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PROPRIETARY RESEARCH: BRINGING NUTRACEUTICALS TO THE NEXT LEVEL

Conducting product- or ingredient-specific research is crucial to the long-term success of this market

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Abstract: The natural products industry has seen tremendous growth in branded combination products over the recent decade. Product manufacturers have used the most cutting edge science and technology to produce novel and innovative branded combination products that hold great promise for advancing consumer health. A potential discovery of a combination therapy that achieves an even greater health benefit can be profitable to product manufacturers in huge proportions, not to mention may potentially revolutionize the direction of conventional and alternative medicine. When such complex science is undertaken, companies are burdened to substantiate their product's benefits with medical evidence. But evidence isn't a universal concept in industry. Some companies with formulated, proprietary products rely solely on existing published data as evidence. The problem with this is that the data does not sufficiently substantiate the claims made and may not appropriately address the specific product in question. Common assumptions are that: 1. a combination product's therapeutic benefit is proportional to the benefits of each individual ingredient and; 2. a mixture's pharmacological intensity and physiological effect is based on the concentration of each active ingredient. However, product makers must be aware that the combination of ingredients gives a unique identity and profile to the finished product, not each separate ingredient or biomarker. When multiple ingredients are mixed together, the combination may result in ingredient interactions (agonistic and antagonistic), alteration of those ingredients chemically and pharmacologically, and worse adverse reactions. Both ingredient interactions and chemical alterations can potentially result in an increase or decrease in efficacy of the combination product, even if the constituent ingredients are considered to be effective and generally recognized as safe (GRAS). Different extraction procedures can also result in different concentrations of components, yielding different biological effects. While third party data can be helpful, it should not be solely relied upon to substantiate complex formulations like those contained in combination products. Proprietary research including in vitro laboratory studies and in vivo human clinical studies provides the most reliable evidence of efficacy and safety.



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There's a story behind every great herbal combination product. Cutting edge technology has made creating these innovative products possible. Savvy marketing is another reason. Most importantly with great products come great science and evidence to support claims of a new product's therapeutic superiority over another. Product makers who recognize the value in engaging in ongoing research are one step ahead in the combination product market. But there are companies developing and marketing combination products that have not yet jumped on the bandwagon of performing laboratory and clinical research.

An all too common problem in the natural products industry is that some companies with formulated, proprietary combination products rely solely on existing published data to make claims, often simply based on the assumption that a mixture works like the sum of the individual components. Such an approach does not sufficiently substantiate or appropriately address the properties of the specific combination product. This can result in combination products that may be ineffective or worse yet, unsafe. Therefore studies, including laboratory research as well as placebo-controlled clinical trials in humans, must be performed when a novel combination product is developed from known pre-existing ingredients. Of course, novel combination products will be developed, and laboratory and clinical studies will be designed based on existing published data on each individual ingredient; however research dedicated to understanding the properties of the novel combination product is absolutely required.

The purpose of this paper is to begin a discussion around this enlightening topic in order to educate our industry on the importance of substantiating the health benefits of novel products with laboratory and clinical research. We will focus on combination products, but

these concepts are applicable to any new health care product. We hope that the recommendation proposed in this paper will become an industry-wide best practice.

The Problem: Substantiating Efficacy with Third Party Data Alone Doesn't Work

Use of borrowed third party data to support the clinical benefits of newly developed combination products is due to the belief that data on individual ingredients sufficiently provides evidence on efficacy for the novel combination product. The problem with this practice is that the published data on individual ingredients does not necessarily substantiate the benefits being claimed for the novel combination product. In addition, data on individual ingredients does not take into account the possibility of ingredient interactions.

Two common assumptions made when borrowing third party data to substantiate a combination product are: (1) the concentration of active ingredients in the combination product is directly proportional to the intensity of the pharmacologic response¹ and (2) when different ingredients are combined, the new combination will produce at least the same, additive or even synergistic pharmacological benefit than that of each individual ingredient. Using such assumptions, natural product marketers believe that substantiation of efficacy is simply based on the sum of the effects of each individual ingredient without fully understanding how these products will work in combination. In reality, such assumptions must be stated as hypotheses that can then be tested with laboratory and clinical research.



The Interaction of Multiple Ingredients In Combination Products: Mechanisms and How to Understand Them

Multi-ingredient interactions: Basic Understandings

Mixing ingredients with known properties and effects can change the properties and effects of those individual ingredients.^{2, 3} Sometimes these changes can be predicted based on previous research and experience, sometimes there are no changes, and other times, unexpected results can arise. In general, ingredient interactions can result in adverse reactions and/or an increase or decrease in the efficacy of any of the components in the mixture. Such increases or decreases in efficacy or adverse reactions can be additive or synergistic (with synergistic meaning a combined effect). Unexpected effects include any properties, either beneficial or adverse, not seen when the ingredients are used separately. The possibility of an ingredient interaction in a novel combination product can also alter efficacy, even when natural ingredients that are considered to be safe and effective are used. Unfortunately, such interactions are not always studied.

It must be noted that for the purposes of this discussion, mixtures should not be limited to just mixing two or more individual components together. Many products use extracts of botanicals; these extracts themselves are complex mixtures of components including phytochemicals, amino acids, antioxidants, hormones, enzymes, various alcohols and alkaloids. Different extraction procedures can result in different concentrations of components. Therefore, even an altered extraction procedure can result in a change in the constituent profile of the final extract.

Additionally, one must also consider the so called inactive ingredients in a mixture. Changes in the inactive ingredients could, although rarely, result in unexpected changes in the active ingredients in the mixture.

Ingredient interactions can result in changes in the efficacy and adverse reactions through a variety of biological mechanisms. Such interactions may result in reactions that are either antagonistic or agonistic. Interactions may alter the activity of enzymes involved in the metabolism or catabolism of the active components of the mixture. There may be changes in the function of transporter proteins that are involved in getting active substances into or out of cells. Or such interactions may just change the structure or availability of the active substances. Therefore, it is critical to understand what the changes in efficacy and adverse reactions are in a clinical setting.

Examples of Changes in Efficacy with Multiple Ingredients in Combination Products

A pair of traditional herbal medicines on the market in Japan, hochuekkito and juzentaihoto, or, more simply, TJ-41 and TJ-48, are used to treat a variety of chronic diseases and ailments including exhaustion, dry skin, restlessness, loss of appetite and post-surgical discomforts.⁴ There is also evidence that TJ-41 and TJ-48 may have a variety of anti-cancer effects, although research in this area is limited at present. In addition, both herbal preparations display properties that appear to activate immune function. Both TJ-41 and TJ-48 are combination products each consisting of 10 herbal preparations each; 5 of the 10 herbal ingredients are common to both TJ-41 and TJ-48. Each of the 10 components of one of the preparations, TJ-48, was studied separately for its ability to activate immune function in the intestinal



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tract of mice.⁵ It was shown that each of the 10 herbal components of TJ-48, when tested separately, was unable to elicit an immune response whereas the combination did elicit a response. This is an example of synergy; the mixture shows an efficacy that none of the separate components had. That research further showed that for the intestinal immune response, only 6 of the 10 components were actually required. Subsequent research compared the efficacies of TJ-41 and TJ-48.⁴ Again, using mice as an experimental model, it was shown that TJ-41 expressed the ability to activate the immune system of upper respiratory mucosal tissue whereas TJ-48 did not. In addition, even though both herbal preparations appeared to work by activating cells of the immune system, TJ-48 appeared to function through activation of macrophage cells, while TJ-41 appeared to function through activation of NK cells. Although 50% of the components of each of the herbal combination products are the same, the medical use and the mechanism of action of each product is different. Thus, each of these preparations is uniquely different in profile and efficacy. And none of these conclusions would have been made without laboratory testing and clinical trials.

A second example is a study that was performed to test the ability of a combination of extracts derived from seven different botanicals to inhibit the growth of prostate cancer cell lines.⁶ The botanicals used were *Scutellaria baicalensis*, *Rabdosia rubescens*, *Panax-pseudo ginseng*, *Dendranthema morifolium*, *Glycyrrhiza uralensis* and *Serenoa repens*. First, each of the seven extracts was tested individually. After identifying four extracts that were most active at inhibiting growth of prostate cancer cells, *S. baicalensis*, *R. rubescens*, *D. morifolium*, and *G. uralensis*, extracts were then tested as two-extract

combinations. The combination of *S. baicalensis*, and *D. morifolium* showed additive to slightly synergist efficacy while the combination of *R. rubescens* and *D. morifolium* was only additive. The remaining combinations showed antagonism; that is, the efficacy was decreased by combining two ingredients that had a common effect individually. Yet combining all four extracts gave the best results. It was concluded that these observations clearly showed the need to test any new combination therapy with actual experimental approaches.

Laboratory experiments and clinical trials are also required when using proprietary extraction procedures to break complex extracts down to its active constituents. This is because certain extraction procedures may compromise the efficacy of those active ingredients. For example, total cranberry extract was much more effective at inhibiting the growth of cultured human cancer cells than any of its isolated fractions representing cranberry sugars, organic acids, total polyphenols, proanthocyanides or anthocyanins.⁷ In this case, taking the total extract apart decreased the efficacy of the remedy. The key to the effectiveness was the synergistic combination of the total extract of cranberry - there was no single active component.

In order to avoid adverse events, clinical testing must always be performed. New product combinations may result in unexpected adverse events – an undesirable side effect or worse, a fatality. The case of *Ephedra sinica*, a traditional medicine used for thousands of years, is a significant example. It is a stimulant with activity on the heart. Ephedra containing multi-component supplements were banned by the FDA due to adverse events.⁸ Had the appropriate clinical trials been performed, adverse events could have been avoided while developing



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proper dosages and ingredient combinations. Such an approach would have required basic clinical trials.

The Importance of Conducting Proprietary Research On Your Novel Proprietary Combination Product

When asked about substantiating health claims, Marc Ullman, Chairman, Legal Advisory Council at Natural Products Foundation and an attorney who represents clients in matters relating to the FDA and Federal Trade Commission said “If you have a single ingredient, you can generally use available research, but for a combination product, if you are claiming that product X does 1, you need to substantiate that product X does 1” and not product X helps promote an activity related to 1. Unless third party data has been thoroughly reviewed, manufacturers cannot assume that data addressing a specific ingredient sufficiently substantiates the efficacy of their specific product. “Borrowed” data leaves too many questions unanswered for proprietary products. However, borrowed data on specific ingredients would allow for companies to “identify common themes and weaknesses [which] will allow them to fill in the gaps with their own research.”⁹ The main question still remains. Will greater therapeutic benefits occur as a result of a combination of ingredients? The answers lie in the pharmacokinetics and pharmacologic effects of the product.

Conclusions

Combination herbal products hold extraordinary promise for their unique ability to show greater efficacy than any of its constituents alone. However, without appropriate laboratory and clinical evidence pertaining to the product at hand, it is impossible for any kind of uniqueness claim to be made. Proprietary

studies utilizing clinical trials would provide the strongest case of efficacy, safety and uniqueness. Research allows efficacy to be verified, dosage and routes of administration to be determined and marketing claims to be made. While third party data can be helpful, it cannot be the sole basis for making claims regarding a combination product, even if that product uses ingredients that have been shown to be effective and safe. Data that refers to a specific product applies only to that specific product, and not all products.

Product or ingredient-specific research is the tool with which companies can build credibility and set their brand apart from competition. It will also help establish such a company as one that truly values science, ethics and integrity. It will help establish long-term success with consumers, retailers and the scientific community. A product is only as good as the evidence to support its efficacy.

We hope that this paper has set a tone for ongoing discussion on this topic and can finally begin to help make company-owned clinical research the “gold” standard for industry.

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