



Considerations on Health Canada's proposed definition of Veterinary Natural Health Products

Prepared by the American Herbal Products Association
April 7, 2009

It has been brought to the attention of the American Herbal Products Association (AHPA) that Health Canada is developing guidelines for the use of natural ingredients in veterinary natural health products. In the list of types of ingredients, items 1 and 2 pertain to botanicals.

- Schedule 1: List of Included substances:
 1. A plant or plant material, an alga, a bacterium, a fungus or a non-human animal material
 2. An extract or isolate of a substance described in item 1, the primary molecular structure of which is functionally equivalent to that which it had prior to its extraction or isolation

Members of AHPA's Animal Products Committee and Standards Committee have reviewed the above-cited language and AHPA offers the following comments on this matter.

Background Information¹

Botanical Constituents and Activity:

Botanicals are complex mixtures that, with some exceptions, have chemical compositions that are generally not well characterized and have biological activity that is generally not well understood.

For any given botanical, normally only a fraction of the chemical composition has been identified. Many botanicals have been characterized with respect to various classes of compounds (alkaloids, flavonoids, etc.) and/or individual constituents. However, very few if any botanicals have been completely characterized; in most cases, the majority of the chemical composition is unknown.

Furthermore, for any given botanical, the "active component" has usually not been conclusively identified. Purified constituents and/or chemical fractions can be shown to exhibit various types of physiologic activity *in vitro* and/or *in vivo*, but it cannot be assumed those constituents or fractions are "the" active component in the botanical. In most cases, one botanical will comprise multiple different types of constituents which contribute to the overall physiologic effect of the botanical. Also, the physiologic activity of any given constituent studied in isolation is often different than the same constituent contained in the broader matrix of constituents native to the botanical. As a

¹ This introductory discussion is abbreviated and somewhat over-simplified. For a complete discussion of related issues, refer to AHPA's white papers "Guidance for the Manufacture and Sale of Bulk Botanical Extracts" (pp. 12-13), "Standardization of Botanical Products" (especially section 7) and "Use of Marker Compounds in Manufacturing and Labeling Botanically Derived Dietary Supplements" (in its entirety), which are hereby incorporated by reference.

result, the only scientifically rigorous approach is to consider the entire chemical composition of a botanical preparation as “the active component.” In such cases, individual constituents are properly referred to as “marker compounds” rather than “active compounds.”

Botanical Preparations:

Botanically derived preparations can be separated into several broad types, based on the degree of purification, degree of novelty, and the degree to which active constituents have been identified.

Preparations derived from botanicals range from wide spectrum extracts, which comprise most of the soluble constituents native to the botanical, through broad spectrum extracts (containing a broad range of native constituents) and narrow spectrum extracts (comprising a narrow range of native constituents) to isolates (single chemicals, which AHPA and others exclude from the definition of an “extract” and may be more accurately described as a “constituent”).

Preparations from botanicals can be divided into “generic” and “proprietary” preparations.

- i. “Generic” (or “traditional”) preparations are made using traditional, relatively unsophisticated manufacturing processes such as maceration, decoction, or pressing, and using traditional solvents such as water, ethanol, or vinegar.² Often, a traditional culture has developed one or more classic preparation methods for each botanical, which may encompass everything from raw material preparation (e.g. drying, curing, etc.) through extraction (e.g. chewing, maceration in a particular solvent, etc.) to administration. The safety and efficacy of such generic and especially traditional preparations has generally been established through centuries or millennia of use.
- ii. “Proprietary” (or “special”) preparations are made by adjusting growing, harvesting, and/or processing conditions and methods to manipulate the chemical composition of the resulting material. Since the chemical composition of such preparations is relatively new, it cannot be assumed that the safety and efficacy of such preparations will match that of the generic or traditional preparation.

It must be noted that “traditional” or “generic” extracts can be both broad spectrum (e.g., a macerate in water) or narrow spectrum (e.g., a macerate in oil). In contrast, “proprietary” extracts tend to have a narrower spectrum since the manufacturer develops the preparation with particular types and levels of marker compounds in mind.

Finally, botanical preparations can be characterized by the extent to which the “active component” is known. In the case of isolated chemicals, the active chemical is obvious (e.g., purified ephedrine hydrochloride). The activity of extracts, on the other hand, ranges from the rare case where a definitive active is known (e.g., ephedra leaf extract

² For a complete discussion of extraction methods, see AHPA’s “Guidance for the manufacture and sale of bulk botanical extracts,” pp. 6-12.

containing a defined amount of ephedrine alkaloids)³, to cases where multiple co-actives are known, to cases where no active is known. In the latter cases, preparations may nevertheless be characterized with respect to various marker compounds, but those markers should not be assumed to necessarily be the most important constituents in the preparation.

It must be noted that “generic” or “traditional” preparations may or may not be characterized with respect to the level of various compounds. For example, one company may sell a hydroethanolic echinacea root extract which is not chemically characterized. Another company may produce exactly the same kind of hydroethanolic echinacea root extract, and test each batch for alkylamide content, and thereby sell the material as a “standardized” extract.⁴ The mere act of performing a chemical analysis does not change the nature of the material in trade; the difference between these two echinacea extracts is only a matter of labeling.

In contrast, “proprietary” extracts are generally characterized with respect to one or more classes of compounds; and since the processing method has been designed specifically to manipulate the content and control the levels of those compounds, the “proprietary” extract will be fundamentally different from “generic” or “traditional” extract even if the nominal levels of marker compounds are the same. For example, a manufacturer might design an extraction process to achieve unusually high levels of alkylamides from echinacea; such an extract would be obviously different from generic echinacea extracts. However, if the manufacturer adds a large amount of corn starch to dilute the level of alkylamides back to more normal levels, the difference between the proprietary extract and the generic extract will not be obvious from the labeling.

In summary, botanical preparations should be evaluated with respect to the specific processing used as well as to the degree of purification, degree of novelty, and degree to which active vs. marker components are known.

Comments Regarding the Proposed Schedule 1 Categories

The first listed category in proposed Schedule 1 is self explanatory and AHPA supports it as written. The second category, however, presents difficulties in interpretation and implementation.

1. What is meant by the “primary” molecular structure? An assumption can reasonably be made that this means that minor chemical modifications, such as esterification, are allowed as long as these arise naturally from the processing conditions.⁵ The reasoning behind this assumption is that the use of the term “primary” has meaning only if a secondary or other molecular structure is present

³ In order for a single “active” compound or group of compounds to be identified, the purported “active” must be studied both in isolation and in the broader native matrix, and the physiologic activity must be shown to be identical in each circumstance. This situation exists for only a few botanicals such as ephedra, opium, digitalis, etc.

⁴ In this example, so long as the manufacturer maintains strict controls over raw material sourcing and processing conditions, the levels of alkylamides in the final material will usually remain reasonably consistent from batch to batch.

⁵ Certain chemical changes such as hydrolysis and transesterification often occur naturally during processes such as extraction.

that does not significantly alter the biological activity of the material in the material from which it can be extracted.

2. How is “functionally equivalent” to be determined or reasonably assumed? As was mentioned above, for most botanicals it is not clear how the activity of the botanical as a whole relates to individual constituents or various groups of compounds. The physiologic activity of any compound or group of compounds will often be different when studied in isolation vs. in the broader native matrix of the botanical, because various constituents can work antagonistically, synergistically, or can otherwise modulate each other’s effect. Furthermore, various compounds in the broader native matrix can affect stability, bioavailability, and other aspects of the preparation. As a result, it is difficult to see how “functional equivalence” can be practically implemented as part of the criteria to be considered.

AHPA therefore recommends that paragraph 2 of proposed Schedule 1 be modified as follows:

2. An extract or isolate of a substance described in item 1:
 - A. An extract manufactured using traditional processing methods and solvents, whose chemical composition is broadly similar to preparations of the substance which have been traditionally used.
 - B. An extract which, due to unique procedures used in cultivation, harvest, processing, or otherwise, has a chemical composition which is not broadly similar to traditional preparations of the substance.
 - C. Isolated constituents derived from the substance.

From a practical standpoint, AHPA believes it would be up to the manufacturer of any extract to provide Health Canada justification for which sub-category their product should fall into (A, B, or C), and for category B and C materials to justify the safety and/or efficacy of their material.

AHPA believes it important to formally recognize the differences between these 3 proposed sub-categories, since differences in chemical composition can change the safety and efficacy of the preparation. The safety and efficacy of traditional, generic preparations is generally known through centuries of use. In contrast, the safety and efficacy of non-traditional preparations, whose overall chemical composition differs significantly from the traditional preparation, may require closer consideration based on the preparation’s history in the marketplace, the types of compounds it contains, etc. Finally, the safety and efficacy of isolated chemicals should never be assumed to be the same as that of the broader complex matrix.

Proper sub-categorization of these materials will be important not only in reviewing product registrations, but may also be important in post-market surveillance of the use of the products.