Use of Marker Compounds in Manufacturing and Labeling Botanically Derived Dietary Supplements

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

EXECUTIVE SUMMARY

This paper is a discussion of marker compounds. It defines them, their common use, their value, and their limitations. Their relationship to active compounds is also considered.

The beneficial uses of marker compounds include their application for purposes of botanical identification, detection of adulteration, and as indicators of product quality during manufacturing, handling, and storage. They can be used as quality control measures for botanical mixtures and as shelf life indicators. Further uses include their employment as an indicator of pharmacological activity when they themselves are active, and for evaluation of material used in clinical trials.

The pitfalls of using marker compounds include limitations on available testing methods, reliance on them as sole identity indicators, misrepresentation of botanical standardization, and misapprehension resulting from an incomplete understanding of their relative importance. This can result in deleterious effects on raw material and product quality through an approach that does not adequately take into account the complexity of botanicals.

It should be remembered that the use of marker compounds is not necessary to the production of quality botanical products. On the contrary, many companies achieve consistently high quality without reference to marker compounds.

This document should serve as an educational piece that stimulates further conversation on the topic of marker compounds. It was developed by industry specialists and reviewed by outside experts with the intent to clarify an evolving aspect of the botanical marketplace.

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1. Introduction.

The use of marker compounds is a powerful tool that can help ensure quality and batch-to-batch reproducibility of botanically derived products. However, misuse of marker compounds through improper selection or measurement, or through other factors, can create misunderstanding about product quality, strength, and potency. Misuse of the marker compound concept can even contribute to the creation of misbranded or adulterated products. The purpose of this white paper is to provide information about the proper use of marker compounds, and to provide education to prevent their improper use.

2. What are marker compounds?

Marker compounds are one or more constituents that occur naturally in the botanical material and that are selected for special attention by a researcher or manufacturer. The levels of the chosen compounds are quantitatively determined in both raw materials and products and are used as a guide for the manufacture of the product.

The choice of marker compounds is based on a variety of factors, including availability of analytical methods and standards, ease of analysis, value in identification of the botanical material, perceived therapeutic or other health relevance, use as an indicator of quality and stability, and previous use of a marker compound by other manufacturers. Some of these factors are discussed further below.

In some cases, more than one type of "marker" is examined, with each serving a different purpose. For example, in the root or dong quai (*Angelica sinensis*) some researchers believe the ubiquitous compound ferulic acid is a useful indicator of stability, while the compound ligustilide (which has a much narrower distribution in the plant kingdom) is more useful for identification. In echinacea, some companies use polysaccharides to help ensure proper handling, but alkylamides or cichoric acid are more often used for verifying *Echinacea* species.

However, even these preferences are often the subject of dispute. There is considerable controversy within both industry and the scientific community about which are the most appropriate markers for any given botanical, and which markers should be used for which purposes.

3. Are marker compounds different from active compounds?

In theory, it is easy to state the difference between an active compound and a marker compound. An active compound is a plant constituent that is known to exert a direct physiological effect. A marker compound is a constituent that is useful for technical purposes but that does not necessarily exert a physiological effect.

In practice, however, it can be very difficult to determine whether a given compound is an active or a marker or both. It is rare that a single compound or group of compounds is solely responsible for the physiological effect of a botanical; rather, there are usually many compounds and types of compounds that are therapeutically relevant. This makes it difficult to identify a single "active compound."

Furthermore, there is often conflicting or inconclusive data about the physiological activity of a compound. Some studies may conclude that the compound has activity, while other studies find no activity at all. Tests performed on an isolated compound may identify activity that the compound does not possess in the highly complex matrix of the botanical or when consumed by a human. Activity found in vitro may not occur in vivo, for a variety of reasons (e.g. degradation in the digestive tract, metabolism into an inactive form, lack of bioavailability, etc.).

In other instances, markers may serve as the precursor to an active compound when, after ingestion, the marker is converted into an active form in the body. For example, the marker compound alliin in garlic (*Allium sativum*) is converted in the body to the active compound allicin. In this case the marker, while strictly speaking not an active, bears significant relevance to the physiological activity of the botanical, and manufacturers may be justified in treating the marker as if it were the active.

Finally, the classification of a particular compound as an active or a marker may depend on the intended use of the product in which it occurs. For example, St. John's wort (*Hypericum perforatum*) contains a variety of unique components, two of which are hypericin and hyperforin. Hypericin has been found to have both some antiviral activity and some anti-depressent activity. Hyperforin also has anti-depressent activity, but is not known to have antiviral properties. Therefore, in a product marketed for "maintaining a healthy state of mind" the hypericin and hyperforin could both be considered actives; but in a product marketed for "supporting the body's natural resistance" only the hypericin might be considered an active, while the hyperforin would be considered a marker.[1]

Because of the complexities outlined above, there is no comprehensive, generally accepted classification of particular compounds as actives or markers. It remains incumbent upon the company that develops a product to determine which, if any, of the compounds should be considered active based on solid scientific research.

However, research and experience have shown time and again that the full physiological activity of a plant can rarely be attributed to a single compound or group of compounds. Furthermore, hypotheses about the source of a plant's activity often change as new data becomes available. Therefore, even when evidence of activity exists for a particular marker, it remains prudent to treat the entire plant or plant extract as the true "active principle." These issues are discussed further in Section 5 (see page 6).

4. What are the beneficial uses of marker compounds?

Marker compounds serve a number of important functions in helping to ensure the quality and consistency of botanical raw materials and products.

Identification. Chemical entities that are uncommon in the plant kingdom can be useful in confirming identity. Markers such as these may be found in only a few botanical species or even in a single part of a single species. When these markers are detected in the raw material or product, it helps to confirm the identity of the

1) Saint John's wort, like any botanical, contains a multiplicity of compounds, and no definitive conclusions can yet be drawn concerning which of its components are physiologically active. The statements made in this paragraph reflect some current views on this subject, and are provided simply to illustrate the complexities of the intersection between marker compounds and marketing. As new research becomes available it is likely that opinions concerning the activities of St. John's wort constituents will continue to change.

material. Although markers alone usually cannot identify a material with 100% confidence, they can help reduce the chance of mix-ups during harvest, processing, and packaging.

Detection of adulteration. The absence of certain markers can be used to ensure that known adulterants are not present in a batch of material. Certain botanicals are occasionally contaminated with other plants; for example, digitalis leaf (especially *Digitalis lanata*) is sometimes mixed with English plantain (*Plantago lanceolata*), and safflower (*Carthamus tinctorius*) with saffron (*Crocus sativus*). Some of these adulterants are toxic and may cause serious injury or harm. To avoid this problem manufacturers can test for known constituents of the adulterating species (negative markers) to be sure the adulterant is not present. For example, shipments of plantain can be tested for digitalis glycosides to exclude the possibility of digitalis adulteration in the material.[2]

Indication of proper handling, manufacturing, packaging, and storage. Markers serve as a useful control for the processing and distribution of the botanical raw materials and products, from pre-harvest to retail sale. Improper handling can cause material degradation at each step in this sequence. This is particularly true of processing steps such as drying, grinding, extraction, packaging, and storage where the material may be exposed to heat, moisture, oxygen, or microbial contamination. If each step is not executed carefully, the overall quality of the material may be diminished.

In this sense markers can play an even more important role for botanical extracts. The manufacture of high quality extracts depends not only on quality raw materials but also on careful control of many variables, including extraction times and temperatures, solvent composition, the proportion of solvent in relation to the plant material, and the particle size of the plant material. Any variation in these factors can change the character of the extraction.

Markers serve to control these processes by providing an objective reflection of the history of the material. If the expected markers are not found at the expected levels, this indicates that some part of the manufacturing process may have gone wrong. Perhaps the material was not dried thoroughly after harvest; perhaps an extraction vessel was allowed to get too hot. While it may not be possible to determine exactly where the failure occurred, the manufacturer will know that something is amiss, and can use that information to decide the fate of the affected lot and review the process and tighten controls where appropriate.

The use of this technique presupposes the need to analyze the marker content of the botanical raw material before it is processed, as well as the availability of suitable analytical methods (see Section 5, "Test Methods"). Information regarding marker content must be available before manufacturing begins so that the "correct" or expected marker content for the finished material can be predicted.

In this context, it is not possible to say that a marker should occur at a certain level in every product in order to demonstrate the quality of the products. What is important is not the marker content in an absolute sense, whether high or low, but simply that the marker(s) be present at levels that are consistent with past history and experience for proper production of the product. In cases where the marker content of raw materials is analyzed but not controlled, the recovery of marker at the end of production should be consistent with historical recoveries. Once a history is

2) In this example, the adulteration can also be detected by examining the material microscopically if the material is not too finely powdered.

established, deviations from the expected marker content or the expected marker recovery are indicative of a possible problem during processing.

Quality control of mixtures. Markers can serve a crucial role whenever a botanical material is mixed with other materials. It is very difficult to determine the amount of a particular botanical present in a mixture. Since a botanical can contain thousands of compounds, the identity of many of which are unknown and for which no test method may be available, it is at best extraordinarily difficult to determine the amount of botanical directly through chemical analysis.

However, it may be possible to determine the amount of a botanical in a mixture indirectly, through the use of marker compounds. For example, if a particular lot of botanical material contains 10% of a certain marker, this may be used as a guide for examining mixtures containing the lot. If the lot makes up 50% of the overall mixture, then the marker should be present at a level of 5% in the mixture; and if it isn't, then something is wrong. This can allow the use of chemical analysis to confirm that the correct mixture was made, as long as no insurmountable analytical difficulties arise (see Section 5, page 6).

Furthermore, analysis of marker content may be used to ensure that complete blending is achieved. If different portions of the mixture show different levels of marker, the blend is not uniform and further mixing is required.[3]

As in the previous section, the use of this technique requires that the marker content of the botanical raw material be analyzed before it is mixed with other materials, so that the target marker content for the blend can be determined. As with other quality control techniques involving markers, the point of this exercise is not that the material or the blend must have a certain marker content every time, or that a higher level of marker is better; it is simply a tool that may be used on a batch-by-batch basis to confirm that blends are correctly made.

Shelf life. Marker compounds are sometimes used as an indicator of shelf life for the product. Formulation, packaging, and storage conditions can all affect the stability of botanical materials. By looking for degradation of marker compounds, manufacturers may be able to establish when product quality begins to deteriorate and to establish a meaningful product shelf life.

However, marker content is not the only guide to product stability. Depending on the product, organoleptic properties, disintegration, pH, viscosity, microbiological characteristics, chromatographic fingerprints, and other characteristics should also be considered.

For product stability purposes, the marker(s) must be chosen carefully. Some markers are highly unstable and begin to degrade almost immediately after harvest of the plant; such markers may be unsuitable for determining the shelf life of a commercial product, especially if they are not pharmacologically relevant. Other markers are extremely stable, which may also make them unsuitable as a guide to the stability of the product overall. Furthermore, there are questions concerning the use of any marker for stability testing if that marker is not a recognized active. As with any other decision involving markers, the choice of markers for stability purposes is often controversial and will be impacted by the perceived therapeutic relevance of the

3) This presupposes that a suitably accurate and precise analytical method is available. The method must give highly reproducible results, with minimal scatter in the data; otherwise it is difficult to determine whether variability in the results is a reflection of heterogeneity in the blend or is simply an artifact of the analysis.

marker, the stability of the marker in relation to other constituents and product characteristics, the stresses to which the product is likely to be exposed,[4] and the presence or absence of a label claim for the marker. (See appendix B for further information concerning markers and label claims.)

Control of pharmacological activity. In plants where marker compounds with known pharmacological activity (i.e. active compounds) occur, the marker compounds can help ensure that each batch of the product will have the same physiological effect. In these cases, controlling the levels of these compounds within well-defined limits is necessary to ensure consistent product efficacy. Upper as well as lower limits should be established for compounds where safety is a concern.

In many cases, the pharmacological activity of the herbal product can be ascribed to more than one marker compound. In such instances, the ratio between the compounds found in a preparation with a history of safe and effective use can provide information important to understanding the biological activity of the preparation. This is similarly important in cases where the bioavailability (e.g. solubility, absorption, gastrointestinal and hepatic stability) of one compound is enhanced or ensured by another.

In cases where the biological activity of an herbal material cannot be fully ascribed to its identified marker compound(s), it is preferable to characterize the material as fully as possible by chromatographic fingerprinting[5] rather than confine the examination to only one marker.

Evaluation of clinical trial data. The presence of a marker or groups of markers is often used in the evaluation of clinical trials. When a clinical trial is conducted, it is important that the material used in the trial be characterized as thoroughly as possible, so that the results of the trial can be extrapolated to other batches of the same product and to similar botanical products. Similarly, the results of the trial should not be extrapolated to products that are significantly different from that used in the trial.

Markers are often used as one component of this characterization. This use is valid to the extent that markers help to control the nature and the consistency of the material. However, it must be borne in mind that markers by themselves do not ensure reproducibility either between batches or between products (see Section 5 below).

5. What are some of the pitfalls of marker compound use?

Although markers can have an important role to play in ensuring product quality, it is important to understand the pitfalls and limitations of their use. The uninformed or misguided use of markers can cause erroneous conclusions to be drawn about the material, and can actually diminish product quality.

Test methods. It is important that test methods be specific as to compound and well-validated as to performance. Non-specific methods can give false positive results, seeming to indicate that the marker is present when in fact it is absent. They can also

4) Different markers can be useful for evaluating the effect of different stressors (heat, light, moisture, air). For example, one marker may be particularly susceptible to oxidation in the presence of air, while another is more susceptible to degradation by light or heat.
5) To obtain the most complete picture of the material, both relatively polar and relatively nonpolar groups of compounds should be fingerprinted.

overestimate the quantity of marker present. In general, chromatographic methods are to be preferred over less-selective methods such as titrations or UV-visible spectroscopy.

It is also important that the test method and sample preparation be suitable for the matrix in which the marker occurs. For example, slightly different methods may be necessary for the analysis of a crude botanical vs. an extract. In addition, whenever a botanical is mixed with other ingredients (e.g. blends and other in-process manufacturing materials, or finished products), some components of the mix may interfere with the sample preparation and/or analysis of other components. For example, excipients such as magnesium stearate, gum arabic, maltodextrin, and silica can interfere with marker recoveries, thereby yielding erroneously low results. Where several botanical ingredients are combined, the multiplicity of similar compounds can make adequate separation and accurate quantification of any particular marker difficult, if not impossible. The test method should be properly optimized and validated for the matrix to be analyzed; otherwise the results obtained may be incorrect.

Once a suitable test method is established it should not be altered, since changes in the method can lead to inconsistent results. If a method must be changed, it is necessary to determine how the change in the method impacts the results obtained. This allows results obtained before and after the change to be properly compared.

Finally, it is always necessary to take the effects of the analytical method into account when evaluating or comparing the marker contents of raw materials or products. Some methods will consistently give higher or lower results than others. As a result, without detailed information about the method it is difficult to interpret statements made concerning the marker content.

Identification. In general, the mere presence of a marker is not adequate to confirm the identity of a material, since similar markers may occur in a wide variety of plants. Furthermore, it may be possible for unscrupulous vendors to pass one plant material off as another by spiking it with the appropriate marker(s).

Rather than rely on the presence of a single marker, it is wise to use all available information about the material. To ensure identification with a high degree of confidence, chromatographic fingerprints for one or more groups of compounds should be examined. Morphologic characteristics should also be examined where available. Ideally, a chain of custody from harvest to product should be established, and botanically verified voucher specimens for the harvest should be maintained.

Standardization. The mere presence of a particular marker at a particular level is often mistakenly confused with the concept of extract standardization.[6] Standardization consists of the body of information and controls that serve to ensure batch-to-batch reproducibility of the extract; as such, it comprises a wide variety of raw material and process controls, as well as use of a consistent recipe. The goal is to control the complete chemical composition of the extract (although a considerable amount of variability will usually remain). The complex nature of standardization cannot be reduced to the mere quantity of one constituent or group of constituents.[7]

This concept of standardization is based on the recognition that the physiological effect of any given compound or group of compounds can be heavily influenced by the matrix in which they occur. Some compounds in the plant may enhance or diminish the physiological effects of others. Other compounds, while having no direct physiological effect, may nevertheless influence the stability, solubility, and

bioavailability of the physiologically relevant compounds. As a result, it is important to consider the entire spectrum of chemicals in the material, and to implement standardization measures that will control the entire spectrum and not just one constituent.

The narrower concept of ensuring that each batch contains a particular content of marker is more properly understood as adjustment, not standardization. Adjustment to a minimum, maximum, or target concentration of a constituent is appropriate only when the constituent is known to be active and should ideally be achieved through the mixing of extract lots rather than by spiking or dilution.

Misapprehensions caused by focusing on markers. The confusion between marker content and standardization has had a number of insidious effects in the U.S. marketplace.

The excessive attention paid to individual compounds has led consumers, retailers, and even extract manufacturers to assume that control of the marker content is equivalent to controlling the physiological effect of the extract. Furthermore, it is also commonly assumed that "more is better," and that higher levels of marker will result in stronger physiological effects.

These assumptions are not always valid. As discussed above, a variety of compounds must work together to determine the plant's physiological effect. Furthermore, many markers may have no physiological effect whatsoever. Even where physiological activity does occur in a marker, there may be a maximum level that is safe or efficacious.

Negative effects on raw material and product quality. Undue attention paid to marker compounds can have the effect of lowering the overall quality of materials in trade. Materials can be manipulated in a variety of ways for the sole purpose of "enhancing" marker content. This can occur, for example, through the development of plant varieties with higher levels of markers, so that label claims can be raised and/or less botanical material will be needed to meet a particular label claim. Similarly, during manufacture of an extract, alterations can be made to raw material specifications, solvent systems, and processing methods to increase marker levels and/or reduce the amount of botanical material consumed in the extraction. In some cases, extracts are even spiked with additional quantities of purified chemicals. Finally, the products in the marketplace are sometimes designed or reformulated to deliver higher and higher levels of markers.

All of the above practices can have negative effects on quality, safety, and efficacy, and in some cases are illegal. Any practice that elevates the level of one compound beyond what has been historically or scientifically demonstrated to be safe and effective must be regarded with caution. This is particularly true when the marker level is elevated at the expense of other constituents. If a marker does possess physiological activity, then higher levels of it may lead to unexpected side effects or even toxicity. If the marker does not possess physiological activity, or if it is responsible for only part of the plant's activity (as is usually the case), then raising it

6) Indeed, there is a common misconception in the U.S. that standardization is equivalent to adding purified compounds to an herb in order to achieve a desired level of marker compound. In fact, nothing could be further from the truth. The addition of purified compounds in order to achieve "standardization" actually defeats the purpose of standardization, and may result in the creation of a misbranded or adulterated product.

7) In cases where a marker with a powerful pharmacological effect occurs, e.g. with certain alkaloids, the content of that compound has an elevated relevance to the standardization of the extract. In such cases it may be justified to focus attention primarily on a single compound or group of compounds.

at the expense of other compounds (some of which may in fact be the primary actives or contribute secondary activity) could diminish the effectiveness of the product.

Inconsistency of products over time caused by "chasing new science." As scientists further their study of botanicals, new information continually emerges. In particular, a primary focus of research is the discovery and investigation of new markers and /or actives. This research is driven by a variety of factors, including (a) the desire to understand and control the physiological effect of the botanical; (b) the protection of patents; (c) the development of new marketing avenues; (d) the desire to replace subjective quality assurance measures, such as the detailed traditional knowledge that often exists concerning the evaluation, harvest and processing of the botanical, with measures that are more objective and hence more widely accessible; (e) basic phytochemical inquiry.

In the current U.S. marketplace, these new discoveries often translate into huge swings in both the advertising and the nature of the materials and products offered to the consumer. New science can make a hot marketing story that can translate into sales. Within months of a new marker being discussed in the scientific literature, dozens of products touting its presence may be found on the retail shelves.

The new focus on a marker can be used both as an additional way to characterize existing materials and products, and as the basis for development of novel materials and products. In the first case the marker is used for quality control and to provide additional information to the consumer. In the latter case the marker can be used to alter the very nature of the products being offered, i.e. the chemical profile of the product is altered in order to highlight the marker currently in fashion.

This latter use of a marker can be beneficial or detrimental to quality. When done responsibly and on the basis of valid scientific data, such "improvements" can be used to create new products or to enhance the safety and efficacy of existing products offered to the consumer. Sometimes, however, they are based on preliminary or incomplete data, and the effects of the alteration(s) are not appropriately investigated beforehand. This can lead to a chaotic profusion of products and "marketing stories" which confuse the consumer and which may or may not deliver the same safety and efficacy as the older type of product.

Conclusion

The preceding discussion should make it clear that the issue of marker compounds is a complex one. Markers can be valuable tools in the production of safe, efficacious, high quality products. However, their proper role must be thoroughly understood. Markers alone don't ensure product quality; in fact, it is possible to ensure a high level of product quality without their use. When markers are used, they must be part of a comprehensive quality assurance program encompassing many other aspects of the materials and processes in order to deliver a safe and effective product.

APPENDIX A

Glossary.

Active compound: A botanical constituent that is wholly or partially responsible for the physiological effect of the botanical. Some active compounds are similarly effective when tested as an isolated substance compared to when tested as part of a botanical preparation, while others are not as effective when isolated.

Marker compound: A constituent present in a botanical that is characteristic of the botanical and that is used for technical purposes (e.g. identification of the botanical or process control). Marker compounds fall into two main categories: (a) Characteristic markers are those constituents which are characteristic of a certain species, genus, or family of plants; (b) Ubiquitous markers are those constituents which appear in several plant families.

Standardization: The complete body of information and controls that serves to enhance the batch to batch consistency of a botanical product, including but not limited to the presence of a marker compound at a defined level or within a defined range.

APPENDIX B

The Relationship of Marker Compounds and Label Claims.

Federal regulations (21 CFR part 101.9(g)(3), 101.9(g)(4), and 101.36(f)(1)) require that products be truthfully labeled with respect to their contents. In clarifying this requirement, the Food and Drug Administration (FDA) has established two different minimum levels that label claims must meet depending on the type of ingredient. These two guidelines are commonly known as "the 80% rule" and "the 100% rule."

The 80% rule applies to constituents that occur naturally in an ingredient and whose level in the ingredient is not controlled.[8] For example, kelp powder contains naturally occurring iodine at a level of approximately 0.5%. Therefore if a product contains 100 mg of kelp powder, it will also contain about 0.5 mg of iodine. However, the content of iodine will not be exactly 0.5% in each batch of kelp. In recognition of this FDA allows up to 20% variation between the labeled and the actual content of iodine. Thus if a kelp product is tested for iodine it will be considered to be truthfully labeled as long as the iodine content is at least 80% of label claim.[9]

The 100% rule applies to components whose content is controlled directly. Thus a product containing pure vitamin C is required to meet 100% of its label claim for vitamin C. Similarly, a product containing guarana seed extract adjusted to 5% caffeine is required to meet 100% of its label claim for caffeine.[10] This is because the caffeine content of the raw material has been controlled.

Whether the 80% rule or the 100% rule applies, FDA requires that the product conform to these guidelines throughout the shelf life of the product.

8) This is the current position taken by FDA. However, some legal experts dispute this interpretation of the regulations, maintaining that the 80% rule applies to all naturally-occurring components whether or not their level is controlled.
9) For maximum legal protection, such a product should be labeled as containing "naturally occurring iodine."
10) See footnote 8.