

Thomas C. Kupiec, PhD

*Analytical Research Laboratories
Oklahoma City, Oklahoma*

Claudia Okeke, PhD

*United States Pharmacopoeial Convention, Inc.
Rockville, Maryland*

Loyd V. Allen, Jr., PhD, RPh

*International Journal of Pharmaceutical Compounding
Edmond, Oklahoma*

Clay Denison

*Analytical Research Laboratories
Oklahoma City, Oklahoma*

Quality-Control Analytical Methods: Glossary of Quality Control/Quality Assurance Terms in Pharmaceutical Compounding

Compounding pharmacists are being introduced to many terms used in chapters of the *United States Pharmacopoeia (USP)*. It is imperative that both pharmacists and technicians understand each term and its application if they are to stay in compliance. This glossary defines many of those terms and is intended to equip pharmacists and technicians with the basic knowledge they need to apply these terms properly. While this glossary of important and sometimes misunderstood terms is not a complete list of the terms that appear in *USP* chapters and the compounding literature, it does provide a starting point for understanding these important definitions.

Activity – The capacity of a substance to take part in a chemical reaction or physiological process.

Antimicrobial effectiveness test – Investigation whose purpose is to determine whether the concentration of preservative present in a formulation is effective at prohibiting microbial growth in the product. Used in *USP* Chapter <51>.

Aseptic preparation – Preparation of sterile dosage units from sterile components using sterile equipment (eg, syringes, needles) and manipulation techniques in a suitable controlled environment so as to keep the dosage units sterile without employing a final sterilization.

Bacterial endotoxins – A toxin that forms an integral part of the cell wall of certain bacteria and is released upon destruction of the bacterial cell. Endotoxins produce a variety of responses in the body, including nonspecific inflammation and fever. Discussed in *USP* Chapter <85>. (Also see **Pyrogen**.)

Bacterial endotoxin units – A unit of measurement of the quantity of bacterial endotoxins present in a bulk chemical or dosage form.

Beyond-use date – The date after which a compounded preparation is not to be used. The date is based on the chemical stability of the drug (see *USP* Chapter <795> for guidelines) or the limits established in *USP* Chapter <797>, whichever is shorter. It is similar to an expiration date, but because compounded preparations are intended for administration immediately or after short-term storage, their beyond-use dates may be based on criteria other than those used to assign expiration dates for manufactured products.

Biological indicators – A preparation of a specific microorganism that provides a defined and stable resistance to a specific sterilization process. A biological indicator can be used to assist in development and establishment of a validated sterilization process for a particular article. Described in *USP* Chapter <1035>.

Bulk chemical/drug – Purified active drug substance for use in preparing dosage units for patient administration. Also termed “raw material,” the bulk drug is combined with various other materials into a preparation suitable for patient administration.

Calibration – Checking or adjusting the accuracy of a measuring instrument by comparing it with a standard.

Certificate of analysis – A document generally provided by the manufacturer or supplier that specifies the results of quality tests to assure that a bulk chemical or finished drug product meets the required specifications.

Compliance – Observance of official requirements.

Consultant/consulting – One who acts in an advisory capacity to a physician, a business, or other entity.

Container/closure – The combination of packaging components used to protect and preserve manufactured drug products (including bulk chemicals) and compounded preparations. These include glass or plastic bottles and caps; glass or plastic vials and rubber stoppers; plastic bags; and glass ampules.

Degradation product – A molecule resulting from a structural change in the drug substance (through oxidation, aggregation, proteolysis, or a similar process) that occurs over time. These changes may be due to processing or storage techniques, and

some degradation products are pharmacologically active or more toxic than the original drug.

Endotoxins – (See **Bacterial endotoxins**.)

Excipients – All materials and substances other than the active drug substance that are incorporated into dosage forms. Also termed “inactive components,” although many excipients have biological activity themselves.

Expiration date – Identifies the interval during which the manufactured formulation may be expected to meet the requirements of the Pharmacopeial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used.

Formulation – The recipe of components (drugs and excipients) used to prepare dosage units for patient administration.

GCPs – Good Compounding Practices: Used in *USP* Chapter <1075>. Guidelines intended to ensure that methods used in compounding medications produce formulations that manifest the quality, purity, and safety needed for the medication’s intended use. Addresses responsibilities of the compounder; training; procedures and documentation; facilities and equipment; ingredient selection; packaging and labeling; compounding controls; and required recordkeeping.

GLPs – Good Laboratory Practices: Quality standards of practice for the operation of laboratories to ensure accurate and reliable results of testing.

GMPs – Good Manufacturing Practices: Guidelines intended to ensure that methods used in preparation of medications, excipients, and bulk chemicals result in products that manifest their purported quality, purity, safety, and suitability for use. Used in *USP* Chapter <1078>.

Growth media – A category of materials designed to serve as food for microorganisms to promote their growth. The growth media most commonly employed in drug testing are soybean casein digest medium and fluid thioglycollate medium.

Heavy metals – Metallic contaminants or impurities of bulk chemicals that may have adverse patient effects. Examples are lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum. The *USP* Heavy Metals test (*USP* Chapter <231>) is a general quality assurance test and is performed on bulk chemicals to ensure compliance of heavy metals with the official monographs.

Identity – The characteristics of an item that make it recognizable. In the pharmacopeia, it states “the identity of an official article, as expressed by its name, is established if it conforms in all respects to the requirements of its monograph and other relevant portions of the compendia.”

Impurity – Any component of the drug substance or final drug product that is not the chemical entity defined as the drug substance, an excipient, or other additive to the drug product.

ISO Certified – International Organization for Standardization Certification is intended to provide confidence that the organization meets at least minimum agreed standards. Because these standards are agreed on by many different countries and usually apply to all industries, they simply reflect good management practice.

LAL – Limulus amebocyte lysate test: A test methodology based on the blood of the horseshoe crab (*Limulus polyphemus*) that quantifies the amount of gram-negative bacterial endotoxins present in a bulk chemical or parenteral dosage form. Refer to *USP* Chapter <85> for more information.

Media fill validation/verification – Quality-assurance procedures designed to evaluate the acceptability of processing and preparation steps used in sterile drug preparation and the individuals employed in preparing sterile dosage units. Growth medium that promotes the growth of microorganisms is substituted for drug solutions in the preparation process. If the individuals and process are working properly, no microorganisms should be present in the growth medium. This is different than sterility testing. The procedure is described in *USP* Chapter <797>. (Also see **Sterility testing**.)

Microbial contamination risk levels – The *USP* lists three risk levels for compounded sterile preparations (CSPs) on the basis of potential for contamination. Refer to *USP* Chapter <797> for complete descriptions of risk levels.

- Low-risk level – Involves measuring, transferring, or mixing no more than three already sterile products using aseptic technique under Class 100 conditions.
- Medium-risk level – Involves complex and long-duration procedures using already sterile products or the combining of many small dosage forms into a large dosage form. Also includes items that do not contain broad-spectrum bacteriostatic agents and are administered over several days.
- High-risk level – Involves using nonsterile ingredients or devices before final sterilization.

Particulate matter – A quality-control test of finished injections and ophthalmic solutions to determine whether the particulate burden in the drug solution is below the limit set in the *USP*.

pH – A system for quantifying the amount of hydrogen ions in a solution.

Pharmacopeia/Pharmacopoeia – A reference issued by an officially recognized authority, which describes drugs, chemicals, and medicinal preparations and serves as a standard reference. In the United States this is the *United States Pharmacopeia*.

Policy – A high-level, overall plan embracing the general goals and acceptable procedures of the *USP*.

Potency – The pharmacological activity of a compound.

Preparation – A substance or compound prepared for a particular patient and purpose.

Preservative effectiveness test – (See **Antimicrobial effectiveness test**.)

Procedure – A systematic process that allows consistent achievement of the same results.

Product – A finished manufactured medication.

Protocol – A set of formal rules describing how something should be done.

Purity – Assurance that the item contains what it is labeled to contain.

Purity rubric – A set of authoritative criteria with a fixed scale used in subjective assessments of purity by describing the level of quality for each criterion (eg, poor, average, excellent).

Pyrogen – Any substance that produces a fever (eg, endotoxin).

Quality assurance – The overall systematic program of building quality into a product or preparation and the verification procedures used to ascertain that the quality program worked as expected.

Quality-control testing – Tests and evaluative procedures designed to ascertain the conformance of a specific drug batch or compound to established quality criteria and specifications. May include drug concentration analysis, pH, color, clarity, particulate matter, sterility, and endotoxin testing, among others. (Also see **Release testing**.)

Reference standard – A material for which the true value is known (meets *USP* requirements), which is used to determine validity.

Related compounds – Molecular entities similar to the active drug (but not identical) that are present in the bulk chemical as contaminants, usually resulting from the synthesis or purification procedures.

Release testing – Tests that must be completed before the compound can be released from the pharmacy for administration. Includes sterility and endotoxin testing, physical inspection, and compounding accuracy checks.

Residual solvents – Solvents that are used in bulk chemical preparation and purification processes and remain in the bulk drug as contaminants.

Sample – A portion of a preparation that will offer a true representation of the entire preparation and can be used for testing purposes.

Stability – The extent to which a preparation retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding.

Stability-indicating method – A test that accurately and selectively detects changes in the pertinent properties of a drug that occur with time, and can measure either the active ingredient or its degradation products without interference from other degradation products, processing impurities, excipients, or other potential impurities.

Stability study – A study designed to test the stability of a preparation over a predefined time period in predetermined environmental parameters.

Standard – An accepted measure of comparison.

Standard operating procedure (SOP) – Established methods to be followed while performing a given operation (eg, calibration of an instrument).

Sterile/Sterility – The quality of a material or dosage form of being free of viable (living) organisms, including microorganisms.

Sterility testing – Used in *USP* Chapter <71>. Tests designed to ascertain whether any viable microorganisms are present in specific dosage units, typically a batch of dosage units. This is different than media fill verification. (Also see **Media fill validation/verification**.)

Sterilization – Any process used to remove or destroy viable (living) microorganisms present in nonsterile drug products and preparations and devices. Typical processes include autoclaving (steam sterilization), filtration, and radiation.

USP Chapter <795> – The chapter of the *United States Pharmacopeia* that addresses pharmacy nonsterile compounding.

USP Chapter <797> – The chapter of the *United States Pharmacopeia* that addresses pharmacy sterile compounding.

USP Chapter <1075> – The chapter of the *United States Pharmacopeia* that addresses Good Compounding Practices.

USP Chapter <1160> – The chapter of the *United States Pharmacopeia* that addresses pharmaceutical calculations in prescription compounding.

Validation – The process that establishes through studies that the procedure used meets the requirements for the intended use.

Verification – Confirmation that the product meets established requirements.

ANALYTICAL TESTING
GREAT PRICES - FAST RESULTS

**STERILITY, ENDOTOXIN,
PARTICULATES**

**ACTIVE DRUG SUBSTANCE
ASSAYS**

**OSMOLARITY AND
VISCOSITY**

with results in three days!

Now you can test your products without excessive delay or expense that can interfere with your business. Send us one sample and see for yourself!

R_x Analytical, Inc.
Call us at 520.219.2900 or visit our website: www.rxanalytical.com

Address correspondence to Thomas C. Kupiec, PhD, Analytical Research Laboratories, 840 Research Parkway, Suite 546, Oklahoma City, OK 73104. E-mail: tkupiec@arlok.com ■