



U.S. PHARMACOPEIA
The Standard of QualitySM

Food Additives Stakeholder Forum
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Conference Center
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Appropriate Analytical Methods

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Outline

- ◆ Requirements for FCC monographs
 - ▶ Categories of monographs
- ◆ Validation of compendial methods <1225>
- ◆ USP Reference standards
 - ▶ USP's plans for RS
 - ▶ FCC Section 4 Infrared spectra
- ◆ Harmonization
 - ▶ Improvement of existing Test methods and procedures
 - ▶ Special topics supported by Project teams
 - e.g., Heavy Metals



Requirements for FCC Monographs

FCC V, General Information p. XX

- ◆ Substance is permitted for use in food or in food processing in the US (or in other countries where recognized)
- ◆ It is commercially available
- ◆ Suitable specifications and **analytical test procedures are available to determine its Identity and Purity**
- ◆ Specifications published in FCC V based on
 - ▶ Preparation under GMP conditions
 - ▶ Safe (the additive, its associated impurities, or its degradation products)



Requirements for FCC Monographs, cont.

Procedures for submission of specifications or revision of specifications

- ◆ Submission by regulatory bodies, manufacturers, suppliers, or users of the ingredients; by the committee itself; or by any other interested parties
- ◆ Accompanied by supporting data



Requirements for FCC Monographs, cont.

- ◆ Revision of test procedures and analytical methods require comparative data for both existing and suggested procedures
- ◆ Limit changes: supporting data on representative production batches
 - ▶ Limit on impurities (arsenic, cadmium, lead, flouride or mercury) may require supporting safety data and information concerning daily intake of the substance
- ◆ Other manufacturers, if involved and identified, also asked to comment



Monograph Content

- ◆ Monograph includes:
 - ▶ Packaging and storage, Function
 - ▶ Specification
 - Universal tests (description, identification, assay, impurities)
 - Specific tests, (LOD, pH, viscosity, micro.)
 - one or more analytical procedures for each test,
 - acceptance criteria



Monograph Specification

- ◆ Description (e.g., physical form, odor, color, and solubility). Food additives derived from natural sources, the sources themselves should be clearly identified.
- ◆ Identification tests
- ◆ An assay of purity
- ◆ Physico-chemical characteristics (e.g., ash content, moisture content, melting point, density, refractive index, pH).
- ◆ Limits for impurities and contaminants.
- ◆ For food additives, a limit for lead should be proposed. In addition, limits for arsenic and heavy metals, such as cadmium and mercury, should be considered when their presence needs to be controlled.
- ◆ Limits for any known natural toxicants or for microbial contaminants in or on a food additive derived from a natural source should be proposed.
- ◆ Limits for residual reactants, reaction by-products, and residual solvents.



USP Guideline for Submitting Request for Revision to the *USP-NF*

- ◆ Guideline is the work of Expert Committees and Project Teams
- ◆ Chapter 3: Excipients
- ◆ Template for writing a monograph in the USP style
 - ▶ Posted at the USP website
 - ▶ <http://www.usp.org/USPNF/submitMonograph/subGuide.html>
- ◆ Provides guidance for submission of monograph proposal where
 - ▶ *USP-NF* monographs do not exist
 - ▶ *USP-NF* monographs exist or proposals for new or revised monographs have appeared in *PF*



USP-NF Monograph Content

Submission guidelines - Microsoft Internet Explorer

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Address <http://www.usp.org/USPNF/submitMonograph/subGuide.html> Go

- Priority new monograph items
- Monographs needing improvement
- Submission guidelines**
- General Chapters status
- ▶ Expert committee meeting summaries
- ▶ Pharmacopeial Harmonization
- ▶ Frequently asked questions

REFERENCE STANDARDS

USP VERIFIED

PATIENT SAFETY

HEALTHCARE INFORMATION

EDUCATION & EVENTS

PRODUCTS

▶ **USP Revision Guideline** (522KB)

or you may download sections of interest as follows:

- ▶ **Revision History** (25KB)
- ▶ **Introduction** (29KB)
- ▶ **Glossary** (39KB)
- ▶ **Chapter One: Small Molecule Drug Substances and Products** (211KB)
- ▶ **Chapter Two: Biologics and Biotechnology Drug Substances or Products** (143KB)
- ▶ **Chapter Three: Excipients** (128KB)
- ▶ **Chapter Four: Vaccines** (59KB)
- ▶ **Chapter Five: Blood, Plasma, and Cellular Blood Components** (39KB)
- ▶ **Drug Substance Template** (159KB)
- ▶ **Tablets and Capsules Template** (157KB)
- ▶ **Excipients Monograph Template** (140KB)
- ▶ **Injection and for Injection Template** (47KB)
- ▶ **Oral Solution and Suspension Template** (35KB)
- ▶ **Cream and Ointment Template** (35KB)
- ▶ **Topical Lotion/Suspension Template** (32KB)
- ▶ **Transdermal Delivery System Template** (27KB)

Trusted sites

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USP Guideline for Submitting Requests for Revision to *USP-NF*

CHAPTER 3 EXCIPIENTS.....	47
Name.....	47
Definition.....	47
Other Requirements.....	48
Universal Tests.....	48
Description.....	48
Identification.....	49
Impurities.....	51
Inorganic Impurities.....	53
Other Impurities.....	53
Heavy Metals and Other Residual Metals	53
Inorganic Salts.....	54
Residual Solvents.....	54
Assay.....	54
Titration.....	55
Chromatography.....	55
Specific Tests.....	55
pH.....	55
Antimicrobial Agent Test.....	56
Microbial Limit Test.....	56
Bacterial Endotoxins.....	56
Formulas.....	56
REFERENCE STANDARD MATERIAL.....	56
REAGENTS.....	57



Monographs by Category

Possible suggestions:

- ◆ Macromolecular: Natural origin; oils, proteins, polysaccharides, polymeric forms
- ◆ non Macromolecular: alcohols, sugars, salts
- ◆ Categories:
 - ▶ Food additives
 - ▶ Processing aids
 - ▶ Flavor chemicals
 - ▶ Colors
 - ▶ Enzymes



<1225> Validation of Compendial Methods

FCC V p XXIV

- ◆ Validation of FCC methods
 - ▶ General Information section

USP 30 NF 25

- ◆ Validation of Compendial methods <1225>
 - ▶ General Information chapter



Comparison

Validation of FCC Methods

Rationale

Suggested analytical method

Data elements

Validation

Accuracy

Precision

Specificity

LOD

LOQ

Linearity and range

Ruggedness

Robustness

Data elements req'd for assay
validation

USP <1225>

- ◆ SUBMISSION TO THE COMPENDIA
 - ▶ Rationale
 - ▶ Proposed analytical procedure
 - ▶ Data elements
- ◆ VALIDATION
- ◆ ANALYTICAL PERFORMANCE CHARACTERISTICS
 - ▶ Accuracy
 - ▶ Precision
 - ▶ Specificity
 - ▶ Detection Limit
 - ▶ Quantitation Limit
 - ▶ Linearity and range
 - ▶ Ruggedness
 - ▶ Robustness
 - System suitability
- ◆ Data elements req'd for assay validation



- ◆ Section 4/ Infrared spectra
 - ▶ ~500 spectra used in Monograph/Flavor chemical ID test
 - ▶ **Identification** The infrared absorption spectrum of the sample exhibits relative maxima at the same wavelengths as those of a typical spectrum as shown in the section on *Infrared Spectra*, using the same test conditions as specified therein.



Almond Oil, Bitter, FFPA

FCC 5th Edition, p. 21

Almond Oil, Bitter, FFPA

Bitter Almond Oil Free from Prussic Acid

CAS: [8013-76-1]

DESCRIPTION

Almond Oil, Bitter, FFPA, occurs as a colorless to slightly yellow liquid with a strong almond aroma and a slightly astringent, mild taste. It is a volatile oil obtained from the nuts of the bitter almond tree, *Prunus amygdalus* Batsch var. *amara* (De Candolle) Focke (Fam. Rosaceae), apricot kernel (*Prunus armeniaca* L.), and other fruit kernels containing amygdalin. It is prepared by steam distillation of a water-macerated, powdered, and pressed cake that has been specially treated and redistilled to remove hydrocyanic acid. It is soluble in most fixed oils and in propylene glycol, slightly soluble in mineral oil, and insoluble in glycerin.

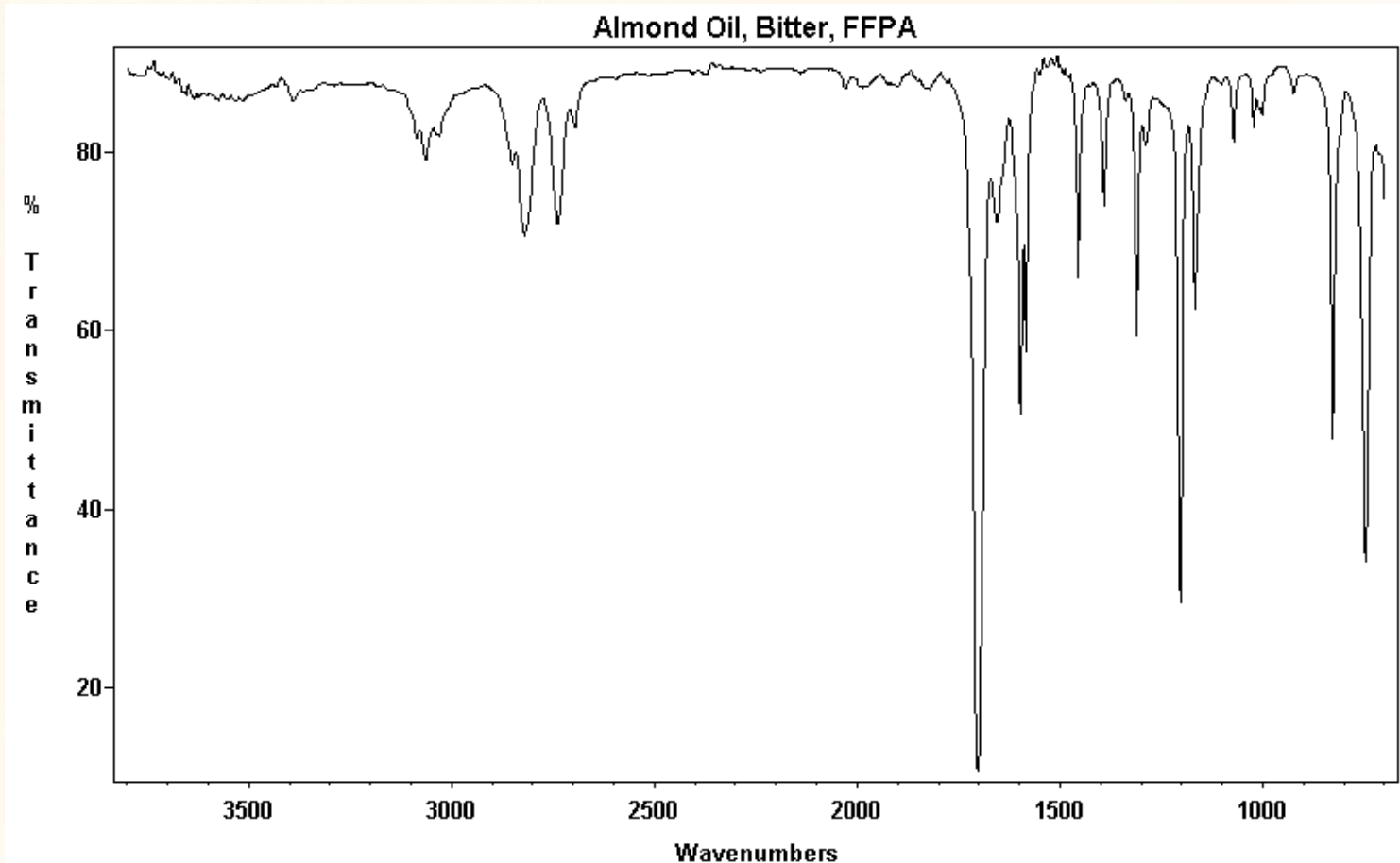
Function Flavoring agent.

REQUIREMENTS

Identification The infrared absorption spectrum of the sample exhibits relative maxima at the same wavelengths as those of a typical spectrum as shown in the section on *Infrared Spectra*, using the same test conditions as specified therein.



Almond Oil, Bitter, FFPA Infrared Spectrum p. 648





Monographs with Reference to Infrared Spectrum LIST

- ◆ 164 FCC Monographs reference IR spectrum section 4
- ◆ All Section 3 Flavor chemicals reference IR Spectra section 4 (~500)



Monographs with Reference to Infrared Spectrum LIST

N-Acetyl-L-Methionine

DL-Alanine

L-Alanine

Almond Oil, Bitter, FFPA

Ambrette Seed Oil

Amyris Oil, West Indian Type

Angelica Root Oil

Angelica Seed Oil

Anise Oil

L-Arginine

L-Arginine Monohydrochloride

L-Asparagine

Aspartame-Acesulfame Salt

DL-Aspartic Acid

L-Aspartic Acid

Balsam Peru Oil

Basil Oil, Comoros Type

Basil Oil, European Type

Bay Oil

Bergamot Oil, Coldpressed

Biotin

Birch Tar Oil, Rectified

Black Pepper Oil

Bois de Rose Oil

Butadiene-Styrene Rubber

Cananga Oil

Candelilla Wax

Caraway Oil

Cardamom Oil

Carrot Seed Oil

Cascarilla Oil

Cassia Oil

Cedar Leaf Oil

Celery Seed Oil

Chamomile Oil, English Type

Chamomile Oil, German Type

Cinnamon Bark Oil, Ceylon Type

Cinnamon Leaf Oil

Clary Oil

Clove Leaf Oil



Monographs with Reference to Infrared Spectrum LIST, cont.

- Clove Oil
- Clove Stem Oil
- Cognac Oil, Green
- Copaiba Oil
- Coriander Oil
- Costus Root Oil
- Cubeb Oil
- Cumin Oil
- gamma-Cyclodextrin
- L- Cysteine Monohydrochloride
- L-Cystine
- Dill Seed Oil, European Type
- Dill Seed Oil, Indian Type
- Dillweed Oil, American Type
- Dimethyl Dicarbonate
- Eucalyptus Oil
- Fennel Oil
- Fir Needle Oil, Canadian Type
- Fir Needle Oil, Siberian Type
- Garlic Oil
- Geranium Oil, Algerian Type
- Ginger Oil
- L-Glutamic Acid
- L-Glutamic Acid Hydrochloride
- L-Glutamine
- Glycerol Ester of Gum Rosin
- Glycerol Ester of Partially Dimerized Rosin
- Glycerol Ester of Partially Hydrogenated Gum Rosin
- Glycerol Ester of Partially Hydrogenated Wood Rosin
- Glycerol Ester of Polymerized Rosin
- Glycerol Ester of Tall Oil Rosin
- Glycerol Ester of Wood Rosin
- Glycine
- Grapefruit Oil, Coldpressed
- 4-Hexylresorcinol
- L-Histidine
- L-Histidine Monohydrochloride
- Hops Oil
- Isobutylene-Isoprene Copolymer
- DL-Isoleucine



Monographs with Reference to Infrared Spectrum LIST, cont.

L-Isoleucine

Juniper Berries Oil

Labdanum Oil

Laurel Leaf Oil

Lavandin oil, Abrial Type

Lavender Oil

Lemongrass Oil

Lemon Oil, Coldpressed

Lemon Oil, Desert Type, Coldpressed

Lemon Oil, Distilled

DL-Leucine

L-Leucine

Lime Oil, coldpressed

Lime Oil, Distilled

Linaloe Wood Oil

Lovage Oil

L-Lysine Monohydrochloride

Mace Oil

Mandarin Oil, Coldpressed

Marjoram Oil, Spanish Type

Marjoram Oil, Sweet

Mentha Arvenis Oil, Partially Dementholized

DL-Methionine

L-Methionine

Methyl Ester of Rosin, Partially Hydrogenated

Monoammonium L-Glutamate

Monopotassium L-Glutamate

Monosodium L-Glutamate

Morpholine

Mustard Oil

Myrrh Oil

Neotame

Nutmeg Oil

Olibanum Oil

Onion Oil

Orange Oil, Bitter, Coldpressed

Orange Oil, Coldpressed

Orange Oil, Distilled

Origanum Oil, Spanish Type

Orris Root Oil



Monographs with Reference to Infrared Spectrum LIST, cont.

Palmarosa Oil	L-Proline
Paraffin, Synthetic	Rice Bran Wax
Parsley Herb Oil	Rosemary Oil
Parsley Seed Oil	Rose Oil
Pennyroyal Oil	Rue Oil
Pentaerythritol Ester of Partially Hydrogenated Wood Rosin	Sage Oil, Dalmatian Type
Pentaerythritol Ester of Wood Rosin	Sage Oil, Spanish Type
Peppermint Oil	Salatrim
Petitgrain Oil, Paraguay Type	Sandalwood Oil, East Indian Type
Petroleum Wax	Savory Oil (Summer Variety)
Petroleum Wax, Synthetic	DL-Serine
DL-Phenylalanine	L-Serine
L-Phenylalanine	Spearmint Oil
Pimenta Leaf Oil	Spike Lavender Oil
Pimenta Oil	Sucrose Acetate Isobutyrate
Pine Needle Oil, Dwarf	Tangerine Oil, Coldpressed
Pine Needle Oil, Scotch Oil	Tarragon Oil
Polyethylene	L-Threonine
Polyisobutylene	Thyme Oil
Polyvinyl Acetate	DL-Tryptophan



Monographs with Reference to Infrared Spectrum LIST, cont.

L-Tryptophan

L-Tyrosine

L-Valine

Wintergreen Oil



FCC Monographs That Use FTIR but no Reference Spectra or Standard

Aconitic Acid

Butane

Glycerin

Isobutane

Propane

Talc

Aconitic Acid

Identification The infrared spectrum of the sample, determined neat as a potassium bromide dispersion, exhibits infrared absorption bands at 3030, 2630, and 1720 cm^{-1} . An aqueous solution of the substance exhibits major absorption peaks at 411 and 432 nm, with little or no absorption at 389 nm.



32 Monographs Reference a USP RS in ID

Ascorbic Acid

Aspartame

Caffeine

Calcium Disodium EDTA

Calcium Lactobionate

Calcium Pantothenate

Calcium Pantothenate, Racemic

L-Carnitine

beta-Cyclodextrin

Dehydroacetic Acid

Dexpanthenol

Dimethylpolysiloxane

Diocetyl Sodium Sulfosuccinate

Disodium EDTA

Ethyl Maltol

Fructose

Fumaric Acid

Malic Acid

Niacin

Niacinamide

Niacinamide Ascorbate

DL-Panthenol

Potassium Gluconate

Propylene Glycol

Sodium Stearyl Fumarate

Sucralose (other std comparison)

D-Tagatose (other std comparison)

Thiamine Hydrochloride

Vitamin D2

Vitamin D3

Vitamin K

Xylitol



RDL Project : Replace Spectrum with USP RS for Following Monographs

L-Alanine

Anethole

L-Arginine

L-Arginine Monohydrochloride

L-Asparagine

Aspartame-Acesulfame Salt

L-Aspartic Acid

Benzyl Alcohol

Benzyl Benzoate

d-Camphor

L-Cysteine Monohydrochloride

Ethyl Acetate

Ethyl Vanillin

Eugenol

L-Glutamic Acid

L-Glutamine

Glycerin

Glycine

L-Histine

L-Isoleucine

L-Leucine

L-Lysine Monohydrochloride



Harmonization

- ◆ Provide an available and reliable test method and procedure
- ◆ Replace methods and procedures that don't work, old, outdated (e.g., packed column replaced with capillary column, GC replaced with HPLC; Heavy metals replaced with AA, ICP methods)
- ◆ Method should not be exclusionary.
 - ▶ Possible flexible monograph approach
 - Method I AASGF
 - Method II ICP AES



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Thank You