefore, by convention, $\mathcal{K}$ is cleaned by a specified method immediately before a measurement comparison (with the assumption that it has been restored to its original state). Any uncertainty in this process is combined with other uncertainties inherent in the measurement process and is assigned to the object being compared, and not to $\mathcal{K}$.

The United States has artifacts $\mathcal{K}4$ and $\mathcal{K}20$. Because of historical happenstance, $\mathcal{K}20$ is the national standard of mass for the United States. These artifacts are in the custody of the National Institute of Standards and Technology in Gaithersburg, MD (the US National Metrology Institute) and have been used to assign values to sets of stainless steel weights that have been distributed to each of the US states, districts, and territories. In turn, state and local governments use these weights to calibrate the weights used in commerce in their jurisdictions, e.g., the scale in the butcher shop. In this way, through an unbroken chain of measurements, the pound of hamburger purchased in California has identical mass to one purchased in New York—within a prescribed uncertainty—based on the propagation of uncertainties through the measurement chain. In fact, one can be assured that it is the same one-pound amount (by mass) of hamburger that is purchased in London (but expressed there as 0.45 kg), because the mass values in all three locations can be traced back directly to the kilogram $\mathcal{K}$ at BIPM. This consistency in measurement through traceability ensures confidence in trade and reliability in quality and quantity, and today, for most commodities and in most industries, this consistency is taken for granted.

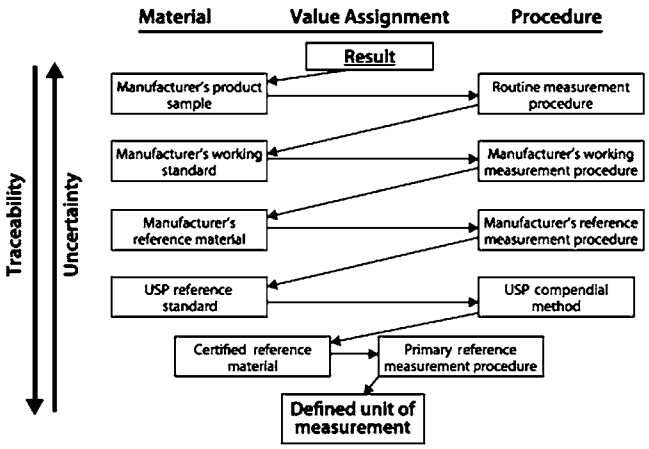

Fig. 1 Metrology cascade.

In summary, the application of these principles of metrology leads to confidence in the results of the measurement, consistency in measurements across time, space, and technology, and assurance of the validity of the results as a basis for decision making. When one considers legal quality for trade in food and drugs between practitioners and patients, e.g., in terms of strength, quality and purity, one is necessarily referring to metrologic concepts.

Compendial Applications

Food and Drugs

Application of these concepts to USP's monograph tests, procedures, and acceptance criteria for food and drug articles involves development of analytical procedures to acquire information about the measurands (attributes) that control the quality of a given article. Of many procedures used for purposes of characterization, a subset will be defined to use in ensuring compliance with specified acceptance criteria (12). Frequently, but not always, these analytical procedures and their acceptance criteria are developed privately and later are subjected to regulatory review and acceptance. Thereafter, they may form the basis for the public tests, procedures, and acceptance criteria of a compendial monograph. The reference material associated with the procedure may be a drug substance or an excipient, food ingredients or their products, or a more highly purified sample of any of these—or it can even be another material. The food or drug product is usually a matrix that contains ingredient articles and allowed impurities. There can be a primary procedure (e.g., direct measurement via isotope dilution–mass spectrometry analysis or mass balance) that can determine content of the active ingredient in the drug substance and can also be used

to assign value to the reference material. This primary procedure and material then form the foundation for subsequent procedures and materials (Fig. 1). The content of the reference material has a component of uncertainty (caused, for example, by heterogeneity and instability) in addition to the uncertainty arising from the analytical procedure. More typically, however, the primary procedure and reference materials either are in the public domain or are maintained privately by the manufacturer and are subject to regulatory control. USP's task is to work with all manufacturers to bring the procedure and its corresponding materials into the public domain.

Although the language of regulatory agencies and compendia readily accommodates the language of metrology, the realization and implementation thereof have not yet occurred. For example, the ICH quality document Q2 and USP's General Chapter *Analytical Validation* <1225> were created approximately 15 years ago, at a time when the language of measurement science as applied to chemistry was evolving (13,14). Neither the ICH guidelines nor USP's <1225> adopt the language of metrology, nor do they work to ensure traceability of results.

Out-of-Specification Results

Regulatory documents (15) describe comparisons of measurement results of an ingredient or product against typically predetermined acceptance criteria. The acceptance criteria are usually given as a range for desirable ingredients (active pharmaceutical ingredient, excipient, or food ingredient) or limits (impurities) but without uncertainty. USP and many others believe that these acceptance criteria should be based on safety and benefit and not process considerations (16). Manufacturers and conformity assessment bodies become concerned when a measurement yields results that approach a fixed limit. For a measurement scientist, the solution is clear: Design a measurement system of sufficient accuracy (trueness and precision) in order to control manufacturing and measurement variability relative to predefined acceptance criteria. Such a well-designed measurement system will necessarily involve reference materials and traceability, as called for in ISO 17025 and in a guideline from the American Society of Mechanical Engineers (ASME) (5,17). The guideline speaks to release criteria narrower than the legal acceptance criteria that add assurance of releasing an acceptable article into commerce. Concepts of measurement science and manufacturing science, emphasized recently through terms such as quality by design, accord well and work in a complementary way. In fact, modern manufacturers of food and drugs, and their overseeing regulatory bodies, can expect that a sound understanding of science will allow much better understanding of the variability in ingredient and product manufacture that, together with analytical variability, uses up the space reflected in the acceptance criteria (Fig. 2). Keeping this variability to a minimum allows good products and ingredients into the marketplace, thus reducing both manufacturer and consumer risk and promoting practitioner and patient/consumer confidence. In some ways, the term *uncertainty* is a misnomer because a sound measurement system, coupled with understanding of manufacturing variability, provides greater certainty that manufactured articles will conform through testing to the legal standard.

Non-SI Measurements

In some settings involving measurements of food and drugs, modern metrologic approaches to ensure traceability of results and specified uncertainty estimates to SI units are only partially possible or are not possible at all. For potency and other types of measurements for natural-source or recombinant biologicals, traceability may involve a specified unit relative to a specified material, e.g., WHO's IU for some biologicals. Similarly, for dissolution, a specified material may be provided (18,19). Partial solutions may be emerging, e.g., the katal, which for enzymatic assays allows a ratio of two SI units (moles transformed relative to time).

DISCUSSION

Metrological traceability and determination of uncertainty, when feasible, appear essential and thus inevitable for food and drug measurements. If two measurements are made for a particular food or drug article (either two sources or two laboratories for same source), results must be comparable. Buyers (second parties) of food and drug ingredients must ensure the quality of materials purchased from suppliers

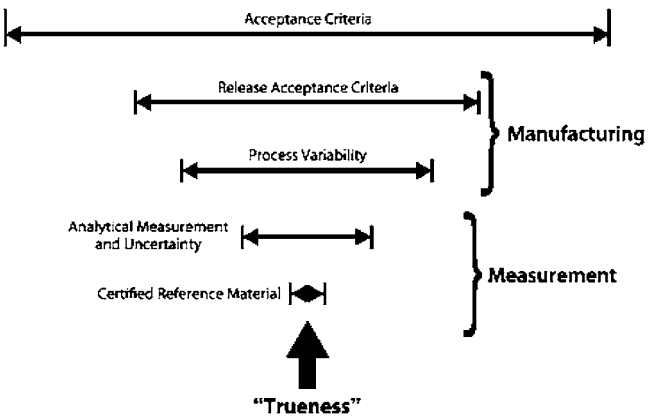

Fig. 2 Realms of specifications and measurements.

(first parties). Conformity assessment bodies (regulatory or other third parties) must ensure by measurement that food and drug articles in commerce meet established acceptance criteria. Practitioners, patients, and consumers must be assured that food and drug articles are of good quality by testing according to modern measurement science and good manufacturing practices according to modern manufacturing science. Both manufacturing and measurement science speak to knowledge that ensures comparability of results without regard to time or space (20).

If appropriately established and maintained, the entire system of measurement for food and drug articles assures all parties that good quality food and drugs are being purchased and used. Food and drug measurements will record values either in units of mass or units. Different methods or procedures, or even execution of the same procedure at different times or places, may introduce biases. Without traceability, the magnitude of these biases remains unknown. A common reference material somewhere higher in the cascade allows measurement results to be comparable (Fig. 1). A supplier who releases material at the acceptance criteria without understanding both traceability and uncertainty of results may unknowingly release adulterated material into commerce. A buyer who purchases from a supplier and conducts testing must rely on a common reference material to confirm that the supplier's results are acceptable, or the buyer risks using poor quality material. Testing of different procedures to ensure that they are acceptable, equivalent, or better must use a common reference material. Regulatory agencies and purchasers who monitor the quality of food and drug articles in commerce must necessarily determine comparability of results relative to a common reference material. Harmonization can advance with the understanding that reference materials downstream can be declared equivalent to one another by testing to a common material. Also, results from different procedures can be declared equivalent or better when compared to equivalent or common material.

Indeed, measurement science offers the hope of much more rapid harmonization of regulatory (private) and compendial (public) specifications for articles of food and drug commerce than heretofore has been considered possible. A globally harmonized measurement system for food and drugs would a) reduce testing, b) reduce likelihood of failure, particularly when coupled with modern manufacturing science (16), and c) promote harmonization. Although initial costs might be incurred, the value of measurement results that are comparable across time, space, and technology appear to be high both in terms of direct costs and payor and consumer confidence.

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