

## CHAPTER 31

# Supplements Evaluated in Clinical Trials: Why Specific Formulations Matter

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The decision to take a botanic product or advise a patient to take a botanic substance is based on an expected therapeutic benefit. This expected benefit can be based upon traditional use and/or on the results of modern clinical or pharmacological studies. The assumption is that the product selected from the shelf will be similar enough to the reference product to have the same therapeutic effect. This assumption is based upon working with drugs that are mandated to conform to official specifications for generics.

Perhaps because of this, in the United States an herbal preparation is often not specified beyond the common name of the plant. Simply “valerian,” “echinacea,” or “garlic” is used to describe the preparation. That might suffice if all valerian, echinacea, or garlic products were equivalent. But they are not. For example, valerian root preparations are available as teas (aqueous extracts) and aqueous alcoholic extracts (70% ethanol with an herb to extract ratio of 4-7:1). As for echinacea products, three different species are used in commerce and the preparations are as diverse as the expressed juice of *Echinacea purpurea* flowering tops and an aqueous alcoholic extract of the roots of *Echinacea angustifolia* roots. Garlic is available raw, dried, aged (aqueous alcoholic extract), and as an oil. None of these preparations can be assumed to be chemically and therapeutically equivalent.

For products sold as dietary supplements in the United States, there are suggested guidelines on establishing bioequivalence. However, there are no mandated criteria to use to compare products which might be considered equivalent. The Federal Trade Commission, in its advertising guide for the dietary supplement industry, states that “...advertisers should examine the underlying research to confirm that it is relevant to the advertiser’s product..., ...dosage and formulation are comparable..., ...an advertiser should not rely on studies where ... the advertisers product is made using a different extraction method...” (1).

In contrast, for drugs there are established mandated criteria to define a generic product. Generic drugs are pharmaceutically and therapeutically equivalent to the reference product as established by United States Food and Drug Administration mandates (2). A substance is considered pharmaceutically equivalent if it contains the same active pharmaceutical ingredient (API), same chemical composition, same strength, same dosage form, same route of administration, and labeled for the same condition of use. Therapeutic equivalency is established by measuring disintegration (the ability of the capsule or tablet to dissolve), dissolution (release of active components), and bioavailability (metabolism, distribution, and excretion). Often, bioequivalence is estab-

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lished with a clinical study that includes a time course of plasma concentrations after single administration of the original and test products. The study is usually a two-way, crossover study with 24 to 36 healthy volunteers that demonstrates identical plasma exposure over time. Critical parameters are the extent of absorption of the active constituent, measured as the area under the plasma concentration time curve (AUC) and the rate of absorption as measured by maximum plasma concentration ( $C_{\max}$ ).

The challenge with defining a generic botanic product lies in establishing the API. Is the API the whole plant, an extract, an extract of selected groups of compounds, or a specific chemical constituent? What about a multicomponent mixture? This question can be addressed by referring to the original material that delivered the specific benefit. As an example, there is a “nerve tea” formula in the German Pharmacopoeia 7 that is based upon traditional use. The formula includes valerian root, balm leaves, and peppermint leaves in a ratio of 2:1:1 (3). In this example, the whole formula is the API. As another example, most of the clinical and pharmacological data for ginkgo leaf extracts is based upon a proprietary extract (EGb 761) that is a 50:1 concentrate (4). In this example, the specialized concentrated ginkgo extract is the API. Although preparations of ginkgo-powdered leaf are offered for sale in the United States, it is highly improbable that this preparation will offer the same benefits. A third example is the sennosides, found in senna leaves and pods. The sennosides are purgative laxatives and these specific compounds, which can be purified from the plant, are the API (3).

A more subtle distinction in establishing the API is the type of extract prepared from the plant material. Different solvents can pull different chemical compounds from the plant and this may affect the therapeutic efficacy of the preparation. As an illustration, an experiment was conducted to determine the effects of different extraction solvents on hawthorn preparations. Extracts were prepared using aqueous ethanol (40% to 70% volume/volume), aqueous methanol (40% to 70%), and water. Chemical characterization determined that the contents (procyanidin, flavonoid, total vitexin, and total phenolic) were qualitatively and quantitatively different in the water extract compared with the aqueous alcoholic extracts. In addition, the ability of the water extract to have a relaxant effect on aortic tissue *in vitro* was reduced by more than half compared with the aqueous alcoholic extracts (5). This data suggest that the tea would be less effective than the tincture or dried aqueous alcoholic extract in treating cardiac insufficiency.

A rational approach to evaluating the APIs and phytoequivalence of herbal products was developed by an international group, the Herbal Medicinal Products Working Group of the International Pharmaceutical Federation (FIP). This group produced three categories of products according to the extent of information on APIs (6).

In the first category (A) are extracts containing constituents (single compounds or families of compounds) with known and acknowledged therapeutic activity deemed solely responsible for the clinical efficacy. In this category, the API can be established chemically. Tests for pharmaceutical equivalency and bioavailability can be conducted in the same way as they are for drugs. Examples of category (A) botanics in the European Pharmacopoeia are aloe dry extract, buckthorn bark dry extract, senna leaf dry extract, and belladonna leaf dry extract. Examples in the German Pharmacopoeia are ipecacuanha dry extract, rhubarb dry extract, milk thistle fruit dry extract, and horse chestnut seed dry extract (6).

In the second category (B) are extracts containing chemically defined constituents (single or groups) possessing relevant pharmacological properties that are likely to contribute to the clinical efficacy. However, proof that they are solely

responsible for the clinical efficacy has not been provided. The API is the whole extract and there is a need for product manufacturing details as well as chemical markers. In some cases, biological activity testing may replace chemical assays. Examples of category (B) botanics are ginkgo leaf dry extract and St. John's wort dry extract, listed in the German and European Pharmacopoeia, respectively (6).

Extracts that do not contain any constituents that are regarded as being responsible for the therapeutic activity are placed in category (C). For these botanics, chemically defined constituents (markers) may be used for quality control purposes to monitor Good Manufacturing Practices or to determine the contents in the product. Establishment of bioequivalency requires specification of the species, the plant part (root, rhizome, leaf, seed, etc.), and manufacturing processes (e.g., the solvent, the extraction conditions, the ratio of plant material to solvent, and final ratio of starting material to final product). An example of a category (C) botanic in the German Pharmacopoeia is valerian root dry extract (6).

Once chemical equivalency has been established, then bioavailability is the next step in establishing therapeutic equivalency. The biological effect of any substance is dependent upon the extent to which it is absorbed by the body. An array of factors influences bioavailability including the route of administration (oral, intravenous, topical) and the formulation of the product. Formulation in liquid or solid form along with the specifics of the excipients will influence the absorption of the product.

The importance of formulation in bioavailability was demonstrated in a study comparing two ginkgo products. Both preparations contained extracts characterized as containing 24% flavone glycosides and 6% terpene lactones. The reference product was Ginkgold, containing the EGb 761 extract which is the basis for the Commission E monograph (7). Dissolution studies, which are designed to detect the presence and quantity of the API in simulated digestive fluid, were conducted on Ginkgold and the test product. The assay indicated that Ginkgold released more than 99% of its terpene lactone content in 15 minutes, whereas the test product released less than 33% in 60 minutes. These two products were then alternately given to 12 healthy volunteers using a crossover trial design. After administration the plasma concentrations of ginkgolides A, B, and bilobalide were determined. The result of the study was that EGb 761 caused statistically significant greater  $C_{max}$  and AUC for ginkgolides A, B, and bilobalide compared to the test product. Statistical analysis, using 90% confidence intervals, showed that these two products were not bioequivalent (8). As with drugs, information on chemical characterization, as well as bioavailability, is required to establish therapeutic equivalency.

Product characterization can also influence the safety of a product. Experimental evidence with St. John's wort extract suggests that two different types of preparations might be effective in treating mild depression, although one type of preparation may be less safe than the other due to drug-herb interactions. Previous to 1998 it was thought that hypericin was the chemical constituent in St. John's wort that was largely responsible for the antidepressant effect. At that time, research by a group of scientists demonstrated evidence that another compound, hyperforin, was more active than hypericin in treating depression (9). However, a St. John's wort extract that did not contain any significantly amounts of hyperforin was also clinically active (10). It was soon established that St John's wort extracts interacted with specific drugs via the induction of cytochrome P450 enzymes (particularly CYP3A4) and/or P-glycoprotein (11). Further studies determined that the degree of enzyme induction correlated with the amount of hyperforin in the extract. Thus, St. John's wort extracts that did not contain substantial amounts of hyperforin (<1%) do not appear to produce clinically

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relevant enzyme induction (12–15). Thus, there are St. John's wort extracts with different chemical profiles that have demonstrated clinical efficacy in treating mild to moderate depression. Depending on the chemical profile of the extract, St. John's wort products may or may not interact with certain drugs.

Guidance on the characterization of botanic products comes from sources such as pharmacopoeias, government guidelines, and journal editors. Pharmacopoeial monographs specify the identity of the plant material, the plant part, and chemical composition. As an example, goldenseal is defined in the United States Pharmacopoeia (USP) as the dried roots and rhizomes of *Hydrastis canadensis* L that contain not less than 2% hydrastine and not less than 2.5% berberine (16). The goldenseal extract is defined as having a ratio of starting crude plant material to powdered extract of 2:1.

Pharmacopoeial monographs can also specify tests for disintegration and dissolution of capsules and tablets. As an example, the USP monograph for milk thistle capsules specifies that, using the described method, not less than 75% of the labeled amount of silymarin as silybin is dissolved in 45 minutes (17). Compliance with the USP specifications on dietary supplement ingredients is not mandatory in the United States. In contrast, compliance is mandatory for drugs sold in the United States. Botanic products are regulated differently in other countries. For example, Canada and Germany require either compliance with a monograph or individualized approval before marketing.

Guidelines for botanic characterization are given on the Web site for the National Center for Complementary and Alternative Medicine (NCCAM) of the US National Institutes of Health. In its guidelines for clinical trial grant applications, NCCAM suggests that when plant material is used in a trial, it be accompanied by a botanic description, extraction procedure, the quantity of any known active constituent(s), as well as identity and stability tests. When a product is used, information about the manufacturing process, analysis for impurities, and quality controls for manufacturing must be included. In addition, where appropriate, disintegration/dissolution rates are required to estimate bioavailability (<http://grants.nih.gov/grants/guide/notice-files/NOT-AT-05-004.html>).

Some journals give precise details on the information needed to characterize botanic products. The *Journal of Natural Products*, published by the American Chemical Society and the American Society of Pharmacognosy, provides such guidance to its authors. The journal requires that experimental biological material be authenticated as to its identity and that the herbarium that holds the voucher specimen be given along with the voucher number. It further requires that the scientific name (genus, species, authority citation, and family) be given. It also requires authors who purchase dried "herbal remedies" or other materials from companies to deposit a specimen in an herbarium for future access. It requires that the extraction procedure be specified when studying a commercially available extract and that the identification of the extract be supported by an HPLC trace of known secondary metabolite constituents (<http://pubs.acs.org/page/jnprdf/submission/authors.html>).

In summary, therapeutic efficacy cannot be assumed when substituting one botanic product for another. Regulatory guidance on establishing bioequivalence (generics) in dietary supplements is suggested but not specified or mandated. The risks associated with assumption of generic status include efficacy different from expected, unknown safety status, and uninformed /misleading decisions made by health care providers, consumers, and policy makers.

Practical steps that can be taken to move toward identifying botanic products with therapeutic equivalency are listed below. In addition, Table 31.1 lists select

**TABLE 31.1** Select Proprietary Products That Have Been Clinically Tested<sup>a</sup>

<b>Indication</b>	<b>Botanic</b>	<b>Product; Manufacturer</b>	<b>Characteristics</b>	<b>Daily Dose in Trials</b>
Benign prostatic hyperplasia	Grass Pollen (Flower Pollen)	Cernilton; AB Cernelle, Sweden; Graminex, USA	Pollen; water and acetone extracts (Cernitin)	180–360 mg
Benign prostatic hyperplasia	Pygeum	Tadenan; Lab. Fournier, France	Bark; lipophilic extract	100–200 mg
Benign prostatic hyperplasia	Saw palmetto	Permixon; Pierre Fabre, France	Berries; hexane extract (PA 109)	320 mg
Cardiovascular risk	Garlic	Kwai; Lichtwer Pharma, Germany	Dried bulb; standardized to 1.3% alliin, 0.6% allicin (LI 111)	900 mg
Chronic heart failure	Hawthorn	Crataegutt, HeartCare; Schwabe, Germany	Leaves and flowers; hydroalcoholic extract (WS1442)	160–180 mg
Chronic venous insufficiency	Grape seed	Leukoselect; Indena, Italy	Seed; extract standardized to 80%–85% oligomeric proantho-cyanidins	100–300 mg
Chronic venous insufficiency	Horse chestnut	Venastat, Venostasin; Pharmaton, Switzerland	Seed; extract standardized to 16% aescin	600 mg; 100 mg aescin
Cognitive function	Ginkgo	Ginkoba, Gingold, Schwabe, Germany	Leaf; 50:1 extract standardized to 24% flavonoids, 6% terpenes (EGb 761)	120–240 mg, up to 600 mg
Depression	St John's wort	Kira, Jarsin; Lichtwer, Germany; Indena, Italy	Flowers; extract standardized to 0.3% hypericin, >3% hyperforin (LI 160)	900 mg
Insomnia	Valerian	Sedonium; Lichtwer, Germany	Root/rhizome; ethanolic extract (LI 156)	600 mg before bed
Liver disease/ alcoholic cirrhosis	Milk thistle	Legalon; Madaus, Germany	Seeds; extract standardized to 80% silymarin	210–800 mg

(continued)

**TABLE 31.1** (Continued)

Indication	Botanic	Product; Manufacturer	Characteristics	Daily Dose in Trials
Menopause symptoms	Black cohosh	Remifemin; Schaper & Brummer, Germany	Root/rhizome; isopropanolic extract	2 or 4 tablets – equivalent to 40 mg root/ day
Physical performance	Ginseng (Asian)	Ginsana; Pharmaton, Switzerland	Root/rhizome; extract standardized to 4% ginsenosides (G115)	200–600 mg

<sup>a</sup> Information in this table is excerpted from Barrett, 2004 (18).

proprietary products that have been tested clinically for various indications. This information is excerpted from *The Handbook of Clinically Tested Herbal Remedies* (18).

## PRACTICAL STEPS TOWARD BIOEQUIVALENCE

1. Identify the source of the information on expected efficacy. For example, is the source of information on efficacy a book on traditional Chinese medicine or clinical studies conducted on a specific product?
2. Look at the source for information of the characteristics of the product. Note the scientific name of the plant, the plant part and any information on the way it is prepared (dried, heated, extracted, etc), as well as any available information on chemical constituents.
3. Identify sources for products that look like they might be similar to the original preparation. Ask pharmacies that specialize in dietary supplements or search the Web. Look for information on the label of the new product that correlates with the information you gathered above. *The Handbook of Clinically Tested Herbal Remedies* (Barrett, 2004) lists proprietary products that have been tested clinically and possible sources of these products in the United States (18).

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