USP's Monographs in Support of FDA's OTC Monograph System: Modernization Opportunities

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ABSTRACT This Stimuli article outlines a proposal to advance modernization of US Pharmacopeial Convention (USP) quality monographs that apply to over-the-counter (OTC) products marketed under the Food and Drug Administration (FDA) OTC monograph system. USP monographs play a critical and unique role in ensuring the quality of these products, which can consist of numerous combinations of FDA-sanctioned drug substances and are not required to undergo a preapproval review (New Drug Application or Abbreviated New Drug Application) process at FDA. However, in addition to the general challenges USP faces in obtaining the information and material it needs to maintain up-to-date monographs, development and maintenance of monographs for OTC products present particular challenges because of the wide variety and rapidly changing nature of these products. To address these challenges, USP is developing novel approaches to accelerate the development and modernization of drug substance and drug product monographs for products marketed under the FDA OTC monograph system. These approaches, which are presented in this Stimuli article, include: updating testing technology, eliminating non–value added testing, increasing the USP in-house effort to develop and validate methods, implementing the use of performance-based monographs, and using a product-class monograph strategy. These new approaches will enable USP to more quickly build and maintain meaningful public standards to ensure the continued high quality of products in commerce.

FDA OTC MONOGRAPH SYSTEM

Drugs legally manufactured or sold in interstate commerce are subject to clearance by one of the marketing pathways provided by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (FDCA) (1). Drugs that require the supervision of a practitioner can be dispensed only by prescription (Rx), but drugs that do not require such supervision can be dispensed over-the-counter (OTC). Many OTC drugs, particularly those first cleared for marketing as Rx only, obtain marketing approval via one of FDA's pathways that require review and approval (e.g., New Drug Application, Abbreviated New Drug Application, or Biologics License Application). However, FDA also has provided a pathway known as the OTC drug monograph system that does not require review and preapproval for certain OTC drugs that qualify as “generally recognized as safe and effective” (GRASE) (2).

FDA's OTC drug monograph system (also called the OTC Drug Review process) arose following the 1962 Kefauver–Harris Amendments to FDCA that added a requirement for demonstration of efficacy to the existing safety requirement (3). These amendments resulted in FDA's Drug Efficacy Study Implementation (DESI) initiative launched in 1968 to investigate the effectiveness of drugs first marketed between 1938 and 1962 (4). This in turn led to the OTC Drug Review process, which began in 1972 to evaluate the safety
and efficacy of OTC active ingredients then in the market. Under FDA's OTC drug monograph system, OTC drugs are recognized as GRASE and therefore are appropriate for marketing without review and preapproval if they satisfy all of the requirements in 21 CFR Part 330 and in each respective monograph. In addition to providing the general conditions and procedures for GRASE determination, this regulation calls on FDA to create monographs in various therapeutic categories that specify acceptable ingredients, doses, formulations, indications, and labeling for products in that category. Since the system began, FDA has completed work on more than 75% of the OTC monographs that were originally envisioned. OTC monographs are created via the standard rulemaking process: First FDA typically convenes an expert Advisory Panel, then issues an advance notice of proposed rulemaking, then publishes a proposed rule including a Tentative Final Monograph, and then publishes a final rule/monograph in the Code of Federal Regulations (see, for example, the monograph for the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug category, 21 CFR Part 341).

For sponsors who wish to market a drug that is not covered by an FDA OTC monograph, FDA has created regulatory mechanisms that allow amendment of the OTC monograph system. In the case of products that were marketed before 1975, a sponsor can submit a Citizen Petition to seek an amendment. In the case of OTC products marketed in the United States after the FDA monograph system began or were marketed outside the United States, a Time and Extent Application (TEA) can be submitted to demonstrate that the drug has been used to a “material extent” and for a “material time” under the proposed labeling conditions (see 21 CFR 330.14). These procedures for adding a new active ingredient or product to the FDA OTC monograph system are challenging but represent an important means of obtaining marketing clearance.

As an alternative to amending an FDA OTC monograph, manufacturers can file an NDA or ANDA, which is reviewed like an application for a prescription drug product. A final way to OTC status available for prescription drugs already on the market is to undergo a switch from a prescription drug to a nonprescription drug, but meeting labeling requirements can be cumbersome and complex.

FDA's OTC monograph system offers considerable manufacturing flexibility as a means of promoting self-care. The system has taken on additional significance in recent years with FDA's Unapproved Drugs Initiative, which is intended to ensure that all drugs are marketed only in accordance with the new drug approval or OTC monograph system and includes enforcement policies that FDA will use to bring unapproved drugs into compliance or to remove them from the market (4). This has focused attention on the FDA OTC monograph system and increased FDA and manufacturer efforts to ensure that it is continuously modernized and updated.

**USP AND OTC PRODUCTS**

**Role in Law**

USP compendial quality standards have had a role in US food and drug laws since 1906. Under FDCA, any drug (including PHS Act biologics) recognized in an official USP compendium must use the USP-specified nonproprietary name in its labeling, must comply with compendial identity, and also must conform to compendial standards for strength, quality, and purity (or must plainly state any differences on the label). Drugs that fail to comply may be deemed adulterated and/or misbranded under FDCA Sections 501(b) and 502(e). Drugs recognized in official USP compendia also may be deemed misbranded unless they conform to compendial packaging and labeling requirements under FDCA §502(g). These compendial standards serve as a reference for the pharmaceutical industry to ensure the quality and safety of products.
requirements apply regardless of whether a drug is Rx or OTC and also regardless of the means by which the drug has been cleared for marketing (NDA, ANDA, BLA, or pursuant to FDA's OTC drug monograph system).

FDA also has established a role for USP's compendial standards in the regulations governing the agency's OTC drug monograph system and for inclusion in a drug final monograph or in a notice of enforcement policy. Further, 21 CFR 330.14(i) requires that the active ingredient or botanical drug substance be recognized in an official *United States Pharmacopeia–National Formulary (USP–NF)* drug monograph that sets forth its standards for identity, strength, quality, and purity. There is no specific requirement in law or regulation for a USP drug product monograph in FDA's OTC drug monograph system, although as noted above §501(b) of FDCA states that drug products must meet USP standards if they exist and further provides for FDA to inform USP about deficiencies in its standards and to request timely corrections.

**Council of Experts**

Within USP's Council of Experts, responsibility for OTC monographs lies with the four Small Molecules Expert Committees that support USP (Figure 1). Each of these Expert Committees focuses on different therapeutic areas (Table 1). Small Molecules Expert Committee 3 has responsibility for approximately one-third of the existing USP OTC monographs, and responsibility for the remainder is divided roughly equally among the other three committees.
Staff Support
Staff support for the Small Molecules Expert Committees is provided primarily by the Chemical Medicines Department, led by Shawn Dressman, PhD, Vice President, Chemical Medicines, USP–NF. Dr. Dressman reports to Srini Srinivasan, PhD, Executive Vice President of USP's Global Science and Standards division. Within the Chemical Medicines Department, scientific liaisons and reference standards scientists who work on documentary standards and reference materials, respectively, are assigned to each of the expert committees. Other staff support comes from USP's laboratories, including both the Rockville, MD, and Hyderabad, India, sites that participate in procedure development, procedure evaluation, and collaborative testing of reference materials. The Compendial Affairs group within the Global Alliances and Organizational Affairs division also plays a key support role, providing administrative support for expert committees, as does the Executive Secretariat that oversees the balloting process for USP's expert committees and ensures that the will of the Council of Experts is accurately reflected in USP's standards.

STATUS OF USP'S OTC MONOGRAPHS

USP–NF: General
USP's documentary standards (monographs) for food and drugs are approaching 10,000, and its reference material collection is approaching 3000 (Figure 2; all estimates as of August 2012). The majority of USP's documentary (> 75%) and reference materials (> 60%) originate from donations from manufacturers. Despite impressive efforts, all of USP's compendia are incomplete for both documentary and reference material standards (compared to the number of drugs and ingredients that are legally marketed). In USP–NF many monographs are missing or require updating, and most of these are in the small molecules area.
USP–NF: OTC Monographs

USP's OTC monographs represent a subset of the total outdated and missing small molecules monographs shown in Figure 2. USP currently has monographs for all of the drug substances covered by the FDA OTC monograph system because such monographs are a precondition under FDA regulations for initiating or finalizing FDA OTC monographs. However, of the approximately 240 OTC drug substance monographs that currently exist in USP, an estimated 140 are in need of modernization.

At the drug product level, USP currently has about 500 monographs for OTC drug products, but many of these are out of date. In addition, many OTC products are not covered by a USP monograph. Examples include toothpastes, medicated mouthwashes, lip balms, and shampoos, among others, as well as myriad combination products composed of substances covered by the FDA OTC drug monograph system. The large number of OTC products on the market and the frequent changes that occur to OTC products have made it virtually impossible for USP to develop and maintain monographs for these products through its traditional approach, which involves creating a monograph for each individual product by means of a process that requires 18–24 months to complete.

Collaboration among USP, FDA, and Industry to Improve USP's OTC Monographs

Early efforts to implement new approaches to USP's OTC monographs occurred in the 1990s when USP briefly experimented with the concept of creating monographs for multiple combinations of OTC ingredients. This initiative was confined to the cold and cough area and resulted in seven monographs (see example in Figure 3). However, this effort did not continue.
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine

Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine contain not less than 90.0 per cent and not more than 110.0 per cent of the labeled amounts of acetaminophen \((C_{6}H_{11}NO_{2})\), chlorpheniramine maleate \((C_{16}H_{25}ClN_{2} \cdot C_{6}H_{11}O_{2})\), dextromethorphan hydrobromide \((C_{18}H_{25}NO \cdot HBr \cdot H_{2}O)\), and pseudoephedrine hydrochloride \((C_{19}H_{33}NO \cdot HCl)\) or pseudoephedrine sulfate \([C(C_{18}H_{35}NO_{2}) \cdot H_{2}SO_{4}]\). 

NOTE—The heading of this monograph does not constitute the official title. It is not intended that the name described herein be recognized as the official title or the common or usual name. The name for each article encompassed by this monograph shall be composed of the names of the active ingredients contained therein, as well as the quantitative amount of each active ingredient, and a statement of the function (or purpose) of the ingredient in the article.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards (17)—
USP Acetaminophen RS
USP Chlorpheniramine Maleate RS
USP Dextromethorphan Hydrobromide RS
USP Pseudoephedrine Hydrochloride RS
USP Pseudoephedrine Sulfate RS

Labeling—The label for each article encompassed by this monograph bears a name composed of the active ingredients. The label states the name and quantity of each active ingredient and indicates its function (or purpose) in the article. When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

Identification—
A: If pseudoephedrine hydrochloride or pseudoephedrine sulfate is claimed in the labeling to be present, the chromatogram of the Assay preparation, obtained as directed in the Assay for pseudoephedrine hydrochloride or the Assay for pseudoephedrine sulfate, exhibits a major peak for pseudoephedrine, the retention time of which corresponds to that exhibited by the Standard preparation.

B: If acetaminophen is claimed in the labeling to be present, the chromatogram of the Assay preparation, obtained as directed in the Assay for acetaminophen, exhibits a major peak for acetaminophen, the retention time of which corresponds to that exhibited by the Standard preparation.

C: If chlorpheniramine maleate is claimed in the labeling to be present, the chromatogram of the Assay preparation, obtained as directed in the Assay for chlorpheniramine maleate, exhibits a major peak for chlorpheniramine, the retention time of which corresponds to that exhibited by the Standard preparation.

Dissolution, Procedure for a Pooled Sample (711)—

Medium: pH 5.8 phosphate buffer (see Buffer Solution, Reagents, Indicators, and Solutions); 900 mL.
Apparatus 2: 50 rpm.
Time: 45 minutes.

Test preparation—Mix 9.0 mL of a filtered portion of the solution under test with 1.0 mL of 1% phosphoric acid.

Procedure—Determine the amounts of pseudoephedrine hydrochloride or pseudoephedrine sulfate (as appropriate) and dextromethorphan hydrobromide dissolved, employing the procedures for the Assay for pseudoephedrine hydrochloride or Assay for pseudoephedrine sulfate, Assay for acetaminophen, Assay for chlorpheniramine maleate, and Assay for dextromethorphan hydrobromide, respectively, making any necessary volumetric adjustments.

Tolerances—Not less than 75% \((\Omega)\) of the labeled amounts of pseudoephedrine hydrochloride \((C_{10}H_{15}NO \cdot HCl)\) or pseudoephedrine sulfate \([C(C_{18}H_{35}NO_{2}) \cdot H_{2}SO_{4}]\), acetaminophen \((C_{6}H_{11}NO_{2})\), chlorpheniramine maleate \((C_{16}H_{25}ClN_{2} \cdot C_{12}H_{11}O_{2})\), and dextromethorphan hydrobromide \((C_{18}H_{25}NO \cdot HBr \cdot H_{2}O)\) are dissolved in 45 minutes.

TEST 2—If the product complies with this test, it indicates that it meets USP Dissolution Test 2.
Medium: water; 900 mL.
Apparatus, Time, Test preparation, Procedure, and Proceed as directed for Test 1.

Uniformity of dosage units (905): meet the requirements of USP General Notice 905.

Assay for pseudoephedrine hydrochloride (when pseudoephedrine hydrochloride is the salt form used, if pressure formulation)

Mobile phase—Prepare a filtered and degassed mixture of methanol and water \((68:40)\) containing 0.34 g of monopotassium phosphate, 0.3 g of triethylamine hydrochloride, 0.15 g of sodium lauryl sulfate, and 0.1 mL of phosphoric acid in each 100 mL of solution. Make adjustments if necessary to System suitability solution under Chromatography (621).

Standard preparation—Dissolve an accurately weighed quantity of USP Pseudoephedrine Hydrochloride RS in water to obtain a solution having a concentration of about 0.02 mg per mL. Transfer 1.0 mL of this solution to a 25-mL volumetric flask, add 2.5 mL of methanol, dilute with 0.1% phosphoric acid to volume, and mix.

Chlorpheniramine standard preparation—Prepare a Standard preparation in the Assay for chlorpheniramine maleate.

Dextromethorphan standard preparation—Prepare a Standard preparation in the Assay for dextromethorphan hydrobromide.

System suitability solution 1 (for Tablets that contain the four ingredients or a combination of three containing chlorpheniramine maleate)—Mix equal volumes of the Standard and the Chlorpheniramine standard preparation.

System suitability solution 2 (for Tablets that contain chlorpheniramine maleate)—Mix equal volumes of the Standard and the Dextromethorphan standard preparation.

Assay preparation—Weigh and finely powder not more than 20 Tablets. Transfer an accurately weighed quantity, equivalent to about 6 mg of pseudoephedrine hydrochloride, to a 100-mL volumetric flask, and prepare Assay solution 1 or Assay solution 2.
2050 Acetaminophen / Official Monographs

10 μL of System suitability solution 1 or System suitability solution 2, as appropriate. The resolution, R, between pseudoephedrine and chlorpheniramine or between pseudoephedrine and dextromethorphan is not less than 2.0.

Procedure—Separately inject equal volumes (about 10 μL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the pseudoephedrine peaks. Calculate the quantity, in mg, of pseudoephedrine hydrochloride ([C₁₅H₂₁NO₂]·HCl) in the portion of Tablets taken by the formula:

\[ 50C(r_0 / r_s) \]

in which C is the concentration, in mg per mL, of USP Pseudoephedrine Hydrochloride RS in the Standard preparation, and r₀ and rₛ are the pseudoephedrine peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Assay for chlorpheniramine maleate (if present)

Mobile phase and Chromatographic system—Proceded in the Assay for pseudoephedrine hydrochloride

Standard preparation—Dissolve an accurately weighed quantity of USP Chlorpheniramine Maleate RS in water to obtain a solution having a known concentration of about 0.8 mg per mL. Quantitatively dilute a portion of this solution with phosphoric acid to obtain a solution having a known concentration of about 8 μg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 2 mg of chlorpheniramine maleate, to a 250-mL volumetric flask. Add 25 mL of methanol, a cate to disperse the powder. Add 1 mL of phosphoric acid to volume, mix, and filter.

Procedure—Separately inject equal volumes (about 20 μL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the chlorpheniramine maleate peaks. Calculate the quantity, in mg, of chlorpheniramine maleate ([C₁₅H₂₁NO₂]·C₂H₅O₂) in the portion of Tablets taken by the formula:

\[ 250C(r_0 / r_s) \]

in which C is the concentration, in mg per mL, of USP Chlorpheniramine Maleate RS in the Standard preparation, and r₀ and rₛ are the peak responses for chlorpheniramine maleate obtained from the Assay preparation and the Standard preparation, respectively.

Assay for dextromethorphan hydrobromide (if present)

Mobile phase and Chromatographic system—Proceded in the Assay for pseudoephedrine hydrochloride

Standard preparation—Dissolve an accurately weighed quantity of USP Dextromethorphan Hydrobromide RS in water to obtain a solution having a known concentration of about 0.6 mg per mL. Quantitatively dilute a portion of this solution with 0.1% phosphoric acid to obtain a solution having a concentration of about 0.06 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 6 mg of dextromethorphan hydrobromide, to a 100-mL volumetric flask. Add 10 mL of methanol, and sonicate to disperse the powder. Add phosphoric acid, dilute to volume, mix, and filter.

Procedure—Separately inject equal volumes (about 20 μL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the dextromethorphan hydrobromide peaks. Calculate the quantity, in mg, of dextromethorphan hydrobromide ([C₁₅H₂₁NO · HBr · H₂O]·C₂H₅O₂) in the portion of Tablets taken by the formula:

\[ 200C(r_0 / r_s) \]
Figure 3. Example of an OTC combination monograph: Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine.

More recent attention to USP's OTC monographs followed a letter USP received from Janet Woodcock, MD, in October 2010 calling attention to the need to modernize USP monographs, particularly those relating to OTC products (letter available on USP website at http://www.usp.org/usp-nf/key-issues/monograph-modernization). Although USP had begun during the 2005–2010 cycle to identify monographs in need of modernization, including OTC monographs, this letter accelerated the effort to identify and begin work to update such monographs. Dr. Woodcock's letter was followed in November 2010 by a letter from Larry Ouderkirk and Paul Seo, PhD, co-chairs of FDA's newly created Monograph Modernization Task Force, which specifically requested that USP begin work on the acetaminophen and diphenhydramine drug substance and related drug product monographs (letter available on the USP website at www.usp.org/usp-nf/key-issues/monograph-modernization). USP has continued to work diligently on updating these and other high-priority monographs identified by FDA.

To help focus broader attention on the need to update USP's OTC monographs and to explore solutions with stakeholders, USP hosted a September 2011 workshop at which Dr. Woodcock was the keynote speaker (the workshop objectives and agenda are posted on the USP website at http://www.usp.org/usp-nf/key-issues/monograph-modernization). Dr. Woodcock emphasized that preservation of the current system relied on sound standards in order to avoid repeats of negative patient and consumer experiences regarding poor-quality medicines and foods. Participants discussed the challenges presented by OTC monographs, and there was general consensus that creative approaches were required and that collaboration among USP, FDA, and industry are essential. USP's CEO closed the workshop by calling for novel approaches that allow USP to work both independently of donors as well as collaboratively with them in advancing new and updated monographs for USP. The possibility of developing broader, “product class” monographs for OTC products also was considered briefly as a way to accommodate manufacturers' need for flexibility with these products while specifying critical quality requirements that could be enforced by FDA.

USP's workshop was followed by a Product Quality and Operations Workshop organized by the Consumer Healthcare Products Association (CHPA) in October 2011, which included a track on modernization of USP's OTC monographs. Sessions at this workshop further explored potential approaches for updating USP's monographs and again emphasized the importance of close cooperation among USP, FDA, and industry. At this session USP's CEO again briefly reviewed new opportunities to advance USP's monographs.

Meanwhile, USP has continued to work on identifying OTC monographs that require updating and on modernizing those identified as outdated. It also has continued to develop and refine ideas about how best to approach modernization of OTC monographs, especially OTC drug product monographs, and to discuss these ideas with FDA and CHPA. This ongoing work and collaborative discourse among the parties have led to the present Stimuli article and presentation of the proposed approaches discussed below.

**PROPOSAL FOR OTC MONOGRAPH MODERNIZATION**

**Drug Substance**
The drug substance monograph is the anchor of the monograph family (i.e., the collective term for a particular active ingredient and its associated drug product monographs), and thus these monographs are the logical starting point for OTC monograph modernization efforts. Procedures established for the drug substance through the routes described below also can be used as the basis for drug product testing.

Monograph Procedures

CURRENT APPROACHES

Modernization of OTC monographs can follow established standards-setting and internal USP processes for elaboration of the documentary standard, development of reference standards, and interactions and balloting by relevant expert committees. USP already has completed the important step of comprehensively reviewing these monographs and determining which require modernization, and work on some of these is already in progress. However, obtaining procedures to support the modernization efforts is a significant challenge. Currently, USP has multiple sources for procedures:

- Donation from manufacturers
- Development in USP's Research and Development (R&D) lab
- Adaptation from alternative sources such as European Pharmacopoeia (EP) monographs
- Development under FDA Cooperative Research and Development Agreement (CRADA), which includes as one of its objectives the development of procedures to support monograph modernization.

The current level of effort in R&D yields about 50 procedures per year, which is slightly above the number of donations from manufacturers. The FDA CRADA work is just beginning, and annual output has not yet been determined. Adaptation of procedures from EP drug substance monographs is a viable option, and efforts are underway to determine how many procedures can be obtained by this approach.

In order to increase the information donated by manufacturers to update OTC monographs, USP is engaging CHPA and its member organizations and is inviting them to submit proposals. The response from CHPA and its members has been largely positive and supportive of the modernization effort, but all parties acknowledge that this may not result in sufficient submission of procedures from CHPA and OTC manufacturers, leaving a substantial amount of work for USP.

NEW APPROACHES

One strategy being considered is to adopt the approach used by USP-India labs for the Medicines Compendium (MC), which involves creation of a performance-based monograph (PBM) that specifies performance criteria for monograph procedures (5). The creation of the PBM is followed by development of source-independent reference procedures that are not optimized for any single manufacturer but rather can be used across different manufacturers' products. This contrasts with the approach that traditionally has been used in USP–NF, where a monograph generally results from the submission by a manufacturer of specific procedures presumably optimized for that manufacturer (albeit deemed appropriate for general use by the approving Expert Committee). In order to accommodate subsequent manufacturers who may prefer or require different procedures, USP has created the flexible monograph approach, which allows these procedures to be added as alternative procedures with appropriate labeling to reflect the procedures used. Although this approach has worked fairly well, it can be cumbersome and can require multiple...
revisions to a monograph to allow compliance by multiple manufacturers. By creating source-independent reference procedures, the MC approach should obviate the need for the flexible monograph. Finally, in order to expedite the modernization of OTC monographs, USP is considering expanding its current in-house laboratory efforts for the development and validation of procedures. By using USP's own labs for the development of the PBM and reference procedures, the MC approach reduces USP's reliance on external sources. Submissions from manufacturers and other donors always will be important to USP, but being able to also work independently will allow USP to progress more quickly in updating and expanding its OTC drug substance monographs.

Modernization Categories

IDENTIFICATION
The goal in modernizing the Identification section of OTC monographs is to include two orthogonal procedures that include at least one specific identification test. This can be accomplished with a specific test such as infrared spectroscopy (performed against a USP Reference Standard) combined with high-performance liquid chromatography (HPLC) based on the monograph Assay or a similar test. Depending on the monograph, it may be necessary to replace an outdated procedure (e.g., wet chemistry) with a more current procedure.

General chapter Identification Tests—General 〈191〉 is referenced in about 1000 USP–NF monographs as part of Identification testing. The modernization of this chapter is underway and will help to modernize any monograph in which it is referenced. The current chapter includes procedures that use wet chemistry procedures (e.g., the endpoint is a color change or formation of a precipitate) and outdated methodology such as a flame test for sodium. Potential updates include ion chromatography for the presence of ions (sodium, potassium, chloride, etc.). The work on 〈191〉 is parallel to the monograph modernization efforts and will have a positive effect.

ASSAY
For modernization of the Assay portion of monographs, the goal is to replace outdated, relatively nonspecific procedures such as titrations and spectrophotometry with validated, specific chromatographic procedures. It is anticipated that HPLC will be the primary methodology or perhaps ultrahigh-performance liquid chromatography (UHPLC), which is the next evolution. For some drug substances (about 12 in the OTC drug substance list), titration may be the best approach, particularly for salts/organic salts such as potassium chloride and sodium citrate and materials with narrow content control limits. Even if titrimetry is used for these monographs, it may be possible to update the type of titration used. Switching to a method such as ion chromatography also could be considered.

A small portion of OTC drug substance monographs (< 10) currently lack an Assay. The monographs are for substances such as activated charcoal, and an Assay in the usual sense may not be applicable. These monographs must be reviewed to determine the appropriate action(s).

IMPURITIES
As with the Assay, the goal is to replace outdated methodology such as thin-layer chromatography with a validated, specific procedure using HPLC/UHPLC. Some monographs currently lack a test for impurities. Because some of the OTC drug substances were not the basis of NDAs or ANDAs, the limits of some
impurities were not vetted through a formal regulatory review process. USP could rely on manufacturers to
generate data using new proposed monograph methods to support currently marketed products that have
limits that are higher than ICH thresholds. Perhaps USP laboratories could test products to determine what
impurities are present and whether ICH limits are appropriate. Further, literature searches may help
provide information about appropriate impurity levels in currently marketed materials. In the absence of
other data, ICH limits can be used as the default values.

OTHER
Some tests may be deleted to remove non–value added tests (e.g., melting point, noncarbonizable
substances, etc.). We anticipate that there will be no need to replace these tests.

Implications for Reference Standards
The monograph modernization effort will result in the identification of new USP Reference Standards (RS)
and new uses for existing USP RS. It is critical that the current RS be evaluated for use in new procedures,
particularly in cases when the existing RS was originally established as a qualitative RS and the new
procedure will use it in a quantitative procedure that requires a purity assignment. The suitability of these
new RS and new uses for existing RS will be subject to approval by the Expert Committee responsible for
the documentary standard, in accordance with the Rules and Procedures and Council of Experts.

OTC DRUG PRODUCT CLASS MONOGRAPHS

Rationale
As noted above, trying to develop and keep current traditional individual monographs for the multitude of
OTC products is not feasible. Therefore, USP is planning to establish class monographs for product
categories based on the FDA OTC monograph therapeutic categories and subcategories. The idea is to
develop a monograph that will cover all, or particular subcategories of, the individual and combination
products allowed in the corresponding FDA OTC monograph. Examples of categories include analgesics
(internal), analgesics (external), nighttime sleep aids, and oral health care. This approach builds and
expands on the prior experiment with combination product monographs. As new class monographs are
established, USP can incorporate information from existing USP product-specific monographs into the
class monographs and then omit the individual monographs from the compendium.

STRUCTURE

The class monograph will provide tests, procedures, and acceptance criteria to establish the identity,
strength, quality, and purity of the products covered by the monograph. The planned monograph format is
consistent with the current USP format and will include identification, assay, impurities, and performance
tests, but it also will cover both single- and multi-active products. The class monographs will reference the
 corres ponding route of administration general chapters such as proposed chapter Oral Drug Products—
Product Quality Tests 2 and official chapter Topical and Transdermal Drug Products—Product Quality Tests 3 for oral and topical/dermal routes, respectively. USP will map each of the existing USP drug
product monographs to the corresponding new class monograph. An example of the OTC drug product
class monograph for Nighttime Sleep Aids is shown in Figure 4.
1 Nighttime Sleep Aids / Draft Monograph

Nighttime Sleep Aids—Oral, Solid, Immediate Release

DEFINITION
Capsules or Tablets containing one or more of the following active ingredients—Acetaminophen \((\text{C}_8\text{H}_9\text{NO}_2)\), Aspirin \((\text{C}_9\text{H}_8\text{O}_4)\), Diphenhydramine Citrate \((\text{C}_{13}\text{H}_{22}\text{NO}_2\cdot\text{C}_6\text{H}_5\text{O}_7)\), Diphenhydramine Hydrochloride \((\text{C}_{13}\text{H}_{22}\text{NO} \cdot \text{HCl})\), Doxylamine Succinate \((\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4 \cdot \text{C}_6\text{H}_5\text{O}_4)\), and Ibuprofen \((\text{C}_{13}\text{H}_{12}\text{O}_2)\) containing NLT 90.0% and NMT 110.0% of the labeled amounts.

This monograph covers the following articles:
1. Acetaminophen and Diphenhydramine Citrate Tablets
2. Aspirin and Diphenhydramine Citrate Tablets
3. Diphenhydramine Citrate and Ibuprofen Tablets
4. Diphenhydramine Hydrochloride Capsules
5. Doxylamine Succinate Tablets

IDENTIFICATION
- A. Infrared Absorption <197>
Extract the active ingredient using a suitable procedure (see <XXX>). Evaporate to dryness and obtain an IR spectrum of the isolated material using an appropriate method according to <197> and compare to the spectrum concomitantly obtained for the corresponding USP RS.

The following procedure may work for products containing Aspirin. If this procedure does not work for your product, see <XXX> for alternative extraction options.

Identification—for Aspirin
**Infrared Absorption <197K>**—Prepare the test specimen as follows. Shake a quantity of finely powdered Tablets, equivalent to about 500 mg of aspirin, with 10 mL of alcohol for several minutes. Centrifuge the mixture. Pour off the clear supernatant, and evaporate it to dryness. Dry the residue in vacuum at 60° for 1 h.

- B. For each active ingredient claimed on the labeling to be present, the retention time of the peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay for that ingredient.

Assay for acetaminophen—
**Mobile phase**—Prepare a suitable degassed and filtered mixture of water and methanol (60:40), making adjustments if necessary (see System Suitability under Chromatograms <621>).

**Internal standard solution**—Prepare a solution of 1 g in a mixture of water and methanol (4:1) to obtain a solution containing 8.0 mg/mL.

**Standard preparation**—Transfer about 50 mg of USP Acetaminophen RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in 2.5 mL of methanol, dilute to volume, and mix. Transfer 2.0 mL of this solution to a 50-mL volumetric flask, add 5.0 mL of internal standard solution, dilute with Mobile phase to volume, and mix.

**Assay preparation**—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powdered material, equivalent to about 500 mg of acetaminophen, to a 100-mL volumetric flask, add 25 mL of methanol, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a 50-mL volumetric flask, add 5.0 mL of internal standard solution, dilute with Mobile phase to volume, and mix.

**Chromatographic system** (see CHROMATOGRAPHY <621>)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm x 15-cm column that contains 5-μm particles. The flow rate is about 1 mL/min. The column temperature is maintained at about 35 ± 0.5°C. Chromatograph the preparation, and record the responses as directed.**

**Procedure**—Separately inject equal volumes (about 20 μL) of the Standard preparation and the Assay preparation.
Calculate the quantity, in mg, of acetaminophen \( \left( \text{C}_8\text{H}_9\text{NO}_2 \right) \) in the portion of Tablets taken by the formula:
\[
10 \frac{W_2}{R_2/R_3}
\]
in which \( W_2 \) is the weight, in mg, of USP Acetaminophen RS taken; and \( R_2 \) and \( R_3 \) are the ratios of the peak response of acetaminophen to that of the internal standard obtained from the Assay preparation and the Standard preparation, respectively.

**Assay for aspirin**

**Mobile phase**—Dissolve 2 g of sodium 1-heptanesulfonate in a mixture of 850 mL of water and 150 mL of acetonitrile, and adjust with glacial acetic acid to a pH of 3.4.

**Diluting solution**—Prepare a mixture of acetonitrile and formic acid (99:1).

**Standard preparation**—Dissolve an accurately weighed quantity of USP Aspirin RS in Diluting solution to obtain a solution having a known concentration of about 0.5 mg/mL.

**Assay preparation**—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 100 mg of aspirin, to a suitable container. Add 20.0 mL of Diluting solution and about 10 beads. Shake vigorously for about 10 min, and centrifuge (Stock solution). Quantitatively dilute an accurately measured volume of the Stock solution with 9 volumes of Diluting solution (Assay preparation). Retain the remaining portion of Stock solution for the test for Limit of free salicylic acid.

**Chromatographic system** [see CHROMATOGRAPHY <621>—The liquid chromatograph is equipped with a 265-nm detector and a 3.9-mm × 30-cm column containing packing L1. The flow rate is about 2 mL/min. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not greater than 2.0; and the relative standard deviation is NMT 2.0%.

**Procedure**—Separately inject equal volumes (about 10 \( \mu L \)) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of aspirin \( \left( \text{C}_8\text{H}_9\text{O}_4 \right) \) in the portion of Tablets taken by the formula:
\[
200 \frac{C(r_2/r_3)}
\]
in which \( C \) is the concentration, in mg/mL, of USP Aspirin RS in the Standard preparation; and \( r_2 \) and \( r_3 \) are the peak responses of the aspirin peaks obtained from the Assay preparation and the Standard preparation, respectively.

**Assay for diphenhydramine citrate**

**Mobile phase**—Prepare a suitable degassed and filtered mixture of methanol, water, and glacial acetic acid (61:38:1) containing 1.0813 g of sodium 1-octanesulfonate in each

**Solvent mixture**—Prepare a mixture of methanol and water (1:1).

**Internal standard solution**—Prepare a solution of xylometazoline hydrochloride in water having a concentration of about 8 mg/mL.

**Standard preparation**—Transfer about 38 mg of USP Diphenhydramine Citrate RS, accurately weighed, to a volumetric flask containing 500 mg of acetaminophen and 5.0 mL of Internal standard solution and about 50 mL of Solvent mixture, and mix until solution is complete. Add Solvent mixture to volume and mix.

**Assay preparation**—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 38 mg of diphenhydramine citrate, to a 100-mL volumetric flask, add about 65 mL of Solvent mixture, and shake by mechanical means for about 10 min. Add 5.0 mL of Internal standard solution, dilute Solvent mixture to volume, and mix.

**Chromatographic system** [see CHROMATOGRAPHY <621>—The column is a liquid chromatograph is equipped with a 265-nm detector and a 3.9 mm × 30-cm column containing packing L1. The flow rate is about 1.5 mL/min. The column temperature is maintained at about 35 ± 0.5°C. Chromatograph the Standard preparation, and record the responses as directed for Procedure: the column efficiency as determined from the analyte peak is NLT 1000 theoretical plates; the tailing factor for the analyte peak is NMT 1.7; the resolution, \( R_b \) between the analyte and internal standard peaks is NLT 2.5; and the relative standard deviation of the peak response ratio of replicate injections is NMT 2.0%.

**Procedure**—Separately inject equal volumes (about 10 \( \mu L \)) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses for the diphenhydramine citrate and xylometazoline hydrochloride peaks. The retention times are about 0.3 for acetaminophen, 0.7 for diphenhydramine citrate, and 1.0 for xylometazoline hydrochloride, respectively. Calculate the quantity, in mg, of diphenhydramine citrate \( \left( \text{C}_{13}\text{H}_{22}\text{NO-C}_8\text{H}_9\text{O}_3 \right) \) in the portion of Tablets taken by the formula:
\[
W_3\frac{(r_2/r_3)}
\]
in which \( W_3 \) is the weight, in mg, of USP Diphenhydramine Citrate RS taken; and \( r_2 \) and \( r_3 \) are the ratios of the peak responses of diphenhydramine citrate to that of the internal standard obtained from the Assay preparation and the Standard preparation, respectively.
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pH of 6.5, filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography). Standard preparation—Dissolve an accurately weighed quantity of USP Diphenhydramine Hydrochloride RS in water to obtain a solution having a known concentration of about 0.5 mg/mL.

Assay preparation—Weigh and combine the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the combined Capsule contents, equivalent to about 50 mg of diphenhydramine hydrochloride, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and filter.

System suitability solution—Dissolve about 5 mg of benzophenone in 5 mL of acetonitrile, dilute with water to 100 mL, and mix. Transfer 1.0 mL of this solution and 5 mg of diphenhydramine hydrochloride to a 20-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see Chromatography)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 1 mL/min. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, R, between the benzophenone and diphenhydramine peaks is NLT 2.0. Chromatograph replicate injections of the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation is NMT 2.0%; and the tailing factor for the diphenhydramine hydrochloride peak is NMT 2.0.

Procedure—Proceed as directed for Procedure in the Assay under Diphenhydramine Hydrochloride. Calculate the quantity, in mg/mL, of C_{17}H_{22}N_{2}O_{3}C_{6}H_{4}O_{3} in the Capsules taken by the formula:

$$\frac{100 \times C \times (r_3/r_2)}{5}$$

in which C is the concentration, in mg/mL, of USP Diphenhydramine Hydrochloride RS in the Standard preparation, and r_3 and r_2 are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Assay for ibuprofen—

Mobile phase—Dissolve 4.0 g of chloroacetic acid in water, and adjust with ammonium hydroxide to pH 3.0. Add 600 mL of acetonitrile, filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography).

Internal standard solution—Prepare a solution of valerophenone in Mobile phase having a concentration about 0.35 mg/mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Ibuprofen RS in Internal standard solution to obtain a solution having a known concentration of mg/mL.

Ibuprofen-related compound C standard solution—Quantitatively dissolve an accurately weighed quantity of ibuprofen-related Compound C RS in acetonitrile to obtain a stock solution having a known concentration of about mg/mL. Add 2.0 mL of this stock solution to 100 mL Internal standard solution, and mix.

Assay preparation—Weigh and finely powder not f...
are coated, place an accurately counted number of Tablets, equivalent to not less than 1200 mg of ibuprofen, in a container, add an accurately measured volume of internal standard solution, sufficient to obtain an Assay preparation containing about 12 mg of ibuprofen per mL, and about 15 glass beads, and shake until the Tablets are completely disintegrated. Centrifuge a portion of the suspension so obtained, and use the clear supernatant as the Assay preparation.

Chromatographic system [see Chromatography (<631>)]—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL/minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.75 for ibuprofen and 1.0 for valerophene; the resolution, R, between ibuprofen and valerophene is NLT 2.5; the tailing factors for the individual peaks are NMT 2.5; and the relative standard deviation for replicate injections is NMT 2.0%.

Chromatograph the ibuprofen-related compound C standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.0 for valerophene and 1.2 for ibuprofen-related compound C; the resolution, R, between valerophene and ibuprofen-related compound C is NLT 2.5; the tailing factors for the individual peaks are NMT 2.5; and the relative standard deviation for replicate injections is NMT 2.0%.

Procedure—Separately inject equal volumes (about 5 μL) of the Standard preparation, the Assay preparation, and the ibuprofen-related compound C standard solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ibuprofen (C₁₃H₁₈O₂) in each Tablet taken by the formula:

\[ \text{mg/Tablet} = \frac{C(A/W)(R_2/\bar{R})}{100} \]

in which C is the concentration, in mg/mL, of USP Ibuprofen RS in the Standard preparation; A is the average weight, in mg, of a Tablet; W is the weight, in mg, of Tablet powder taken to prepare the Assay preparation; and R₀ and R₃ are the ratios of the ibuprofen peak response to the valerophene peak response obtained from the Assay preparation and the Standard preparation, respectively; or where intact Tablets were taken, calculate the quantity, in mg, of C₁₃H₁₈O₂ in each Tablet taken by the formula:

\[ \frac{(C/V)(N)(R_2/\bar{R})}{100} \]

in which V is the volume, in mL, of Internal standard solution used to prepare the Assay preparation; N is the number of Tablets taken; and the other terms are as defined above.

Apparatus 2: 50 rpm.
Time: 30 min.

Procedure—Determine the amount of C₆H₇NO₂ dissolved employing UV absorption at the wavelength of max absorbance at about 243 nm on filtered portions of solution under test, suitably diluted with Dissolution if necessary, in comparison with a Standard solution known concentration of USP Acetaminophen RS in t Medium.

Tolerances—NLT 80% (Q) of the labeled amount of dissolved in 30 min.

- Reference dissolution procedures are included in the monograph, however, if it is determined that the procedure does not work for your product, a suitable dissolution procedure may be used in accordance Section 6.30 of the General Notices.

Dissolution <711>—Aspirin

Medium: 0.05 M acetate buffer, prepared by mixing sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain 1000 mL of solution having a pH of 0.05; 500 mL.

Apparatus 1: 50 rpm.
Time: 30 min.

Procedure—Determine the amount of C₉H₈O₄ dissolved at the wavelength of the isosbestic point of aspirin and salicylic acid at 265 ± 2 nm of filtered portion of solution under test, suitably diluted with Medium if necessary, in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same Medium.

[NOTE—Prepare the Standard solution at the time of filtration or to exceed 1% of the total vol the Standard solution may be used to bring the Rs Standard into solution before dilution with Medium if necessary.]

Tolerances—NLT 80% (Q) of the labeled amount of dissolved in 30 min.

Dissolution, Procedure for a Pooled Sample <711>—Diphenhydramine Hydrochloride

Medium: water; 500 mL.
Apparatus 1: 100 rpm.
Time: 30 min.

Mobile phase and Chromatographic system—Prepare and direct in the Assay.

Procedure—Inject a measured volume (about 50 μL) filtered portion of the solution under test into the chromatograph, record the chromatogram, and measure the response for the major peak. Determine the quantity of C₁₃H₁₈NO·HCl dissolved in comparison with a Standard solution having a known concentration of USP...
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**Dissolution**<sup>711</sup>—Doxylamine succinate

**Medium:** 0.01 N hydrochloric acid; 900 mL.

**Apparatus 2:** 50 rpm.

**Time:** 30 min.

**Procedure**—Determine the amount of C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>C<sub>4</sub>H<sub>8</sub>O<sub>4</sub> dissolved by employing UV absorption at the wavelength of maximum absorbance at about 262 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, in comparison with a Standard solution having a known concentration of USP Doxylamine Succinate RS in the same Medium.

**Tolerances**—NLT 80% (Q) of the labeled amount of C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>C<sub>4</sub>H<sub>8</sub>O<sub>4</sub> is dissolved in 30 min.

**Dissolution**<sup>711</sup>—Ibuprofen

**Medium:** pH 7.2 phosphate buffer (see under Buffers in the section Reagents, Indicators, and Solutions); 900 mL.

**Apparatus 2:** 50 rpm.

**Time:** 60 min.

**Procedure**—Determine the amount of C<sub>13</sub>H<sub>18</sub>O<sub>2</sub> dissolved from UV absorbances at the wavelength of maximum absorbance at about 221 nm of filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Ibuprofen RS in the same medium. [NOTE—Where the Tablets are labeled as gelatin-coated, determine the amount of C<sub>13</sub>H<sub>18</sub>O<sub>2</sub> dissolved from the UV absorbance at the wavelength of maximum absorbance at about 266 nm from which is subtracted the absorbance at 280 nm, in comparison with the Standard solution similarly measured.]

**Tolerances**—NLT 80% (Q) of the labeled amount of C<sub>13</sub>H<sub>18</sub>O<sub>2</sub> is dissolved in 60 min.

**- UNIFORMITY OF DOSAGE UNITS <905>**—Meets the requirements.

**Impurities**

Reference impurity procedures are included in this monograph; however, if it is determined that the reference procedure does not work for your product, a suitable procedure may be used in accordance with Section 6.30 of the General Notices.

**Limit of Free Salicylic Acid (for Products Containing Aspirin)**—Mobile phase and Diluting solution—Prepare as directed in the Assay.

**Standard solution**—Dissolve an accurately weighed quantity of USP Salicylic Acid RS in the Standard preparation prepared as directed in the Assay, to obtain a solution having a known concentration of salicylic acid.

Chromatographic system—Use the Chromatograph described in the Assay. Chromatograph the Standard and record the peak responses as directed for Process retention times are about 0.7 for salicylic acid; the resolution, R, between salicylic acid and aspirin is NLT 2.0; and the relative standard deviation of the salicylic acid peak responses is NLT 4.0%. 

**Procedure**—Proceed as directed for Procedure in the Assay. Calculate the percentage of salicylic acid (C<sub>9</sub>H<sub>8</sub>O<sub>4</sub>) in the portion of Tablets taken by the formula:

\[ \frac{2000(C/Q_A)(r_1/r_2)}{ } \]

where D<sub>9</sub>H<sub>8</sub>O<sub>4</sub> is the quantity, aspirin (C<sub>9</sub>H<sub>8</sub>O<sub>4</sub>) in the portion of Tablets taken, as determined in the Assay, and r<sub>1</sub> and r<sub>2</sub> are the peak of the salicylic acid peaks obtained from the Test and the Standard solution, respectively; NMT 0.3% is for case of Tablets that are coated, NMT 3.0% is found.

**Diphenhydramine Citrate and Ibuprofen**

**Buffer A:** 1 mL of phosphoric acid in 1 L of water. Adjust triethanolamine to a pH of 3.2.

**Buffer B:** 1 mL of phosphoric acid and 1.0 g of monobasic potassium phosphate in 1 L of water. Adjust with triethanolamine to a pH of 3.7.

**Solution A:** Acetonitrile and Buffer A (1:4).

**Solution B:** Acetonitrile and Buffer B (1:1).

**Mobile phase:** See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>45</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>80</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>85</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Standard solution: 0.004 mg/mL of USP Diphenhydramine Citrate RS and 0.02 mg/mL of USP Ibuprofen RS in Solution A.

System suitability solution: 0.004 mg/mL of USP Diphenhydramine-related Compound A RS, 0.8 mg/mL Diphenhydramine Citrate RS, and 4 mg/mL of USP Ibuprofen RS in Solution B.

Sample solution: Transfer an amount of powder from Tablets (NLT 20) to a suitable volumetric flask. Add flask volume of Solution B, sonicate for 20 min, and with Solution B to volume to obtain a solution cont.
Chromatographic system
(See Chromatography <621>, System Suitability.)

Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 15-cm; 5-μm packing L1
Flow rate: 1 mL/min
Injection size: 10 μL

System suitability
Samples: Standard solution and System suitability solution
Suitability requirements
Resolution: NLT 0.8 between diphenhydramine and diphenhydramine-related compound A, System suitability solution
Tailing factor: NMT 2.0 for both diphenhydramine and ibuprofen, Standard solution
Relative standard deviation: NMT 5.0% for both diphenhydramine and ibuprofen, Standard solution

Analysis
Samples: Standard solution and Sample solution
Identify the ibuprofen and diphenhydramine impurities using the relative retention times given in Table 2. Calculate the percentage of each diphenhydramine impurity and unspecified impurities in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times (1/F) \times 100 \]

where
- \( r_U \): peak response of each impurity from the Sample solution
- \( r_S \): peak response of diphenhydramine from the Standard solution
- \( C_S \): concentration of USP Diphenhydramine Citrate RS in the Standard solution (mg/mL)
- \( C_U \): nominal concentration of diphenhydramine citrate in the Sample solution (mg/mL)
- \( F \): relative response factor (see Table 2).

Calculate the percentage of the ibuprofen-related impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times (1/F) \times 100 \]

where
- \( r_U \): peak response of the ibuprofen related impurity from the Sample solution
- \( r_S \): peak response of ibuprofen from the Standard solution
- \( C_S \): concentration of USP Ibuprofen RS in the Standard solution (mg/mL)
- \( C_U \): nominal concentration of ibuprofen in the Sample solution (mg/mL)
- \( F \): relative response factor (see Table 2).

Acceptance criteria: See Table 2.

Table 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>A</th>
<th>C</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine-related compound A</td>
<td>0.95</td>
<td>1.3</td>
<td>0.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>1.00</td>
<td>1.0</td>
<td>0.</td>
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<td></td>
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<tr>
<td>Unidentified diphenhydramine degradation product</td>
<td>1.32</td>
<td>1.0</td>
<td>0.</td>
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<td></td>
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<tr>
<td>Unidentified diphenhydramine degradation product</td>
<td>1.46</td>
<td>1.0</td>
<td>0.</td>
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<td></td>
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<td>Unidentified ibuprofen degradation product</td>
<td>1.49</td>
<td>1.0</td>
<td>0.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl ibuprofen</td>
<td>1.86</td>
<td>1.0</td>
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<tr>
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<td>1.96</td>
<td>1.0</td>
<td>0.</td>
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<tr>
<td>Benzhydrol bromide</td>
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<td>2.4</td>
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<td></td>
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<tr>
<td>Ibuprofen amide</td>
<td>2.87</td>
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<tr>
<td>Isopropyl ibuprofen</td>
<td>3.45</td>
<td>---</td>
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<tr>
<td>n-Propyl ibuprofen</td>
<td>3.71</td>
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<tr>
<td>meta-ibuprofen</td>
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<tr>
<td>Ibuprofen</td>
<td>5.31</td>
<td>---</td>
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<td></td>
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<tr>
<td>n-Butyl ibuprofen</td>
<td>5.68</td>
<td>---</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Any other individual unspecifed degradation product</td>
<td>---</td>
<td>1.0</td>
<td>0.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total impurities</td>
<td>---</td>
<td>---</td>
<td>1.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) 2-(Diphenylmethoxy)-N-methylethanamine.
\( ^b \) Process impurity provided for information only; this is not calculated and is not reported.
\( ^c \) 2-p-Tolylpropanoic acid.
\( ^d \) [Bromomethylene]dibenzene.
\( ^e \) 2-(4-Isobutylphenyl)propanoic acid.
\( ^f \) 2-(4-Isopropylphenyl)propanoic acid.
\( ^g \) 2-(4-Propylphenyl)propanoic acid.
\( ^h \) 2-(3-Isobutylphenyl)propanoic acid.
\( ^i \) 2-(4-Butylphenyl)propanoic acid.

 Exclude peaks that elute before 4 min or after 80 min.

Total impurities excludes ibuprofen-related compo.
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- **LIMIT OF IBUPROFEN-RELATED COMPOUND C (FOR PRODUCTS CONTAINING IBUPROFEN)**

Buffer: 10 g/L of chloroacetic acid in water. Adjust with ammonium hydroxide to a pH of 3.0.

**Mobile phase:** Acetonitrile and Buffer (3:2).

Internal standard solution: 0.35 mg/mL of valerophenone in mobile phase.

Standard stock solution: 0.6 mg/mL of USP ibuprofen-related Compound C RS in acetonitrile.

Standard solution: 0.012 mg/mL of USP ibuprofen-related Compound C RS in internal standard solution; prepared by diluting 2 mL of standard stock solution with internal standard solution to 100 mL.

Sample solution: Transfer an amount of powder equivalent to 1200 mg of ibuprofen from ground Tablets (NLT 20) to a suitable volumetric flask. Add 100 mL of internal standard solution, and sonicate for 20 min to obtain a solution containing about 12 mg/mL of ibuprofen. Pass through a suitable filter, and use the filtrate. [NOTE—Do not dilute to volume.]

**Chromatographic system**

(See *Chromatography* <621>, *System Suitability.*)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection size: 5 µL

**System suitability**

Sample: *Standard solution*

[NOTE—The relative retention times for valerophenone and ibuprofen-related Compound C are 0.86 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.5 for both valerophenone and ibuprofen-related Compound C

Relative standard deviation: NMT 2.0%

Resolution: NLT 2.5 between the valerophenone and ibuprofen-related Compound C peaks

**Analysis**

Samples: *Standard solution and Sample solution*

Calculate the percentage of ibuprofen-related compound \((C_{12}H_{18}O)\) in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{R_D}{R_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 \]

\( R_D \) = peak area ratio of ibuprofen to valerophenone Sample solution

\( R_S \) = peak area ratio of ibuprofen to valerophenone Standard solution

\( C_S \) = concentration of USP ibuprofen-related Compound C in the Standard solution (mg/mL)

\( C_U \) = nominal concentration of ibuprofen in the Sample solution (mg/mL)

Acceptance criteria: NMT 0.1% of ibuprofen-related Compound C

**ADDITIONAL REQUIREMENTS**

- <2> Default Conditions for Solid Oral Dosage Forms

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.

- **LABELING:** The label for each article encompassing monograph bears a name composed of the act's ingredients. The label states the name and quantity of active ingredient and indicates its function or purpose of the article.

- **USP REFERENCE STANDARDS <11>**

  - USP Acetaminophen RS
  - USP Aspirin RS
  - USP Diphenhydramine Citrate RS
  - USP Diphenhydramine Hydrochloride RS
  - USP Doxylamine Succinate RS
  - USP Ibuprofen RS
  - USP Ibuprofen-related Compound C RS
Figure 4. Example of OTC drug product class monograph: Nighttime Sleep Aids.

The title of this example monograph corresponds to the FDA OTC monograph for this product category. The tests, procedures, and acceptance criteria in this example class monograph were taken from currently official *USP* monographs. USP acknowledges that there may be editorial inconsistencies (e.g., a combination of classic and new monograph formats) and scientific and compliance gaps in this example, but its purpose is to illustrate the concept rather than to serve as a formal revision proposal.

**Further Issues**

Creation of class monographs has its own challenges, including compendial and regulatory compliance considerations. Some of the outstanding issues that merit further discussion within USP and with FDA include the inclusion of USP-approved drug product names to ensure proper recognition, use of reference procedures, and less-prescriptive procedures that could enable a reasonable degree of flexibility for manufacturers while still providing a basis for enforcement of compendial requirements.

**CONCLUSION**

USP is pleased to provide this *Stimuli* article as a means of facilitating further discussion about ways to modernize its OTC monographs, which play a key role in supporting FDA's OTC monograph system and helping to ensure the quality of OTC products. This *Stimuli* article offers novel approaches for both drug substance and drug product monographs that offer the possibility of accelerating—perhaps dramatically—the pace of development and modernization. USP understands that these approaches require careful consideration. USP is committed to these approaches as a general means of updating *USP–NF*, which can support provisions of FDCA and implementing regulations.

**REFERENCES**

1. 21 CFR §201.
3. 21 CFR §508; Pub L 87-781.
   Accessed 26 September 2012.

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