GUIDANCE

FOR MANUFACTURE AND SALE OF BULK BOTANICAL EXTRACTS

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Prepared by the Botanical Extracts Committee of the American Herbal Products Association

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INTRODUCTION

The American Herbal Products Association (AHPA) initiated this compilation of information to improve the industry's understanding of the terminology, materials, and processes used in the manufacture of botanical extracts. Our goal in publishing this work is to reduce the confusion that exists in the marketplace about extracts and their purchase.

Creation of this Document

This document is the result of a long and sometimes arduous process. It began in 1992, when a group of AHPA members first got together to write down what they knew about extracts. Over the course of almost a decade, it has been taken up by different groups of members, added to, expanded upon, clarified, honed.

The current version was begun in 1999, when Bill Critchlow advocated to the AHPA Board of Trustees the creation of a Botanical Extracts Committee to address issues related to extracts. A committee was formed; a subcommittee was formed; and after months of weekly conference calls, the document assumed its current shape and dimension. As the conclusive step in this process, AHPA's Board of Trustees authorized publication of the final draft presented here in September 1999.

We have no doubt that this version of the document, too, will not be the final one. Although it was written with the participation of a broad diversity of industry members (including many different extract manufacturers, dosage form manufacturers, marketing companies, and herbal practitioners) and was reviewed by members of AHPA's Scientific Advisory Board, the fact is that our best efforts can only reflect current practices and current thinking. Portions of this document will undoubtedly have to be revised in the future.

Scope of the Document

This document is the first in a series that will address various aspects of the manufacture, sale, labeling, and marketing of botanical extracts.

The series begins at a logical point, with the manufacture of the extract. This document begins with definitions of terms important in describing extracts, and then describes the most common processes involved in the manufacture of extract. The document also addresses quality assurance and quality control as they relate to the manufacture of botanical extracts, and discusses several broad categories into which extracts can be divided based on manufacturing goals. Finally, the document sets forth guidelines for the labeling of extracts sold in bulk.

Future documents in the series will build on this foundation. Such subjects as the retail labeling of extracts; marketing of extracts; dosage form manufacture using extracts; the significance of extract ratios; and phytoequivalence will be addressed in subsequent installments.

Limitations of the Document

This document is intended as a guidance and educational document only. It sets forth the goals toward which industry members should strive in order to achieve quality, consistency, safety, and efficacy in their products.

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DEFINITIONS

General definitions

Biomass: The botanical material from which an extract is made. Outside the United States, the biomass is often called the "drug" or "crude drug."

Excipient: Material, such as carriers, flow agents, preservatives, stabilizers, etc. that is added to the extract for technical purposes. Where the extraction solvent (see below) remains in the finished extract, it too constitutes an excipient.

Extract: The complex, multicomponent mixture obtained after using a solvent to dissolve components of the biomass. Extracts may be in dry, liquid, or semi-solid form. Excipients may be added to extracts in order to adjust the concentration; enhance stability; limit microbial growth; and to improve drying, flow, or other manufacturing characteristics. Extracts are not the same as expressed juices, pure chemicals isolated from an herb, or synthetically modified plant constituents.[1]

Extractives: Soluble components removed from the biomass during the extraction process.

Juice: The liquid obtained by pressing a botanical material without the addition of solvent.

Marc (a.k.a. bagasse): The spent botanical material that remains after the extraction process is complete.

Menstruum: The solvent or combination of solvents used in the manufacture of an extract.

Miscella (a.k.a. mother liquor): The liquid intermediate obtained by extracting the botanical material with solvent. When the extract is manufactured by percolation (see section below), the miscella may be called the "percolate"; when the process is maceration, it may be called the "macerate."

Native extract: Material consisting only of components native to the original plant or naturally formed during extraction, excluding any excipients or other added substances. This term may refer to a concentrated liquid extract from which the added solvent has been removed, or may refer to an extract or that portion of a finished extract that is comprised solely of native components.

Solvent: The liquid used to extract the biomass.

Types of extracts

Aqueous extract: An extract made using water as the sole solvent.

Alcohol-free liquid extract: A liquid extract containing less than 0.5% ethyl alcohol.

Compound (a.k.a. combination) preparation: A preparation made from more than one species of herb or plant part.

Combination preparation: See compound preparation.

Decoction: A liquid extract made by boiling the biomass in water.

Dry extract: See powdered extract.

1) However, it should be noted that some chemical modifications might occur as the natural consequence of the extraction process, for example transesterification, hydrolysis, etc.

Fluid extract: An alcoholic or hydroalcoholic liquid extract in which one part by volume contains the extractives of one part by weight of the original dried biomass, unless otherwise specified; but in any case, not more than 2 parts by volume must contain the extractives of one part by weight of the original dried biomass. Fresh biomass may be used, but the excess water must be subtracted for the purpose of determining the ratio. The traditional preparation in the U.S. uses only dried biomass and a dilution ratio of 1:1.

Fresh-frozen plant extract: An extract made from biomass that was frozen in its fresh state.

Fresh plant extract: An extract made from fresh biomass which has not been preserved by freezing, canning, pickling, salting, drying, or other means.

Glycerin extract (a.k.a. glycerite): An alcohol-free liquid extract containing not less than 50% by weight of glycerin. The glycerin may be used to extract the biomass or to reconstitute the extractives.

Glycerite: See glycerin extract.

Homeopathic tincture: A tincture made in accordance with the Homeopathic Pharmacopoeia of the United States (HPUS).

Infusion: A liquid extract prepared by steeping or soaking the biomass in water without boiling.

Liquid extract: Any extract in liquid form.

Oil extract: An extract made using an oil as the solvent.

Pillular extract: See soft extract.

Powdered (a.k.a. dry) extract: An extract which has been dried into a powder.

Reconstituted extract: A liquid extract made by dissolving a powdered or semi-solid extract in a liquid base or carrier.

Semi-solid extract: See soft extract.

Simple preparation: See single preparation.

Single (a.k.a. simple) preparation: A preparation made from a single plant part from a single species of herb.

Soft (a.k.a. pilular, semi-solid, or solid) extract: An extract having a consistency of a thin to thick liquid or paste.

Solid extract: See soft extract.

Spagyric: A liquid extract in which the ashed marc is combined with the miscella.

Tincture: An alcoholic or hydroalcoholic liquid extract in which 1 part by weight of the original dried botanical material or extractives are dissolved in more than 2 parts by volume but not more than 10 parts by volume of the solvent. The use of fresh biomass, while permissible, must be stated in the labeling. Where fresh biomass is used, the excess water should be subtracted for the purpose of determining the ratio; if the fresh weight is used for calculating the ratio, this must be stated in the labeling. The traditional preparation in the U.S. uses only dried biomass and a dilution ratio of 1:5 or 1:10.

Vinegar: An alcohol-free liquid extract made using vinegar or dilute acetic acid as the sole solvent.

MANUFACTURE OF EXTRACTS

1.1 Materials

a. Herb. The botanical material used for the manufacture should be of high quality and defined as to species and plant part. The extent to which the material has been processed should also be documented (e.g. drying, curing, charring, steaming, etc.). Additional information about the raw material should also be documented, including but not limited to country or region of origin, cultivation or collection procedures, time of harvest, processing methods (e.g. drying method), and dates of harvest and drying.

b. Solvents. Solvents are the extracting agents used in the manufacture of extracts. The choice of solvents for a particular herb or herb combination will affect the spectrum of native components solubilized from the biomass, the total amount of extractives obtained, and the activity of enzymes in the extract. In products in which the solvents are not removed, they will also act as a vehicle in which to adjust the potency, taste and feel of the extract, and, in some cases, to preserve the extract.

i. Alcohols. The most common traditional solvents used for the manufacture of extracts are mixtures of water and alcohol.

There are several types of alcohol available. The alcohol traditionally used for extraction is ethyl alcohol or ethanol, which is sometimes simply referred to as "alcohol." Ethanol used for the production of extracts should comply with the requirements of the United States Pharmacopeia (USP), National Formulary (NF), or the Food Chemicals Codex (FCC). Ethanol is the only alcohol suitable for oral consumption.

Currently, other alcohols are sometimes used instead of ethanol, including methanol, isopropyl alcohol (rubbing alcohol), and butanol.

All alcohols other than ethanol must be removed from the final product to within limits defined in the USP or other compendia. The only exception is that isopropyl alcohol may remain in botanical extracts for external application only.

ii. Glycerin. Glycerin is a colorless, odorless, syrupy, sweet liquid used as a solvent, preservative, carrier and fixative. Glycerin used for the production of extracts should comply with the requirements of USP/NF or FCC.

iii. Oils. The most common oils used as solvents are olive, sesame, coconut and almond. Oils used for extraction should comply with the requirements of USP/NF or FCC, and must not be rancid. Oil-based extracts are typically used for salves and other external applications.

iv. Steam. Steam is used as a solvent in the distillation of volatile oils.

v. Supercritical gases. Certain gases such as carbon dioxide can be liquefied at certain temperatures and pressures, and can then be used as extraction solvents, either alone or in combination with other solvents.

vi. **Vinegar.** Vinegar is a fermented or manufactured product containing acetic acid. It is available in various concentrations, commonly about 5% acetic acid. Vinegar used in the preparation of extracts should comply with USP/NF or FCC.

vii. **Water.** Water is used either as the sole solvent in extracts such as decoctions and infusion, or in combination with other solvents. It is often purified by distillation, reverse osmosis or some other technique prior to use.

viii. **Other solvents.** A variety of other solvents such as petroleum distillates (e.g. hexanes), chlorinated hydrocarbons (e.g. methylene chloride), ketones (e.g. acetone), esters (e.g. ethyl acetate), ethers, and other chemicals are also used in the manufacture of extracts. These solvents are generally unsuitable for internal or external use and must be removed from the final product to within limits specified by USP or other compendia.

c. **Carriers and other excipients.** A carrier is a substance added to a botanical extract to adjust the final concentration to an established level, or to improve its manufacturing characteristics. The marc itself is sometimes used as a carrier.

Other excipients may be added to stabilize or preserve the extract, or to improve flow, grindability, and other characteristics.

The excipients used in extracts should be defined in USP/NF, FCC, or other compendia. Those commonly used include gum arabic (acacia gum), corn syrup solids, glucose, lactose, maltodextrin, methylcellulose, tricalcium phosphate, silica, and the extraction solvent itself.

1.2 Processes

a. **Milling (a.k.a. comminution).** Milling is a process of particle size reduction commonly used for the raw material; it may also be used for powdered extracts.

The particle size of the raw material should be carefully defined, since it significantly affects the extraction process. Smaller particles have a larger surface area, thereby allowing more of the raw material to come in immediate contact with the solvent. However, particles which are too small may lose volatile components such as essential oils, and may also cause physical problems during percolation.

i. **Method.** The most suitable milling method depends upon the hardness of the material, the particle size desired, and the volatile oil content of the material. In general, the milling method should be chosen to minimize the amount of heat generated, since high temperatures can degrade the botanical components. If necessary, the mill and the material should be cooled, or excipients should be added to improve the flow.

ii. **Degree.** The degree of milling for various herbs undergoing specific extraction methods is given in many pharmacopoeias. The degree of comminution is normally listed by a designation that is defined by the mesh size through which a specified percent of particles will pass.

iii. **Excipients.** Excipients can increase flow and output of the mill and allow the mill to operate at a lower temperature, thereby decreasing degradation of the material. They may improve the lubricity of the material, decrease static charge, or counteract a material's hygroscopicity. Excipients commonly used for these purposes include tricalcium phosphate, silica, magnesium stearate, liquid nitrogen, and frozen carbon dioxide (dry ice). Excipients should comply with the requirements of USP/NF, FCC, or other compendia.

b. Extraction methods. The following are a few of the basic extraction methods used in commercial production. No matter which specific extraction method is used, the manufacturer should carefully define the raw material cut size; the menstruum; all process times; all process temperatures; and the quantities of botanical material and menstruum to be used, in order to obtain a consistent product from batch to batch. The appropriate processing parameters will vary depending on the plant and plant part, type of extraction, and the particular components desired in the finished product.

i. **Distillation.** Steam distillation is used to extract volatile oils. The biomass is placed in or above water in a retort and exposed to steam, which carries the volatile oils into a condenser where the mixture is cooled. The oils separate from the water and can be collected. The process and product are strongly controlled by two factors: the rate of passage of steam through the biomass and duration of the distillation process.

ii. **Maceration.** A common manufacturing process in which the biomass is allowed to soak in the menstruum until the cellular structure of the herb material is thoroughly penetrated and the soluble portions are dissolved. During maceration, soluble components will leach into the menstruum only until an equilibrium is reached; after that, no further extraction will occur. Thus maceration will not completely (exhaustively) extract the soluble components from the biomass. Specialized types of maceration include:

- **Kinetic maceration** — maceration with stirring or other agitation;
- **Remaceration** — extraction of the marc a second time with fresh solvent;
- **Digestion** — maceration at elevated temperatures, usually 40-50° C;
- **Vosraction extraction** — use of an electromagnetic field to improve extraction.
- **Ultrasound extraction** — stirring the herb in the menstruum with a high-shear mixer or homogenizer;
- **Extraction with electrical energy** — use of an electromagnetic field to improve extraction.

iii. **Percolation.** A common manufacturing process in which the biomass is exhaustively extracted with fresh solvent until no further soluble components remain. This may be done at room temperature or elevated temperatures.

Extracts prepared with percolation often also employ maceration at some stage. Specialized types of percolation include:

- **Repercolation** — use of the initial percolate as the solvent to extract a further portion of biomass;
- **Countercurrent extraction** — a process in which the biomass and solvent flow in opposite directions, so that herb which has been partially extracted contacts fresh solvent and fresh herb contacts solvent which has already been used;
- **Fractional percolation** — collection of separate fractions of percolate ("part percolates") throughout the percolation process;
- **Pressure percolation** — the use of force to push solvent through the percolator;
- **Vacuum percolation** — the use of vacuum to draw solvent through the biomass.

iv. **Supercritical fluid extraction.** Under special conditions of temperature and pressure, chemicals which are normally gases (such as carbon dioxide) can be condensed into liquids. These liquids are particularly convenient as extraction solvents, since the solvent will quickly revert to a gas and evaporate as soon as the temperature and pressure are returned to atmospheric. Additional solvents (cosolvents or chemical modifiers, e.g. alcohols, esters, or amines) may be used to modify the solvent system; these solvents usually need to be removed at a later point in the process. Supercritical fluid extraction can be used to extract desired components in a highly selective manner.

c. Purification methods.

i. **Removal of the marc**: The marc is separated from the miscella by several mechanical methods. These processes do not change the chemical composition of the miscella.

- **Straining (a.k.a. colation)** — The process of separating a liquid from a solid by pouring it through a relatively coarse strainer such as a sieve or muslin.
- **Decantation** — The process of pouring a liquid off material which has settled out from it. This process does not always give complete separation and therefore may need to be repeated.
- **Filtration** — The process of separating a liquid from a solid by passing it through a relatively fine separating element such as filter paper or a bed of insoluble particles.
- **Pressing** — The process of squeezing liquid out of the marc in a press.
- **Centrifugation** — The process of separating the liquid from the marc by centrifugal force.

ii. **Other purification steps.** The miscella may be subjected to a number of other purification steps which will change its chemical composition. These steps may serve to remove contaminants or toxins, or to concentrate or isolate a particular group of desirable components. Some common purification steps include:

- **Adsorption —** Adsorption is the adhesion of a substance to a matrix. This process can be used to selectively separate components from the miscella by passing the miscella through an adsorptive filter or chromatography column. This process can be used either to remove impurities or to concentrate specific desired components.
- **Ion exchange —** This process works by the attraction of positive and negative charges. A matrix with positive charges (cations) will attract negatively-charged components, while a matrix with negative charges (anions) will attract positively-charged components. Ion exchange is usually used to concentrate a specific group of desirable components from the miscella, but can also be used to remove impurities.
- **Liquid-liquid extractions —** Solvents can be characterized by their polar nature. In general, chemicals with highly disparate polarities (such as oil and water) cannot be mixed together; they will tend to separate. If other chemicals are present in such a mixture, some of those chemicals will be more attracted to one solvent (e.g. the oil), while others will be more attracted to the second solvent (e.g. the water). This principle can be used to segregate the components in the miscella, either to remove impurities or to concentrate desirable compounds.
- **Size exclusion chromatograph —** This type of chromatography separates components based on their molecular size. The chromatography column is packed with porous beads; small molecules will be able to enter the beads and will therefore travel more slowly than large molecules, which flow outside the beads. This process is commonly used to separate large molecules such as proteins and to purify smaller molecules such as flavonoids.

d. **Addition of excipients.** After any purification steps, additional excipients may be added according to an established recipe. This may include excipients to preserve or stabilize the extract, to adjust the strength of the extract, to aid in later manufacturing steps such as drying, or for other technical purposes such as flavor masking. It is common for the recipe to give ranges for the amounts of excipients to be added, thus allowing the manufacturer to compensate for the inherent variability of botanical materials.

e. **Concentration of the miscella.** Before or after addition of any excipients, some of the solvents may be removed from the miscella; this is usually accomplished by raising the temperature and/or by reducing the pressure to evaporate the solvent.

f. **Drying the extract.** If a powdered extract is desired the extract will be dried, generally to a moisture content of less than 5%. This removal of the remaining liquid from the extract is accomplished under reduced pressure and often using heat. Heat can be supplied by conduction (e.g. a heated vessel), convection (e.g. heated air), or radiation (e.g. microwaves). The most common means of drying extracts are:

   ii. **Freeze drying.** The extract is frozen and then reheated at a specified rate under reduced pressure. The temperature of the frozen extract must be maintained below its melting point so that the ice crystals are vaporized rather than melted. The material is dried a second time at a higher temperature and under vacuum to remove any residual water.

   ii. **Spray drying.** The extract is sprayed through a nozzle to form very fine droplets, from which the solvent quickly evaporates. During this process the extract is exposed to heat for a brief time.

   iii. **Vacuum drying.** The extract is dried under reduced pressure, often while spread on trays or a conveyer belt. The use of reduced pressure allows the solvent to evaporate at a lower temperature than it would under atmospheric conditions.

   iv. **Shelf drying.** The extract is dried by convection in a chamber at a temperature usually not exceeding 80° C. This method is often used to dry traditional-style extracts, especially Chinese tonics, where prolonged heating is part of the extraction and drying process.

g. **Sanitization of the extract.** The microbiological load of the extract may be reduced through pasteurization or ultra-high-temperature (UHT) treatment while the extract is still a concentrated liquid. Pasteurization entails heating the liquid to over 70° C for at least 30 minutes, while UHT uses temperatures of 135-150° C for 6-10 seconds.

VARIOUS APPROCHES TO EXTRACT PREPARATION

2.1 Traditional-style extracts.[2]

Traditional extracts are made according to long-standing recipes and processes, which are often defined in pharmacopoeia or other compendia. Most traditional-style commercial extracts are manufactured using the same basic steps: milling, extraction with a hydroethanolic or similar solvent, decanting or filtration, concentration, and drying if appropriate. These steps result in an extract whose composition is complex, containing numerous groups of chemicals and a multitude of individual compounds, many of which are not identified and for which no analytical method exists.

The relative safety and efficacy of many traditional-style extracts are predominantly based on their centuries of use and the experience of modern herbal practitioners. Numerous traditional-style extracts have been subjected to controlled clinical, animal, and in vitro studies. Many have not and remain in use due to anecdotal experience.

2.2 Semi-purified extracts.[3]

The manufacture of semi-purified extracts is targeted to the isolation of one or more specific groups of components. The production process for these extracts is usually unique to each manufacturer and each product. By using selective solvents and/or purification steps, unwanted components are removed while the desired components are retained. Semi-purified extracts are often less chemically complex than traditional-style extracts, but still contain many different components.

Because of differences in chemical composition, the physiological effect of a semi-purified extract may not be directly correlated to that of the traditional extract of the same herb. Depending on their nature and intended use, the safety and/or efficacy of novel semi-purified extracts may merit investigation through toxicological, in vitro, animal, and/or controlled clinical studies. Some semi-purified extracts have extensive scientific data demonstrating safety and value, and enjoy a history of safe and effective use.

2.3 Standardization.

Standardization refers to the body of information and controls necessary to produce material of reasonable consistency. This is achieved through minimizing the inherent variation of natural product composition through quality assurance practices applied to agricultural and manufacturing processes.

Some crude extracts and most semi-purified extracts, especially those in powdered form, are manufactured to contain a defined amount of a particular constituent or

2) The categories "traditional-style" and "semi-purified" constitute, at best, descriptions of the two ends of a continuum. Many extracts fall somewhere in between the two. Furthermore, these categories are based primarily on the manufacturing method, not on the composition of the final extract. Some extracts, although made by a very simple process, will contain high levels of particular compounds (e.g. green tea infusions containing up to 70% catechins); others, while made by a highly complex and sophisticated process, nevertheless maintain a diversity of compounds (e.g. gingko extract containing 24% flavone glycosides, 6% terpene lactones, and 70% other components). As a result, although there are real distinctions between these approaches to extract manufacture, it is difficult at this point to draw a clear boundary between the categories, especially one based on the final extract composition. In general, only the extract manufacturer can determine which category any given extract falls into.

3) The term "semi-purified" should not be confused with the term "standardized," which is discussed in the next section. These terms are neither synonymous nor mutually exclusive.

group(s) of constituents. Constituents whose content is thus controlled are called "marker compounds." Batch to batch reproducibility of marker compound content is an important aspect of standardization. However, contrary to popular use, the identification of the concentration of a marker compound(s) in and of itself does not equate to a standardized product. Standardization requires careful control of raw material quality and manufacturing processes.

Standardization can serve a number of important purposes:

- Provide material of reasonably consistent composition for the conduction of reliable clinical trials.
- Allow dosage-form manufacturers to confirm that the dose contains the correct amount of extract by quantitatively and qualitatively analyzing the content of marker substances in a tablet or capsule.
- Act as a positive control for the manufacturing process. Loss or degradation of marker components may indicate possible problems in manufacturing processes. For this purpose relatively labile marker compounds should be chosen, as their continued presence is likely to indicate that the more stable compounds are also preserved.

In general, the presence of predetermined amount(s) of marker compound(s) does not guarantee the potency of an extract. The term potency, as used herein, requires a biological assessment of an extract and cannot be determined solely by marker or active compound measurement for incompletely chemically defined mixtures.

Biological activity of any compound, even a marker compound with demonstrated bioactivity, depends on the composition of the rest of the extract. Other components of the extract, even those with no direct physiological effect, may influence the uptake, distribution, metabolism, and excretion of other components. Furthermore, this background matrix may affect the solubility, stability, and bioavailability of any given compound. For these reasons, and by pharmaceutical definition, potency should not be confused with mere chemical measurement of marker or active substances in an extract.

Batch to batch standardization is achieved primarily through careful control of raw materials and manufacturing processes; however, marker compound content may still vary. Furthermore, marker constituent levels may vary independently of other constituent levels. Therefore, the addition of fillers to adjust the content of marker constituents in the finished extract is acceptable only within narrow limits. Large adjustments are appropriate only in select cases where it has been established that the marker is primarily responsible for the physiological effect (e.g. ephedrine in *Ephedra* spp., aescin in *Aesculus hippocastanum*). A better post-production method of achieving marker compound consistency is through the mixing of extract lots. The combining of similar lots of different strengths minimizes the dilution of other important components.

The addition of marker constituent(s) to an extract is not an acceptable method to achieve chemical standardization. In fact, if an added constituent were not disclosed as a separate ingredient, this practice would result in the creation of an adulterated product.

For a more in-depth discussion of this topic, see AHPA's *Use of Marker Compounds in ManuFacturing and Labeling Botanically Derived Dietary Supplements* (Eisneret al, 2001)

QUALITY ASSURANCE FOR EXTRACT MANUFACTURING

Quality assurance practices are the steps taken by the manufacturer to ensure the proper outcome of the process and batch to batch reproducibility of the product. This should not be confused with quality control practices, which are the specific chemical, physical, and microbiological tests performed on each batch. Quality assurance involves such global aspects of operations as process validation, control and monitoring of manufacturing parameters, environmental control, and stability testing.

Due to their complex nature, botanical products often defy complete characterization through quality control. Therefore, good quality assurance practices assume an especially important role in their manufacture.

3.1 Process development.

Where the recipe for an extract is not completely defined in a pharmacopoeia or other compendium, the manufacturer should carefully investigate the process to be used. This entails performing a number of careful experiments in which manufacturing parameters are varied, including the milling method, cut size, extraction solvent, extraction method, extraction temperature and time, ratio of solvent to biomass, purification methods, excipients to be used, drying methods, and sanitization methods. The chemical, physical, and/or microbiological characteristics of the resulting experimental extracts are then evaluated to determine which combination of parameters is most suitable, so that the extract obtained has the desired composition and/or other attributes. The "best" manufacturing process will depend on the specifications the manufacturer wishes to achieve.

3.2 Process control.

Once a suitable manufacturing process is identified, comprehensive specifications should be established for the raw materials, manufacturing process, and finished product. Careful control of raw materials and manufacturing parameters is critical for ensuring the consistency and reproducibility of each batch. Raw material specifications should include suitable limits for contaminants such as pesticides, heavy metals, and aflatoxins. A complete batch record should be generated for each batch produced, including information about the raw materials used, the manufacturing steps completed, the process parameters used, and the final outcome of the process.

3.3 Environmental control.

Careful environmental control throughout the manufacturing process will protect the product from contamination and degradation. The processing environment should conform to current good manufacturing practices (cGMPs) for the product. The manufacturing facility should be well lighted and ventilated, provide ample room for the required operations, and should be constructed to facilitate ease of cleaning. In general, materials should be protected from extremes of temperature. Furthermore, it is desirable to control humidity, so as to minimize microbial and fungal growth and prevent hygroscopic materials from becoming sticky. Sterile products must be handled and packaged under aseptic conditions.

3.4 Stability testing.

Manufacturers should ensure each product will remain stable through its labeled shelf life. Stability testing can be performed using techniques such as organoleptic properties, TLC or other chromatographic fingerprinting, content of marker substances, pH, viscosity, and microbial content. The choice of proper packaging material is critical to ensuring adequate shelf life; many products require protection from light, oxygen, and/or moisture. Sensitive products will require packaging in impervious containers, such as glass bottles or metal-lined bags.

QUALITY CONTROL FOR EXTRACT MANUFACTURING

Quality control entails a battery of chemical, physical, and microbiological tests and examinations, which ensure that the raw materials and finished product conform to appropriate specifications. Although it is generally impossible to completely characterize a material as complex as an herb, quality control tests are an important tool for producing quality extracts.

4.1 Raw materials.

Tests for raw materials may include the following:

a. Identity;

b. Content of any desired marker substances;

c. Water- and alcohol-soluble extractives;

d. Contaminants and impurities, such as foreign organic matter, pesticide residues, heavy metals, microbial load, aflatoxins, and radioactivity;

e. Other tests such as total ash, acid-insoluble ash, water-soluble ash, crude fiber, starch content, and water content.

4.2 Finished extracts.

When the finished extract is purchased as a raw material for further processing, the quality control test results and the methods on which those results are based should be made available to the purchaser. Tests for finished products may include the following:

a. Identity;

b. Content of any claimed marker substances;

c. Contaminants and impurities, such as microbial contamination. Depending on the contaminants in the raw material and/or the processing method used, testing for pesticide residues, heavy metals, aflatoxins, ethylene oxide residues, and radioactivity may also be appropriate;

d. Other tests for liquid extracts may include refractive index, density or specific gravity, viscosity, pH, total dissolved solids, and residual solvents;

e. Other tests for powdered extracts may include tapped or bulk density, particle size distribution or mesh size, water content, and solvent residues.

Labeling of Extracts Intended for Further Processing

The following information should be made available to the purchaser on shipping labels, product specifications, or other documentation.

5.1 Liquid extracts.

- **a.** Part or item number.
- **b.** Lot or batch number.
- **c.** Brand name, if applicable.
- **d.** Latin name and authority, and/or common name per *Herbs of Commerce*.
- **e.** Plant part, in English.
- **f.** Solvent used for extraction.
- **g.** Dilution ratio of the finished extract. If the dilution ratio is based on the weight of fresh rather than dried herb, this fact must be disclosed.
- **h.** Description and amount, in percent or range of percents, of all added ingredients, including all solvents remaining in the product.
- **i.** Overview of the manufacturing process, including a general description of each process step.

5.2 Traditional-style powdered extracts.

- **a.** Part or item number.
- **b.** Lot or batch number.
- **c.** Brand name, if applicable.
- **d.** Latin name and authority, and/or common name per *Herbs of Commerce*.
- **e.** Plant part, in English.
- **f.** Solvent used for extraction.
- **g.** Concentration ratio or range of concentration ratios of the finished extract. If the concentration ratio is based on the weight of fresh rather than dried herb, this fact must be disclosed.
- **h.** Description and amount, in percent or range of percents, of all added ingredients.
- **i.** Content, minimum content, or range of content of any marker substances, in percent.
- **j.** Overview of the manufacturing process, including a general description of each process step.

5.3 Semi-purified powdered extracts.

a. Part or item number.

b. Lot or batch number.

c. Brand name, if applicable.

d. Latin name and authority, and/or common name per *Herbs of Commerce*.

e. Plant part, in English.

f. Description and amount, in percent or range of percents, of all added ingredients.

g. Content, minimum content, or range of content of each group of components quantified in the extract.

h. Overview of the manufacturing process, including a general description of each process step.

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