be accurately weighed (see *Weights and Balances* (41) and *Volumetric Apparatus* (31)). Due account should also be taken of the potential errors associated with weighing small masses (see also Section 6.50.20.1 *Adjustments to Solutions in the General Notices and Requirements*). Reference Standards that are defined on a content-per-container basis are an exception, as noted above.

USP RS instructions for use include the following:

- **As Is**: Use without any prior treatment or correction for volatiles. This is the preferred option, and is selected whenever valid data indicate that the volatiles content is constant over time.
- **Dry Before Use**: Use immediately after drying under stated conditions. Drying should not be performed in the original container. A portion of the material should be transferred to a separate drying vessel.
- **Determine Water Content Titrimetrically At Time of Use**: Use with a correction for the water content or the loss on drying, determined on a separate portion of material. Where the titrimetric determination of water is required at the time a Reference Standard is to be used, proceed as directed for Method I under *Water Determination* (921). Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts (about 50 mg of the Reference Standard), titrate with a 2- to 5-fold dilution of the reagent. Where the determination of the loss on drying on a separate portion of USP RS is required, proceed as directed on the label. Sample sizes smaller than those required in the general test chapter *Loss on Drying* (751) may be used for a USP RS provided that the user can obtain a sufficiently accurate result. Whenever the labeled directions for use require drying or a correction for volatiles, it should be performed at the time of use. Further experimental details should be controlled by the user’s Standard Operating Procedures and good laboratory practices.

**STORAGE**

USP RS should be stored in the packaging configuration provided by USP (e.g., vials that are packaged in hermetically sealed bags). When special storage conditions are specified, label directions should be followed. Unopened vials should be stored as indicated on the label. The user is responsible for ensuring that the contents of opened vials continue to be suitable for their intended use and that value assignment and uncertainty information are maintained.

### Diagrams

**Apparatus for Tests and Assays**

**16** AUTOMATED METHODS OF ANALYSIS

Where a sufficiently large number of similar units are to be subjected routinely to the same type of examination, automated methods of analysis may be far more efficient and precise than manual methods. Such automated methods have been found especially useful in testing the content uniformity of tablets and capsules and in facilitating methods requiring precisely controlled experimental conditions. Many manufacturing establishments, as well as the laboratories of regulatory agencies, have found it convenient to utilize automated methods as alternatives to Pharmacopeial methods (see *Procedures under Tests and Assays in the General Notices and Requirements*). In addition, the detection system and calculation of results for automated methods are often computerized.

Before an automated method for testing an article is adopted as an alternative, it is advisable to ascertain that the results obtained by the automated method are equivalent in accuracy and precision to those obtained by the prescribed Pharmacopeial method, bearing in mind the further principle stated in the *General Notices and Requirements* that "where a difference appears, or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive."

It is necessary to monitor the performance of the automated analytical system continually by assaying standard preparations of known composition frequently interspersed among the test preparations. Where immiscible solvents are employed in the automated apparatus for rapid extractions, they are often separated for analysis before complete extraction is attained, and the chemical reactions utilized in automated methods rarely are stoichiometric. Both the accuracy and the precision of the determinations depend upon precise adjustment of the equipment, so maintained that all standard and test preparations are exposed to identical physical and chemical manipulations for identical time intervals. Excessive variability in the response of the standard preparations indicates that the analytical system is malfunctioning and that the test results are therefore invalid. However, where automated systems are shown to operate reliably, the precision of the automated method may surpass that of the manual procedure employing the same basic chemistry.

Many of the manual methods given in this Pharmacopeia can be adapted for use in automated equipment incorporating either discrete analyzers or continuous flow systems and operating under a variety of conditions. On the other hand, an analytical scheme devised for a particular automated system may not be readily transposable for use either in a manual procedure or in other types of automated equipment.

The apparatus required for manual methods is, in general, less complicated than the apparatus of automated systems, even those systems used for the direct automated measurement of a single analyte (i.e., the substance being determined or analyzed for) in a binary mixture. However, because of their versatility, automated systems designed for the rapid determination of a specified substance often can be readily modified by the addition of suitable modules and accessories to permit the determination of one or more additional substances in a dosage form. Such extended systems have been utilized, for example, in the automated analysis of articles containing both estrogens and progestogens.

The accompanying pertinent diagrams represent examples of automated methods. Diagrams for official methods are reproduced here rather than in the individual monographs. The descriptions of the procedural details in these methods exemplify the general approach in automated analysis applicable to dosage forms. It should be noted that the diagrams, with many minutiae, are an indispensable part of the directions for conducting the analysis.

**DIAGRAMS**

The diagrams shown below are arranged in alphabetic order by the name of the drug first mentioned, where the diagram is for a procedure for a specific article. Where there is no procedure in this chapter for a particular diagram, reference is to be made to the named monograph.
ANTIBIOTICS—HYDROXYLAMINE ASSAY

The following procedure is applicable for the assay of those Pharmacopeial antibiotics, such as cephalosporins and penicillins, that possess the beta-lactam structure.

Apparatus—Automatic analyzer consisting of (1) a liquid sampler, (2) a proportioning pump, (3) suitable spectrophotometers equipped with matched flow cells and analysis capability at 480 nm, (4) a means of recording spectrophotometric readings, and/or computer for data retrieval and calculation, and (5) a manifold consisting of the components illustrated in the accompanying pertinent diagram.

Reagents—

Hydroxylamine Hydrochloride Solution—Dissolve 20 g of hydroxylamine hydrochloride in 5 mL of polyoxyethylene (23) lauryl ether solution (1 in 1000), and add water to make 1000 mL.

Acetate Buffer—Dissolve 173 g of sodium acetate and 20.6 g of sodium acetate in water to make 1000 mL. Dilute 75 mL of this solution with water to 500 mL, and mix.

Ferric Nitrate Solution—Suspend 233 g of ferric nitrate in weighed quantity of USP Ascorbic Acid RS in 500 mL of water, cool and dilute with water to 500 mL, and mix.

USP Reference Standards (11)—Use the USP Reference Standard as directed in the individual monograph.

Standard Preparation—Unless otherwise directed in the individual monograph, dissolve an accurately weighed quantity of the USP Reference Standard in water, and quantitatively dilute with water to obtain a solution having a known concentration of about 1 mg per mL.

Assay Preparation—Unless otherwise directed in the individual monograph, using the specimen under test, prepare as directed under Standard Preparation.

Procedure—With the sample line pumping water, the other lines pumping their respective reagents, and the spectrophotometer set at 480 nm, standardize the system until a steady absorbance baseline has been established. Transfer portions of the Standard Preparation and the Assay Preparation to sampler cups, and place in the sampler. Start the sampler, and conduct determinations of the Standard Preparation and the Assay Preparation typically at the rate of 40 per hour, using a ratio of about 2:1 for sample and wash time. Calculate the potency by the formula given in the individual monograph, in which Ç is the concentration, in mg per mL, of USP Reference Standard in the Standard Preparation; P is the potency, in µg per mg, of the USP Reference Standard; and Åo and Åt are the absorbances, corrected for the absorbances of the respective blanks, of the solutions from the Assay Preparation and the Standard Preparation, respectively.

ASSAY FOR ASCORBIC ACID

The following procedure is applicable for the assay of ascorbic acid in Pharmacopeial multivitamin-minerals combination products (solid and liquid dosage forms) that contain components that interfere in other methods of assay.

Apparatus—Automatic analyzer consisting of (1) a liquid sampler; (2) a proportioning pump; (3) a suitable fluorimeter equipped with a flow cell and filters: primary—335 nm, and secondary—426 nm; (4) a means of recording fluorimeter readings; and (5) a manifold consisting of the components illustrated in the accompanying pertinent diagram.

Reagents—

Extracting Solution—Dissolve 600 g of metaphosphoric acid in 1200 mL of water. Add 400 mL of glacial acetic acid, dilute with water to 2000 mL, and mix.

Dilute Extracting Solution—Dissolve 60 g of metaphosphoric acid in 1200 mL of water. Add 160 g of sodium acetate, dilute with water to 2000 mL, and mix.

Hydroxylamine Hydrochloride Solution—Dissolve 200 mg of hydroxylamine hydrochloride in 5 mL of polyoxyethylene (23) lauryl ether by melting 150 g in a container on a steam bath and slowly adding approximately 250 mL of water with continuous stirring. Cool and dilute with water to make 500 mL.

Wash Solution—Add 1 mL of Surfactant Solution to 3000 mL of Dilute Extracting Solution, and mix.

Surfactant Solution—Prepare a 30% solution of polyoxyethylene (23) lauryl ether by dissolving 150 g in a container on a steam bath and slowly adding approximately 250 mL of water with continuous stirring. Cool and dilute with water to make 500 mL.

Carbon Extraction Solution—Dissolve 0.206 g of sodium acetate trihydrate in water to make 1000 mL, mix, and filter.

Phenylenediamine Solution—Dissolve 200 mg of o-phenylenediamine dihydrochloride in water to make 1000 mL, and mix. Prepare fresh daily.

USP Reference Standards (11)—USP Ascorbic Acid RS.

Standard Stock Solution—Dissolve an accurately weighed quantity of USP Ascorbic Acid RS in Dilute Extracting Solution to obtain a solution having a known concentration of about 0.1 mg per mL.

Standard Preparations—Transfer 1.00, 2.00, 3.00, 4.00, and 5.00 mL of Standard Stock Solution to separate 100-mL volumetric flasks, dilute the contents of each flask with Carbon Extraction Solution to volume, mix, and filter to obtain Standard Preparations A, B, C, D, and E having known concentrations of 10 µg, 20 µg, 30 µg, 40 µg, and 50 µg of USP Ascorbic Acid RS per mL, respectively.

Assay Preparation—

For Liquid Preparations—Transfer an accurately measured volume of the liquid preparation, equivalent to 150 mg of ascorbic acid, to a 100-mL volumetric flask. Add 10 mL of Extracting Solution and 6 mL of glacial acetic acid. Dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with Carbon Extraction Solution to volume, mix, and filter.

For Tablet Preparations—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quanti-
tity of the powder, equivalent to about 250 mg of ascorbic acid, to a 250-mL volumetric flask. Add 25 mL of Extracting Solution, 15 mL of glacial acetic acid, and about 100 mL of water, and swirl to mix. Heat for 15 minutes in a 70° water bath, swirling after about 7 minutes. Cool, and dilute with water to volume. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with Carbon Extracting Solution to volume, mix, and filter.

For Capsule Preparations—Empty the contents, if necessary by cutting open with a sharp blade, of not fewer than 20 Capsules in a suitable container, and mix thoroughly. Transfer a portion of the capsule contents, equivalent to about 250 mg of ascorbic acid, to a 250-mL volumetric flask, and proceed as directed for Tablets above, beginning with “Add 25 mL of.”

Procedure—With the sample line pumping the Wash Solution, the other lines pumping their respective reagents, and the fluorimeter equipped with proper filters, standardize the system by pumping until a steady baseline has been established. Transfer portions of the Standard Preparations and the Assay Preparation to sample cups, and place in the sampler. Start the sampler, and conduct determinations of each Standard Preparation and the Assay Preparation at the rate of 40 per hour, using a ratio of about 2:1 for sample and wash time. Derive a standard response line by plotting the respective Standard Preparation concentration (10.0, 20.0, 30.0, 40.0, and 50.0 μg per mL) versus transmittance. From the measured transmittance and the standard response line, determine the ascorbic acid concentration, C, in μg per mL of the Assay Preparation. Calculate the quantity, in mg, of C₆H₈O₆ in the portion of liquids, tablets, or capsule contents taken by the appropriate formula:
For Liquids: $5C/V$ in which $V$ is the volume, in mL, of liquid preparation taken to prepare the Assay Preparation.

For Tablets or Capsules: 12.5C.

**ASSAY FOR IODIDE**

**Apparatus**—Automatic analyzer consisting of (1) a liquid sampler, (2) a proportioning pump, (3) a heating bath, (4) a suitable colorimeter equipped with a 2.0- × 50-mm flow cell and analysis capability at 420 nm, (5) a means of recording colorimetric readings, and (6) a manifold consisting of the components illustrated in the accompanying pertinent diagram.

**Reagents**—

**Acetic Acid Carrier Solution**—Transfer 3.0 mL of glacial acetic acid to a 2000-mL volumetric flask containing about 800 mL of water. Add 2 mL of polyoxyethylene (23) lauryl ether, and dilute with water to volume.

**Surfactant Solution**—Prepare a 30% solution of polyoxyethylene (23) lauryl ether by melting 150 g in a container on a steam bath and slowly adding approximately 250 mL of water with continuous stirring. Cool, and dilute with water to make 500 mL.

**Arsenious Acid Solution**—Transfer 19.6 g of arsenic trioxide and 14.0 g of sodium hydroxide to a 2000-mL volumetric flask. Add about 150 mL of water, and dissolve with stirring. Dilute with water to a volume of about 800 mL, and add 66 mL of sulfuric acid. Cool to room temperature. Transfer 50.0 g of sodium chloride to the solution, and mix to dissolve. Add 2 mL of Surfactant Solution, dilute with water to volume, mix, and filter.

**Ceric Ammonium Sulfate Solution**—Transfer 12.65 g of ceric ammonium sulfate to a 1000-mL volumetric flask. Add about 700 mL of water followed by 100 mL of sulfuric acid, swirling to mix. Heat to dissolve, and cool to room temperature. Add 1 mL of Surfactant Solution, dilute with water to volume, mix, and filter.

**3% Acetic Acid Solution**—Transfer 30 mL of glacial acetic acid to a 1000-mL volumetric flask containing about 300 mL of water. Dilute with water to volume, and mix.

**Standard Preparations**—

**Standard Stock Solution**—Transfer an accurately weighed quantity of 1.3080 g of potassium iodide, previously dried for 24 hours at 105°, to a 1000-mL volumetric flask. Dilute with water to volume, and mix to obtain a solution having an iodide concentration of 1000 μg per mL.

**Intermediate Standard Solution**—Quantitatively dilute a suitable volume of Standard Stock Solution with water to obtain a solution having an iodide concentration of 1 μg per mL.

**Working Standard Preparations**—Transfer 2.0, 4.0, 6.0, 8.0, and 10.0 mL of Intermediate Standard Solution to separate 100-mL volumetric flasks. Add 5 mL of 3% Acetic Acid Solution. Dilute the contents of each flask with water to volume, and mix to obtain Standard Preparations A, B, C, D, and E having known iodide concentrations of about 0.02 μg per mL, 0.04 μg per mL, 0.06 μg per mL, 0.08 μg per mL, and 0.1 μg per mL, respectively.

**Assay Preparation**—

**For Liquid Preparations**—Transfer an accurately measured volume of the liquid preparation, equivalent to 16 μg of iodide, to a 200-mL volumetric flask. Add 10 mL of 3% Acetic Acid Solution to dissolve, dilute with deionized water to volume, mix, and filter. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, add 5.0 mL of 3% Acetic Acid Solution, dilute with deionized water to volume, mix, and filter to obtain a solution having an iodide concentration of about 0.08 μg per mL.

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Diagram for Automated Aspirin Determinative Step of the Dissolution Test for Aspirin, Alumina, and Magnesium Oxide Tablets


For Tablet Preparations—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 250 μg of iodide, to a 250-mL volumetric flask. Add 100 mL of 1 N hydrochloric acid, and mix with the aid of sonication for 30 minutes. Dilute with water to volume, mix, and filter. Transfer 8.0 mL of the filtered solution to a 100-mL volumetric flask, add 5 mL of 3% Acetic Acid Solution, dilute with water to volume, and mix to obtain a solution having an iodide concentration of about 0.08 μg per mL.

For Capsule Preparations—Empty the contents, if necessary by cutting open with a sharp blade, of not fewer than 20 Capsules into a suitable container, and mix thoroughly. Transfer a portion of the capsule contents, equivalent to about 250 μg of iodide, to a 250-mL volumetric flask and proceed as directed for Tablets above, beginning with “Add 100 mL of .”

Procedure—With the sample line pumping the Acetic Acid Carrier Solution, the other lines pumping their respective reagents, and the colorimeter equipped with 420-nm filters, standardize the system until a steady baseline has been established. Transfer portions of the Standard Preparations and the Assay Preparation to the sampler cups, and place in the sampler. Start the sampler, and conduct determinations of each Standard Preparation and the Assay Preparation at the rate of 30 per hour, using a ratio of about 1:4 for sample and wash time. Derive a standard response line by plotting the respective Standard Preparation concentration (0.02, 0.04, 0.06, 0.08, and 0.10 μg per mL) versus absorbance. [NOTE—This is an indirect absorbance relationship: the greater the iodide amount, the less the absorbance.] From the measured transmittance and the standard response line, determine the iodide concentration, C, in μg per mL, of the Assay Preparation. Calculate the quantity, in μg, of iodide in the portion of liquids, tablets, or capsules contents taken by the formula:

For Liquids: \(2000C/V\) in which \(V\) is the volume, in mL, of the liquid preparation taken to prepare the Assay Preparation.

For Tablets and Capsules: 3125C.

CONTENT UNIFORMITY OF NITROGLYCERIN TABLETS

This is not to be considered as the official method. It is detailed here for further illustration of descriptions of automated methods.

Apparatus—Automatic analyzer consisting of (1) a liquid sampler, (2) a proportioning pump, (3) a heating bath, (4) a suitable spectrophotometer equipped with a 5-mm flow cell and analysis capability at 545 nm, (5) a means of recording spectrophotometric readings, and (6) a manifold consisting of the components illustrated in the accompanying pertinent diagram.

Reagents—

1 Percent Strontium Hydroxide Solution—Dissolve 20.0 g of strontium hydroxide \([\text{Sr(OH)}_2 \cdot 8 \text{H}_2\text{O}]\) in 1800 mL of carbon dioxide-free water, heating if necessary. Cool to room temperature, dilute with carbon dioxide-free water to 2000 mL, and mix. Allow to stand overnight, and filter. Store the clear solution in tightly closed containers, protected from carbon dioxide.

0.3 Percent Procaine Hydrochloride Solution—Dissolve 3.0 g of procaine hydrochloride in water to make 1000 mL.

0.1 Percent N-(1-Naphthyl)ethylenediamine Dihydrochloride Solution—Dissolve 1.0 g of N-(1-naphthyl)ethylenediamine dihydrochloride in 1000 mL of water, dilute to 1000 mL, and mix.

Diagram for Automated Iodide Assay
dihydrochloride in water to make 1000 mL. Prepare fresh each week.

**Standard Preparation**—Dissolve an accurately weighed portion of 10% nitroglycerin-betalactose absorbate, previously standardized, in water, and dilute quantitatively and stepwise with water to obtain a solution having a known concentration of about 30 μg per mL.

**Test Preparation**—Dissolve 1 Nitroglycerin Tablet in water to obtain a solution having a concentration of about 30 μg of nitroglycerin per mL.

**Procedure**—With the sample line pumping water, the other lines pumping their respective reagents, and the spectrophotometer set at 545 nm, standardize the system by pumping until a steady absorbance baseline has been established. Transfer portions of the Standard Preparation and the Test Preparation to sampler cups, and place in the sampler. Start the sampler, and conduct determinations of the Standard Preparation and the Test Preparation at a rate of 30 per hour, using a ratio of 1:1 for sample and wash time. First, run two standards, discarding the first value, then continue the run using one standard after each five samples, recording the absorbance values. Calculate the quantity, in mg, of C₃H₅N₃O₉ in the Tablet taken by the formula:

\[
\frac{T}{D} \cdot \frac{T}{A_s} - \frac{C}{A_s} = \text{mg of nitroglycerin in the Tablet}
\]

in which T is the labeled quantity, in mg, of nitroglycerin in the Tablet; D is the concentration, in μg per mL, of nitroglycerin in the solution from the Tablet, based on the labeled quantity per Tablet and the extent of dilution; C is the concentration, in μg per mL, of nitroglycerin in the Standard Preparation; Aₜ is the absorbance of the Test Preparation; and Aₛ is the average of the absorbances of the two Standard Preparations that bracket the Test Preparation.
Diagram of Dissolution Test Method for Erythromycin Ethylsuccinate Tablets Labeled as Chewable

Diagram for Automated Drug Release and Content Uniformity Test for Propranolol Hydrochloride and Hydrochlorothiazide Extended-Release Capsules
Diagram for Automated Dissolution and Content Uniformity Test for Reserpine Tablets

Diagram for Automated Content Uniformity Test for Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets
Add the following:

**PRESCRIPTION CONTAINER LABELING**

**INTRODUCTION**

Medication misuse has resulted in more than 1 million adverse drug events per year in the United States. Patients’ best source (and often only source) of information regarding the medications they have been prescribed is on the prescription container label. Although other written information and oral counseling sometimes may be available, the prescription container label must fulfill the professional obligations of the prescriber and pharmacist. These obligations include giving the patient the most essential information needed to understand how to safely and appropriately use the medication and to adhere to the prescribed medication regimen.

Inadequate understanding of prescription directions for use and auxiliary information on dispensed containers is widespread. Studies have found that 46% of patients misunderstood one or more dosage instructions, and 56% misunderstood one or more auxiliary warnings. The problem of misunderstanding is particularly troublesome in patients with low or marginal literacy and in patients receiving multiple medications that are scheduled for administration using unnecessarily complex, nonstandardized time periods. In one study, patients with low literacy were 34 times more likely to misinterpret prescription medication warning labels. However, even patients with adequate literacy often misunderstand common prescription directions and warnings. In addition, there is great variability in the actual auxiliary warning and supplemental instructional information applied by individual practitioners to the same prescription. The specific evidence to support a given auxiliary statement often is unclear, and patients often ignore such information. The essential need for, and benefit of, auxiliary label information (both text and icons) in improving patient understanding about safe and appropriate use of their medications vs. explicit simplified language alone require further study.

Lack of universal standards for labeling on dispensed prescription containers is a root cause for patient misunderstanding, nonadherence, and medication errors. On May 18, 2007, the USP Safe Medication Use Expert Committee established an Advisory Panel to: 1) determine optimal prescription label content and format to promote safe medication use by critically reviewing factors that promote or distract from patient understanding of prescription medication instructions and 2) create universal prescription label standards for format/appearance and content/language.

In November 2009, the Health Literacy and Prescription Container Labeling Advisory Panel presented its recommendations to the Safe Medication Use Expert Committee, which then requested that USP develop patient-centered label standards for the format, appearance, content, and language of prescription medication instructions to promote patient understanding. These recommendations form the basis of this general chapter.

Note—These standards do not apply when a prescription drug will be administered to a patient by licensed personnel who are acting within their scope of practice.

**PRESCRIPTION CONTAINER LABEL STANDARDS TO PROMOTE PATIENT UNDERSTANDING**

Organize the prescription label in a patient-centered manner: Information shall be organized in a way that best reflects how most patients seek out and understand medication instructions. Prescription container labeling should feature only the most important patient information needed for safe and effective understanding and use.

Emphasize instructions and other information important to patients: Prominently display information that is critical for patients’ safe and effective use of the medicine. At the top of the label specify the patient’s name, drug name (spell out full generic and brand name) and strength, and explicit clear directions for use in simple language.

The prescription directions should follow a standard format so the patient can expect that each element will be in a recognized order each time a prescription is refilled.

Other less critical but important content (e.g., pharmacy name and phone number, prescriber name, fill date, refill information, expiration date, prescription number, drug quantity, physical description, and evidence-based auxiliary information) should not supersede critical patient information. Such less critical information should be placed away from dosing instructions (e.g., at the bottom of the label or in another less prominent location) because it distracts patients, which can impair their recognition and understanding.

Simplify language: Language on the label should be clear, simplified, concise, and familiar, and should be used in a standardized manner. Only common terms and sentences should be used. Do not use unfamiliar words (including Latin terms) or medical jargon.

Use of readability formulas and software is not recommended to simplify short excerpts of text like those on prescription labels. Instead, use simplified, standardized sentences that have been developed to ensure ease of understanding the instructions correctly (by seeking feedback from samples of diverse consumers).

Give explicit instructions: Instructions for use (i.e., the SIG or signatur) should clearly separate the dose itself from the timing of each dose in order to explicitly convey the number of dosage units to be taken and when (e.g., specific time periods each day such as morning, noon, evening, and bedtime). Instructions shall include specifics on time periods. Do not use alphabetic characters for numbers. For example, write “Take 2 tablets in the morning and 2 tablets in the evening” rather than “Take two tablets twice daily”.

Whenever available, use standardized directions (e.g., write “Take 1 tablet in the morning and 1 tablet in the evening” if the prescription reads b.i.d.). Vague instructions based on dosing intervals such as twice daily or 3 times daily, or hourly intervals such as every 12 hours, generally should be avoided because such instructions are implicit rather than explicit, they may involve numeracy skills, and patient interpretation may vary from prescriber intent. Although instructions that use specific hourly times (e.g., 8 a.m. and 10 p.m.) may be implied rather than implicit vague instructions, recommending dosing by precise hours of the day is less readily understood and may present greater adherence issues due to individual lifestyle patterns, e.g., shift work, work that changes on a periodic basis such as in the morning, in the evening, after breakfast, with lunch, or at bedtime. Consistent use of the same terms should help avoid patient confusion.

Ambiguous directions such as “take as directed” should be avoided unless clear and unambiguous supplemental instructions and counseling are provided (e.g., directions for use that will not fit on the prescription container label). A clear statement referring the patient to such supplemental materials should be included on the container label.