**Table 3. Sample Data for MKT Calculations**

| Intervals | Low Temperature (in °C) | High Temperature (in °C) | Average Temperature (in °C) | Average Temperature (in K) | $\Delta H/RT$ | $e^{-\Delta H/RT} \times 10^{16}$ |
|---|---|---|---|---|---|---|
| 1 | 0 | 5 | 2.5 | 275.6 | 36.284 | 1.746 |
| 2 | 2 | 8 | 5 | 278.1 | 35.958 | 2.419 |
| 3 | 3 | 9 | 6 | 279.1 | 35.829 | 2.752 |
| 4 | 3 | 14 | 8.5 | 281.6 | 35.511 | 3.782 |
| 5 | 7 | 15 | 11 | 284.0 | 35.211 | 5.106 |
| 6 | 1 | 6 | 3.5 | 276.6 | 36.153 | 1.990 |
| 7 | 5 | 15 | 10 | 283.1 | 35.323 | 4.565 |
| 8 | 2 | 14 | 8 | 281.1 | 35.575 | 3.548 |
| 9 | 2 | 6 | 4 | 277.1 | 36.088 | 2.124 |
| 10 | 3 | 10 | 6.5 | 279.6 | 35.765 | 2.934 |

# ⟨1163⟩ QUALITY ASSURANCE IN PHARMACEUTICAL COMPOUNDING

## INTRODUCTION

The need for a quality assurance system is well documented in *United States Pharmacopeia (USP)* chapters for compounded preparations (see *Quality Control* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩ and *Quality Assurance (QA) Program* under *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩). A quality assurance program is guided by written procedures that define responsibilities and practices that ensure compounded preparations are produced with quality attributes appropriate to meet the needs of patients and health care professionals. The authority and responsibility for the Quality Assurance program should be clearly defined and implemented and should include at least the following nine separate but integrated components: (1) training; (2) standard operating procedures (SOPs); (3) documentation; (4) verification; (5) testing; (6) cleaning, disinfecting, and safety; (7) containers, packaging, repackaging, labeling, and storage; (8) outsourcing, if used; and (9) responsible personnel.

The definition of compounding for the purpose of this chapter is defined in general test chapter ⟨795⟩.

The safety, quality, and efficacy and/or benefit of compounded preparations depend on correct ingredients and calculations; accurate and precise measurements; appropriate formulation, facilities, equipment, and procedures; and prudent pharmaceutical judgment. As a final check, the compounder shall review each procedure in the compounding process. To ensure accuracy and completeness, the compounder shall observe the finished preparation to ensure that it appears as expected and shall investigate any discrepancies and take appropriate corrective action before the prescription is dispensed to the patient.

The water used in all aspects of compounding should meet the requirements of *Waters for Pharmaceutical Purposes* ⟨1231⟩.

Radiopharmaceuticals and radiolabeled materials have unique characteristics requiring additional quality assurances described in *Radiopharmaceuticals for Positron Emission Tomography—Compounding* ⟨823⟩ and the *Radiopharmaceuticals as CSPs* section under ⟨797⟩.

The responsibilities of the compounder and compounding personnel can be found in chapters ⟨795⟩ and ⟨797⟩.

## TRAINING

Personnel involved in nonsterile or sterile compounding require additional, specific training and periodic retraining beyond the training needed for routine dispensing duties. A thorough quality assurance program for compounded preparations requires documentation of both training and skill competency. In addition, the authority and responsibility for the QA program should be clearly defined as implemented. Training for nonsterile compounders should meet or exceed the standards set forth in ⟨795⟩, and personnel training for sterile preparation compounders should meet or exceed the standards set forth in ⟨797⟩.

## STANDARD OPERATING PROCEDURES

SOPs for pharmaceutical compounding are documents that describe how to perform routine and expected tasks in the compounding environment, including but not limited to procedures involving:

- Beyond-Use dating
- Chemical and physical stability
- Cleaning and disinfecting
- Component quality evaluation
- Compounding methods
- Dispensing
- Documentation
- Environmental quality and maintenance
- Equipment maintenance, calibration, and operation
- Formulation development
- Labeling
- Materials and final compounded preparation handling and storage
- Measuring and weighing
- Packaging and repackaging
- Patient monitoring, complaints, and adverse event reporting
- Patient or caregiver education and training
- Personnel cleanliness and garb
- Purchasing
- Quality Assurance and Continuous Quality Monitoring
- Safety
- Shipping
- Testing
- Training and retraining

SOPs are itemized instructions that describe when a task will be performed, how a task will be performed, who will perform the task, why the task is necessary, any limitations in performing the task, and what action to take when unacceptable deviations or discrepancies occur.

SOPs must be reviewed regularly and updated as necessary. Auditing and verifying compliance with established SOPs should be performed periodically. The SOP should be specific to each device and process used in compounding.

Properly maintained and implemented SOPs are vital to preparation quality.

## DOCUMENTATION

The purpose of documentation is to provide a record of all aspects of compounding operations and procedures that are described in this chapter, in ⟨795⟩, and in ⟨797⟩. Information on the compounding record should ideally be entered as the tasks are performed or as testing data is received. Compounding records should be reviewed for accuracy, completeness (as appropriate) and approved by QA personnel, prior to dispensing. Additionally, beyond-use dating and sterility studies, where appropriate, should be documented by reference to at least one of the following:

- Stability studies published in peer-reviewed literature,
- In-house or laboratory conducted stability and/or sterility studies,
- National compendia, or
- An extrapolation of above based on professional judgment.

## VERIFICATION

Verification involves authoritatively signed assurance and documentation that a process, procedure, or piece of equipment is functioning properly and producing the expected results. The act of verification of a compounding procedure involves checking to ensure the calculations, weighing and measuring, order of mixing, and compounding techniques and equipment were appropriate and accurately performed. The quality of ingredients should be verified upon receipt (e.g., Certificate of Analysis, manufacturer's label on commercial products, etc.). Verification may require outside laboratory testing when in-house capabilities are not adequate. Equipment verification methods are sometimes available from manufacturers of the specific equipment or can be developed in-house. The responsibility for assuring that equipment performance is verified, including work completed by contractors, resides with the compounder.

See *Component Selection, Handling, and Storage* under ⟨795⟩.

## TESTING

A quality assurance program for compounded preparations should include testing during the compounding process and of the finished compounded preparation, when appropriate, as described in chapters ⟨795⟩ and ⟨797⟩. The compounder should have a basic understanding of pharmaceutical analysis to ensure that valid results are obtained when tests are being conducted, whether they are done in-house or outsourced. Acceptance criteria shall be determined prior to testing. Testing every compounded preparation is neither practical nor officially required, but compounders should conduct visual inspections and know: (1) the importance of testing in the overall quality program in the compounding facility, (2) when to test, (3) what to test, (4) what appropriate method(s) and equipment to use, (5) how to interpret the results, (6) the limits of the test, and (7) specific actions required when a preparation does not meet specifications. Investigative and corrective action should extend to other preparations that may have been associated with the specific failure or discrepancy. Testing may involve one or more quality attributes, and each test will have one or more acceptable procedures, usually with well-defined acceptance criteria.

The goal in testing is to determine accurately the adequacy of the compounding process and the quality of the preparation. Any testing procedure used should have accuracy, reproducibility, and specificity. No single testing procedure is suitable for all drugs or preparations because a number of factors determine the validity and reliability of results.

Compounding professionals have two options for the testing that is required for compounded preparations or their ingredients. Some testing methods can easily be performed at the compounding site, but some may need to be outsourced to a contract laboratory. Some testing methods can be conducted in-house by an individual who possesses a good understanding of pharmaceutical analysis and proper training. See *Table 1* for a list of compendial testing methods and *USP* chapters for reference.

**Table 1. U.S. Pharmacopeia Chapters for Selected Quality Testing Methods and Procedures**

| | Chapter Title | Chapter |
|---|---|---|
| **General Testing** | | |
| Boiling point | Distilling Range | ⟨721⟩ |
| Density | Density of Solids | ⟨699⟩ |
| Ion selective potentiometry | — | — |
| Loss on drying | Loss on Drying | ⟨731⟩ |
| | Pharmaceutical Calculations in Prescription Compounding | ⟨1160⟩ |
| Melting point | Melting Range or Temperature | ⟨741⟩ |
| Osmolality and osmolarity | Pharmaceutical Calculations in Prescription Compounding | ⟨1160⟩ |
| | Osmolality and Osmolarity | ⟨785⟩ |
| Particle size | Powder Fineness | ⟨811⟩ |
| Particulate matter in injections | Particulate Matter in Injections | ⟨788⟩ |
| pH | pH | ⟨791⟩ |
| Refractive index | Refractive Index | ⟨831⟩ |
| Viscosity change | Viscosity | ⟨911⟩ |
| Volumetric | Prescription Balances and Volumetric Apparatus | ⟨1176⟩ |
| Weight | Prescription Balances and Volumetric Apparatus | ⟨1176⟩ |
| **Spectroscopy** | | |
| Flame emission and atomic absorption spectroscopy | Spectrophotometry and Light-Scattering | ⟨851⟩ |
| Fluorescence/phosphorescence spectroscopy | Spectrophotometry and Light-Scattering | ⟨851⟩ |
| Infrared spectroscopy | Spectrophotometry and Light-Scattering | ⟨851⟩ |
| Ultraviolet/visible spectroscopy | Spectrophotometry and Light-Scattering | ⟨851⟩ |

**Table 1. U.S. Pharmacopeia Chapters for Selected Quality Testing Methods and Procedures** *(Continued)*

| | Chapter Title | Chapter |
|---|---|---|
| **Chromatography** | | |
| Column chromatography (CC) | Chromatography | ⟨621⟩ |
| Gas chromatography (GC) | Chromatography | ⟨621⟩ |
| High-performance liquid chromatography (HPLC) | Chromatography | ⟨621⟩ |
| Paper chromatography (PC) | Chromatography | ⟨621⟩ |
| Thin-layer chromatography (TLC) | Chromatography | ⟨621⟩ |
| **Microbiology** | | |
| Endotoxin testing | Bacterial Endotoxins Test | ⟨85⟩ |
| Microbial limit testing | Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests | ⟨61⟩ |
| | Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms | ⟨62⟩ |
| Preservative effectiveness testing | Antimicrobial Effectiveness Testing | ⟨51⟩ |
| Sterility | Sterility Tests | ⟨71⟩ |

If testing is done at the compounding site, appropriate equipment shall be obtained and qualified either by the manufacturer upon sale or by the compounding professional upon receipt and shall be maintained, calibrated, and used properly. If testing is outsourced, the compounding professional should determine what to outsource, how to select a laboratory, and should develop an ongoing relationship with the laboratories chosen. Contract laboratories shall follow standards set forth in *USP* general chapters, as appropriate, and preferably should be registered with the U.S. Food and Drug Administration (FDA).

**Selection of a Testing Method**—One general consideration in testing procedure selection is the type of information needed, such as quantitative (strength, concentration), semiquantitative (where a tolerance level is involved, as in endotoxin levels), or qualitative (presence/absence testing, including substance identification, sterility). Another consideration involves the physical and chemical characteristics of the analyte, including solubility, partition coefficient, dissociation constant (pKa), volatility, binding, and the quantity present. The testing method selected also depends upon factors such as sample handling/preparation/purification requirements; type of data needed; and accuracy, reproducibility, and specificity required.

The degree of quantitative measurement and specificity must be considered in the verification process. The typical analytical characteristics used in method verification include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and ruggedness. Generally, the greater the level of accuracy, precision, or specificity required, the more sophisticated and expensive the testing methods needed. The methods used are also governed by the types of instrumentation available and the standards available for comparison.

Pharmaceutical analysis decisions include procedure selection, obtaining a representative sample (the number of preparation units selected to adequately represent the entire formulation, e.g., 10 randomly selected capsules from a preparation of 100 capsules), storage/shipping of the sample, sample preparation for analysis, the actual analysis, data acquisition, data treatment, and interpretation.

The compounding professional is responsible for implementing a program using selected testing methods for the preparations compounded in the facility. *USP* chapters on spectroscopy and chromatography methods are referenced in *Table 1*. Examples of general and microbiological testing methods are discussed later in this chapter. Examples of selected testing methods for bulk substances and various dosage forms (see *Pharmaceutical Dosage Forms* ⟨1151⟩) are shown in *Table 2*.

**Sampling Requirements**—Before collecting samples for testing, compounding professionals should consider the following factors:

- Quantity of preparation being compounded, for a specific prescription versus in anticipation of prescriptions routinely received
- Number of samples needed
- Destructive or nondestructive testing
- Appropriate methods of obtaining representative samples
- Physical state of the samples (solid, liquid, or gas)
- Type of container required for collection and storage
- Any special handling and shipping requirements or restrictions (e.g., controlled drug substances, dangerous or hazardous chemicals, flammable or caustic substances, and refrigerated or frozen preparations)

**Storage Requirements**—Storage requirements for samples must be specified, including type of container, temperature, humidity, and light protection (see *General Notices and Requirements* and the *Containers, Packaging, Repackaging, Labeling, and Storage* section in this chapter).

The effect(s) that any substance has on the compounded preparation that may interfere or alter the results must be known beforehand. When sending a preparation to a contract laboratory, the compounder should provide the complete written formulation so that the laboratory can quickly determine if there may be any interfering substances present.

**Data Interpretation Requirements**—The collection of raw data from the testing process must be completed accurately. One must ensure that appropriate and valid descriptive statistics (e.g., mean, standard deviation) are used to analyze the data and that the operating parameters of the analytical instruments are well-established. Reference values, if available, should be provided with the analytical results. A description of the analytical controls used by the laboratory is important for documentation, as is the source of reference standards used to establish standard curves.

**Personnel Requirements and Considerations**—If testing is done in-house, personnel involved in this activity must be appropriately trained and evaluated with documentation of the training and evaluation. If testing is outsourced, the compounder must be assured of the credentials, proper training, and continuing competency activities of the personnel in the contract laboratory.

## PHYSICAL TESTING OF DOSAGE UNITS

NOTE: In this section the terms "unit" and "dosage unit" are synonymous. To ensure the consistency of dosage units, each unit in a batch should have a uniform weight within a narrow range. Dosage units are defined as dosage forms containing a single dose or a part of a dose in each unit. If multiple dose units are compounded in a batch formulation, the total number of units should not deviate outside of ±10% of the theoretical number of units.

**Table 2. Selected Compendial Testing Methods for Bulk Substances and Various Dosage Forms**

| Bulk Substances and Dosage Forms | Testing Method[a] | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Wt** | **Vol** | **pH** | **Osm** | **RI** | **Sp Gr** | **MP** | **UV/Vis** | **HPLC** | **GC** | **IR** | **Sterile** | **Endotoxin** | **PM** |
| Bulk substances | – | – | + | – | + | – | + | + | + | + | + | – | +[b] | – |
| Capsules | + | – | – | – | – | – | – | – | + | + | – | – | – | – |
| Emulsions | + | + | + | – | – | + | – | – | + | + | – | – | – | – |
| Gels | + | + | + | – | + | + | – | – | + | + | – | – | – | – |
| Inhalations | + | + | + | + | + | + | – | + | + | + | – | + | + | – |
| Injections | + | + | + | + | + | + | – | + | + | + | – | + | + | + |
| Inserts | + | – | – | – | – | + | + | – | + | + | – | – | – | – |
| Irrigations | + | + | + | + | + | + | – | + | + | + | – | + | + | – |
| Lozenges | + | – | – | – | – | – | – | – | + | + | – | – | – | – |
| Nasals | + | + | + | + | + | + | – | + | + | + | – | *[c] | – | – |
| Ophthalmics | + | + | + | + | + | + | – | + | + | + | – | + | – | +[d] |
| Otics | + | + | + | + | + | + | – | + | + | + | – | – | – | – |
| Powders | + | – | – | – | – | – | – | – | + | + | – | – | – | – |
| Semisolids | + | – | + | – | – | + | + | – | + | + | – | – | – | – |
| Solutions, nonsterile | + | + | + | + | + | + | – | + | + | + | – | – | – | – |
| Sterile implant gels | + | + | + | + | + | + | – | + | + | + | – | + | + | – |
| Sterile implant solids | + | + | – | – | – | – | + | + | + | + | – | + | + | – |
| Sticks | + | – | – | – | – | + | + | – | + | + | – | – | – | – |
| Suppositories | + | – | – | – | – | + | + | – | + | + | – | – | – | – |
| Suspensions, nonsterile | + | + | + | – | – | + | – | – | + | + | – | – | – | – |
| Tablets | + | – | – | – | – | – | – | – | + | + | – | – | – | – |

[a] Wt, weight; Vol, volume; Osm, osmolality/osmolarity; RI, refractive index; Sp Gr, specific gravity; MP, melting point; UV/Vis, ultraviolet/visible spectroscopy; HPLC, high-performance liquid chromatography; GC, gas chromatography; IR, infrared spectroscopy; PM, particulate matter; +, test applicable; –, test not applicable.

[b] Endotoxin testing may be needed for bulk substances used in compounding some sterile preparations.

[c] *, microbial limits (see *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* ⟨1111⟩ and *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩).

[d] Solutions only, not suspensions or ointments.

## WEIGHT ASSESSMENT

First, zero or tare the balance. During the compounding process intermediate weighing may be necessary to ensure that all substances have been included and weighed accurately.

At the end of the compounding process, for the dosage form and quantity designated, take care to preserve the integrity of each dosage unit during the following assessment procedures. Assume the concentration (weight of drug substance per weight of dosage unit) is uniform. The following are examples of weight assessment.

**Hard Capsules—**

- Zero or tare balance with an empty capsule.
- Accurately weigh each individual filled capsule from a representative sample of the finished batch (for example, a minimum of 5% of total capsules or 10 individual capsules, whichever is less) and record the weight of each finished capsule on the compounding record.
- Calculate the theoretical weight of a finished capsule's contents.
- Compare the actual content weight of each finished capsule in the representative sample with the theoretical weight of a finished capsule's contents.
- Determine if there is a deviation outside ±10% with any weight of a finished capsule's contents and the theoretical weight of a finished capsule, and if so,
  - — Review the compounding record to ensure no steps were omitted.
  - — Repeat with a larger representative sample of the finished batch (10% of total capsules or 20 individual capsules, whichever is less). Do not mix with the first batch tested.
- If a deviation outside of ±10% is discovered in the second representative sample, then destroy the batch.

**Other Solids (Including Tablets, Suppositories, Inserts, and Lozenges)—**

- Accurately weigh each individual dosage unit from a representative sample of the finished batch (for example, a minimum of 5% of total tablets or 10 individual tablets, whichever is less) and record the weight of each dosage unit on the compounding record.
- Calculate the theoretical weight of the dosage unit.
- Compare the actual weight of each dosage unit in the representative sample with the theoretical weight of a dosage unit.
- Determine if there is a deviation outside ±10% with any weight of a finished dosage unit and the theoretical weight of a finished dosage unit, and if so,
  - — Review the compounding record to ensure no steps were omitted.
  - — Repeat with a larger representative sample of the finished batch (10% of total tablets or 20 individual tablets, whichever is less). Do not mix with the first batch tested.
- If a deviation outside of ±10% is discovered in the second representative sample, then destroy the batch.

**Semi-Solids (Including Creams, Gels, and Ointments)—**

- Accurately weigh an empty container and record the weight on the compounding record.
- Fill an empty container with the final compounded preparation.
- Calculate the theoretical weight of the compounded preparation.
- Weigh the filled container.
- Determine if there is a deviation outside of ±10%, and if so, review the compounding record to ensure no steps were omitted. If the deviation cannot be explained, destroy the batch and prepare a new one.

*Additional Quality Assurance Checks Before Packaging Semi-Solids*—
- — Visually inspect the preparation for foreign materials and expected appearance.
- — Measure pH, when applicable.

## MICROBIOLOGICAL TESTING

Microbiological testing for pharmacy compounding includes sterility, endotoxin, preservative effectiveness testing, and microbial limit testing (see ⟨797⟩).

**Sterility Testing**—Sterility tests may be conducted using commercial kits or by developing and verifying USP sterility testing protocols. Standards and procedures are explained in ⟨71⟩.

**Endotoxin Testing**—Endotoxin tests may be conducted using commercial kits or by purchasing the components separately. Endotoxin testing may be performed in-house with appropriate training and experience. See ⟨85⟩.

**Preservative Effectiveness Testing**—Preservative effectiveness testing may be conducted when preparing a frequently compounded formulation that contains a preservative. When such a test is performed, the results shall support the beyond-use-date (BUD) assigned to the compounded preparations. See ⟨51⟩.

**Microbial Limit Testing**—Microbial limit testing may be conducted to provide an estimate of the number of viable aerobic microorganisms (see ⟨61⟩) or to demonstrate freedom from designated microbial species (see ⟨62⟩).

## CLEANING, DISINFECTING, AND SAFETY

This section applies to both equipment and facilities (see ⟨795⟩, ⟨797⟩, and *Disinfectants and Antiseptics* ⟨1072⟩).

## CONTAINERS, PACKAGING, REPACKAGING, LABELING, AND STORAGE

For storage, packaging, repackaging, and labeling of compounded preparations and repackaging of manufactured products (when defined as compounding in *USP*), refer to *USP General Notices and Requirements* and the following general chapters:
- *Containers—Glass* ⟨660⟩
- *Containers—Plastic* ⟨661⟩
- *Elastomeric Closures for Injections* ⟨381⟩
- *Good Packaging Practices* ⟨1177⟩
- *Good Repackaging Practices* ⟨1178⟩
- *Good Storage and Shipping Practices* ⟨1079⟩
- *Injections* ⟨1⟩
- *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨1146⟩
- *Packaging—Unit-of-Use* ⟨1136⟩
- *Pharmaceutical Dosage Forms* ⟨1151⟩
- *Pharmaceutical Stability* ⟨1150⟩
- *Repackaging into Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms* ⟨681⟩

## OUTSOURCING

NOTE: This section addresses only the purchasing or selling of compounded preparations from pharmacy to pharmacy, not the outsourcing of analytical testing of compounded preparations.

For pharmacies that prepare outsourced compounded preparations or repackaged commercial products, documentation of beyond-use dating, as defined previously in the *Documentation* section of this chapter, is required and shall be provided upon request. In addition, documentation of compliance with *USP* chapters ⟨795⟩ and ⟨797⟩ is required and shall be provided upon request.

For facilities that receive outsourced compounded preparations or repackaged commercial products, documentation shall be on file for all BUDs assigned to those preparations or products.

## RESPONSIBLE PERSONNEL

The responsibility and authority for a quality assurance program should be clearly defined and implemented. Personnel responsible for the quality assurance program should have the education, training, and experience necessary to perform the assigned functions. Quality assurance personnel should assure that documentation, verification, and testing are performed in accordance with written policies and procedures. If deviations from approved policies and procedures occur, it is the responsibility of the quality assurance personnel to investigate and to implement appropriate corrective action. Documentation of any investigations and corrective actions is the responsibility of the quality assurance personnel. Responsible personnel in the quality assurance program are essential in assuring the safety, identity, strength, quality, and purity of compounded drug preparations.

## SUMMARY

A quality assurance program is necessary to ensure the quality of compounded preparations. A sound quality assurance program includes detailed SOPs, documentation, verification, analytical and microbiological testing as appropriate to particular compounded preparations, and responsible quality assurance personnel. Compounding professionals must determine the types of testing and degree of testing that will be a part of their quality assurance program. They also must decide whether to perform testing in-house or outsource it to a contract laboratory.

# ⟨1171⟩ PHASE-SOLUBILITY ANALYSIS

Phase-solubility analysis is the quantitative determination of the purity of a substance through the application of precise solubility measurements. At a given temperature, a definite amount of a pure substance is soluble in a definite quantity of solvent. The resulting solution is saturated with respect to the particular substance, but the solution remains unsaturated with respect to other substances, even though such substances may be closely related in chemical structure and physical properties to the particular substance being tested. Constancy of solubility, like constancy of melting temperature or other physical properties, indicates that a material is pure or is free from foreign admixture except in the unique case in which the percentage composition of the substance under test is in direct ratio to solubilities of the respective components. Conversely, variability of solubility indicates the presence of an impurity or impurities.

Phase-solubility analysis is applicable to all species of compounds that are crystalline solids and that form stable solutions. It is not readily applicable to compounds that form solid solutions with impurities.

The standard solubility method consists of six distinct steps: (1) mixing, in a series of separate systems, increasing quantities of material with measured, fixed amounts of a solvent; (2) establishment of equilibrium for each system at