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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0454

To Whom It May Concern:

CFSAN has solicited comments on FDA's pre-market notification for new dietary ingredients (NDIs).

AIBMR Life Sciences, Inc., (AIBMR) is a private R & D and consulting company that has over 25 years of experience in commissioning studies of dietary supplement products and ingredients; possibly more years of experience than any other firm of its nature in the United States.

Over the past 25 years alone, AIBMR has advised nearly 500 foreign and domestic companies in the marketing or distribution of dietary supplements in matters related to scientific substantiation of the safety and efficacy of their products. We have also had to assist clients with product registrations in over 40 countries. AIBMR's technical staff possesses post-graduate degrees in a diverse range of disciplines. Our recent medical director now holds a post in the School of Medicine, University of Washington, and our last research director resigned to accept a post-doctoral fellowship with the National Cancer Institute at NIH. AIBMR maintains one of the largest natural products research libraries in the world, which requires a full time librarian to maintain. Tens of thousands of books, reference works, journals and a much larger collection of published papers, provide staff with ready access to a substantial literature base on ingredients found in natural products beyond the information accessible via Internet databases. This is because the considerable literature on ingredients found in dietary supplements has only recently begun to be included in various databases that researchers rely upon.

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Among AIBMR's diverse range of services is the determination of the product's safety based on assays, nonclinical and clinical studies. AIBMR commissions laboratories around the world to perform GLP or GCP compliant assays, tests and/or clinical studies on ingredients and products submitted to us for independent evaluation. AIBMR has also submitted results of assays and studies it commissioned on behalf of sponsors that have been included in NDI notifications. This experience has provided AIBMR a working knowledge of the challenges in providing information and data for such submissions. We have also reviewed most of the NDI notifications submitted to the agency over the years since the statutes related to the NDI's became enforceable.

AIBMR appreciates the opportunity of commenting on the NDI notification process.

The most serious weakness in the NDI process is the lack of criteria in evaluating a NDI to determine if there is a reasonable expectation of safety. We would suggest that for both the submitter's and agency's benefit, FDA make available models of real or imagined NDI notifications that contains the quality of data the NDI review team would prefer to find in a submission. Such models might include comments by FDA as to why the information submitted would assist FDA in making a determination that the NDI has a reasonable expectation of safety. We realize that such models may not cover the gamut of ingredients subject to NDI reviews, but it would provide valuable guidance on the qualitative aspects needed for successful submissions to help preparers consider if they have adequate information, evidence and data, to submit an NDI so the agency can make a determination of the ingredient's safety.

The statute related to the NDI asks: What is the ingredient? Too many NDI notifications have simply provided the name of the product, thinking that this is what was being asked for. We believe FDA should provide advice in the form of a guidance document that it wants the chemical composition of the ingredient based on a validated analytical methodology that relies on either a published analytical method or is supported by a validation package for that method. It is AIBMR's opinion that a review of a NDI notification cannot be made without FDA staff being able to answer the most fundamental question, namely, what is the composition of the new dietary ingredient to be reviewed. FDA should make it very clear that the rest of the submission cannot be reviewed if this basic information is not provided.

Information about the ingredient being submitted in the NDI should include the chemical name, common name(s) and synonym(s), Chemical Abstract Service (CAS) registry number, if available, along with empirical, structural, and quantitative information. Chemicals manufactured by using genetic bioengineering, such as via the use of genetically modified organisms (GMOs) should not be accepted; they should be subject to review as a drug.

In the case of a botanical NDI, the chemical composition of the ingredient should include the Latin binomial and its known common name(s) and synonym(s). The plant part should be specified and information provided on whether it is harvested from cultivated fields, wild-crafted, or acquired by tissue culture. Botanical ingredients that are derived from genetically modified organisms (GMOs) or whose seeds are bioengineered should not be accepted; they should be subject to review as a drug.

Analytical data should be based on published validated analytical methods or supported by a validation package of the analytical method(s) relied upon. Information on what chemicals are used to grow the botanical, including post-harvest applications and/or storage should be identified. Evidence of a lack of such chemical residue(s) should be provided at the lowest possible detection levels possible by LC/MS or GC/MS.

Based on AIBMR's experience, botanical extracts that are water extracted have been shown to have the least risk of toxicity based on in vitro assays or in vivo nonclinical toxicology studies in animals. Methods of extraction that do not conform to traditional methods of concentrating active components in the botanical should require more rigorous evidence of lack of toxicity. This brings us to the subject of what kinds of information might be included in an NDI notification in order to establish a reasonable expectation of safety.

Currently, FDA provides no guidance on the kinds of toxicology studies it desires reviewing in determining whether there is a reasonable expectation of safety. AIBMR suggests that when toxicology studies are submitted they include genotoxicity, nonclinical toxicology data, drug interaction assays, and preferably human safety data (especially, in the absence of a history of traditional use).

For genotoxicity data, the notification should include either of the following two studies:

- 1) The Bacterial Reverse Mutation Test (AMES Assay). The AMES assay should be performed in accordance with the Principles of Good Laboratory Practice (as revised in 1997), Environmental Directorate, Organization for Economic Co-operation and Development (OECD), Paris 1998. The laboratory performing the test should be certified by a governmental body with the authority to certify such a laboratory. The test system should include the histidine auxotrophic strains of *Salmonella typhimurium* viz., using: a) the TA 98 & TA 1537 for frame shift mutation; b) the TA 100 & TA 1535 for base substitution; and, the tryptophan auxotrophic strain of *Escherichia coli* viz., WP2 uvrA (pKM101) for base pair substitution.
- 2) The L-5178Y +/- Mouse Lymphoma assay. Mammalian cell culture systems can be used to detect mutations induced by substances. One of the most

commonly used mammalian cell mutagenesis system; the L-5178Y TK+/- mouse lymphoma-TK assay detects mutations at the thymidine kinase locus caused by base pair changes, frameshift and small deletions. The mutagenicity of the test agents is indicated by the increase in the number of mutants after treatment.

Nonclinical toxicology tests:

1) Non-clinical toxicology studies should include both the acute and sub-acute toxicity tests in rats, performed in succession, not parallel. Each study should conform to OECD and FDA Title 21 requirements and be performed by a certified GLP laboratory. The test material to be administered should be validated by the laboratory. The laboratory should be provided the method of analysis for the ingredient.

2) The acute toxicity test should be the 14-day limit test. Ten male and ten female animals should be administered the ingredient orally by gavage at a dose of 2,000 mg/kg of body weight (BW). After administering the acute dose on day 1, there should follow a 14-day observation period. Mortality observations should be made twice daily. Daily food consumption should be measured and recorded. A full gross necropsy should be performed on day 15 and the weights for organs determined and reported. Any significant toxicology finding should be evaluated by histopathology. The NDI notification should include the complete signed and certified report from the laboratory, not just a summary page from the report, even if the results of the study have been published.

3) The subacute toxicology study should be of 90 days duration. The study should conform to OECD and FDA Title 21 requirements and be performed by a certified GLP compliant laboratory. In this study, 160 animals should be included in the study, divided into groups of 40 animals (20 of each gender). Three doses and a "zero" dose should be administered daily by gavage, representing a dose that is subacute based on the dose given in the acute toxicity study (limit test). The study should include behavioral assessment, urinalysis, blood analysis, and histopathologies of all organs. Body weight at arrival, on the day of randomization, at weekly intervals and the day of necropsy, should be performed in all animals. Selected validated laboratory tests should be carried out before the initiation of treatment and at certain intervals from blood samples of all animals. Urinalysis should be performed. The NDI notification should include the complete signed and certified report from the laboratory, not just a summary page from the report, even if the results of the study have been published.

Based on AIBMR's experience commissioning dozens of nonclinical toxicology studies on dietary supplement ingredients over the years, we have not found

additional value in conducting chronic toxicity studies performed if both the acute and subacute toxicity studies, done in succession, demonstrated no toxicological findings of significance. This may be because the 90-day sub-acute study in rats represents an allometric equivalent daily exposure of approximately 1.5 human years. The only exception seen has been with products that have historically been indicated for short periods of use (several days) but that are given to animals for much longer periods (months).

In the area of establishing a reasonable expectation of safety, we would ask that FDA consider animal feeding history if the same ingredient or product had been fed over more than several years in monogastric mammals (e.g. pigs, dogs) in allometric equivalents to the amount proposed for human consumption. For example, an animal feed product that has been found to support healthy growth without evidence of adverse effects.

Clinical studies

FDA should consider data acquired in the course of any clinical study to determine the products efficacy if the protocol included a safety panel. Phase-1 pharmacokinetic studies in at least 4 healthy volunteers of each gender (when appropriate), performed under Good Clinical Practices (GCP) compliant guidelines and requirements should be considered in determining a reasonable expectation of safety.

Dietary Supplement-Drug Interactions

It would be difficult to assume that there is a reasonable expectation of safety for an ingredient if the ingredient relies solely on historical use for the simple reason that the vast majority of prescription medications taken today did not exist previously. Human cytochrome P450 (P450), CYP3A4, is responsible for approximately 60% of P450-mediated metabolism of drugs in use today, implicating this enzyme as important with respect to the action, duration, and disposition of agents and their metabolites.

The role CYP3A4 plays in drug metabolism, hepatic and intestinal expression of P450 can mediate the outcome of many agents. The mammalian xenobiotic response is mediated primarily by two broad specific sensors: the nuclear receptors SXR/PXR (human steroid and xenobiotic receptor/rodent pregnane X receptor); and, the constitutive androstane receptor (CAR). SXR/PXR plays a critical role in the regulation of phase I (P450), phase II (conjugating), and phase III detoxifying enzymes, that coordinate and regulate drug and xenobiotic clearance in the liver. SXR/PXR is activated by a diverse group of hormones, dietary compounds (e.g., phytoestrogens), prescription, medicinal herbs (e.g., St. John's wort), and xenobiotics that are all substrates for the SXR-induced

enzyme. To determine if there may be a potential for adverse supplement ingredient-drug reaction, the PXR reporter gene assay is a complementary method to assess the CYP3A4 induction potential of drugs and xenobiotics and should be considered if submitted in the notification as evidence in support of a reasonable expectation of safety.

Thank you for considering our comments.