should be set to a representative output, dictated by the requirements of the analytical measurement and the laser power measured. The output should be measured and checked against the output measured at instrument qualification. The power (in milliwatts or watts) should vary by no more than 25% compared to the qualified level. If the power varies by more than this amount, the instrument should be serviced (as this variation might indicate, among other things, a gross misalignment of the system or the onset of failure of the laser).

For instruments with an automatic, internal laser power meter, the accuracy of the values generated from the internal power meter should be compared to a calibrated external laser power meter at an interval of not more than 12 months. The internally calculated value should be compared to that generated by the external power meter. Performance is verified by matching the current value to that generated during the previous instrument qualification. The manufacturer might provide software to facilitate this analysis. If the instrument design prevents the use of an external power meter, then the supplier should produce documentation to ensure the quality of the instrument and provide a recommended procedure for the above analysis to be accomplished during a scheduled service visit.

METHOD VALIDATION

Validation of Raman methods will follow the same protocols described in *Validation of Compendial Procedures* ⟨1225⟩ in terms of accuracy, precision, etc. However, several of these criteria are affected by variables specific to Raman spectrometry. Fluorescence is the primary variable that can affect the suitability of a method. The presence of fluorescent impurities in samples can be quite variable and have little effect on the acceptability of a material. The method must be flexible enough to accommodate different sampling regimes that may be necessary to minimize the effects of these impurities.

Detector linearity must be confirmed over the range of possible signal levels. Fluorescence might drive both the signal baseline and the noise higher than that used in the validation, in which case the fluorescence must be decreased, or the method modified to accommodate the higher fluorescence levels. This is also true for the precision, limit of detection, and limit of quantification of the method, as increased baseline noise will negatively impact all of these values. Because fluorescence can also affect quantification caused by baseline shifts, acceptable quantification at different levels of photobleaching, when used, should also be confirmed.

The impact of the laser on the sample must be determined. Visual inspection of the sample and qualitative inspection of the Raman spectrum for measurements with differing laser powers and exposure times will confirm that the sample is not being altered (other than by photobleaching). Specific variables to confirm in the spectrum are shifts in peak position, changes in peak height and band width, and unexpected changes in background intensity.

Method precision must also encompass sample position. The sample presentation is a critical factor for both solids and liquids, and must be either tightly controlled or accounted for in the calibration model. Sample-position sensitivity can often be minimized by appropriate sample preparation or sample holder geometry, but will vary from instrument to instrument based on excitation and collection optical configuration.

DEFINITION OF TERMS AND SYMBOLS

CALIBRATION MODEL is a mathematical expression that relates the response from an analytical instrument to the properties of samples.

INSTRUMENT BANDPASS (OR RESOLUTION) is a measure of the capability of a spectrometer to separate radiation of similar wavelengths.

OPERATIONAL QUALIFICATION is the process by which it is demonstrated and documented that the instrument performs according to specifications, and that it can perform the intended task. This process is required following any significant change such as instrument installation, relocation, major repair, etc.

PERFORMANCE QUALIFICATION is the process of using one or more well-characterized and stable reference materials to verify consistent instrument performance. Qualification may employ the same or different standards for different performance characteristics.

RAMAN SPECTRA[4] are plots of the radiant energy, or number of photons, scattered by the sample through the indirect interaction between the molecular vibrations in the sample and monochromatic radiation of frequency much higher than that of the vibrations. The abscissa is usually the difference in wavenumber between the incident and scattered radiation.

(NORMAL) RAMAN SCATTERING[4] is the inelastic scattering of radiation that occurs because of changes in the polarizability, of the relevant bonds during a molecular vibration. Normal Raman spectra are excited by radiation that is not in resonance with electronic transitions in the sample.

RAMAN WAVENUMBER SHIFT[4],

$$\Delta\tilde{\nu}$$

is the wavenumber of the exciting line minus the wavenumber of the scattered radiation. SI unit: m^{-1}. Common unit: $cm^{-1} = 100\ m^{-1}$.

$$\beta\Delta\tilde{\nu}$$

where β is the differential Raman cross section, is positive for Stokes scattering and negative for anti-Stokes scattering.

⟨1121⟩ NOMENCLATURE

The *USP* (or *NF*) titles for monograph articles are legally recognized under the Federal Food, Drug, and Cosmetic Act as the designations for use in labeling the articles to which they apply.

The value of designating each drug by one and only one nonproprietary[1] name is important in terms of achieving simplicity and uniformity in drug nomenclature. In support of the U.S. Adopted Names program (see *Mission and Preface* in *USP–NF*), of which the U.S. Pharmacopeial Convention is a cosponsor, the USP Council of Experts gives consideration to the adoption of the U.S. Adopted Name, if any, as the official title for any compound that attains compendial recognition.

A compilation of the U.S. Adopted Names (USAN) published from the start of the USAN program in 1961, as well as other names for drugs, both current and retrospective, is provided in the *USP Dictionary of USAN and International Drug Names.* This publication serves as a book of names useful for identifying and distinguishing all kinds of names for drugs, whether public, proprietary, chemical, or code-designated names.[2]

[4] Chalmers, J., Griffiths, P., Eds. *Handbook of Vibrational Spectroscopy;* John Wiley & Sons, Ltd: New York, 2002.

[1] The term "generic" has been widely used in place of the more accurate and descriptive term "nonproprietary" with reference to drug nomenclature.

[2] *USP Dictionary of USAN and International Drug Names* is obtainable on order from U.S. Pharmacopeia, Customer Service Department, 12601 Twinbrook Parkway, Rockville, MD 20852.

A nonproprietary name of a drug serves numerous and varied purposes, its principal function being to identify the substance to which it applies by means of a designation that may be used by the professional and lay public free from the restrictions associated with registered trademarks. Teaching in the health sciences requires a common designation, especially for a drug that is available from several sources or is incorporated into a combination drug product; nonproprietary names facilitate communication among healthcare providers; nonproprietary names must be used as the titles of the articles recognized by official drug compendia; a nonproprietary name is essential to the pharmaceutical manufacturer as a means of protecting trademark rights in the brand name for the article concerned; and, finally, the manufacturer is obligated by federal law to include the established nonproprietary name in advertising and labeling.

Under the terms of the Drug Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act, which became law October 10, 1962, the Secretary of Health and Human Services is authorized to designate an official name for any drug wherever deemed "necessary or desirable in the interest of usefulness and simplicity."[3]

The Commissioner of Food and Drugs and the Secretary of Health and Human Services published in the *Federal Register* regulations effective November 26, 1984, which state, in part:

"**Sec. 299.4 Established names of drugs.**"

"(e) The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common and usual name of the drug. Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names*."[4]

It will be noted that the monographs on the biologics, which are produced under licenses issued by the Secretary of the U.S. Department of Health and Human Services, represent a special case. Although efforts continue toward achieving uniformity, there may be a difference between the respective title required by federal law and the USP title. Such differences are fewer than in past revisions of the Pharmacopeia. The USP title, where different from the FDA Center for Biologics Evaluation and Research title, does not necessarily constitute a synonym for labeling purposes; the conditions of licensing the biologic concerned require that each such article be designated by the name appearing in the product license issued to the manufacturer. Where a USP title differs from the title in the federal regulations, the former has been adopted with a view to usefulness, simplicity, and conformity with the principles governing the selection of monograph titles generally.

GENERAL NOMENCLATURE FORMS

Some monograph titles existing in the *USP–NF* do not conform to the formats outlined in this general information chapter. Typically, these monograph titles were adopted before the establishment of the title formats and nomenclature policies presented in this general information chapter. Such monograph titles may be subject to subsequent revision and should not be interpreted as precedents for other monograph titles.

Standardized forms of nomenclature have been devised in the interest of achieving uniformity for naming compendial articles. The general nomenclature forms that follow illustrate the terminology used throughout the official compendia for consistency in establishing titles of monographs on official pharmaceutical dosage forms and preparations. Examples are shown for the more frequently encountered categories of dosage forms.

For a variety of dosage forms, titles are in the following general form: [DRUG] [ROUTE OF ADMINISTRATION] [DOSAGE FORM].

Examples:
- Calcium Carbonate Oral Suspension
- Cetylpyridinium Chloride Topical Solution
- Dexamethasone Ophthalmic Suspension
- Epinephrine Bitartrate Ophthalmic Solution
- Isosorbide Dinitrate Sublingual Tablets
- Miconazole Nitrate Topical Powder
- Triple Sulfa Vaginal Cream

The term "Vaginal Inserts", rather than "Vaginal Tablets", "Vaginal Capsules", or "Vaginal Suppositories" is used in the title of this type of vaginal preparation to avoid the potential for misuse of these products if the term "Tablets" or "Capsules" or "Suppositories" were to appear in the title.

Example:
- Clotrimazole Vaginal Inserts

The term for route of administration is omitted for those dosage forms for which the route of administration is understood. The general form then becomes simply [DRUG] [DOSAGE FORM]. Thus, capsules, tablets, and lozenges are administered via the oral route unless otherwise indicated by the title.

Examples:
- Acetaminophen Capsules
- Aminophylline Delayed-Release Tablets
- Aspirin Extended-Release Tablets
- Hexylresorcinol Lozenges
- Meperidine Hydrochloride Tablets

Drugs that are injected may be administered via the intravenous, intramuscular, subcutaneous, etc., route; the route being specified in the labeling rather than in the name.

Examples:
- Aurothioglucose Injectable Suspension
- Epinephrine Injection
- Fluorouracil Injection
- Hydrocortisone Acetate Injectable Suspension
- Phytonadione Injectable Emulsion

Creams, ointments, lotions, and pastes are applied topically, unless otherwise indicated by the name.

Examples:
- Benzoyl Peroxide Lotion
- Betamethasone Dipropionate Cream
- Estradiol Vaginal Cream
- Nystatin Ointment
- Zinc Oxide Paste

The term "Suppositories" is used in the titles of preparations that are intended for rectal administration.

Example:
- Aspirin Suppositories

The term "for" is included in names, as appropriate, of preparations for which a solid drug substance must be dissolved or suspended in a suitable liquid to obtain a dosage form, and the general form becomes [DRUG] for [ROUTE OF ADMINISTRATION] [DOSAGE FORM].

Examples:
- Ampicillin for Oral Suspension
- Epinephrine Bitartrate for Ophthalmic Solution
- Nafcillin for Injection
- Spectinomycin for Injectable Suspension

In some instances, the drug is supplied in one dosage form for the preparation of the intended dosage form.

Examples:
- Aspirin Effervescent Tablets for Oral Solution
- Methadone Hydrochloride Tablets for Oral Suspension
- Papain Tablets for Topical Solution

Systems are preparations of drugs in carrier devices that are applied topically or inserted into body cavities, from which drugs are released gradually over extended times, after which the carrier device is removed. The general form for a system is [DRUG] [ROUTE] [SYSTEM].

[3] F.D.&C. Act, Sec. 508 [358].
[4] 53 Fed. Reg. 5369 (1988) amending 21 CFR § 299.4.

Examples:
Nicotine Transdermal System
Progesterone Intrauterine Contraceptive System

Some drugs are available as concentrated solutions that are not intended for direct administration to humans or animals, but are to be diluted with suitable liquid vehicles to obtain the intended preparation. The general form for these preparations, which are not dosage forms, is [DRUG] [CONCENTRATE].

Examples:
Isosorbide Concentrate (used to prepare Isosorbide Oral Solution)
Glutaral Concentrate (used to prepare Glutaral Disinfectant Solution)

For products intended for parenteral administration, the use of the word "Concentrate" in the monograph title is restricted to one specific monograph, Potassium Chloride for Injection Concentrate. The word "Concentrate" should not appear in the monograph title for any other parenteral product; rather, this issue is to be addressed in the product labeling.

Some drugs are supplied as preparations that may be intermediates used for convenience in formulating finished dosage forms. The general form for such preparations, which are not finished dosage forms, is [DRUG] [PREPARATION].

Examples:
Vitamin E Preparation
Cranberry Liquid Preparation

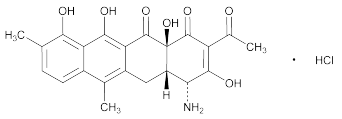
MONOGRAPH NAMING POLICY FOR SALT DRUG SUBSTANCES IN DRUG PRODUCTS AND COMPOUNDED PREPARATIONS

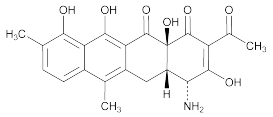
The titles of USP monographs for drug products and compounded preparations formulated with a salt of an acid or base use the name of the active moiety, as defined below. The strength of the product or preparation also is expressed in terms of the active moiety.

An active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance, without regard to the actual charged state of the molecule in-vivo.

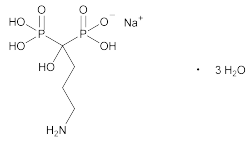
For example, the active moiety of a hydrochloride salt of a base will be the free base and not the protonated form of the base. The active moiety of a metal acid salt will be the free acid.

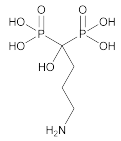
i. Example: Chelocardin Hydrochloride active moiety is Chelocardin





ii. Example: Alendronate Sodium active moiety is Alendronic Acid





This Policy is followed by USP in naming drug products and compounded preparations that are newly recognized in the USP. Revising existing monographs to conform to this Policy is not intended, except where the USP Council of Experts determines that, for reasons such as safety, a nomenclature change is warranted.

Related Issues

Labeling—The labeling clearly states the specific salt form of the active moiety that is present in the product/preparation, as this information may be useful to practitioners and patients. The names and strengths of both the active moiety and specific salt form (where applicable) are provided in the labeling.

Exceptions—In those rare cases in which the use of the specific salt form of the active moiety in the title provides vital information from a clinical perspective, an exception to this Policy may be considered. In such cases, where the monograph title contains the specific salt form of the active moiety, the strength of the product or preparation also is expressed in terms of the specific salt form.

POLICY FOR POSTPONEMENT SCHEDULES

It is the practice of USP to postpone the official dates of nomenclature and labeling revisions for a reasonable time primarily to allow for product label changes to be made and to allow health practitioners and consumers time to become familiar with the new terminology. A postponement period of 18 months is usually applied when only one or a small number of products is affected. A postponement period of 30 months is usually applied when names or labeling of multisource products or multiproduct lines of a firm's preparations are being changed. A postponement period of 60 months is usually applied for title and labeling changes that affect excipients, because such changes would require relabeling of very large numbers of prescription-only and OTC preparations.

There may be exceptions to this postponement schedule where a shorter time is needed in order to specify nomenclature and labeling changes in cases where public health and safety are a concern.

The assignment of a postponement schedule is handled by the USP Expert Committee on Nomenclature. The postponement schedules are presented below. USP's implementation of a postponement schedule is automatic, unless an exception is sought. Exceptions to the postponement schedule are rarely made, and must have suitable justification as well as the approval of the Expert Committee on Nomenclature. Any questions or concerns regarding this postponement schedule may be addressed to the USP staff liaison assigned to the Expert Committee on Nomenclature.

18 months—Schedule for title and labeling changes for a drug product. One or few companies are involved. *Example:* Sterile [Drug] change to [Drug] for Injection.

30 months—Schedule for title and labeling changes for prescription-only and OTC products.

1. Extensive product line for a company. *Examples:* syrups and elixirs.
2. Several companies are involved. *Examples:* syrups and elixirs; lotions; sunscreens.

60 months—Schedule for title and labeling changes for excipient monographs. Ingredient names in numerous multisource products are affected.

⟨1125⟩ NUCLEIC ACID-BASED TECHNIQUES—GENERAL

SCOPE

Nucleic acid-based assays are used in a variety of settings, the most common of which include the detection of infectious agents (viruses, bacteria, etc.), and cellular materials, as well as disease profiling. More recently such assays have also been used for forensic purposes and for the detection of trace contamination in biological materials. The latter include pharmaceutical development applications, such as viral clearance and adventitious agent testing in vaccine seed lots and tissue culture cell banks. This chapter introduces a series of general information chapters that provide techniques that support procedures for the detection and analysis of nucleic acids (see *Figure 1*). The assays using these techniques may be presented in a USP general chapter or in a private specification.

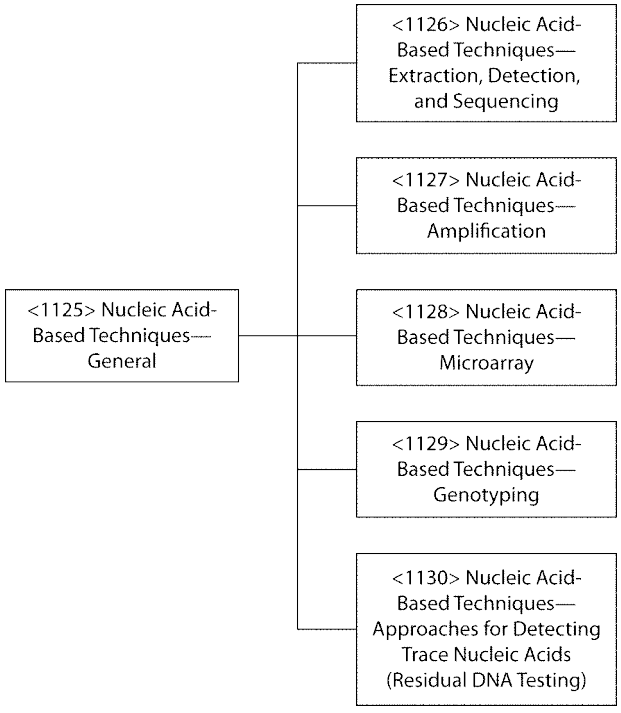


Figure 1

The major requirement for any nucleic acid analytical procedure is the availability of pure, intact nucleic acids for analysis. The information in *Nucleic Acid-Based Techniques—Extraction, Detection, and Sequencing* ⟨1126⟩ discusses procedures available for nucleic acid extraction and handling. Hybridization is the core mechanism underlying many molecular biology techniques, and in addition to the detection of nucleic acids by absorbance and fluorescence measurements and size measurement by gel electrophoresis, this chapter also covers blotting and identification of nucleic acid species by hybridization assays using labeled probes. Hybridization probes are oligonucleotides that have a sequence that is complementary to the target of interest. Probes contain radioactive, fluorescent, biotin, digoxigenin, or other tags that, upon binding of the probe to the target, allow visualization and identification of the target. Probes are capable of detecting target sequences that are present in concentrations too low to be detected by absorbance measurements or gel electrophoresis.

These analytical procedures require a minimum quantity of nucleic acid, typically in the nanogram to microgram range. However, in the vast majority of cases, e.g., in the detection of viruses or rare cellular RNA species, the nucleic acid under assay is present in minute quantities (in the picogram to femtogram range), and an amplification step must be performed before the nucleic acid can be detected and identified. The amplification step may be directed either at the signal used for detection (signal amplification), such as the branched DNA assay (bDNA assay), or at the target as in nucleic acid amplification technologies (NAT).

In 1983 a revolutionary yet simple process termed polymerase chain reaction (PCR) was developed for amplifying the number of specific nucleic acid fragments present in a sample, and in just a few years after its discovery PCR became the most frequently used procedure for amplifying nucleic acids, especially DNA. Since the inception of PCR, the number of applications has expanded rapidly, and the technique, which now includes quantitative and multiplex assays, is currently used in almost every field of research and development in biology and medicine. Numerous variations of assay procedures have been developed for specific analytes. The general information chapter, *Nucleic Acid-Based Techniques—Amplification* ⟨1127⟩, describes amplification procedures used for DNA and RNA analysis as well as qualitative and quantitative NAT assays. Signal amplification procedures in which the signals, typically fluorescent signals, are used to detect the nucleic acid of interest, are not very common. The major signal amplification procedure, the branched DNA or bDNA assay, is used predominantly for viral nucleic acid detection.

Quality assurance aspects of the methodology are also covered, together with a summary of current regulatory requirements for NAT assays. The need for globally comparable, accurate, and reliable results in the diagnostics field has driven the quest for, and development of, national and international standards within an increasingly sophisticated and metrologically sound, highly developed international regulatory environment devoted to the highest standards of regulatory science. Because NAT has become the most widely used of nucleic acid techniques, the majority of guidance documents and standards are related to NAT. The general information chapter, *Nucleic Acid-Based Techniques—Microarrays* ⟨1128⟩, addresses a still-emerging field that is of increasing relevance to molecular DNA analysis. Detailed treatment of various microarrays, including data analysis and validation, are excluded from ⟨1128⟩ at this time. The general information chapter, *Nucleic Acid-Based Techniques—Genotyping* ⟨1129⟩, focuses on the specific modifications of the techniques that are necessary to enable detection of single base differences and common genetic variations, e.g., single nucleotide polymorphisms (SNPs). The final general information chapter in the series, *Nucleic Acid-Based Techniques—Approaches for Detecting Trace Nucleic Acids (Residual DNA Testing)* ⟨1130⟩, describes residual DNA testing in the context of pharmaceutical manufacturing. Applications relevant to viral adventitious agents, however, are discussed in the general information chapter *Virology Test Methods* ⟨1237⟩.

Two major uses of nucleic acid testing are excluded from this family of NAT chapters: viral testing for blood and blood product safety and genetic testing. The traditional