GUIDANCE:
Liquid Extract Specifications for cGMP Compliance

August 2022

Prepared by the American Herbal Products Association

Disclaimer

The information contained herein is not and should not be considered legal advice. This AHPA publication is not a substitute for the actual statutes and regulations that apply to the products and activities that are discussed herein. The information contained herein is not intended to replace or supersede any applicable federal or state statutes, regulations, policies, or guidance.

This document is specifically relevant to addressing the current legal status of the ingredients identified herein. No other issues related to the manufacture, marketing, or sale of food, dietary ingredients, dietary supplements, cosmetics, or any other class of consumer goods are addressed herein.

While AHPA believes the information herein is accurate, AHPA advises all individuals and entities using this information to discuss all aspects of their application of this information with an attorney, a qualified consultant, or personnel at relevant regulatory agencies.

Table of Contents

Introduction

This Guidance for Liquid Extract Specifications for cGMP Compliance was developed to support liquid extract manufacturers in documenting compliance with current U.S. good manufacturing practices (cGMPs) and labeling requirements for dietary supplement products. The current U.S. dietary supplement regulations' requirements to establish product specifications as well as certain labeling requirements can prove challenging to apply to liquid extract products. The guidance provides a point of reference when corresponding with U.S. Food and Drug Administration (FDA) staff about how to apply cGMPs to specific liquid extract product types by incorporating key regulatory citations and providing suggested narrative justifications.

This guidance provides a menu of options with illustrative examples of different approaches to presenting liquid extract product information in various contexts, including Supplement Facts boxes, master formulas, and product specifications. The examples include narrative content that explains the alignment of the elements and their relationship to the product specifications. The examples provided are intended to function as customizable templates.

Guidance is provided for the following extract categories:

- Ratio liquid extracts
- Marker liquid extracts
- Liquid extracts with no ratio and no marker
- Concentrated liquid extracts
- Liquid extract blends
- Liquid group extractions

This guidance was developed by a working group of AHPA members who produce liquid extracts and other interested parties. Particular appreciation is due to Staci Eisner of Cortex Scientific Botanicals who served as the primary editor of the document. Comments on this guidance and suggestions for additional examples to include or other improvements are welcome and should be submitted to AHPA at the email or physical address listed below. Revisions may be made to this guidance as additional insights are gained through its practical use.

American Herbal Products Association
8630 Fenton St., Suite 918
Silver Spring, Maryland 20910
USA
info@ahpa.org

1. Ratio liquid extracts

1.1 Supplement Facts examples

Supplement Facts information is required on the retail label for all dietary supplements unless the company claims an exemption.[1]

Serving Size. The "serving size" in the header of the panel may be presented using any appropriate measure such as drops, dropperfuls, teaspoons, milliliters, etc. (21 C.F.R. § 101.36(b)(1)).

- The conversion between the serving size declared on the label and the volume equivalent to that serving needs to be known in order for the company to properly to create the product formula and manufacturing procedures and records.

- If the serving size is in drops, the actual average number of drops per mL or per mg needs to be determined for each product, since it will vary depending on density and viscosity. It will also vary with temperature; AHPA recommends using the average value based on the expected range of temperatures.[2]

- If measuring lines are indicated on the dropper, the average quantities dispensed according to the lines needs to be determined for each product and each model of dropper. This volume may vary slightly with temperature (since the size of the drop that remains at the end of the tube when the filled dropper is removed from the retail container may change depending on how temperature affects the surface tension of the liquid), but any amounts expressed by weight will vary much more significantly depending on the temperature (due to expansion or contraction of the entire column of liquid in the dropper). AHPA recommends using the average value based on the expected range of temperatures.

- If the serving size is in dropperfuls, the actual average quantity dispensed by the bulb needs to be determined for each product and each model of bulb. Also, to avoid consumer confusion it may be appropriate to clarify on the label that one dropperful equals one squeeze of the bulb, lest consumers believe they must completely fill the dropper.

- Some companies describe the serving size and servings per container with qualifiers such as "about" or "approximately" (e.g., "about 30 servings"). However, AHPA advises against using such descriptors.

Throughout these examples a serving size of 1 ml is frequently used. This is merely an example; the serving size may be whatever quantity the company deems appropriate.

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[1] See information about claiming an exemption at https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm2006867.htm.

[2] FDA labeling regulations define the serving size as the largest serving consumed at one time, but AHPA doubts that FDA considered cases where both the number of units (i.e., drops) and the volume would vary. AHPA believes in such cases, to use the maximum volume (i.e., the volume at the lowest expected temperature) would almost always overstate the actual serving, which would be confusing and misleading to the consumer. Therefore, it is more appropriate to use the average volume.

Nutritional Data. Nutritional data such as Calories, Total Carbohydrate, etc. must be disclosed in the Supplement Facts box if the amounts per serving exceed the thresholds established in the labeling regulations (21 C.F.R. §§ 101.9 and 101.36). In practice, for typical liquid extract serving sizes the amounts of Calories or Total Carbohydrate will generally fall below the threshold for disclosure.

Dietary Ingredients. The amount of each dietary ingredient (in this case, the amount of Echinacea Root Extract) in the body of the table may be presented in metric weight or volume units, e.g., grams, milligrams, or milliliters (21 C.F.R. § 101.36(b)(3)(ii)(A) and (B)).

Use of fresh plant material. If fresh rather than dry crude botanicals are used to make the extract, this fact must be disclosed for each such dietary ingredient per 21 C.F.R. § 101.36(b)(3)(ii)(B). Where this is done, the term "fresh" to describe the crude botanical should similarly be used in Master Formula information and elsewhere as appropriate for clarity. For example, a liquid extract made from fresh echinacea root should be called "fresh echinacea root extract" and the crude botanical should be called "fresh echinacea root" in the master manufacturing record (MMR), raw material specifications, etc. In addition, extracts made with fresh raw materials will generally have higher levels of moisture or water reflected in the finished extract specifications.

Extract Ratio. The extract ratio is a measure of the concentration or dilution level of an extract (in the form Y:Z where Y is the weight of the starting material and Z is the volume of solvent).

Some FDA districts have taken the position that extract ratios cannot be stated in the Supplement Facts box, and other districts have taken the position that extract ratios cannot be stated on the label at all, unless the ratio can be tested in the finished product. However, there is no scientifically valid method to test for "extract ratio." AHPA opposes FDA assertions that labels cannot include extract ratios. Expressing extract strength as a ratio is a practice with historical roots going back more than a century and has always been based on manufacturing inputs, not analytical test results. Extract ratio specifications defined based on manufacturing inputs are widely recognized – often even required - by food and drug authorities around the world, and consumers often expect to see ratio information provided on product labels. Furthermore, FDA labeling regulations explicitly provide for disclosure of the extract ratio (21 C.F.R. § 101.36(b)(3)(ii)(B)) on the basis of information that is easily determined from the batch record, requiring no test to verify (nor is there any scientifically valid way to test for "extract ratio"). In view of these facts, AHPA believes statement of the extract ratio in specification documents, labels, and elsewhere is perfectly appropriate, and that the ratio is determined based on batch record data. See additional discussion below in the Bulk Liquid Extract Specifications.

The extract ratio may be established as a single fixed value or as a range. If a range is allowed in manufacturing, then for product labels the ratio is usually stated based on the midpoint of the range. (For example, a product whose ratio ranges from 1:4 to 1:6 would be labeled as 1:5.) Ratio ranges are more common with powdered extracts than with liquid extracts.

Ingredients Statement. The "Ingredients" or "Other ingredients" statement below the Supplement Facts box must disclose either all ingredients or all ingredients not listed in the body of the Supplement Facts box. For example, with "Echinacea root extract" listed in the Supplement Facts box, the "Ingredients" could be listed as water, ethanol, and echinacea root or the "Other Ingredients" could be listed as water and ethanol. In either case, the ingredients or other ingredients must be listed in descending order of predominance by weight (not volume). In the case of 50% ethanol by volume, the weight of the water will be greater than the weight of the ethanol, so it should be listed first.

Solvent Disclosure. Where the name(s) of the solvent(s) used are not stated in the Supplement Facts panel, they must be named in the ingredient statement. For hydroethanolic extracts, the alcoholic component of the solvent may be named as "alcohol," "ethanol," or "ethyl alcohol."

The quantitative proportion of solvent (e.g., 70% ethanol) may be stated for the liquid extract, but it is not required. AHPA recommends that solvent percentages should always be stated on the volume/volume (v/v) basis, rather than weight/weight (w/w) or weight/volume (w/v).

If a solvent percent is stated on the label, then it must reflect the solvent composition in the finished product, which may differ somewhat from the solvent proportions used in manufacturing the extract (e.g., due to selective evaporation). At least one FDA district requires that the firm have test data to support the accuracy of the stated number, for example, by gas chromatography (GC) testing; several other FDA districts permit verification of the ethanol percent based on the batch record, allowing a range of ±5% absolute (e.g., if the ethanol percent is 50%, the range is 45-55%).

Since the ethanol content varies somewhat from batch to batch of product, some companies state a range of alcohol content (e.g., "40-50% ethanol") or an upper limit "NMT 70% alcohol." Some attorneys recommend against this practice, but AHPA is not aware of any objections by FDA to it or of any principled reason why it should not be allowed. However, the average ethanol content is most commonly stated.

See additional comments in the Bulk Liquid Extract Specification section.

Crude Herb Equivalents. In addition to or instead of disclosing the extract ratio, some companies also state the amount of herbal raw material per serving, e.g., "Each serving provides extractives from xx mg of herb" or "X mg of herb was used to make each serving." Any amounts stated must be consistent with the extract ratio specified. AHPA recommends:

- If fresh herb is used as the raw material, this fact should be disclosed in such statements (e.g., "X mg of fresh echinacea root was used per serving").
- Such statements should not appear in the Supplement Facts box or otherwise in between the Supplement Facts box, the (other) ingredients list, and the name and place of business of the manufacturer, packer, or distributor per 21 C.F.R. § 101.22(e).
- Companies should NOT use the phrases "equivalent to X amount of herb" (because extraction efficiency is always less than 100%) or "contains X amount of herb" (because the herb is not actually present after extraction).

Dietary ingredient quantity claimed by volume:

Supplement Facts

Serving Size: 1 ml (28 drops)[3]

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Echinacea Root Extract 1:10	1 mL	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Ingredients: water, organic alcohol (40%), organic echinacea root.

Dietary ingredient quantity claimed by weight:

Supplement Facts

Serving Size: 1 ml (28 drops)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Echinacea Root Extract (in 40% alcohol)	940 mg	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, 190 proof organic alcohol.

As a reminder, there are numerous options for the content of Supplement Facts panels. For example, the extract ratio may be disclosed or not; the proof and/or percentage or range of percentages of ethanol (or other solvent composition) may be disclosed or not; and "alcohol" may be called "ethanol." The illustrations provided herein are examples only.

[3] The labeling regulations allow the serving size to be stated in any appropriate unit of measure and do not require the weight or volume of the serving to be stated. The volume is included in each of the examples in this document simply to facilitate the reader's ability to see the correlation between the Supplement Facts panel information and the Master Formula information.

1.2 Master formula examples

The information in what may be called the Master Formula is a required part of the MMR; it is described in 21 C.F.R. § 111.210(b) through (e), although without using the term "Master Formula." This required information may be presented in the MMR in any manner the company deems appropriate. For clarity and conciseness, throughout these examples the Master Formula is presented in table form.

The Master Formula information should be configured in a manner that is easy to correlate with the Supplement Facts panel (e.g., same serving size, same amounts per serving and same units of measure) and with the dispensing instructions in the MMR (i.e., same amounts of ingredients per batch and same units of measure).

It can be useful to maintain the Master Formula information all in one place, e.g., summarized on one page or table in the MMR so that the manufacturing process can be readily correlated to the Supplement Facts information. It may also be maintained as a separate document from the rest of the MMR so that manufacturing instructions may be updated separately from the formula (however, by regulation the Master Formula still remains part of the overall MMR). Alternately, the information may be integrated into the MMR in whatever manner the company prefers, so long as the required elements are included.

If the product is not labeled with a Supplement Facts box (i.e., if the firm claims a labeling exemption for the product as per the FDA Small Business Nutrition Labeling Exemption[4]), then the "each contains" element of the Master Formula information may be omitted.

Four examples are provided on the following pages –

- The retail label claims 1 ml of echinacea root extract per 1 ml serving (i.e., the claimed amount is a volume measurement), made by maceration.

- The retail label claims 1 ml of echinacea root extract per 1 ml serving (i.e., the claimed amount is a volume measurement), made by percolation.

- The retail label claims 940 mg of echinacea root extract per 1 ml serving (i.e., the claimed amount is a weight measurement), made by maceration. In this case, the volume of the extract is converted to weight using the density of the extract.

- The retail label claims 1 ml of echinacea root extract per 1 ml serving made by maceration, and the manufacturing process includes raw material preparation steps that will cause losses.

(Throughout the remainder of this document, all examples are by maceration unless otherwise specified.)

Ratios and Percentages. Whenever percentages or ratios are used, it is important to consider whether they are on the weight/volume basis (w/v), volume/volume basis (v/v), or weight/weight basis (w/w). For example, 190 proof ethanol in the United States contains 95% ethanol on the v/v basis; it contains

[4] Available at https://www.fda.gov/food/labeling-nutrition-guidance-documents-regulatory-information/small-business-nutrition-labeling-exemption.

less ethanol on the w/w basis. For solvents, AHPA recommends all proportions be expressed on the v/v basis.

Densities. The density of a liquid will vary with temperature, so it is important to control the temperature when making measurements by volume or when making measurements of density.

AHPA recommends, for purposes of the Master Formula information and calculating label claims, using the average density of the product. AHPA believes this to be justified since FDA commonly makes allowances for analytical variability and other factors that are beyond the firm's direct control; for example, Class II nutrients as defined in 21 C.F.R. § 101.9(g)(3)(ii) are permitted to deviate from label claim by +/- 20%, while the variation in density will be much less than that. However, firms who wish to be conservative should use the lowest likely value for the density rather than the average, as this will correspond to the lowest weight for the label claim.

1.2.1 Master Formula for 1:10 (w:v) ratio extract with label claim by volume, made with maceration

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE001 Version #: 001 Batch Size: 100 L (100,000 ml)

Product: Echinacea Root Liquid Extract 1:10 (w:v)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 1 mL contains	U/M	Multiplier* %	Overage* %	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1									
2			100	0	50345	Echinacea root, chopped organic dry†	10	kg	1
3									
4						Theoretical subtotal for dry ingredients:	10	kg	
5									
6					70001	Water, purified	50	L	5
7									
8					70002	Ethanol, 190 proof	50	L	5
9									
10						Theoretical subtotal for liquid ingredients: **	100	L	
11									
12	1	ml	100	0		Theoretical output total: ***	100	L	
13									
14									
15									

[Filename] / [date] / [initials] [Company name and address]

* The "multiplier" is a mathematical conversion factor to take into account the strength/potency/content of the raw material, as applicable to the type of ingredient (e.g., an herb that contains 3% of a marker, an ingredient that contains 1 million IU/g of a certain vitamin, an ingredient that contains 57% of a certain mineral element). In this example, the strength of the echinacea root is 100%.

* The "overage" is the proportion by which the batch quantity of an ingredient exceeds the bare minimum theoretically required to meet the label claim. In this example, no overage is used.

See additional scenarios below and the "Marker Liquid Extract" and "Liquid Extract Blend" sections for additional information and examples.

† The firm's documentation system must identify the appropriate genus and/or species of each botanical; this is typically done in raw material specification documents, but it may also be appropriate in the Master Formula and/or finished product specifications, especially if the Latin name is stated on the product label. Per 21 C.F.R. § 101.4(h)(2), the Latin name is required on retail labels if the common name used on the labels differs from the Standard Common Name established in AHPA's "Herbs of Commerce." Whatever naming system is used, it is generally preferable for the names to be consistent throughout the related paperwork from raw material to finished product.

** For extracts made by maceration, this number is used in calculating the extract ratio, which is defined as Y:Z where Y is the weight (mg) of the starting material and Z is the volume (ml) of solvent. The actual volume of the combined solvents will vary from the theoretical volume due to shrinkage; for hydroethanolic solutions this effect is typically 2% or less, an effect too small to affect the calculated extract ratio.

*** This is the theoretical yield for the batch. The master manufacturing record (MMR) must establish the allowed range of actual yields beyond which a quality assurance or quality control investigation is required. The allowed range should account for, for example, expected losses due to evaporation, adsorption of solvent to the marc, and expected gains from water and extractives contributed by the herb.

1.2.2 Master Formula for 1:10 (w:v) ratio extract with label claim by volume, made with percolation

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE001 Version #: 001 Batch Size: 100 L (100,000 ml)

Product: Echinacea Root Liquid Extract 1:10 (w:v)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 1 mL contains	U/M	Multiplier %	Overage %	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1									
2			100	0	50345	Echinacea root, chopped organic dry	10	kg	1
3									
4						Theoretical subtotal for dry ingredients:	10	kg	
5									
6					70001	Water, purified	500	L	5
7									
8					70002	Ethanol, 190 proof	500	L	5
9									
10						Theoretical subtotal for liquid ingredients:	1000	L	
11									
12	1	ml	100	0		Theoretical output total:*	100	L	
13									
14									
15									

[Filename] / [date] / [initials] [Company name and address]

* For extracts made by percolation, this number is used in calculating the extract ratio, which is defined as Y:Z where Y is the weight (mg) of the starting material and Z is the volume (ml) of solvent. Percolation uses much larger volumes of solvent than what actually ends up in the finished extract.

1.2.3 Master Formula for 1:10 (w:v) ratio extract with label claim by weight

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE001 Version #: 001 Batch Size: 100 L (100,000 ml)

Product: Echinacea Root Liquid Extract 1:10 (w:v)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 1 mL contains	U/M	Multiplier %	Overage %	Density (g/ml) (at 20 °C)	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1										
2			100	0		50345	Echinacea root, chopped org dry	10	kg	1
3										
4							Theoretical subtotal for dry ingredients:	10	kg	
5										
6						70001	Water, purified	50	L	5
7										
8						70002	Ethanol, 190 proof	50	L	5
9										
10							Theoretical subtotal for liquid ingredients:	100	L	
11										
12	940	mg	100	0	0.94		Theoretical output total:	100	L	
13										
14										
15										
16										
17										
18										
19										

[Filename] / [date] / [initials] [Company name and address]

1.2.4 Master Formula for 1:10 (w:v) ratio extract with label claim by volume, and raw material preparation losses

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE001 Version #: 001 Batch Size: 100 L (100,000 ml)

Product: Echinacea Root Liquid Extract 1:10 (w:v)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 1 mL contains	U/M	Multiplier %	Overage* %	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1									
2			100	10	50345	Echinacea root, whole organic dry	11	kg	1
3									
4						Theoretical subtotal for dry ingredients:	11	kg	
5									
6					70001	Water, purified	50	L	5
7									
8					70002	Ethanol, 190 proof	50	L	5
9									
10						Theoretical subtotal for liquid ingredients:	100	L	
11									
12	1	ml	100	0		Theoretical output total:	100	L	
13									
14									
15									
16									
17									
18									
19									
20									
21									
22									

* This formula includes a 10% overage for the whole echinacea root, in expectation of up to 10% losses during raw material preparation (e.g., inspection, cleaning, and milling). Increasing the amount of raw material by the maximum expected scrap rate, as is done in this example, is one way to account for such losses. Another option is for the Master Formula to specify 10 kg of prepared raw material, with an overage of 0%, and then the MMR to include a separate dispensing step after raw material preparation, at which point exactly 10 kg of prepared raw material is weighed for use in the batch and any leftover is scrapped. A third option is for the output of the raw material preparation to be weighed and the amounts of solvents to be used in the batch recalculated so as to keep the same proportions called for in the Master Formula; any such adjustments must be documented and approved by the quality department. Other appropriate options may also exist.

1.3 Product specifications

1.3.1 Ratio liquid extract - Bulk liquid extract specification

[Company Name / Logo]

BULK LIQUID EXTRACT SPECIFICATION

CONFIDENTIAL

Item:	Description:	Page:
BLE001	Echinacea root liquid extract 1:10 (w:v), bulk	Page 1 of X

Version:	Supercedes:	Created by / date:	Approved by / date:
01	**		*[This must be a signature]*

Item	**Specification**	**Method**
Identity	Echinacea root liquid extract 1:10 (w;v), bulk	As per batch record
Color	Brown *[or, Pantone color(s) or range, Munsell color values, etc.]*	Organolepsis*
Consistency	Thin liquid *[or, compare to a common liquid such as water, syrup, etc.]*	Organolepsis
Clarity	Clear, with sediment	Organolepsis
Odor	*[describe in detail]*	Organolepsis
Flavor	*[describe in detail]*	Organolepsis
Density	0.93-0.95 g/ml *[or test specific gravity instead]*	Weight/volume
	[other potential identity tests = pH, viscosity, TLC for echinacea root, etc.]	
Purity	100% echinacea root liquid extract 1:10 (w:v)	By input as per batch record†
Strength	1:10 (w:v) as per Master Formula	By input as per batch record††
Composition	1 part Echinacea root, 5 parts water, 5 parts 190-proof ethanol	By input as per batch record
Ethanol	35-45% (v/v) *[the ethanol will not be exactly the amount based on input due to selective evaporation, contributions of moisture from the botanical raw material, and some adsorption of ethanol by the marc]*	Hydrometer *[requires validation**]* *[or use GC, or batch record review***]*
Water	52-63% (v/v) *[or test water activity instead; it's a cheap test and has relevance to microbiological safety]*	Karl-Fischer *[or water activity meter]*
	[other potential composition tests = dry solids]	
Heavy metals	*N/A or set appropriate specifications; see additional comments below*	*N/A or list test method*
Pesticides	*N/A or set specifications as per risk assessment; see additional comments below*	*N/A or list test method*
Salmonella	*N/A or set a specification of "Absent"; see additional comments below*	*N/A or list test method*
E. coli	*N/A or set a specification of "Absent"; see additional comments below*	*N/A or list test method*
	[other potential tests = spoilage organisms, mycotoxins, allergens, etc.]	

* See AHPA's guidance document "Organoleptic Analysis of Herbal Ingredients" for information about organoleptic evaluations. Organoleptic characteristics should be described in as much detail as possible.
† In the preamble to the final cGMP rule, FDA describes the "purity" of a dietary supplement as "that portion or percentage of a dietary supplement that represents the intended product" and provides as examples (a) arginine containing 90% L-enantiomer and 10% D-enantiomer is "90% pure" L-arginine and (b) an oil containing 95% triglycerides and 5% free fatty acids and sterols is "95% pure" triglycerides. As far as AHPA has been able to discern, "purity" specifications as described by FDA in 21 C.F.R. Part 111 serve no purpose that isn't already accomplished by the "strength" specification (i.e., the arginine and triglycerides described above would have strength specifications in the form "900 mg/g L-arginine" or "95 g/100 g triglycerides," and setting additional "purity" specifications provides no additional quality control benefit). In the context of herbal extracts, AHPA believes "purity" to be inapposite, since U.S. federal regulations – consistent with worldwide practice and historical custom – define the quantity of an extract as including the solvents and other excipients.

†† (a) Some FDA districts have stated they require use of UV-visible spectroscopy testing as a measurement of the extract ratio for extracts where the company establishes an extract ratio specification. AHPA believes this to exceed the requirements of the regulation and therefore believes such demands to exceed FDA's authority. AHPA furthermore questions whether use of spectroscopy as a "test" for extract ratio is scientifically valid; UV-visible spectroscopy is a measurement of color intensity, which bears at best an unreliable relationship to the extract ratio. Such tests are more suited to providing evidence of identity (i.e., color) or, in some cases, content of marker substances.
(b) At least one FDA district is reported to have pushed companies to use density as a test for "strength." AHPA is not aware of any evidence that density is a scientifically valid test method to determine extract "strength"; the density will bear at best an unreliable relationship to the extract ratio or any other measure of extract strength, and it will have meaning only in the context of a firm's particular manufacturing process executed on that firm's particular raw materials. As a result, AHPA does not support use of density as a test for strength; rather, review of ingredient and batch records will provide the most reliable evidence (unless marker content is used for the strength specification). AHPA views density measurements as providing evidence of identity rather than strength.

[Some FDA investigators assert that identity, purity, strength, and composition must each be different than the others. AHPA believes this to be erroneous; nothing in the regulation or preamble requires them to be different from each other, although in this example they are.]

** Hydrometer measurements of finished products probably need to be validated on a product-by-product basis; e.g., test the first 3 batches by GC and by hydrometer, then create a chart or graph to correlate hydrometer measurements to GC measurements and use that to correct the hydrometer readings for subsequent batches.

*** At least one FDA district pushes for ethanol determinations by GC testing of the finished product; AHPA believes this to exceed the requirements of the regulation and therefore believes such demands to exceed FDA's authority. Other districts allow firms to test the ethanol concentration at the raw material stage, establish finished product ethanol specifications as a reasonable range around the theoretical value based on the formula (e.g., +/- 5%), and then verify the finished product ethanol content through review of batch records. AHPA believes the latter to be consistent with the regulation and with FDA's authority. AHPA notes that the typical variation in the content of ethanol, which is merely an excipient, is much less than the +/- 20% range FDA allows for Class II nutrients. AHPA therefore sees no justification to require expensive analytical testing of its content, except perhaps for products where the ethanol content is low enough that small fluctuations might permit growth of spoilage organisms or organisms of public health significance.

BULK LIQUID EXTRACT SPECIFICATION (CONT'D)

CONFIDENTIAL

Item:	Description:	Page:
BLE001	Echinacea root liquid extract 1:10 (w:v), bulk	Page 2 of X

Version:	Supercedes:	Created by / date:	Approved by / date:
01	**		*[This must be a signature]*

Narrative justification[5]:

a. Botanicals are complex chemical mixtures whose compositions are not fully known; furthermore, the composition of extracts made from a given botanical will vary depending on the extraction method. Our trade association, the American Herbal Products Association (AHPA), advises that methods do not exist to perform comprehensive chemical testing to quantitate the complete chemical makeup of the echinacea extractives, other than on an aggregate basis as dry solids. Under the Dietary Supplement Health and Education Act, cGMP regulations "may not impose standards for which there is no current and generally available analytical methodology." 21 U.S.C. § 342(g)(2).

   With respect to testing individual marker compounds, AHPA advises that qualitative or quantitative marker testing of individual echinacea constituents does not prove identity, purity, strength, or composition of a botanical supplement (except in those cases where a company has chosen to use the content of a marker compound as a measure of the strength[6]), as isolated markers are readily obtained and these exogenous constituents can be spiked into the product in order to confound the test.[7] Therefore, marker testing of the finished product does not demonstrate that the production and process control system is producing a dietary supplement that meets the established specifications for identity, purity, strength, and composition; these specifications can be reliably determined only by examination of the ingredient records and batch record.[8]

[5] The details of the narrative justification should be tailored for each product to the extent possible, and the justification should reference standard operating procedures (SOPs) and other controls that support how the production and process control system ensure the dietary supplement meets the established specifications for identity, purity, strength, composition, and freedom from contaminants that may adulterate the product. Furthermore, it may be helpful to include detailed, product-specific justifications for any exemptions from testing under 21 C.F.R. § 111.75(c) or (d), although at least some AHPA members in some FDA districts have not found product-specific justifications to be necessary. AHPA does not believe product-specific justifications are required where the details of the justification apply equally to a range of different products; rather, such justifications may be provided in SOPs or similar documents.

[6] Use of marker compounds is entirely at the company's discretion. FDA has explicitly declined to require marker testing for botanical dietary supplements; FDA states in the preamble to the Final Rule, "The final rule does not require any specific testing requirements, such as testing for marker compounds." 72 FR 34851.

[7] As illustrative examples, orange juice cannot reliably be identified by testing for vitamin C, carrot juice cannot reliably be identified by testing for beta carotene, and vanilla extract cannot reliably be identified by testing for vanillin. Similarly, the quantity of actual orange juice in a product labeled as "orange juice" cannot reliably be determined by quantifying the vitamin C; the quantity of actual carrot juice in a product labeled as "carrot juice" cannot reliably be determined by quantifying the beta carotene; and the quantity of actual vanilla extract in a product labeled as "vanilla extract" cannot reliably be determined by quantifying the vanillin.

[8] FDA has acknowledged that batch records are an accurate and practical method for assuring that finished products meet required specifications with respect to ingredients that are chemically complex or for which no validated test method exists, such as soy

Our ingredient control procedures include:

- Assigning a unique lot number to each shipment of raw material as per SOP # 1111;
- Qualifying the accuracy of relevant test results reported in certificates of analysis received from each vendor as per SOP # 2222;
- Reviewing the vendor's certificate of analysis for each lot to ensure the test results meet our specifications as per SOP # 3333;
- Testing each dietary ingredient lot to confirm the identity as per SOP # 4444 and the relevant test methods; and
- Periodically requalifying the accuracy of vendor certificates of analysis as per SOP # 2222[9].
- [other items as appropriate for your operations and the product in question]

Our batch production procedures include:

- Use of calibrated scales and other equipment as appropriate, as per SOP # 5555;
- Use of MMRs that are reviewed and approved by Quality Assurance prior to use and that specify the required ingredient item numbers, quantities, process instructions, process parameters, in-process monitoring, expected yields at applicable points in production, and allowed ranges of yields beyond which investigation by Quality Assurance is required;
- Issuance of a unique batch record for each production batch, consisting of a copy of the MMR, which is used to record the completion of each step specified in the MMR and all data, results, and yields related to the batch;[10]
- Dispensing of each ingredient by one operator and verification of the dispensed quantity by a second operator, as per SOP # 6666;[11]
- Recording the dispensed ingredient quantity and lot number in the batch record;
- Addition of each dispensed ingredient to the batch by one operator and verification of the addition by a second operator, as per SOP # 7777;
- In-process controls [describe] as required by SOP # 8888;
- *[other items as appropriate for your operations and the product in question]*

These controls ensure the finished extract will reliably meet the established specifications for identity, purity, strength, and composition, and they will do so more reliably than testing for markers.

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protein, dietary fiber, added sugars and certain types of Vitamin E. See for example 64 FR 45934 and 79 FR 11956. In the former, FDA states, "…[C]alculation of the soy protein content based on information contained in manufacturers' records is an accurate and practical method for assuring that products bearing the proposed health claim meet the requirement for the qualifying level of soy protein." In the latter, FDA states, "The information contained in manufacturers' records is an accurate and practical method for assuring that the nutrient declarations comply with section 403(q) of the FD&C Act." In 21 C.F.R. § 101.9(g)(10), FDA stipulates that manufacturers may rely on databases, formulae, recipes, or batch records to confirm the content of various nutrients. In addition, FDA provides for use of similar documentation to substantiate nutrient content to support health claims in regulations such as 21 C.F.R. § 101.82(c)(2)(ii)(B).

[9] Rather than relying on vendor certificates of analysis (COAs) and keeping a schedule for requalifying vendor COAs, some companies test each ingredient shipment for each specification established for the ingredient by the company.

[10] Rather than a copy of the MMR, the batch record may consist of a printout of the MMR or may be another document that follows the MMR.

[11] Per 21 C.F.R. § 111.210(h)(3)(ii), double checks for dispensing of ingredients and for adding ingredients to the batch are required only for manual operations.

b. If heavy metal specifications are not applicable for the product, discuss why. If historical heavy metals testing has consistently shown that heavy metal adulteration does not occur in the product, and no changes to the ingredient supply or manufacturing process have occurred, this may support omission of heavy metals testing for the finished product. Alternately, if raw materials are properly controlled for heavy metals (either by testing each lot, or by reviewing vendor COAs for each purchased shipment and by qualifying those COAs on a scheduled basis), this may also support omission of heavy metals testing for the finished product.

c. Discuss why pesticide specifications are not applicable or why particular pesticide specifications have been set. Consider following AHPA's guidance at http://www.ahpa.org/Portals/0/PDFs/Policies/Guidance-Policies/AHPA_Pesticide_Specification_Guidance_FINAL.pdf and/or performing a risk assessment of which pesticides are known or reasonably foreseeable to occur given the particulars of the raw material supply in question. If historical pesticide screening has consistently shown that pesticide adulteration does not occur in the product, and no changes to the ingredient supply or manufacturing process have occurred, this may support omission of pesticide testing for the finished product. Alternately, if raw materials are properly controlled for pesticides (either by testing each lot, or by reviewing vendor COAs for each purchased shipment and by qualifying those COAs on a scheduled basis), this may also support omission of pesticide testing for the finished product.

d. If pathogen specifications (e.g., Salmonella, E. coli) are not applicable for the product, discuss scientific data that establishes why these tests may safely be omitted. This may be based on publicly available scientific literature or on formal challenge studies conducted by the company on the product (or a similar product). FDA is not likely to accept a justification for omission of pathogen testing without scientific evidence to show that these pathogens cannot survive in the product.

END OF DOCUMENT

2. Marker liquid extracts

2.1 Supplement Facts examples

See the "Ratio Liquid Extract" section for a general discussion of Supplement Facts panels.

The following examples give some options for how marker content may be expressed on the Supplement Facts panel for an Echinacea Root Extract containing a claimed amount of echinacoside.

Note that some firms combine use of the marker and the extract ratio. Either or both may be listed in Supplement Facts boxes, and either or both may be used in product specifications.

Only the marker is claimed (note that the source of the marker is then included in the "Ingredients" list):

Supplement Facts

Serving Size: 1 ml (28 drops)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Echinacoside	2.5 mg	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Ingredients: water, organic alcohol (40%), organic echinacea root.

Extract and marker are both claimed quantitatively by weight:

Supplement Facts

Serving Size: 1 ml (28 drops)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Echinacea Root Extract	940 mg	†
Echinacoside	2.5 mg	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, 190-proof organic alcohol.

Extract claimed by volume, marker by weight:

Supplement Facts

Serving Size: 1 ml (28 drops)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Echinacea Root Extract	1 ml	†
Echinacoside	2.5 mg	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic alcohol.

Marker is claimed quantitatively with the extract listed as the source:

Supplement Facts

Serving Size: 1 ml (28 drops)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Echinacoside (from Echinacea Root Extract)	2.5 mg	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic ethanol.

2.2 Master formula examples

See the "Ratio Liquid Extract" section for a general discussion of Master Formulas.

Two examples are provided below for products claiming a marker content –

- The retail label claims echinacoside on the w/v basis.
- The retail label claims echinacoside on the w/w basis.

A detailed explanation of the columns in the Master Formula, and the calculations involved, are provided after the second example.

2.2.1 Master Formula for an extract claiming a marker on the w/v basis

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE001 Version #: 001 Batch Size: 100 L (100,000 ml)

Product: Echinacea Root Liquid Extract (2.5 mg/ml echinacoside)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 1 mL contains	U/M	Multiplier %	Overage %	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1									
2					50345	Echinacea root, whole organic dry	10	kg	1
3	2.5	mg	3	20		Echinacoside			
4									
5						Theoretical subtotal for dry ingredients:	10	kg	
6									
7					70001	Water, purified	50	L	5
8									
9					70002	Ethanol, 190 proof	50	L	5
10									
11						Theoretical subtotal for liquid ingredients:	100	L	
12									
13	1	ml	100	0		Theoretical output total:	100	L	
14									

[Filename] / [date] / [initials] [Company name and address]

2.2.2 Master Formula for an extract claiming a marker on the w/w basis

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE001 Version #: 001 Batch Size: 100 L (100,000 ml)

Product: Echinacea Root Liquid Extract (0.26% (w/w) echinacoside)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 1 mL contains	U/M	Multiplier* %	Overage* %	Density (g/ml) (at 20 °C)	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1										
2						50345	Echinacea root, chopped org dry	10	kg	1
3	2.5	mg	3	20			Echinacoside†			
4										
5							Theoretical subtotal for dry ingredients:	10	kg	
6										
7						70001	Water, purified	50	L	5
8										
9						70002	Ethanol, 190 proof	50	L	5
10										
11							Theoretical subtotal for liquid ingredients:	100	L	
12										
13	940	mg	100	0	0.94		Theoretical output total:	100	L	
14										
15										

[Filename] / [date] / [initials] [Company name and address]

* The "multiplier" is a mathematical conversion factor to take into account the strength/potency/content of the raw material. In this example, the strength of the echinacea root raw material is 3% echinacoside. (Note this is different from the strength of the finished product, which in these examples is defined as 0.26% (w/w) echinacoside or 2.5 mg/ml echinacoside.)

* The "overage" is the proportion by which the batch quantity of an ingredient exceeds the bare minimum theoretically required to meet the label claim. In this example, an overage of 20% is included to compensate for (a) incomplete recovery of the echinacoside from the raw material and (b) degradation of the marker over the shelf life of the product. The actual overage for any product must be determined on a case-by-case basis depending on the marker recovery during extraction and the stability characteristics of the marker. All products must be formulated to meet 100% of label claim throughout the shelf life of the product.

The label claim for echinacoside is translated into the batch quantity of echinacea root through the following calculations:
2.5 mg ÷ 0.03 x 1.2 = 100 mg of echinacea root per serving; then 100 mg per serving x 100,000 servings ÷ 1,000,000 mg/kg = 10 kg echinacea root per batch. In other words, 2.5 ÷ 0.03 x 1.2 x 100,000 ÷ 1,000,000 = 10.

Conversely, the appropriate label claim for echinacoside can be calculated from the batch quantity of echinacea root through the following calculations:
10 x 1,000,000 ÷ 100,000 ÷ 1.2 x 0.03 = 2.5.

† Even though a marker may be stated in the Master Formula, ingredient specifications, and/or product specifications, this does not mean the marker is required to be stated on the retail label. This document includes the marker in the Supplement Facts panel as an illustrative example only.

2.3 Product specifications

2.3.1 Marker liquid extract – Bulk liquid extract specification

[Company Name / Logo]

BULK LIQUID EXTRACT SPECIFICATION

CONFIDENTIAL

Item:	Description:	Page:
BLE001	Echinacea root liquid extract (0.26% (w/w) echinacoside)	Page 1 of X

Version:	Supercedes:	Created by / date:	Approved by / date:
01	**		*[This must be a signature]*

Item	Specification	Method
Identity	Echinacea root liquid extract (0.26% (w/w) echinacoside), bulk	As per batch record
Color	Brown *[or, Pantone color(s) or range, Munsell color values, etc.]*	Organolepsis
Consistency	Thin liquid *[or, compare to a common liquid such as water, syrup, etc.]*	Organolepsis
Clarity	Clear, with sediment	Organolepsis
Odor	*[describe in detail]*	Organolepsis
Flavor	*[describe in detail]*	Organolepsis
Density	0.93-0.95 g/ml *[or test specific gravity instead]*	Weight/volume
	[other potential identity tests = pH, viscosity, TLC for echinacea root, etc.]	
Purity	Echinacea root liquid extract (0.26% (w/w) echinacoside), bulk	By input as per batch record
Strength	NLT 0.265% (w/w) echinacoside *, **	TM-5555 *[HPLC]*
Composition	1 part Echinacea root, 5 parts water, 5 parts 190-proof ethanol	By input as per batch record
Ethanol	35-45% (v/v)	Hydrometer *[or by input as per batch record, or by GC]*
Water	52-63% (v/v) *[or test water activity instead]*	Karl-Fischer *[or water activity meter]*
	[other potential composition tests = dry solids]	
Heavy metals	*N/A or set appropriate specifications*	*N/A or list test method*
Pesticides	*N/A or set specifications as per risk assessment*	*N/A or list test method*
Salmonella	*N/A or set a specification of "Absent"*	*N/A or list test method*
E. coli	*N/A or set a specification of "Absent"*	*N/A or list test method*
	[other potential tests = spoilage organisms, mycotoxins, allergens, etc.]	

* Alternately, the strength may be expressed as NLT 2.5 mg/ml echinacoside, in which case that description should also be included in the extract name and purity specification.

** If the company wants to control both the extract ratio and the marker content then a strength specification may be established for each (e.g., Strength: 1:4 (w:v) by input as per batch record; NLT 2.5 mg/ml echinacoside by HPLC).

See additional information and comments about the bulk extract specifications in the "Ratio Liquid Extract" section.

BULK LIQUID EXTRACT SPECIFICATION (CONT'D)

CONFIDENTIAL

Item:	Description:	Page:
BLE001	Echinacea root liquid extract (0.26% (w/w) echinacoside)	Page 2 of X

Version:	Supercedes:	Created by / date:	Approved by / date:
01	**		*[This must be a signature]*

Narrative justification:

a. Botanicals are complex chemical mixtures whose compositions are not fully known; furthermore, the composition of extracts made from a given botanical will vary depending on the extraction method. Our trade association, the American Herbal Products Association (AHPA), advises that methods do not exist to perform comprehensive chemical testing to quantitate the complete chemical makeup of the echinacea extractives, other than on an aggregate basis as dry solids. Under the Dietary Supplement Health and Education Act, cGMP regulations "may not impose standards for which there is no current and generally available analytical methodology." 21 U.S.C. § 342(g)(2).

   With respect to testing individual marker compounds, AHPA advises that qualitative or quantitative marker testing of individual constituents does not prove identity, purity, or composition of a botanical supplement, as isolated markers are readily obtained and these exogenous constituents can be spiked into the product in order to confound the test. Therefore, marker testing of the finished product does not demonstrate that the production and process control system is producing a dietary supplement that meets the established specifications for identity, purity, and composition; these specifications can be reliably determined only by examination of the ingredient records and batch record. (In general, the same applies to strength; however, for this product we have determined that echinacoside is of particular interest and have therefore established strength specifications based on echinacoside content by HPLC. This testing, when combined with ingredient and batch records, will serve to confirm the strength.)

b. See additional discussions included in the "Ratio Liquid Extract" narrative justification for the bulk liquid extract specifications.

END OF DOCUMENT

3. Liquid extracts with no ratio and no marker

3.1 Supplement Facts example

See the "Ratio Liquid Extract" section for a general discussion of Supplement Facts panels and other examples (e.g., quantity claimed by weight).

Dietary ingredient quantity claimed by volume:

Supplement Facts

Serving Size: 1 ml (28 drops)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Echinacea Root Extract	1 mL	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic alcohol.

3.2 Master formula example

See the "Ratio Liquid Extract" section for a general discussion of Master Formulas. Below is a Master Formula example for a liquid extract with no ratio and no marker claims, with the extract quantity measured by volume.

3.2.1 Master Formula for liquid extract with label claim by volume

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE001 Version #: 001 Batch Size: 100 L (100,000 ml)

Product: Echinacea Root Liquid Extract

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 1 mL contains	U/M	Multiplier %	Overage %	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1									
2			100	0	50345	Echinacea root, chopped organic dry	10	kg	1
3									
4						Theoretical subtotal for dry ingredients:	10	kg	
5									
6					70001	Water, purified	50	L	5
7									
8					70002	Ethanol, 190 proof	50	L	5
9									
10						Theoretical subtotal for liquid ingredients:	100	L	
11									
12	1	ml	100	0		Theoretical output total:	100	L	
13									
14									
15									
16									
17									
18									

[Filename] / [date] / [initials] [Company name and address]

3.3 Product specifications

3.3.1 Liquid extract with label claim by volume – Bulk liquid extract specification

[Company Name / Logo]

BULK LIQUID EXTRACT SPECIFICATION

CONFIDENTIAL

Item:	Description:	Page:
BLE001	Echinacea root liquid extract, bulk	Page 1 of X

Version:	Supercedes:	Created by / date:	Approved by / date:
01	**		*[This must be a signature]*

Item	Specification	Method
Identity	Echinacea root liquid extract, bulk	As per batch record
Color	Brown *[or, Pantone color(s) or range, Munsell color values, etc.]*	Organolepsis
Consistency	Thin liquid *[or, compare to a common liquid such as water, syrup, etc.]*	Organolepsis
Clarity	Clear, with sediment	Organolepsis
Odor	*[describe in detail]*	Organolepsis
Flavor	*[describe in detail]*	Organolepsis
Density	0.93-0.95 g/ml *[or test specific gravity instead]*	Weight/volume
	[other potential identity tests = pH, viscosity, TLC for echinacea root, etc.]	
Purity	100% echinacea root liquid extract	By input as per batch record
Strength	1 part echinacea root per 10 parts solvent	By input as per batch record
Composition	1 part Echinacea root, 5 parts water, 5 parts 190-proof ethanol	By input as per batch record
Ethanol	35-45% (v/v)	Hydrometer *[or by input as per batch record, or by GC]*
Water	52-63% (v/v) *[or test water activity instead]*	Karl-Fischer *[or water activity meter]*
	[other potential composition tests = dry solids]	
Heavy metals	*N/A or set appropriate specifications*	*N/A or list test method*
Pesticides	*N/A or set specifications as per risk assessment*	*N/A or list test method*
Salmonella	*N/A or set a specification of "Absent"*	*N/A or list test method*
E. coli	*N/A or set a specification of "Absent"*	*N/A or list test method*
	[other potential tests = spoilage organisms, mycotoxins, allergens, etc.]	

See additional information and comments about the bulk extract specifications, and the Narrative Justification for the specifications, in the "Ratio Liquid Extract" section.

END OF DOCUMENT

4. Concentrated liquid extracts

4.1 Supplement Facts examples

See the "Ratio Liquid Extract" section for a general discussion of Supplement Facts panels.

The following example is for a ratio extract with the quantity claimed by volume, where the manufacturing process starts with a 1:10 extract and concentrates it to 1:5. (The fact that the extract has been concentrated is not apparent in the Supplement Facts panel but can be seen in the Master Formula.)

Note that 21 C.F.R. § 101.36(b)(3)(ii)(B) provides, "Where the solvent has been partially removed (not to dryness), the final concentration, when indicated, shall be stated (e.g., if the original extract was 1:5 and 50 percent of the solvent was removed, then the final concentration shall be stated as 1:2.5)." In other words, the extract ratio is not required on the label, but, if it is stated, it shall be the ratio after concentration.

Dietary ingredient quantity claimed by volume:

Supplement Facts

Serving Size: 1 ml (28 drops)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Echinacea Root Extract 1:5	1 mL	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic 190-proof alcohol.

4.2 Master formula example

See the "Ratio Liquid Extract" section for a general discussion of Master Formulas. Below is an example of a Master Formula for an extract that is made with a concentration step.

4.2.1 Master Formula for 1:5 (w:v) ratio extract, concentrated from 1:10 (w:v), with label claim by volume

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE001 Version #: 001 Batch Size: 50 L (50,000 ml)

Product: Echinacea Root Liquid Extract 1:5 (w:v)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 1 mL contains	U/M	Multiplier %	Overage %	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1									
2			100	0	50345	Echinacea root, chopped organic dry	10	kg	1
3									
4						Theoretical subtotal for dry ingredients:	10	kg	
5									
6					70001	Water, purified	50	L	5
7									
8					70002	Ethanol, 190 proof	50	L	5
9									
10						Theoretical subtotal for liquid ingredients:	100	L	
11									
12						Theoretical output after pressing:	100	L	
13									
14	1	mL	100	0		Theoretical total after concentration:	50	L	
15									

[Filename] / [date] / [initials] [Company name and address]

4.3 Product specifications

4.3.1 Concentrated liquid extract – Bulk liquid extract specification

[Company Name / Logo]

BULK LIQUID EXTRACT SPECIFICATION

CONFIDENTIAL

Item:	Description:	Page:
BLE001	Echinacea root liquid extract 1:5 (w:v), bulk	Page 1 of X

Version:	Supercedes:	Created by / date:	Approved by / date:
01	**		*[This must be a signature]*

Item	**Specification**	**Method**
Identity	Echinacea root liquid extract 1:5 (w:v), bulk	As per batch record
Color	Brown *[or, Pantone color(s) or range, Munsell color values, etc.]*	Organolepsis
Consistency	Thin liquid *[or, compare to a common liquid such as water, syrup, etc.]*	Organolepsis
Clarity	Clear, with sediment	Organolepsis
Odor	*[describe in detail]*	Organolepsis
Flavor	*[describe in detail]*	Organolepsis
Density	0.97-0.98 g/ml *[or test specific gravity instead]*	Weight/volume
	[other potential identity tests = pH, viscosity, TLC for echinacea root, etc.]	
Purity	100% echinacea root liquid extract 1:5 (w:v)	By input as per batch record
Strength	1:5 (w:v) as per Master Formula	By input as per batch record
Composition	1 part Echinacea root, 5 parts water, 5 parts 190-proof ethanol prior to concentration	By input as per batch record
Ethanol	12-18% (v/v) *[concentration by 50% will disproportionately reduce the amount of ethanol due to selective evaporation]*	Hydrometer *[or by input as per batch record, or by GC]*
Water	79-86% (v/v) *[or test water activity instead]*	Karl-Fischer *[or water activity meter]*
	[other potential composition tests = dry solids]	
Heavy metals	*N/A or set appropriate specifications*	*N/A or list test method*
Pesticides	*N/A or set specifications as per risk assessment*	*N/A or list test method*
Salmonella	*N/A or set a specification of "Absent"*	*N/A or list test method*
E. coli	*N/A or set a specification of "Absent"*	*N/A or list test method*
	[other potential tests = spoilage organisms, mycotoxins, allergens, etc.]	

See additional information and comments about the bulk extract specifications, and the Narrative Justification for the specifications, in the "Ratio Liquid Extract" section.

END OF DOCUMENT

5. Liquid extract blends

The examples in this section are for a product containing a blend of botanical extracts which is manufactured by obtaining the individual botanical extracts and mixing them together. (See the "Group Extraction" section for an example of a similar product manufactured by extracting a blend of crude botanicals as a group.)

5.1 Supplement Facts examples

See the "Ratio Liquid Extract" section for a general discussion of Supplement Facts panels.

Three example Supplement Facts panels are provided here.

In the first example, the quantity of each extract is declared on the label by volume (ml). Alternately, the quantity of each extract may be declared by weight (e.g., mg).

In the second and third examples, the blend of extracts is declared as a Proprietary Blend per 21 C.F.R. § 101.36(c). For a Proprietary Blend, the quantity of each dietary ingredient in the blend is not disclosed; rather, the total quantity of the blend as a whole is stated in the Supplement Facts box. The dietary ingredients within the blend must be listed in descending order of predominance by weight.

There is some debate whether the labeling regulations require the total quantity of a Proprietary Blend to be declared by weight and not by volume. The regulations explicitly permit the net quantity of contents, serving size, and individual dietary ingredients to be stated in either gravimetric or volumetric measurements, but in the context of Proprietary Blends the regulations only explicitly discuss gravimetric measurements. AHPA believes this to be an oversight rather than an intentional omission. In view of the fact that FDA considers both gravimetric and volumetric measures to be acceptable in every other labeling context, AHPA believes that the regulations do not prohibit disclosure of Proprietary Blend quantities by volume; rather, either weight or volume measurements may be used as appropriate for the product.[12]

In addition to the details provided in the examples below, other information such as extract ratio or marker content may be disclosed for any or all of the dietary ingredients. See other sections for examples demonstrating these options.

[12] See AHPA Guidance Policy "Quantifying liquid propriety blends in Supplement Facts under 21 C.F.R. § 101.36"

Each dietary ingredient quantity claimed by volume:

Supplement Facts

Serving Size: 2 ml (2 dropperfuls)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Calories	5	
Echinacea Root Extract	1 mL	†
Goldenseal Root Extract	0.5 mL	†
Elderberry Fruit Extract	0.5 mL	†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic ethanol (45%).

Dietary ingredient quantity claimed by weight as a Proprietary Blend:

Supplement Facts

Serving Size: 2 ml (2 dropperfuls)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Calories	5	
Proprietary Blend	1950 mg	
Echinacea Root Extract		†
Goldenseal Root Extract		†
Elderberry Fruit Extract		†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic alcohol.

Dietary ingredient quantity claimed by volume as a Proprietary Blend:

Supplement Facts

Serving Size: 2 ml (2 dropperfuls)

Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Calories	5	
Proprietary Blend	2 mL	
Echinacea Root Extract		†
Goldenseal Root Extract		†
Elderberry Fruit Extract		†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic 190-proof ethanol.

5.2 Master formula examples

See the "Ratio Liquid Extract" section for a general discussion of Master Formulas.

Two example Master Formulas for a blend of liquid extracts are provided on the following pages; one corresponds to a Supplement Facts box where the quantity of each extract is listed, and the other corresponds to a Proprietary Blend.

5.2.1 Master Formula for an extract blend with label claim(s) by volume

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE9055 Version #: 001 Batch Size: 50 L (25,000 servings**)

Product: Super Immune Liquid Extract Blend

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 2 mL* contains	U/M	Multiplier %	Overage %	Item #	Ingredient	Batch Quantity	U/M	Formula %
1									
2	1.0	mL	100	0	BLE001	Echinacea Root Liquid Extract 1:10 (w:v)	25.0	L	50
3									
4	0.5	mL	100	0	BLE352	Goldenseal Root Liquid Extract 1:5 (w:v)†	12.5	L	25
5									
6	0.5	mL	100	0	BLE102	Elderberry Fruit Liquid Extract 1:2 (w:v)	12.5	L	25
7									
8	2.0	mL				Theoretical output total:	50.0	L	100
9									
10									

[Filename] / [date] / [initials] [Company name and address]

* The "each contains" column is changed from 1 mL (as in other examples) to 2 mL to match the serving size in the Supplement Facts panel. This is optional; companies may express the "each contains" column (and batch size) in whatever form they deem appropriate, but it should be easily related to the Supplement Facts information.

** In other examples, the serving size is 1 mL so it is convenient to state the batch size in mL However, in this example, the serving size is 2 mL to facilitate the necessary calculations to convert between the label claim quantities and the batch quantities. It is preferable to state the batch size in servings rather than mL. However, it is optional to do so.

† Since the amounts of Goldenseal Root Extract and Elderberry Fruit Extract are the same, they may be listed in either order on the Supplement Facts panel of the label.

The label claim quantities in the far-left column can be converted to the batch input quantities through the following calculation:
[label claim in mL] ÷ [multiplier] x [1+overage] x [batch size in servings] ÷ [conversion factor from mL to L] = [batch quantity]. In other words, for the Goldenseal Root Extract in this formula, 0.5 ÷ 1 x 1 x 25,000 ÷ 1000 = 12.5.
Conversely, the appropriate label claim for each extract can be calculated from the batch quantity of the extract through the following calculation:
[batch quantity] x [conversion factor from L to mL] ÷ [batch size in servings] ÷ [1+overage] x [multiplier] = [label claim in mL]. In other words, for the Echinacea Root Extract in this formula, 25.0 x 1000 ÷ 25,000 ÷ 1 x 1 = 1.0.

See the "Ratio Liquid Extract" and "Marker Liquid Extract" Master Formulas for additional information and examples.

5.2.2 Master Formula for a proprietary extract blend with label claim by weight

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE9055 Version #: 001 Batch Size: 50 L (25,000 servings)

Product: Super Immune Liquid Group Extract 1:5 (w:v)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 2 mL contains	U/M	Multiplier %	Overage %	Density (g/ml) (at 20 °C)	Item #	Ingredient	Batch Quantity	U/M	Formula %
1										
2			100	0		BLE001	Echinacea Root Liquid Extract 1:10 (w:v)	25.0	L	50
3										
4			100	0		BLE352	Goldenseal Root Liquid Extract 1:5 (w:v)	12.5	L	25
5										
6			100	0		BLE102	Elderberry Fruit Liquid Extract 1:2 (w:v)	12.5	L	25
7										
8	1950	mg	100	0	0.975		Theoretical output total:	50.0	L	100
9										
10										
11										
12										
13										
14										
15										

[Filename] / [date] / [initials] [Company name and address]

The label claim quantities in the far-left column can be converted to the batch input quantities through the following calculation:
[label claim in mg] ÷ [multiplier] x [1+overage] ÷ [density] x [batch size in servings] ÷ [conversion factor from mL to L] = [batch quantity]. In other words, 1950 ÷ 1 x 1 x 25,000 ÷ 0.975 ÷ 1,000,000 = 50.

Conversely, the appropriate label claim can be calculated from the batch quantity of the extract through the following calculation:
[batch quantity] x [conversion factor from L to mL] ÷ [batch size in servings] x [density] ÷ [1+overage] x [multiplier] = [label claim in mg]. In other words, 50 x 1,000,000 ÷ 25,000 x 0.975 ÷ 1 x 1 = 1950.

See the "Ratio Liquid Extract" and "Marker Liquid Extract" Master Formulas for additional information and examples.

5.3 Product specifications

5.3.1 Liquid extract blend – Bulk liquid extract specification

[Company Name / Logo]

BULK LIQUID EXTRACT SPECIFICATION

CONFIDENTIAL

Item:	Description:	Page:
BLE9055	Super Immune Liquid Extract Blend	Page 1 of X

Version:	Supercedes:	Created by / date:	Approved by / date:
01	**		*[This must be a signature]*

Item	Specification	Method
Identity	Super Immune Liquid Extract Blend, bulk	As per batch record
Color	Amber to brown *[or, Pantone color(s) or range, Munsell color values, etc.]*	Organolepsis
Consistency	Thin liquid *[or, compare to a common liquid such as water, syrup, etc.]*	Organolepsis
Clarity	Clear, with sediment	Organolepsis
Odor	*[describe in detail]*	Organolepsis
Flavor	*[describe in detail]*	Organolepsis
Density	0.97-0.98 g/ml *[or test specific gravity instead]*	Weight/volume
	[other potential identity tests = pH, viscosity, etc.]*	
Purity	100% Super Immune Liquid Extract Blend, bulk	By input as per batch record
Strength	50% Echinacea Root Liquid Extract 1:10 (w:v) 25% Goldenseal Root Liquid Extract 1:5 (w:v) 25% Elderberry Fruit Liquid Extract 1:2 (w:v)	By input as per batch record
Composition	50% Echinacea Root Liquid Extract 1:10 (w:v) 25% Goldenseal Root Liquid Extract 1:5 (w:v) 25% Elderberry Fruit Liquid Extract 1:2 (w:v)	By input as per batch record
Ethanol	40-50% (v/v)**	Hydrometer *[or by input as per batch record, or by GC]*
Water	44-56% (v/v) *[or test water activity instead]*	Karl-Fischer *[or water activity meter]*
	[other potential composition tests = dry solids]	
Heavy metals	*N/A or set appropriate specifications*	*N/A or list test method*
Pesticides	*N/A or set specifications as per risk assessment*	*N/A or list test method*
Salmonella	*N/A or set a specification of "Absent"*	*N/A or list test method*
E. coli	*N/A or set a specification of "Absent"*	*N/A or list test method*
	[other potential tests = spoilage organisms, mycotoxins, allergens, etc.]	

* AHPA does not list TLC or other chromatographic methods for identification of botanical mixtures because scientifically valid methods for identification of herbs in a mixture generally are not publicly available. See Narrative Justification below and in the "Ratio Liquid Extracts" section.

** The ethanol specification of 40-50% is determined based on the ethanol content of the combined liquid extracts and corresponds to the alcohol content stated in one of the Supplement Facts examples (45%).

Narrative justification:

In addition to the typical Narrative Justification described for single extracts in the "Ratio Liquid Extract" section, AHPA suggests including the following after paragraph "a.":

> With respect to multi-ingredient, chemically complex botanical formulations such as this one, AHPA advises that there are rarely if ever any "current and generally available analytical methodologies" for use to identify or quantify individual botanicals or botanical extracts in such mixtures.

See additional information and comments about the bulk extract specifications, and the Narrative Justification for the specifications, in the "Ratio Liquid Extract" section.

END OF DOCUMENT

6. Liquid group extractions

6.1 Supplement Facts examples

See the "Ratio Liquid Extract" section for a general discussion of Supplement Facts panels and the "Liquid Extract Blend" section for a general discussion of Proprietary Blends.

Two example Supplement Facts panels are provided here, with the total quantity declared as a Proprietary Blend. AHPA is not aware of companies making group extractions who declare the quantities of individual extracts.

Per 21 C.F.R. § 101.36(c), the components of a Proprietary Blend must be declared in descending order of predominance by weight. On the native extract basis (where "native extract" refers to the extractives obtained from the crude herb, without including any excipients) it can be difficult to determine the order of ingredients by weight for a group extraction, since the amount of native extract obtained from each raw material is not strictly proportionate to the input weight of the raw material (because different herbs contain different levels of soluble components).

However, labeling regulations do not require labeling on the basis of native extract but rather on the basis of final extract, i.e., the native extract plus excipients, which in the case of liquid extracts includes unremoved solvents. With this in mind, the solvent present can be allocated amongst the ingredients as appropriate. Therefore, the general practice in the industry is to list the raw materials in descending order by input weight; AHPA believes this is the best option.

See other examples for additional options (e.g., marker claims, fresh raw material usage).

Dietary ingredient quantity claimed by weight as a Proprietary Blend:

Supplement Facts

Serving Size: 2 mL (2 dropperfuls)

Servings Per Container: about 30

	Amount Per Serving	% Daily Value*
Calories	5	
Proprietary Blend	1950 mg	
Extracts from:		
Echinacea Root (organic)		†
Goldenseal Root (organic)		†
Elderberry Fruit (organic)		†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic alcohol.

Dietary ingredient quantity claimed by volume as a Proprietary Blend:

Supplement Facts

Serving Size: 2 mL (1 dropperful)

Servings Per Container: about 30

	Amount Per Serving	% Daily Value*
Calories	5	
Proprietary Blend	2 mL	
Organic Echinacea Root Extract		†
Organic Goldenseal Root Extract		†
Organic Elderberry Fruit Extract		†

*Percent Daily Values are based on 2000 calorie diet

†Daily Value not established

Other ingredients: water, organic alcohol.

6.2 Master formula example

See the "Ratio Liquid Extract" section document for a general discussion of Master Formulas.

An example Master Formula for a group extraction is provided below.

6.2.1 Master Formula for a group extraction

CONFIDENTIAL [Company Name]

Page 1 of X

Master Formula

Item #: BLE9055 Version #: 001 Batch Size: 50 L (25,000 servings**)

Product: Super Immune Liquid Group Extract 1:5 (w:v)

Master Approved By: _____ By: _____

(Production) *(Date)* *(Quality Assurance)* *(Date)*

#	Each 2 mL* contains	U/M	Multiplier %	Overage %	Density (g/ml) (at 20 °C)	Item #	Ingredient	Batch Quantity (input to extraction)	U/M	Parts (by input)
1										
2			100	0		50345	Echinacea root, chopped org dry	5	kg	5
3										
4			100	0		51222	Goldenseal root, chopped org dry	3	kg	3
5										
6			100	0		50129	Elderberry fruit, milled org dry	2	kg	2
7										
8							Theoretical subtotal for dry ingredients:	10	kg	
9										
10						70001	Water, purified	25	L	25
11										
12						70002	Ethanol, 190 proof	25	L	25
13										
14							Theoretical subtotal for liquid ingredients:	50	L	
15										
16	1950	mg	100	0	0.975		Theoretical output total:	50	L	
17										

[Filename] / [date] / [initials] [Company name and address]

* The “each contains” column is changed from 1 mL (as in other examples) to 2 mL to match the serving size in the Supplement Facts panel. This is optional; companies may express the “each contains” column (and batch size) in whatever form they deem appropriate, but it should be easily related to the Supplement Facts information.

** In other examples, the serving size is 1 mL so it is convenient to state the batch size in mL However, in this example, the serving size is 2 mL to facilitate the necessary calculations to convert between the label claim quantities and the batch quantities. It is preferable to state the batch size in servings rather than mL. However, it is optional to do so.

The label claim quantities in the far-left column can be converted to the batch input quantities through the following calculation:
[label claim in mg] ÷ [multiplier] x [1+overage] ÷ [density] x [batch size in servings] ÷ [conversion factor from mL to L] = [batch quantity]. In other words, 1950 ÷ 1 x 1 x 25,000 ÷ 0.975 ÷ 1,000,000 = 50.

Conversely, the appropriate label claim can be calculated from the batch quantity of the extract through the following calculation:
[batch quantity] x [conversion factor from L to mL] ÷ [batch size in servings] x [density] ÷ [1+overage] x [multiplier] = [label claim in mg]. In other words, 50 x 1,000,000 ÷ 25,000 x 0.975 ÷ 1 x 1 = 1950.

See the “Ratio Liquid Extract,” “Marker Liquid Extract,” and “Liquid Extract Blend” Master Formulas for additional information and examples.

6.3 Product specification

6.3.1 Liquid group extraction – Bulk liquid extract specification

[Company Name / Logo]

BULK LIQUID EXTRACT SPECIFICATION

CONFIDENTIAL

Item:	Description:	Page:
BLE9055	Super Immune Liquid Group Extract 1:5 (w:v), bulk	Page 1 of X

Version:	Supercedes:	Created by / date:	Approved by / date:
01	**		*[This must be a signature]*

Item	Specification	Method
Identity	Super Immune Liquid Group Extract 1:5 (w:v), bulk	As per batch record
Color	Amber to brown *[or, Pantone color(s) or range, Munsell color values, etc.]*	Organolepsis
Consistency	Thin liquid *[or, compare to a common liquid such as water, syrup, etc.]*	Organolepsis
Clarity	Clear, with sediment	Organolepsis
Odor	*[describe in detail]*	Organolepsis
Flavor	*[describe in detail]*	Organolepsis
Density	0.97-0.98 g/ml *[or test specific gravity instead]*	Weight/volume
	[other potential identity tests = pH, viscosity, etc.]*	
Purity	100% Super Immune Liquid Group Extract 1:5 (w:v)	By input as per batch record
Strength	1:5 (w:v) as per Master Formula	By input as per batch record
Composition	5 parts Echinacea root, 3 parts Goldenseal root, 2 parts Elderberry fruit, 25 parts water, 25 parts 190-proof ethanol	By input as per batch record
Ethanol	35-45% (v/v)	Hydrometer *[or by input as per batch record, or by GC]*
Water	52-63% (v/v) *[or test water activity instead]*	Karl-Fischer *[or water activity meter]*
	[other potential composition tests = dry solids]	
Heavy metals	*N/A or set appropriate specifications*	*N/A or list test method*
Pesticides	*N/A or set specifications as per risk assessment*	*N/A or list test method*
Salmonella	*N/A or set a specification of "Absent"*	*N/A or list test method*
E. coli	*N/A or set a specification of "Absent"*	*N/A or list test method*
	[other potential tests = spoilage organisms, mycotoxins, allergens, etc.]	

* AHPA does not list TLC or other chromatographic methods for identification of botanical mixtures because scientifically valid methods for identification of herbs in a mixture generally are not publicly available. See Narrative Justification below and in the "Ratio Liquid Extracts" section.

Narrative justification:

In addition to the typical Narrative Justification described for single extracts in the "Ratio Liquid Extract" section, AHPA suggests including the following after paragraph "a.":

With respect to multi-ingredient, chemically complex botanical formulations such as this one, AHPA advises that there are rarely if ever any "current and generally available analytical methodologies" for use to identify or quantify individual botanicals or botanical extracts in such mixtures.

See additional information and comments about the bulk extract specifications, and the Narrative Justification for the specifications, in the "Ratio Liquid Extract" section.

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