

CHPA Voluntary Codes and Guidelines

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Introduction

CHPA members, the manufacturers of OTC medicines and dietary supplements, have made numerous improvements in the industry's practices regarding labeling and advertising on a voluntary basis. Since 1934, the Association has administered voluntary guidelines established by its member companies. These guidelines affect the way products are developed, packaged, labeled, distributed and advertised. A number of CHPA voluntary guidelines were put in place well before similar federal laws or regulations were adopted. These include:

- **Guidelines for Product Identification of Solid Dosage Nonprescription Drug Products:** CHPA adopted these voluntary guidelines in 1989. A U.S. Food and Drug Administration (FDA) regulation similar to the industry's voluntary program was published in 1993.
- **Program on Alcohol Content of Monographed Nonprescription Medicines Intended for Oral Ingestion:** CHPA adopted this voluntary program in 1992. In 1995, FDA published a final regulation that closely paralleled CHPA's voluntary program.
- **Child-Resistant Packaging for Alcohol-Containing Mouthwash:** CHPA's voluntary program was adopted in 1993. The U.S. Consumer Product Safety Commission (CPSC) published a final regulation in 1995 that was virtually identical to CHPA's voluntary program.
- **Label Readability Guidelines:** CHPA's label readability guidelines were adopted in 1991. FDA issued a rule on label format and content in 1999. The FDA final rule contains a number of elements that were in the CHPA label readability guidelines.
- **Packaging, Labeling and Formulation of Iron-Containing Dietary Supplements:** CHPA's voluntary program was adopted in 1993. In 1997, FDA issued a final rule, revised in 2003, on labeling of iron-containing drugs and dietary supplements. The final regulation is similar to the industry's labeling suggestions.
- **Child Safety Closures:** Today's child-resistant packaging requirements built upon and expanded voluntary child safety closure programs developed in the 1960s.

All of the voluntary programs were designed by industry and CHPA to better serve the public.

Advertising Practices for Nonprescription Medicines

Introduction.

Since 1934, the Consumer Healthcare Products Association (CHPA) has administered voluntary guidelines established by its member companies. These guidelines help to serve as an assurance to the public that manufacturers of nonprescription medicines are mindful of their responsibility in promoting and protecting the public interest.

The advertising of nonprescription, over-the-counter (OTC) medicines helps acquaint the public with these products and must be truthful, not misleading, and must meet high standards reflecting the nature of the product advertised.

Guideline provisions:

1. The package, label, and accompanying literature of a nonprescription medicine should comply with the pertinent provisions of the federal Food, Drug and Cosmetic Act; and advertising of a nonprescription medicine should comply with the pertinent provisions of the Federal Trade Commission Act.
2. Advertising for nonprescription medicines should be truthful and non-deceptive.
3. Advertisers of nonprescription medicines should have adequate substantiation for all product claims before an advertisement is disseminated.
4. Advertising of a nonprescription medicine should urge consumers to read and follow label directions.
5. A nonprescription medicine should not be advertised in a manner which is likely to lead to its use by young children without parental supervision. A nonprescription medicine should not be advertised on programs or in publications specifically directed toward young children.
6. Advertising of a nonprescription medicine should contain no reference to doctors, nurses, pharmacists, or hospitals unless such representations can be substantiated by independent evidence.

Procedures.

Complaints under the CHPA voluntary guidelines may be resolved in various ways, including, informally by discussing the complaint with the member advertiser directly, utilizing an arbitrator mutually agreed upon by the parties, or by submission to the Council of Better Business Bureau's (CBBB) National Advertising Division under its procedures.

Consumers with complaints may contact their local Better Business Bureau or the National Advertising Division with complaints. Any complaints received by the association will be logged and sent to the official representative of the CHPA member company in question.

The National Advertising Division reviews advertising challenges or complaints, using policies developed by the National Advertising Review Council (NARC) of the Council of Better Business Bureaus. NARC is aware of CHPA's voluntary guidelines on advertising practices. Overall, NARC sets policies to provide guidance and set standards of truth and accuracy for national advertisers, including through voluntary self-regulation.

Neither CHPA's voluntary guidelines nor the NARC policies replace other governmental or non-governmental systems regulating advertising claims. For example, the major television networks have their own advertising preclearance standards and processes, and the Federal Trade Commission (FTC) can and does take enforcement action against false or misleading advertising claims. Rather, CHPA's guidelines seek to encourage voluntary cooperation with industry standards. Where advertisers participating in the NAD process do not comply with

NAD's guidance and recommendations, the offending claims can be referred to the FTC for formal investigation.

Adopted: 1934

Revised: 1944, 1951, 1955, 1966, 2009 and 2015

"Flag the Label"

Manufacturers of over-the-counter (OTC) medicines often make changes in their products to improve safety or increase effectiveness, either as a result of the development and recognition of new scientific data or by providing more detailed labeling information. Additionally, OTC manufacturers often introduce, under an existing brand name, new products which may contain different single ingredients or new combinations of ingredients, in order to provide a broader range of available self-care options. The advent in 1972 of the Food and Drug Administration's massive, unprecedented and still-ongoing review of all categories of OTC medicines has acted as a catalyst for these changes which still occur at a frequent rate.

A noteworthy program - "Flag the Label" - has been adopted by members of the Consumer Healthcare Products Association to aid in alerting consumers to significant changes in nonprescription medicines. The "Flag the Label" campaign is a consumer information program approved by the Consumer Healthcare Products Association in 1977 and amended in 1993 and 1995. ("Flag" is a term used by industry to designate an attention-getting label signal which alerts consumers to read the label carefully because of significant new information.) Members of the Association have agreed to implement the flagging program as they make significant changes in their nonprescription medicines or introduce new products under an existing brand name.

Flag the Label for Significant Changes in a Currently Marketed Nonprescription Medicine

Manufacturers of nonprescription medicines should flag the label when significant changes are made in currently marketed (i.e., not new) products or labels. "Significant Changes" are defined as:

1. Expansion or limitation of indications (claims);
2. Material modification of dosage level;
3. Change in active ingredients or in directions for use;
4. New warnings or new contraindications; and
5. Any other significant new information.

This guideline is met by using phrases such as the following (or words of similar meaning), with the goal of being as specific as possible in relation to the significant change that is being undertaken:

"See new directions"

"See new label directions"

"New information: Read entire label"

"See label for new ingredients"

"See new warnings"

"Read label for current directions and warnings"

"See new uses"

"See new use"

"See new dosage"

"See new Drug Facts"

To ensure that consumers are alerted to these changes, the language of the flag should:

- appear on the principal display panel;
- be prominent and conspicuous; and
- be carried for at least six months after such a change is made.

Manufacturers should select appropriate means to make the flag conspicuous consistent with their trade dress.

Flag the Label for New Products Introduced Under Existing Brand Names

Manufacturers of nonprescription medicines should flag the labels of all new products introduced under an existing brand name.

The statement in the flag should be an accurate representation of the unique/new product feature(s). For example, if the brand name line extension is the addition of a second (or third or fourth) ingredient to a single ingredient brand name product, then such phrases as the following (or similar applicable phrases) should be used to meet this guideline:

"Added new ingredient"

"Added new ingredients"

"See label for new ingredients"

"Added [insert pharmacological class – e.g., Decongestant]"

If, for example, the brand name line extension is a change in the single ingredient that is (or had been) in the brand name product, then the guideline could be met with the following phrase (or phrase of similar applicable meaning):

"Contains no (insert type of ingredient that is in the brand name product, such as 'antihistamine')" - i.e., "Contains no antihistamine"

"(insert name of new ingredient, such as 'decongestant'), no (insert name of ingredient that is in the brand name product, such as 'antihistamine')" - i.e., "decongestant, no antihistamine"

If, for example, the brand name line extension is an extension of a line of products into new pharmacologic categories (e.g., an antacid product now expanded to relief of constipation, gas, or diarrhea), then this guideline could be met by the use of the following phrases (or phrases of similar meaning):

"For (insert new indication category, such as 'constipation', or 'diarrhea')" - i.e., "For constipation"

If, for example, the brand name line extension is a new dosage or dosage form, then the use of the following phrases (or phrases of similar applicable meaning) would meet this guideline:

"New dosage"

"New timed release formula"

"New dosage form"

The above examples are not meant to cover all possible examples of line extensions, but rather to provide known examples as models in helping companies to address other possible situations, such that specificity is added to the words/phrases used in the flag to describe the new brand name line extensions.

To ensure that consumers are alerted to these changes, the language of the flag should:

- *appear on the principal display panel;*
- *be prominent and conspicuous; and*
- *and be carried for at least six months after such a change is made.*

The indication(s)/purpose(s) for which the brand name line extension is intended should be displayed prominently and conspicuously, and be clearly distinguishable from other labeling on the principal display panel.

Additional Considerations

Note: Current requirements for the statement of identity are: "The statement of identity shall be presented in bold face type on the principal display panel, shall be in a size reasonably related to the most prominent printed material on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed." [See Code of Federal Regulations, 21 CFR 201.61 (c).]

Adopted: 1977

Amended: 1993, 1995 and 2015

Guidelines for Unsolicited Consumer Sampling of Nonprescription Medicines

Many members of the Consumer Healthcare Products Association (CHPA) provide unsolicited free samples of nonprescription, over-the-counter (OTC) medicines to consumers through the mail or by other means to promote their products. This is an economical and efficient way to accomplish mass sampling. It has been successfully followed for many years, and accidental ingestion of sample OTC medicines by children has been kept to a minimum.

The purpose of these guidelines, adopted for bulk mail sampling in 1967, amended in 1968 and 1969, and further amended in 1994, 1995 and 2015 to include other means of unsolicited consumer sampling, is to catalogue and strengthen standards of care which have evolved in this practice. While these guidelines may be employed in other forms of product promotion, they are not intended to cover transactions in which samples are provided in response to requests from consumers, are delivered to adult consumers in person or are mailed to professionals, such as physicians or dentists, at their office addresses. The company should require that a non-covered transaction, whether carried out by the company itself or by a third party, is conducted in a manner that minimizes potential risk to a child, and is not conducted in such a way that it becomes subject to the guidelines and is not in conformance with them.

These guidelines, carefully observed by the industry, should help guarantee the continued safety and success of this marketing practice. The guidelines read as follows:

1. Child-resistant packaging should be used when required either by regulation or additionally via an internal company safety assessment.
2. The total amount of the product supplied in any one sample should not be great enough to cause bodily injury to a child if ingested.
3. Where there is an objective safety concern such that ingestion of multiple samples thereof represents a reasonable hazard to a small child, the inner and/or outer container should be of such design, either through strength of closures or other methods, to inhibit accidental ingestion by a small child.
4. The outer container of every sample (such as the envelope or other package that the consumer receives in the mail or by other means) should be clearly and conspicuously labeled to show that it contains a medicinal product, and should avoid use of designs or pictures with cartoons or other juvenile themes that could encourage children to open it.
5. Multiple dwellings should not be included in samplings when such sampling would present a reasonable hazard to a small child.
6. Members of the packaging industry should be consulted periodically to ensure the latest advances in the art of safe packaging are utilized in sampling.
7. The company should also require that each of the guidelines is followed when the sampling has been contracted to a third party, rather than done by the company itself.

Adopted: 1967

Amended: 1967, 1969, 1994, 2015

Voluntary Labeling Program for Dietary Supplements

Proposed Pregnancy/Nursing Label Statement

Members of the Consumer Healthcare Products Association (CHPA) which market dietary supplements formally initiated a voluntary labeling program on March 22, 2000 which relates to the use of the following label statement on dietary supplement products:

If you are pregnant or nursing a baby, ask a health professional.

This statement (or its reasonably substantial equivalent; see 2.b.), when included in the labeling of dietary supplement products defined by the voluntary program, will be prominent and conspicuous and may appear in one of a number of alternative forms which convey essentially the same information intended by the label statement cited above (see below re: Alternative Statements). Certain dietary supplements logically do not need such a label statement because, for example, their intended uses are not for women of child-bearing age, or because they have recognized uses for women of child-bearing age (e.g., prenatal vitamins and minerals) or have data to support the use of the product by women who are pregnant and/or nursing a baby. Types of products that fall in these categories are listed below under "Exemptions."

The implementation time for this program is at the next label printing, but no later than April 2, 2001.

1. **Voluntary Pregnancy/Nursing Statement:** If you are pregnant or nursing a baby, ask a health professional.
2. **Provisions:** The following provisions apply to the voluntary use of this label information statement by CHPA members marketing dietary supplements:
 - a. **Scope:** This label information statement is intended for use on dietary supplements defined by the Dietary Supplement Health and Education Act (DSHEA), with certain exemptions:
 - (1.) **DSHEA Definition of Dietary Supplements:** "a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients."
 - (2.) **Exemptions:**
 - (a.) Dietary supplements with recognized nutrient value that have adult recommended daily intake values (RDIs) and are labeled at or below the RDI, subject to 2.c. below;
 - (b.) Dietary supplements with recognized nutrient values which are intended for prenatal use and/or for use during nursing and which solely contain vitamins and minerals with RDIs at levels safe for these intended uses;
 - (c.) Dietary supplements that may be used during pregnancy and/or by nursing mothers based on recognized compendia and/or based on determinations or pending recommendations of other authoritative bodies such as the National Academy of Sciences and United States Pharmacopeia or others and/or based on company-generated research, or information, etc.;

- (d.) Dietary supplements that are labeled exclusively for pediatric use;
- (e.) Dietary supplements that are labeled exclusively for postmenopausal women; and
- (f.) Dietary supplements that are labeled exclusively for use by men.

(3.) **Stay of Use of Structure/Function Claims for Certain Conditions Associated with Pregnancy:** Under this voluntary program, member companies would not make claims relating to edema associated with pregnancy.

- b. **Alternate Statements:** As with other CHPA voluntary label statements, this proposed pregnancy/nursing statement may be used in reasonably substantially equivalent wording, such as:
 - consult (*or, ask; or contact*) a (*or, your*) doctor (*or, health professional; or, health practitioner*) if you are pregnant or nursing (*or, breast feeding*) a baby;
 - before using (*or, before using this product*) consult (*or, ask; or contact*) a (*or, your*) doctor (*or, health professional; or, health care practitioner*) if you are pregnant or nursing a baby (*or, lactating; or, breast feeding*);
 - ask (*or, consult; or contact*) a (*or, your*) doctor (*or, health professional; or, health care practitioner; or, doctor or other health professional*) before using (*or, before using this product*) if you are pregnant or nursing a baby;
 - if you are pregnant or nursing a baby, ask (*or, consult; or, contact*) a (*or, your*) doctor (*or, health professional; or doctor or other health professional; or, health care practitioner*);
 - not for use during pregnancy and lactation, unless directed by a health care practitioner (*or, doctor; or, doctor or other health professional*); or
 - other substantially equivalent statements.
- c. **Combination of the Voluntary Pregnancy/Nursing Label Statement with Other Similar Voluntary Label Statements:** The voluntary pregnancy/nursing label statement may be combined with other voluntary labeling statements provided the combined language creates a logical construct (e.g., If you are taking a prescription medicine, or, if you are pregnant or nursing a baby, ask a doctor).
- d. **Implementation Date:** At the next label printing, but not later than April 2, 2001.

Words in italics represent examples of reasonably equivalent wording, and are not to be considered inclusive of all possible reasonably equivalent statements

Adopted: March 2000

Voluntary Labeling Program for Dietary Supplements

Proposed St. John's Wort Information Statement

Members of the Consumer Healthcare Products Association (CHPA)¹ who market dietary supplements containing St. John's wort initiated a voluntary labeling program April 2, 2000, which related to the use of the following label statement (or its reasonably substantial equivalent) on dietary supplement products containing St. John's wort:

If you are taking a prescription drug, ask a health professional.

This statement (or its reasonably substantial equivalent; see 2.c.), when included in the labeling of dietary supplement products defined by the voluntary program, will be prominent and conspicuous and may appear in one of a number of alternative forms which convey essentially the same information intended by the label statement cited above (see below re: Alternative Statements).

The implementation time for this program is at the next label printing, but no later than April 2, 2001.

1. **Voluntary St. John's Wort Label Statement:** If you are taking a prescription drug, ask a health professional (see 2.c.).
2. **Provisions:** The following provisions apply to the voluntary use of this label information statement by CHPA members marketing dietary supplements containing St. John's wort:
 - a. **Scope:** Dietary supplements containing St. John's wort
 - b. **Exemptions:** None.
 - c. **Alternate Statements:** As with other CHPA voluntary label statements, this proposed statement may be used in reasonably substantially equivalent wording, such as:
 - ask (*or, consult; or, contact*)² a (*or, your*) doctor (*or, health professional; or, health care practitioner*) if you are taking a prescription medicine (*or, drug*);
 - ask (*or, consult; or, contact*) a (*or, your*) doctor (*or, health professional, or doctor or other health professional; or, health care practitioner*) before using this product if you are taking a prescription medicine (*or, product*);
 - if you are taking a prescription medicine (*or, product*), ask (*or, consult*) a (*or, your*) doctor (*or, health professional, or doctor or other health professional; or, health care practitioner*);
 - if you are taking (*or, currently taking*) a prescription medicine (*or, product*), ask (*or, consult; or, contact*) a (*or, your*) doctor (*or, health professional, or doctor or other health professional; or, health care practitioner*) before using (*or, before using this product*); or
 - other reasonably substantially equivalent statements.
 - d. **Combination of the Voluntary St. John's Wort Label Statement with Other Similar Voluntary Label Statements:** The voluntary St. John's wort label statement may be combined with other voluntary labeling statements, such as the CHPA pregnancy/nursing label statement, provided the combined language creates a logical construct (e.g., If you are taking a prescription medicine, or if you are pregnant or nursing a baby, ask a doctor).

e. **Implementation Date:** At the next label printing, but not later than April 2, 2001.

¹CHPA, founded in 1881, represents manufacturers and distributors of dietary supplements. CHPA has over 200 members across the manufacturing, distributing, supply, research testing and advertising sectors of the self-care industry.

²Words in italics represent examples of reasonably equivalent wording, and are not to be considered inclusive of all possible reasonably equivalent statements.

Adopted: May 2000

Voluntary Program for Dietary Supplements: Adulterants, Known

Consumer Healthcare Products Association (CHPA) members agree voluntarily to take appropriate steps to assure that the following raw materials have not been substituted in whole or in part with known toxic adulterants, noted below. These steps are to be based on validated analyses by the processor or manufacturer, or, in lieu of such analysis, a guarantee or certificate of analysis from a supplier provided that the processor or manufacturer establishes the reliability of the supplier's analysis:

Herb in Commerce	Adulterant
a. Siberian Ginseng root (<i>Eleutherococcus senticosus</i>)	a. <i>Periploca sepium</i> root
b. Plantain leaf (<i>Plantago lanceolata</i>)	b. <i>Digitalis lanata</i> leaf
c. Skullcap herb (<i>Scutellaria lateriflora</i>)	c. Germander herb (<i>Teucrium chamaedrys</i>)
d. Stephania root (<i>Stephania tetrandia</i>)	d. <i>Aristolochia fangchi</i> root

Adopted: March 8, 2001

Voluntary Program for Dietary Supplements: Goldenseal

Consumer Healthcare Products Association (CHPA) members agree voluntarily to refrain from labeling or marketing products that contain goldenseal (*Hydrastis canadensis*) in any manner that suggests that the product masks drug testing.

Adopted: March 8, 2001

Voluntary Program for Dietary Supplements: Kava

Consumer Healthcare Products Association (CHPA) members agree voluntarily to market products containing kava (*Piper methysticum*) with the following dosage and labeling:

- **Labeled Content:** Products containing kava should be formulated and labeled to limit consumption of total kavalactones to 300 mg per day.
- **Labeling:** Labels of all products containing kava should bear the following statements, or their substantial equivalent and where appropriate consistent with other CHPA voluntary labeling programs:

Caution: Not for use by persons under the age of 18. If pregnant, nursing a baby, or taking a prescription drug, ask a health professional prior to use. Do not exceed recommended dose. Excessive consumption may impair ability to drive or operate heavy equipment. Not recommended for consumption with alcoholic beverages.

Adopted: March 8, 2001

Voluntary Program for Dietary Supplements: Lady's Slipper

Whereas the roots of lady's slipper, *Cypripedium* spp. (notably *C. acaule* and *C. parviflorum*) have historically been traded as wild botanicals and, given the recognition of the threatened status of these and other orchids (resulting from extirpation for commercial purposes and other causes), Consumer Healthcare Products Association (CHPA) members agree voluntarily to refrain from trade in wild-harvested lady's slippers.

Adopted: March 8, 2001

Voluntary Program for Pyrrolizidine Alkaloids

Consumer Healthcare Products Association (CHPA) members agree voluntarily to the following provisions pertaining to pyrrolizidine alkaloids. All products with botanical ingredients which contain toxic pyrrolizidine alkaloids * should not be taken orally and should therefore bear the following cautionary statement on the label:

"For external use only. Do not apply to broken or abraded skin. Do not use while nursing."

Including but not limited to: *Alkanna tinctoria* (alkanet), *Anchusa officinalis* (bugloss), *Borago officinalis** (borage), *Crotalaria spp.*, *Cynoglossum spp.*, *Erechtites hieraciifolia*, *Eupatorium cannabinum* (hemp agrimony), *Eupatorium purpureum* (Joe Pye), *Heliotropium spp.*, *Lithospermum officinale* (European gromwell), *Packera candidissima*, *Petasites spp.* (e.g., Butterbur), *Pulmonaria spp.* (e.g., lungwort), *Senecio jacobaea* (European ragwort), *Senecio vulgaris* (groundsel herb), *Symphytum spp.* (comfrey), and *Tussilago farfara* (coltsfoot).

*Borage seed oil is specifically exempt from the above label recommendation.

In view of the fact that by statutory definition botanicals that are not orally ingested are not dietary supplements, pyrrolizidine alkaloids encompassed by this voluntary program are not dietary supplements.

Adopted: March 8, 2001

Voluntary Program for Dietary Supplements: Stimulant Laxatives

With the exception of those products containing senna, cascara sagrada, or aloe that are labeled in accordance with the Tentative Final Monograph for OTC laxatives, or the leaf gel of Aloe vera, Consumer Healthcare Products Association (CHPA) members agree voluntarily that any product that contains as an ingredient any of the herbs listed below shall include the following information on its label:

1. The standard common name and plant part should be listed on all labeling and literature as follows:

Botanical Name	Common Name	Plant Part
<i>Aloe spp.</i>	Aloe	dried latex
<i>Frangula alnus</i>	frangula	bark
<i>Frangula purshiana</i>	cascara sagrada	bark
<i>Rhamnus cathartica</i>	buckthorn	fruit
<i>Rheum officinale</i>	Chinese rhubarb	root
<i>Rheum palmatum</i>	Chinese rhubarb	root
<i>Senna spp.</i>	senna	leaf
<i>Senna spp.</i>	senna	fruit or pod

NOTE: Senna was formerly listed in the genus Cassia, including the following species: *Cassia angustifolia*, *C. obtusifolia*, *C. senna*, and *C. tora*. Bulk raw materials labeled as a species of Cassia should be identified on finished consumer packages as "senna."

2. A dietary supplement including a claim in an OTC monograph per the Final Rule on structure/function claims and containing a quantity of stimulant laxative to warrant such a claim, shall also include on the label all warnings pertaining to that claim as found in the applicable OTC monograph, as stipulated in FDA's final rule on structure/function claims [Fed. Reg. 65: 1031, 2000].

Adopted: March 8, 2001

Voluntary Labeling Program for Dietary Supplements: Disclosure of Added Constituents

Whereas the Federal labeling regulations for dietary supplements require that the label of a dietary supplement list all ingredients in order of predominance, CHPA members recommend, for any botanical raw material, whether sold as a botanical or as a concentrate; metabolite; constituent; or extract of a botanical, that:

- The ingredient declaration of bulk botanical raw material declare all ingredients by their common or usual name and in order of predominance, including but not limited to botanical extractives; excipients; fillers; binders; solvents that have not been removed; and added constituents;
- Specification sheets for bulk botanical raw materials indicate for each such ingredient the percentage, or range of percentages, of the entire raw material represented by the ingredient, so that finished product manufacturers can determine the order of ingredients in a finished product containing the raw material;
- The common name of a botanical raw material to which a constituent has been added be in the form of: botanical; plant part; form; "with added" constituent, e.g., "guarana seed extract with added caffeine," "goldenseal leaf powder with added berberine"; and
- Manufacturers and marketers of finished products containing any botanical raw material as described here label such products to include all ingredients as described here in order of predominance.

Adopted: March 8, 2001

Program on OTC Oral Pediatric Cough and Cold Medicines

Members of the Consumer Healthcare Products Association (CHPA) who make OTC oral pediatric cough and cold medicines are committed to enhancing the safe and effective use of these products by parents and other caregivers with children under their care.

Under a voluntary program which began in November 2007, with amendments in 2008, and formal adoption by the CHPA Board of Directors on November 18, 2008, manufacturers of OTC oral pediatric cough and cold medicines should take the following steps in the labeling, packaging, and promotion of these medicines:

A. Changes Within the “Drug Facts” Label

1. **Label directions for children under age four, products without antihistamines.** For OTC oral cough and cold medicines with labeling for use in children under 12 with nasal decongestants, cough suppressants, or expectorants, but without antihistamines, the FDA-required direction for “children under 2 years of age: ask a doctor” should instead direct that “children under 4 years of age: do not use” in the directions section of the label.
2. **Label directions for children under age four, products with antihistamines.** For OTC oral cough and cold medicines with labeling for use in children under 12 that include antihistamines under the relevant OTC Review monograph, the FDA-required direction to “ask a doctor” for children under 6 years of age should instead include the direction “do not use” for children under 4 years of age in the directions section of the label.
3. **Cold products containing monograph antihistamines with labeling for children.** OTC oral cough and cold products with labeling for use in children under 12 containing an antihistamine under the relevant OTC Review monograph should include a statement: “Do not use unless directed by a doctor” in place of the pre-existing direction to “ask a doctor” in children under 6 years of age in the directions section of the label.
4. **Products containing monograph antihistamines with labeling for children.** The warnings section of the label for all OTC oral medicines (whether for cough and cold, or allergy) with labeling for use in children under 12 containing an antihistamine under the relevant OTC Review monograph should include a warning: “Do not use to sedate children” or, alternatively, “Do not use to make a child sleepy”.

B. Additional Labeling Changes

1. **Principal display panel.** For OTC oral cough and cold medicines with labeling for use in children under 12, the principal display panel of products containing more than one active ingredient should include the name of all active ingredients, adjacent to the purposes.
2. **Professional recommendation claims.** While companies have a right to use truthful, not misleading claims where appropriately substantiated regarding recommendations by health professionals, the industry recognizes that “doctor recommended” claims for OTC oral cough and cold medicines have been questioned by regulatory officials and health professional organizations. Companies should stop use of “doctor recommended” and similar claims in labeling for OTC oral cough and cold medicines. Any reintroduction of similar terms after November 18, 2008, would be on the basis of robust support.

C. Packaging Changes

1. **Dosing devices.** Packaging of OTC oral cough and cold medicines in liquid form with labeling for use in children under 12 should include a dosing device appropriate to the product. Markings on such dosing devices should not include extraneous marking systems that do not correspond to a marking system on the label (i.e., "teaspoon" [tsp], or "ml"). Such dosing devices should include markings for amounts directed in the product's labeling.
2. **Child-resistant packaging.** All OTC oral cough and cold medicines with labeling for use in children under 12 should come in child-resistant packaging.

D. Promotion Changes

1. **Professional recommendation claims.** While companies have a right to use truthful, not misleading claims where appropriately substantiated regarding recommendations by health professionals, the industry recognizes that "doctor recommended" claims for OTC oral cough and cold medicines have been questioned by regulatory officials and health professional organizations. Companies should stop use of "doctor recommended" and similar claims in advertising for OTC oral cough and cold medicines. Any reintroduction of similar terms would be on the basis of robust support.

E. Implementation

The implementation time for the labeling and promotion paragraphs of this program is at the next label printing, but no later than December 31, 2008.

The implementation time for the packaging change paragraphs of this program is no later than December 31, 2009.

OTC oral cough and cold medicines subject to a new drug application approved after the date of adoption of this program are exempt from section A of this program.

Adopted: November 2008

Guideline for the Stability Testing of Nonprescription (OTC) Drug Products Not Regulated by an NDA/ANDA

INTRODUCTION

Prior to this guideline, the nonprescription industry did not have directly applicable stability testing guidance for over-the-counter (OTC) monograph drug products not regulated by an NDA/ANDA. Historically, nonprescription drug companies developed their stability testing programs based upon their best interpretation and practical application of the most current FDA and/or ICH guidance for new drug products. Because of the unique requirements associated with new drug products, the direct application of the FDA and ICH guidance is sometimes inappropriate and impractical. Drug products with an OTC monograph will typically be well characterized with a significant body of information, a well-known safety profile, and a long history of use in multiple dosage forms. For this reason, the OTC industry is proposing this guideline for OTC drug products not regulated by an NDA/ANDA. For simplicity, OTC drug products not regulated by an NDA/ANDA will be referred to as OTC monograph drug products.

OBJECTIVES OF THE GUIDELINE

To define the minimum stability data package to support the commercial distribution of OTC monograph drug products in the United States per climatic zone II. The stability data package will be based on development stability studies. These studies will be used to establish the tentative expiration dating period and label storage statement for the OTC monograph drug product.

This guideline recognizes that a significant body of scientific information may exist for OTC drug products. Alternative approaches may be used when there are scientifically justifiable reasons.

SCOPE OF THE GUIDELINE

This guideline applies specifically to OTC monograph drug product stability. This guideline does not currently seek to cover the stability testing of:

- Nonprescription drug products regulated by an NDA/ANDA
- Drug substances
- Drug products used in clinical trials
- Marketed product stability

Additionally, this guideline is not applicable to:

- Specific details of the sampling and testing for particular dosage forms in their proposed container closures
- Safety studies

GENERAL PRINCIPLES

The purpose of product stability testing is to provide evidence on how the quality of a drug product in a specific package configuration varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a shelf-life period for the drug product and recommended storage conditions.

The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions only in the United States.

The design of the stability studies for the OTC monograph drug product should be based on knowledge of the behavior and properties of the drug substance and drug products that use the same active ingredient(s), manufacturing process, quantity of excipients, and container/closure system. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

PHOTOSTABILITY TESTING

Stability data should be available to demonstrate that the drug product is not susceptible to light. At least one batch of the drug product packaged in the container closure proposed for market should be tested for photostability effects. This testing may be omitted, if a scientific justification can be provided to show that the drug product in the container closure proposed for market will not be susceptible to photostability effects.

The irradiation of the packaged drug product is to be conducted according to the ICH Q1B guidance for photostability testing of drug products. Generally, not all test parameters are required in order to assess photostability effects. Scientific judgment should be used in order to determine the appropriate subset of parameters required for the photostability assessment.

SELECTION OF BATCHES

Stability data should be available on at least one primary batch of the drug product. Additional primary batches may be necessary for new product formulations and instances where no similar formulations exist. The primary batch(es) should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batch(es) should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. The batch(es) should be at least pilot scale (1/10 Production Scale); a scientific rationale may be used to justify a smaller batch size. Where practical, if multiple batches are studied, the drug product should be manufactured using different batches of the drug substance. Stability studies should be performed on each individual strength, container size, or other attribute unless a reduced sampling and testing program can be scientifically justified (e.g. bracketing and/or matrixing approaches can be used).

CONTAINER / CLOSURE SYSTEM

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing.

SPECIFICATIONS

A specification is composed of a list of tests with references to analytical procedures and the proposed acceptance criteria. The acceptance criteria can be numerical limits or ranges, textual descriptions, or other requirements depending on the type of test specified.

The list of tests should include an assessment for all of the drug product attributes that are susceptible to change during storage and that are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Analytical test procedures should be fully validated and stability indicating. There are some test methodologies where it may not be necessary or

appropriate, using good scientific judgment, to validate a test procedure (e.g., tablet hardness, where a calibrated test instrument is used).

Acceptance criteria for shelf-life specifications should be based on all of the available stability information and compendial requirements. Specifications for product release may be more restrictive than shelf-life specifications in order to account for changes observed during storage of stability samples.

For multi-dose liquid and semi-solid drug products, antimicrobial preservative effectiveness testing (AET) should be demonstrated in the multi-dose container(s). If differences between the release and shelf-life acceptance criteria for AET are necessary, the difference should be scientifically justified based on a correlation between preservative content and preservative effectiveness.

TESTING FREQUENCY

The frequency of testing, for the primary stability studies, should be designed in order to adequately determine the stability profile for the drug product. This testing frequency will typically be 0, 3, 6, 9, 12, 18, 24 months and annually thereafter through the proposed shelf-life. Justification for doing less than these time points should be provided.

At the accelerated storage condition, a minimum of three time points are recommended to be tested over a three month period (including the initial and final time; e.g. 0, 1, and 3 months). When the drug product fails to meet the established shelf-life criteria at the accelerated storage condition (such as 40C/75%RH), intermediate accelerated conditions may be used to insure that at minimum, some acceptable accelerated data is available to show that the product can withstand the typical excursions experienced in the distribution chain once the product is marketed. In addition, a drug product that fails to meet shelf-life specifications for accelerated conditions will require additional data from long term and/or intermediate accelerated conditions in order to establish an acceptable tentative expiration dating period for market.

STORAGE CONDITIONS

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Long term and accelerated storage conditions for drug products are detailed in the sections below. The general case applies if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used, if justified.

Container orientation should be considered when designing stability study protocols for liquid and semi-solid products.

STORAGE CONDITIONS – GENERAL CASE

Study	Storage Condition
Long Term	25 ± 2°C / 60 ± 5% RH
Intermediate	30 ± 2°C / 65 ± 5% RH
Accelerated	40 ± 2°C / 75 ± 5% RH

If at the accelerated storage condition the drug product fails to meet the established shelf-life criteria, alternative accelerated conditions may be used to insure that at minimum, some acceptable accelerated data is available to show that the product can withstand the typical excursions experienced in the distribution chain once the product is marketed.

STORAGE CONDITIONS – DRUG PRODUCTS PACKAGED IN IMPERMEABLE CONTAINERS

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

STORAGE CONDITIONS – DRUG PRODUCTS PACKAGED IN SEMI-PERMEABLE CONTAINERS

Aqueous-based based (those containing $\geq 50\%$ water) products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage Condition
Long Term	$25 \pm 2^\circ\text{C}$ / $40 \pm 5\%$ RH
Intermediate	$30 \pm 2^\circ\text{C}$ / $65 \pm 5\%$ RH
Accelerated	$40 \pm 2^\circ\text{C}$ / NMT 25% RH

A 5% loss in water from the initial value is recommended to be the limit of acceptability for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40°C /NMT 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40°C /NMT 25% RH may be appropriate, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated. For example, at a given temperature, e.g., 40°C , the calculated water loss rate during storage at NMT 25% RH is

the water loss rate measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative Relative Humidity	Reference Relative Humidity	Ratio of water loss rates at a given temperature
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

STORAGE CONDITIONS – SPECIAL CASE

Drug products intended for storage in a refrigerator, freezer, below -20°C, or under other conditions should be treated on a case-by-case basis.

POST-LAUNCH STABILITY REQUIREMENTS

Post-launch marketed product stability testing will be conducted to confirm the assigned expiration dating period as required by the current Good Manufacturing Practices (cGMPs).

EVALUATION

A scientific approach should be adopted in the presentation and evaluation of stability information for establishing a tentative expiry period. Results from research and development batches on similar or closely related formulations, on similar or closely related marketed products, and data published in the literature, as well as results from the specific stability study may be considered a body of knowledge that can be used in the scientific assessment. Results from physical, chemical and microbiological tests as appropriate for the dosage form should be included in this evaluation.

The purpose of the accelerated stability study is to establish, based on testing a minimum of one batch of the drug product, a tentative expiry period and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances.

When the data from an accelerated stability study remains within established limits, while maintaining potency, a tentative expiry period can be assigned prior to marketing the product. A twenty-four month expiry period may be assigned upon successful completion of three months accelerated testing. For those products that cannot tolerate 40C accelerated testing, stability data at the intermediate condition may be used to support a tentative expiry period of twenty-four months. Using sound scientific judgment, shorter expiry periods may be assigned based on less than three months of accelerated testing and longer tentative expiry periods may be justified using extended periods of accelerated testing or a combination of long term and accelerated testing. Any longer tentative expiry period or extension of an expiration dating period should be made based on scientific justification, historical data on same/similar formulas/products, and calculations using the Arrhenius equation (all with appropriate documentation).

When the data clearly exhibits no change or stability trend over time, a formal statistical analysis is not necessary.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean intersects the acceptance criterion. If analysis shows that the batch-to-batch or among package configuration variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches or package configurations. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance. If it is inappropriate to combine data from several package configurations, then each configuration should be evaluated separately with an expiry period being assigned to the individual package configuration rather than to the product as a whole.

STATEMENTS/LABELING

A storage statement should be established for the labeling in accordance with current FDA or USP requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instructions should be provided, particularly for drug products which require special storage conditions.

GLOSSARY

The following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing

Studies designed to increase the rate of chemical or physical change of a drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. However, results from accelerated studies are not always representative of similar results from the long-term label storage studies.

Bracketing

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all-time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Container/Closure system

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Development studies

Stability studies initiated during the development of a drug product. If these studies are to

be used for the purpose of assigning a tentative expiration dating period, they are sometimes called "formal" stability studies.

Dosage form

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product

The dosage form in the final immediate packaging intended for marketing.

Drug Substance

The unformulated active pharmaceutical ingredient that may subsequently be formulated with excipients to produce the dosage form.

Excipient

Anything other than the drug substance in the dosage form.

Expiration date

The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal stability studies

Stability studies initiated during the development of a drug product in a specific package according to a prescribed stability protocol in order to establish or confirm the shelf life or expiration dating period for the product.

Impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Long term testing

Stability testing of samples that have been stored at the proposed (or approved) labeled storage condition for a drug product in a specific package. Samples are stored and tested through the entire shelf life period.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Pilot scale batch

A batch of a drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Primary batch

A batch of a drug product used in a formal stability study for the purpose of establishing an

expiration dating period. A primary batch of a drug product should be at least a pilot scale batch; a scientific rationale may be used to justify the use of a smaller batch.

Production batch

A batch of drug product manufactured at production scale using production equipment in a production facility.

Semi-permeable containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient.

Shelf life (also referred to as expiration dating period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification – Release

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification - Shelf life

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product throughout its shelf life.

Storage condition tolerances

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guideline. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Supporting data

Data, other than those from formal stability studies, that support the analytical procedures, the proposed shelf life, and the label storage statements. Such data include (1) stability data on small scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

Tentative Expiry Period

A shelf-life for a drug product in a specific package that has been established using either accelerated or less than full term stability data. A tentative expiry period becomes a shelf-life period once acceptable long term stability data are available to confirm the tentative period.

REFERENCES

ICH Q1A "Stability Testing of New Drug Substances and Drug Products"

ICH Q1B "Photostability Testing of New Drug Substances and Products"

ITG-41 (FDA) "Expiration Dating and Stability Testing for Human Drug Products"

Adopted: June 24, 2009

Revised: June 26, 2012

Guideline for the Stability Testing in Support of Changes to Nonprescription (OTC) Monograph Drug Products Not Regulated by an NDA/ANDA

INTRODUCTION

Due to the great variety of changes that may be encountered after an OTC monograph drug is marketed, it is impossible to address stability requirements for all changes in an exhaustive manner in this guideline. Some of the more common examples of changes that can occur are listed below. However, since a significant body of information typically exists for these OTC monograph drug products, general guidance from the examples provided within this guideline can be used in the decision making process as to the extent of additional stability testing necessary to support a given product change.

The parent guideline "Guideline for the Stability Testing of Non-Prescription (OTC) Drug Products Not Regulated by an NDA/ANDA" describes the requirements for stability testing and data package(s) for new products. The parent guideline can be followed to generate stability data for OTC monograph drug product launches in the U.S. per climatic zone II.

Three underlying assumptions within this additional guidance to post-market changes are that 1) a post-market stability program is in place with pre-defined initial and ongoing requirements and 2) the capability exists to conduct accelerated stability testing concurrently or upfront prior to marketed product stability 3) the capability exists to assign a different expiration dating period to the changed product in the event that it is warranted.

Because of the significant body of information that typically exists for OTC monograph drug products, the significance of the change can be categorized into one of the three following categories:

- Minor – A change that has a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product.
- Moderate – A change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product.
- Major – A change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product.

In the case of multiple changes occurring simultaneously, the combined changes may or may not have an additive effect as to their impact and must be considered as well. Each situation should be evaluated appropriately.

Table 1 presented below outlines the recommended pre- and post-market stability requirements for each of the three types of changes. Within a given change category, the presence or absence of a significant body of information can lead to a more or less conservative approach. In general, the net impact to a product's expiration dating period is that only certain types of major changes would warrant a change in the current expiration dating period. For moderate or minor category changes, it is anticipated that the current expiration dating period will be maintained for the changed product. If the generated stability data for the change is not comparative, a reevaluation of the change should be performed.

Table 1: Stability Data Packages to Support Product Changes

Type of Change	Pre-Market Stability Data ¹	Post-Market Stability Data	Expiry Dating Period
Minor	None	None beyond the regular annual batches.	Maintain current expiration dating period if supported; can market product immediately.
Moderate	Comparative accelerated data on minimum of 1 batch ² of drug product with the proposed change based on product history / knowledge base.	1st production batch (minimum of one batch) on long-term stability through expiry period. ³	Maintain current expiration dating period if supported; can market product immediately.
Major	3-months of comparative accelerated data and available long-term data generated up-front on minimum of 1 batch ² of drug product with the proposed change.	1st production batch (minimum of one batch) on long-term stability through expiry period. ³	Maintain current expiration dating period if supported; market product after 3-months comparative data.

¹Alternative methods (i.e., MVTR, Extractables) and knowledge base are also used when deciding how much data is required to support a change.

²Pilot scale batches acceptable

³ If already part of the comparative stability package, no additional commercial lots are required.

SITE CHANGES

A change in the manufacturing, packaging or testing site of the OTC monograph drug product can be supported by a sufficient body of data (Table 2) to show that such a change does not affect the stability of the drug product. If the data are found acceptable, the established expiration period may be retained.

Table 2: Stability Data to Support Manufacturing Site Changes

Definitions / Examples	Type of Change
a. Manufacturing site change within a facility with the same equipment, SOP's, environmental conditions, controls, personnel (eg. Remodeling an existing building, add-on to an existing facility).	Minor
b. Packaging site change for solid oral dosage form drug products.	Minor
c. Test laboratory site change to a new location.	Minor
a. Change within a contiguous campus, or between facilities in adjacent city blocks, with the same equipment, SOP's, environmental conditions, controls, personnel.	Minor
a. Manufacturing site change to a different facility with the same equipment, SOP's, environmental conditions, controls.	Moderate

FORMULATION CHANGES

Historically, all changes in drug product formulation were grouped together and required stability documentation to support the change. An exception was the deletion of a color. Excipients may play a critical role in certain complex dosage forms. Table 3 provides information on stability recommendations to support formulation changes.

Table 3: Stability Data to Support Formulation Changes

Definition/Examples	Type of Change
a. All Dosage Forms: Deletion or partial deletion of an ingredient intended to affect the color, taste or fragrance of the drug product.	Minor
b. Solid Oral and Semisolid Dosage Forms: The total additive effect of all excipients changes does not exceed 10% with individual changes within the limits specified in SUPAC-IR and –SS.	Minor
c. Semisolid Dosage Forms: Change in supplier of structure-forming excipient which is primarily single chemical entity (purity > 95%).	Minor
a. Semisolid Dosage Forms: Change in supplier or grade of a structure forming excipient.	Moderate
b. Semisolid Dosage Forms: Change in the particle size distribution of active drug substance, if the drug is in suspension.	Moderate
a. Modified Release Dosage Forms: Change in the technical grade and/or specifications of a nonrelease controlling excipient.	Minor
b. Modified Release Dosage Forms: change in release controlling excipient quantity or quality.	Major
a. All Dosage Forms: Any qualitative or quantitative change in total excipients beyond the range greater than 10% (of total formula composition).	Moderate
b. Change of the formula added on to a fabric substrate (i.e., lotion on a fabric wipe, baby wipe, hand sanitizing wipe).	Moderate
c. Semisolid Dosage Forms: Change in the crystalline form of the drug substance, if the drug is in suspension.	Major
b. Semisolid Dosage Forms: Change in the particle size distribution of active drug substance, if the drug is in suspension.	Moderate

a. Modified Release Dosage Forms: Change in the technical grade and/or specifications of a nonrelease controlling excipient.	Minor
b. Modified Release Dosage Forms: change in release controlling excipient quantity or quality.	Major
a. All Dosage Forms: Any qualitative or quantitative change in total excipients beyond the range greater than 10% (of total formula composition).	Moderate
b. Change of the formula added on to a fabric substrate (i.e., lotion on a fabric wipe, baby wipe, hand sanitizing wipe).	Moderate
c. Semisolid Dosage Forms: Change in the crystalline form of the drug substance, if the drug is in suspension.	Major

ADDITION OF A NEW STRENGTH

The addition of a new strength for a monograph OTC drug product is permissible provided the new active concentration is within the approved drug monograph. Demonstration of equivalent stability between the current OTC drug product and the new strength will allow extension of the current OTC drug product expiration dating to the new strength. Depending on issues specific to the drug products (e.g. dosage form), availability of a significant body of information for the current OTC drug dosage form, a minor, moderate, or major category stability data package may be appropriate as shown in Table 4. New strengths intermediate to those of a current monograph OTC drug products may be supported by bracketing/matrixing studies.

Table 4: Stability Data to Support Addition of a New Strength

Definition/Examples	Type of Change
New strength of identical qualitative and quantitative composition*:	
a. Addition of a score to an immediate release tablet.	Minor
b. Change in the fill of an immediate release gelatin capsule.	Moderate
c. Change in the size of an immediate release tablet or capsule.	Moderate
New strength involving a change in the drug substance (API) to excipient(s) ratio, while maintaining qualitative composition of excipients in the formula:	
a. Simple solutions	Moderate
b. Semisolid topical dosage forms	Moderate
c. Immediate release solid oral dosage forms	Moderate
d. Semisolid and modified release oral dosage forms	

*No change in drug substance (API) to excipient(s) ratio from the current monograph OTC drug product.

CHANGES IN MANUFACTURING PROCESS AND/OR EQUIPMENT

A change limited to the manufacturing process of the OTC monograph drug product, such as a change in the type of equipment used, can be supported by a sufficient body of data to show that such a change does not compromise the stability of the drug product. The commitment to conduct stability studies on product produced by the revised manufacturing process may be appropriate as shown in table 5 below to generate a stability data package

to support the manufacturing process or equipment change. If the data are found acceptable, the established expiration period may be retained.

Table 5: Stability Data to Support Manufacturing Process Changes

Definition/Examples	Type of Change
<u>Process</u> : Changes in processing parameters such as mixing times, operating speeds within application/validation ranges.	Minor
<u>Equipment</u> :	
a. Change to equipment of the same design and operating principles.	Minor
b. Changes to equipment of different design and/or operating principles Solids Semisolid Liquids	Moderate
<u>Process</u> : Changes in processing parameters such as mixing times, operating speeds outside of application/validation ranges: a. Solids b. Semisolids c. Liquids	Moderate
<u>Equipment</u> : Changes to equipment of different design and/or operating principles a. Solids b. Semisolid c. Liquids	Moderate
<u>Process</u> : Changes in types of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder: a. Solids b. Semisolids c. Liquids	Major

CHANGE IN BATCH SIZE

A key question in considering an increase in batch size beyond the production batch size used to establish an expiration period is whether the change involves a change in equipment or its mode of operation, or other manufacturing parameters described for the approved batch size. If no equipment change is made, then the next concern is the size of the change relative to the approved batch size with larger changes expected to present a greater stability risk in the drug product. Table 6 below presents the recommended stability data packages for a variety of batch size situations not involving equipment or mode of operation changes.

If an equipment change is part of the batch size change, please refer to the previous section on manufacturing process and/or equipment changes.

Table 6: Stability Data to Support Batch Size Changes

Definition/Examples	Type of Change
<u>Solids (i.e. tablets, capsules, powders, for reconstitution), semisolids, and liquids</u> : A change in batch size up to and including a factor of ten times the size of the pre-market batch.	Minor
<u>Solids (i.e. tablets, capsules, powders, for reconstitution), semisolids, and liquids</u> : A change in batch size beyond a factor of ten times the size of the pre-market batch.	Moderate

CHANGE IN CONTAINER/CLOSURE SYSTEM (PRIMARY PACKAGING)

The Stability data packages for changes in container and closure of OTC drug products vary (Table 7). The first factor used in determining the stability data package recommendation is whether or not the protective properties of the container/closure system are affected by the proposed change. Protective properties of the container/closure system include, but are not limited to, moisture permeability, oxygen permeability, and light transmission. Changes that may affect these properties should be supported by a greater amount of data to support the change. The second factor is the nature of the dosage form itself. A solid dosage form will generally be less affected by a container change than a liquid dosage form.

Table 7: Stability Data to Support Container/Closure Changes

Definition/Examples	Type of Change
<u>Closure changes</u> : Adding or changing a child resistant feature to a packaging system or changing from a metal to a plastic screw cap, while the inner seal remains unchanged	Minor
<u>Changing the secondary packaging</u> : Changing a carton	Minor
<u>Removal or non-drug product material</u> : Removing: a. an insert b. a filler	Minor Moderate
<u>Changing shape of a container or closure</u> : a. Without changing the size – solids b. Without changing the size – liquids and creams	Minor Moderate
<u>Changing size of container/closure</u> : a. Within the established approved package size range and head space ratio b. Outside the established approved package size range and head space ratio	Minor Moderate
<u>Adding or changing a component to increase protection within the same system</u> : a. Adding, or changing to, a heat-induction seal: i. For a solid oral drug product. ii. For a liquid oral drug product b. Adding or changing a desiccant or a filler c. Adding an overwrap or carton.	Minor Moderate Moderate Minor
<u>Changing the manufacturer or formulation of a container/closure component, including bottle or blister resin, cap, liner, seal, laminate, desiccant, filler, etc., within the same system</u> :	Minor Minor Moderate

a. Using an approved or compendia container or closure equivalency protocol for: i. a solid oral drug product ii. a liquid oral drug product. b. Without an approved or compendia container or closure equivalency protocol	
<u>Changing to a different container and closure system:</u> For any solid or liquid oral drug product	Major

Adopted: March 2011

Standard Terminology and Format for Labeling of Volumetric Measures on OTC Pediatric Orally Ingested Liquid Drug Products

1. Summary

In 2008, the Centers for Disease Control and Prevention (CDC) convened a stakeholder meeting to share information and expertise on medication overdoses in children. One of the key initiatives defined by the PROTECT group was to refine dosing measures on product labeling to reduce the possibility of unintentional medication overdose. Use of nonstandard dosing devices (e.g., kitchen spoons) or inconsistent dosing directions on product labeling can result in consumer confusion and administration of an inappropriate medication dose.

As a direct result of the PROTECT initiative, CHPA developed a voluntary guideline for industry suggesting ways to standardize volumetric measures in dosing directions and dosing devices for oral pediatric liquid drug products, including preferred use of “mL” as the unit of measure for dosing instructions. Other recommendations provided in the 2009 CHPA guideline were consistent with those in a concurrently released FDA guidance on OTC dosage delivery devices (finalized in 2011).

CHPA is updating voluntary labeling guidelines for liquid products intended to be given to children under 12 years (previously approved in November 2009). Key changes include deletion of spoon labeling (i.e., teaspoon, tablespoon) in dosing directions and on dosing devices; specifying use of “mL” only in dosing directions and on devices; and deletion of the volumetric unit of measure definition (i.e., mL = milliliter). These changes are based on recent activity from FDA (issued a Draft Guidance on pediatric liquid acetaminophen products specifying that dosing directions be provided in mL only), the National Council on Prescription Drug Programs (issued a White Paper recommending that mL be the standard unit of measure for liquid prescription products), and the CDC (which through the PROTECT initiative encourages the adoption of an mL only standard for dosing directions and devices).

2. Objective and Scope

To improve patient safety by decreasing the potential for overdoses, underdoses and other errors when patients or caregivers measure and administer orally ingested OTC liquid medications, these guidelines identify and support consistent terminology, format, and text for volumetric measures within the dosing directions on the outer packaging, the immediate container label, and the dosing device for OTC orally ingested liquid drug products intended for use in children, defined as <12 years of age. Products covered by this voluntary guidance include those marketed pursuant to an OTC Monograph as well as those approved via a New Drug Application (NDA) or Abbreviated NDA (ANDA). Implementation of these guidelines, once approved as part of a members' label and packaging change process, may take up to several years.

Although similar principles may apply, this document does not address other OTC liquid products such as oral medications indicated for adults and children 12 years and over, prescription medicines or dietary supplements. In addition, the guidance does not address products with children's dosing intended for topical or non-ingested use such as crèmes or pastes, gargles/mouth rinses or sprays.

3. Background

Communications exist for parents and caregivers about the best ways to give medicines to children, especially the proper use of oral liquid medicines (2-7). Key points provided to parents and caregivers are to always read the label carefully, use the dosing device that comes with the product and to understand the types of liquid measure units for dosing liquid medicines. The use of preferred volumetric measure terms, units and abbreviations, as well as potential areas to avoid has also been suggested (7-14).

In response to reports of unintentional overdoses attributed at least in part to products with confusing or inconsistent labels and measuring devices, FDA released a draft voluntary guideline addressing dosage delivery devices for OTC liquid drug products in November 2009. The FDA voluntary guidance for industry (*Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products*) which was finalized in May 2011 provided specific recommendations for aligning dosing devices with the accompanying dosing directions for orally ingested OTC liquid medications (15). In October 2014, FDA also released a draft guidance addressing medication errors and unintentional ingestions of pediatric drug products containing acetaminophen (16). Other authoritative bodies have also released guidance on best practices for reducing medications errors, including those associated with orally ingested liquids (17-21).

In 2009, CHPA conducted an industry-wide survey of OTC oral liquid drug products with dosing directions for children in order to determine potential areas for improving the consistency and standard formatting of volumetric measures. A number of improvements were suggested including standardization of abbreviations, decimals and fractions; representation of volumetric measures in a dosing chart; use of a dosing device (provided with the product); and consistency in volumetric measures between the dosing device and the labeling dosing directions. These recommendations were provided in the CHPA voluntary guideline released in November 2009.

At the time the FDA guidelines were released, a published analysis of product labeling for marketed pediatric oral liquid OTC medications with dosing information for children younger than 12 years found numerous instances of variable dosing directions and inconsistency between dosing directions and measuring devices (22). A more recent study assessed adherence to recommendations provided in the FDA and CHPA guidelines aimed at reducing dosing errors among national brand name orally ingested OTC liquid pediatric medications (23). Recommendations included those which directly addressed potential dosing errors of ≥ 3 -fold (e.g., do not use atypical units, include a dosing device, do not use trailing zeroes, etc.).

Results from this study demonstrated a high level of adherence to the recommendations. Additional opportunities for standardization were noted by the authors including promotion of milliliter (mL) as the standard unit for dosing orally ingested liquid medications as well as the design and marking of dosing devices.

A recently released white paper from the National Council for Prescription Drug Programs (NCPDP - *Recommendations and Guidance for Standardizing the Dosing Designations on Prescription Container Labels of Oral Liquid Medications*, March 2014) provided recommendations and guidance for standardizing the dosing designation used on prescription container labels of oral liquid medications (24). Recommendations included use of milliliter (mL) as the standard unit of measure, a practice shown to reduce dosing errors (25); use of leading zeros before the decimal point for dosage amounts less than one and avoidance of the use of trailing zeros after a decimal point; and use of dosing devices with numeric graduations and units that correspond to the container labeling.

4. Specific Recommendations

The following recommendations address the labeling dosing directions on the outer packaging, the immediate container labeling, and the dosing device, for OTC orally ingested liquid drug products with dosing directions for children.

4.1 OTC Drug Facts Dosing Directions: Outer Package and Immediate Container Labeling

A. Dosing Directions:

Provide a statement(s) that:

1. encourages a consumer to select the right dose
2. use the dosing device that accompanies the product
3. keep dosing device with product/do not discard dosing device

Example dosing directions (see also Appendix)

"Find right dose on chart. Use only enclosed [*insert specific name of product's dosing device (e.g., "dosing cup", "oral syringe")*] specifically designed for use with this product. Do not use any other dosing device.)."

B. Dosing Directions: Guidelines for Volumetric Measures

1. Use a tabular format to provide dosing directions (if space permits)
2. Use milliliter (mL) as the only unit of measure in the dosing directions (*e.g.*, 5 milliliter or 5 mL)
3. Avoid use within labeling dosing directions of the following: teaspoon, tablespoon, cubic centimeters, cc, dram, fluid ounce, Fl. Oz., and dropper(ful) or any other less common or nonstandard volumetric measures.
4. For fractional volumes, use a decimal; if <1 mL volume, use decimal with a leading zero (*e.g.*, 0.5 mL) to help avoid 10-fold dosing errors. Avoid use of trailing zeros after a decimal (*i.e.*, use 1 mL not 1.0 mL) to help avoid 10-fold dosing errors.

4.2 Dosing Device: Dosing Device Accompanying the Product

A. Dosing Device: Guidelines for Volumetric Measures

1. Provide a calibrated dosing device with all orally-ingested liquid products.
2. Dosage delivery devices should not be significantly larger than the largest dose described in the labeled dosage directions and should permit clear measurement and delivery of the smallest labeled dosage.
3. Provide graduated markings on the dosing device that include dosage(s) specified in the dosing directions.
4. Use contrasting graduated markings (*e.g.*, etched or printed) so as to aid the readability of the measured liquid.
5. Use the milliliter (mL) volumetric unit(s) of measure only.
6. For fractional volumes, use the same decimal format and style provided in the dosing directions.

5. Appendix: Examples

5.1 Examples: Dosing Directions Statement(s)

Example A:

"Measure the dose correctly using the enclosed [insert specific name of product's dosing device, *e.g.*, dosing cup, oral syringe]"

Example B:

"For accurate dosing, use the enclosed [insert specific name of product's dosing device, *e.g.* dosing cup, oral syringe] to measure a dose"

Example C: Label statement using only mL (infant acetaminophen products)

"Find right dose on chart below"

"Use only enclosed [insert specific name of product's dosing device, *e.g.*, dosing cup, oral syringe] designed for use with this product. Do not use any other dosing device."

5.2 Examples: OTC Drug Facts Directions

Example A

Drug Facts

Directions

□□for accurate dosing, use the enclosed [insert specific name of product's dosing device, e.g. dosing cup, oral syringe] to measure a dose

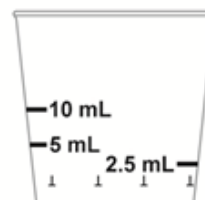
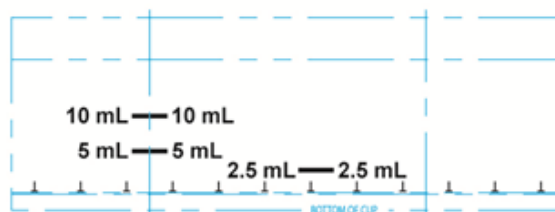
adults and children 6 years and over 10 mL once daily;
do not take more than 10 mL in 24 hours.

adults 65 years and over 5 mL once daily;
do not take more than 5 mL in 24 hours.

children 2 to under 6 years of age 2.5 mL once daily;
do not give more than 2.5 mL in 24 hours.

children under 2 years of age do not use

Directions	
■ use only with enclosed dosing cup ■ find right dose on chart below	
adults and children 6 years and over	5 mL or 10 mL once daily depending upon severity of symptoms; do not take more than 10 mL in 24 hours.
adults 65 years and over	5 mL once daily; do not take more than 5 mL in 24 hours.
children 2 to under 6 years of age	2.5 mL once daily. If needed, dose can be increased to a maximum of 5 mL once daily or 2.5 mL every 12 hours. Do not give more than 5 mL in 24 hours.
children under 2 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor



Example B

Drug Facts

Directions

- ☐ ☐ shake well before using
- ☐ ☐ use only enclosed dosing device

adults and children 6 years and over	30 mL once daily; do not take more than 30 mL in 24 hours.
--------------------------------------	--

adults 65 years and over	15 mL once daily; do not take more than 15 mL in 24 hours.
--------------------------	--

children 2 to under 6 years of age	7.5 mL once daily. do not give more than 7.5 mL in 24 hours.
------------------------------------	--

children under 2 years of age	do not use
-------------------------------	------------

Example C

Drug Facts

Directions

- ☐ ☐ shake well before using
- ☐ ☐ use only with enclosed dosing device
- ☐ ☐ find right dose on chart below. If possible, use weight to dose; otherwise use age.
- ☐ ☐ fill to dose level
- ☐ ☐ dispense liquid slowly into child's mouth, toward inner cheek
- ☐ ☐ if needed, repeat dose every 4 hours
- ☐ ☐ do not use more than 5 times in 24 hours

Weight Dose (lb) (mL)	Age (yr)	
Under 24 doctor	Under 2	Call a
24-35 5 mL	2-3	

Attention: specifically designed for use with enclosed dosing device. Do not use any other dosing device with this product.

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Adopted: November 17, 2009

Revised: November 14, 2014

Voluntary Labeling Guidelines for Dietary Supplement Products Containing Probiotics¹

Objective Statement

This document was developed by members of CHPA Dietary Supplements Committee (DSC) Probiotics Labeling Group (Labeling Group) to provide voluntary guidelines for use by manufacturers of dietary supplement products that contain probiotic ingredients. The voluntary guidelines contained within this document represent the minimum label information for probiotic-containing dietary supplement products from the viewpoint of the Labeling Group. They are not intended to replace, interpret, or circumvent any applicable local, state, or federal regulations, statutes, or guidance. Manufacturers are responsible for ensuring all product labeling is in compliance with applicable law.

Guidelines

1. Colony Forming Units (CFU) count or other appropriate measure of live bacteria at the time of expiration (guaranteed minimum) of the product.
2. Storage conditions: Provide specific directions about the conditions under which the probiotic-containing product must be maintained in order to ensure viability and potency. Storage conditions can vary depending on strain, temperature, humidity, and other factors. Storage conditions should be based on stability testing under various conditions. Each manufacturer should establish adequate storage directions based upon product-specific stability and/or test data.
3. Lot number or production code should be on the point of purchase container for every package and as appropriate, on the immediate container.
4. A clear identification of the probiotic bacteria including the strain (unless there is scientific substantiation that the claimed health benefits are not strain specific) based on widely accepted nomenclature. If a Trademarked name is used to identify the bacteria, the actual genus, species, and strain should also be included on the label. This information gives consumers the knowledge and opportunity to research the strains.
5. Contact information for the company including an address or a telephone number that consumers can call if they have any questions or concerns. For products that don't have adequate space on the label, a company should list a website where the consumer can obtain contact information.
6. Directions for suggested usage.

¹Adapted from the International Probiotics Association (<http://internationalprobiotics.org/home/>), "Voluntary Quality Guidelines for Supplement Products." Assessed at <http://internationalprobiotics.org/news/upload/pdf/2.pdf> on June 13, 2011.

Adopted: November 17, 2011

Voluntary Guideline on Impurities in Monograph OTC Topicals Excluding NDA and ANDA Products

INTRODUCTION

1.1 Objective of the guideline

This white paper provides guidance for the evaluation and reporting of impurities in OTC monograph drug products formulated as topicals and topical rinses. Topicals and topical rinses are not administered per discrete doses and they exhibit complex tissue interactions precluding the development of a single model to regulate impurities. This document serves as the Consumer Healthcare Products Association's (CHPA) member company consensus on this complex issue.

1.2 Background

CHPA formed a sub-committee to address issues regarding the handling of impurities in OTC topical products covered by the CFR monograph system (21 CFR Part 330). Currently, available guidance is based on new drug entities that differ from monograph OTC topical products in that monograph OTC products have a long market experience, may have active pharmaceutical ingredients (APIs) without specific structure-function relationships, and have specific effects based on route of administration. Due to the large body of data that supports monograph OTC products, appropriate guidelines should be developed that take into account the major distinctions between OTC and new drug entities as well as the complications associated with dermal administration.

Monograph OTC topical drug products are widely distributed, generally recognized as safe/effective (GRAS/GRAE), have years of market experience and have a well-characterized, historical record of adverse events. "GRAS/GRAE" is a designation for drugs that are generally recognized, among qualified experts, as having been adequately shown to be safe/effective under the conditions of their intended use. 21 CFR 170.3(i) defines "safe" as a material with a "reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use". Also, most topical OTC consumer products are based on core formulations that have been well characterized by the manufacturer with minor excipient variations for consumer appeal (e.g. fragrance, flavor, color). Finally, market experience accrued over the long life of the products, along with quantitative structure-activity relationship (QSAR) characteristics, estimated bioavailability, and consumption by the population, has provided foundational evidence of the safety of monograph OTC topical drug products.

Monograph OTC topical products may contain APIs that are single molecular entities or "atypical actives" with varied structures and no specific structure-function relationship (such as aloe-vera, petrolatum, or witch hazel). The fact that such compounds do not have discrete active compounds makes impurity qualification challenging. Additionally, topical OTC products are frequently non-dosage-limited with multiple APIs and can be applied to various tissue types. Current guidances make no allowance for the route of administration when considering limits on impurities.

The complexities due to the above factors prevent a single general regulation governing impurities arising from drugs formulated in monograph OTC topical products. Therefore, control strategies for impurities should be developed using a coherent, scientifically based approach on a per formula basis.

1.3 Scope of the guideline

This document serves as a consensus on the appropriate approach to the handling of impurities in FDA monograph topical OTC drug products. Topical OTC drug products cover a breadth of formulations, each with different active ingredient amounts, drug purposes, indications, and other legal requirements for marketing under monograph status. Ref CFR 201.66

Given the complexity of monograph topical OTC formulations, this white paper will only address impurities arising from APIs in topicals and topical rinses. APIs are the chemically active moieties, the drug substances used in GRAS/GRAE drug products in the United States, and are marketed under one of the following regulatory classifications (CHPA Your Health At Hand Book, October 2010):

- Category I ingredients - (GRAS/GRAE for the claimed therapeutic indication) contained in a tentative final monograph or a final monograph (FM).
- Category III ingredients - (insufficient data available to permit final classification) contained in marketed products such as ingredients are referred to as "FM pending."

Monograph drug product impurities addressed in this document include degradation products of the drug substance, reaction products of the drug substance with other drug substances in the formulation, reaction products of the drug substance with an excipient and/or the immediate container closure system (collectively referred to as "degradation products"). All impurities will be considered except the following: impurities arising solely from excipients present in the new drug product and/or extracted or leached from the container closure system, impurities revealed in the course of clinical development, and impurities arising from residual solvents and heavy metals as these are well defined in the USP. Related compounds of the ingredients that are not degradants are controlled in the raw materials and not in the finished product.

APPROACH TO THRESHOLDS

Each manufacturer is responsible for developing limits for the degradation products observed during manufacture and/or stability studies of their OTC monograph products. These limits should be based upon sound scientific appraisal of potential and observed degradation pathways. In addition, the manufacturer should summarize laboratory studies conducted to detect degradation products and any analytical procedures developed for those degradation products that literature references indicate to be unusually potent based on structure, producing toxic or significant pharmacological effects.

Manufacturers should establish limits for degradants in monograph OTC topical products with support based on consideration of the following factors:

- Compendial limits for API raw material
 - Limits for impurities in the product should scale with compendial impurities limits for the API, where compendial limits exist
 - Applicability of limits for topical administration
- Consumer exposure to the product
 - Annual number of doses of product
 - Special sensitivity of the target population (e.g. pediatric, elderly, diabetics)
- Market experience
 - Support with epidemiological data if available
 - Trends of data
 - Adverse events(AEs) associated with product
 - Data relating AEs to actives, excipients, or degradants
 - Length of market history

- Similarities of limits to those in NDA or ANDA products
 - Similarities of limits to those in products approved by other health authorities
- Duration and frequency of the exposure
 - Ease of product absorption through the skin
 - Directions for use mitigate exposure to impurities in product
 - Estimation of the systemic exposure per day (i.e. “rinse-off” products provide lower exposure than “leave-on” products.
- Route of administration and bioavailability
 - Ease of product absorption through the skin
 - Metabolism of product constituents in the dermis
 - Estimation of the systemic exposure per day
- QSARs
 - Toxicity data available for compounds with similar structures
 - Dermal toxicity and toxicokinetic data
 - Photo-irritation/photosensitization data
- Core formulations and similarities to other products
 - History of use of similar formulations
 - Gap analysis of formulas

As manufacturers work on a case-by-case basis to develop impurity limits for monograph OTC topical products, considerations must also be made for the specifics described in Appendix I.

In conclusion, this white paper provides guidance for the evaluation and reporting of impurities in OTC monograph drug substances formulated as topicals and topical rinses. A single model to regulate impurities cannot be developed for these products because they are not administered in discrete doses, may have multiple APIs, and exhibit complex tissue interactions. Consequently, this document serves as a CHPA member company consensus regarding the handling of this complex issue.

APPENDIX I

Topical and topical rinse OTC monograph drug products are complex formulations with numerous OTC variants that prevent the development of a single, robust model that accounts for all associated impurities. The complexity arises from critical physicochemical factors that impact the drug's absorption and bioavailability. Therefore, a rational approach that takes these factors into consideration will provide a clear scientific foundation for addressing impurity limits specific to a given OTC topical or topical rinse product:

Absorption variability – Absorption rate estimation for topical and topical rinses are governed by a simple model - Fick's first law of diffusion at steady state:

$$J = \frac{dQ}{dt} = D \cdot k \nabla C / e \approx K_p \cdot C$$

where dQ/dt is the rate of chemical absorbed, D represents the diffusivity in the stratum corneum), k is the stratum corneum/vehicle partition coefficient, ∇C is the concentration gradient above and below stratum corneum, e (the thickness of the stratum corneum), K_p is the permeability coefficient, and C is the applied chemical concentration.

Fick's law illustrates that both the size and charge of given chemical entity has a pronounced effect on its absorption rate. While calculating absorption is not essential for

every OTC topical product, Fick's Law helps to estimate the possible exposure to an impurity. For example, a lipophilic compound will absorb more readily through the skin than a hydrophilic one because the transfer process used is passive diffusion. Also, smaller molecular weight compounds may have a different dermal retention time than larger compounds (i.e. smaller compounds will move through the skin more quickly than larger ones). Nonpolar compounds will be absorbed at a rate directly proportional to their lipophilicity and inversely proportional to their size. Also, hydrophilic compounds will use appendages such as follicles to transfer across the dermal layer so follicular density should be factored to appropriately assess topical absorption.

Tissue variation (i.e. thickness, type, vascularity) - A primary factor limiting absorption through the skin is the stratum corneum. This outermost skin layer is composed of keratinocytes with thickened cell walls and a dry, keratinous intracellular matrix which prevents fluid loss through the skin and prevents absorption of many xenobiotics. Additionally, if a compound penetrates the stratum corneum, it then must traverse through six distinct layers of skin before entering systemic circulation and becoming bioavailable. The thickness of the stratum corneum varies from one region of the body to another resulting in different absorption rates. Stratum corneum on the palms of the hands and soles of the feet is very thick making absorption across these areas difficult. However the skin on the scrotum has a thin stratum corneum making it fairly easy for impurities to penetrate the skin. The hydration state, temperature, and integrity of the stratum corneum can also impact penetration of the skin. When the stratum corneum is hydrated (normally 7% water by weight), absorption occurs to an approximately 10-fold greater extent than when completely dry. Also, when in contact with water, penetration across the stratum corneum can approximately triple. An increase in temperature will increase dermal blood flow and increase dermal absorption. Damaged or compromised skin (i.e. burns, caustic agents, cuts/abrasions) that no longer has a completely intact stratum corneum has increased permeability.

Another consideration would be topical products that are applied close to the oral cavity (e.g. lips, perioral). These have a greater potential for systemic absorption due to the highly vascular oral mucosa that provides a direct route into systemic circulation and whole body distribution.

Solvents present in a formulation can also impact dermal absorption. Typically less vehicle-soluble compounds will penetrate the skin more easily than compounds that are more soluble in the vehicle. Also, chemicals that increase surface permeability (e.g. dimethyl sulfoxide) results in increasing dermal absorption.

Physical removal of drug substance from application site - Topicals can be inadvertently removed by washing the treated area or rubbed off by clothing, but they can also be removed purposefully as directed for some products. This results in a highly variable total exposure to the topical and its impurities due to uncontrollable and controllable factors.

Exposure duration variability (e.g. rinse off vs. leave on) - Different topical products have different directions for use. Some will remain on the skin for days (leave on) while others may only be in contact with the skin for several minutes. Such instructions result in highly variable exposure to products and their impurities. Impurities in leave-on products will have greater exposure.

Atypical drug components and natural compounds - Atypical compounds such as petrolatum have varied structures and no specific structure-function relationships. These types of compounds do not have discrete related compounds thus challenging a robust determination of their impurity profile.

Voluntary Program for Dietary Supplements: Caffeine

Caffeine is found naturally in a wide variety of beverages (coffee, tea, cola) and food (chocolate) and is an added active ingredient contained in a number of prescription and over-the-counter drugs. Manufacturers of dietary supplements are responsible for ensuring the safety of their products.

This guideline applies specifically to caffeine-containing dietary supplement products. CHPA members marketing caffeine-containing dietary supplements agree to adopt these voluntary guidelines addressing labeling, packaging, and promotion to ensure safe and responsible use of these products.

1. Disclosure of Total Caffeine Content per Serving (mg/serving)

- A. Total caffeine content, resulting from both added caffeine and naturally-occurring caffeine¹, should be declared in milligrams per serving either in the Supplement Facts Box or in a separate statement elsewhere on the label.
- B. Caffeine disclosure provisions in this guideline apply to dietary supplements containing added caffeine and greater than 25 mg per serving of naturally occurring caffeine.

2. Labeling Information

- A. Any supplement containing >100 mg total caffeine per serving should provide the following statements or equivalent language on the product label:
 - i. This product is not intended/recommended for children less than 18 years of age or those sensitive to caffeine.
 - ii. Pregnant or nursing women, those with a medical condition, and those taking medication should consult a healthcare professional before using this product.

3. Serving Size and Daily Intake Recommendations

- A. Labeling should provide serving size and daily intake recommendations that are consistent with current safety information about caffeine established by competent and reliable scientific evidence.
 - Serving size and daily intake recommendations should comply with Section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act, which requires product ingredients to be safe under the conditions of use recommended in labeling, or if no conditions of use are recommended in the labeling, under ordinary conditions of use.

4. Restraints Against Marketing In Combination with Alcohol

- A. CHPA members will not advertise, market, or otherwise promote the use of caffeine-containing dietary supplements in combination with alcohol, or to counter the acute or immediate effects of alcohol.

¹ "Added caffeine" refers to pure anhydrous (powdered) caffeine. "Naturally occurring caffeine" refers to caffeine occurring naturally in other dietary ingredients, including, but not limited to green tea, guarana, cocoa, kola nut, and yerba mate.

5. Restraints Against the Sale and Marketing of Powdered Pure Caffeine

- A. CHPA members should not sell or market powdered pure caffeine in bulk form directly to consumers.² This section is not intended to limit CHPA members from marketing or selling powdered pure caffeine in bulk form to a business entity as part of a business transaction.

6. Implementation

- A. The implementation time for this program is at the next label printing or no later than 12 months following adoption.

Adopted: June 18, 2013

Amended: June 25, 2015 (added "Restraints Against the Sale and Marketing of Powdered Pure Caffeine")

² Pure caffeine is a powerful stimulant and even very small amounts may cause an accidental overdose. In December 2014, FDA recommended that consumers not use powdered pure caffeine noting two recent deaths associated with the use of the product.