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Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements

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Introduction

Threshold Enterprises supports the development of more specific GMPs for dietary supplement products. The dietary supplement health and education act (DSHEA) required that FDA develop GMPs "modeled after" those required for foods, recognizing that dietary supplements are a sub-category of food. We believe FDA has stepped beyond this mandate by incorporating requirements for supplements that are beyond those required for pharmaceuticals and by additionally inserting HAACP requirements, two parameters that are clearly beyond the requirements for conventional food GMPs. We understand that FDA has interpreted the term "modeled after" in a manner that justifies their approach. We do not agree with this assertion. The congressional mandate of modeling supplement GMPs after those for food was based on the recognition of the legal definition of dietary supplements as a category of foods and to prevent the implementation of pharmaceutical GMPs that are overly expensive, overly burdensome, and inappropriate for the dietary supplement category. Everyone involved in the passage of DSHEA was aware of this basic premise. However, direct evidence that FDA has not modeled these proposals after either food or drug GMPs and has stepped beyond the congressional mandate is in the basic premise of the proposed regulations; namely:

> specifications must be established for the "identity, purity, quality, strength, and composition (emphasis added) of components, dietary ingredients, or dietary supplements that you receive." Subpart E—111.35(e)(1)

FDA has required that testing of the composition of a botanical be required. Without specific guidance of how FDA is to interpret what constitutes the composition of the 1200+ herbs in trade, this is an impossibility. Nowhere in the drug cGMPs is composition regarding a drug component made.

Conversely, the requirements for drug GMPs are as follows:

> (b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess. § 211.25 Personnel qualifications.

And;

> (2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. § 211.84 Testing and approval or rejection of components, drug product containers, and closures.

There are a number of other sections in which the current proposals were not modeled after either food or drug GMPs and in some cases are more onerous than the regulations applied to pharmaceuticals.

We have a more significant concern. Because the proposed GMPs focus primarily on consistency of manufacturing practices and conformity to internal specifications, rather than the development of independent standards, there is a real potential for these

proposals to have an opposite of their intended effect. By requiring manufacturers to confirm the validity of every criteria that is established as a specification may encourage manufacturers to implement less quality assurance specifications for each ingredient. Also, manufacturers may not have the necessary testing equipment for a desired specification but their vendor of an ingredient may, and the vendor may be able to provide confirmatory data that the specification has been met to the satisfaction of the manufacturer. In these cases, the manufactures has only two choices; 1. Reduce the specification; 2. Incur the added cost of independently verifying the vendor's test findings. Manufacturers should have a third option of determining the validity of the vendor's test through an audit or random testing program. Under the current proposals, some manufacturers will surely choose to reduce their quality assurance specifications to the bare minimum.

We hope the FDA will take note of this and propose corrective actions. Our suggestions for doing so are provided. Moreover, any reliable quality assurance program requires written procedures. The original industry GMP proposal submitted several years ago had significant requirements for written procedures. According to the preamble, FDA stated that the need for written procedures were reduced so as not to place undue cost on manufacturers. Developing written procedures is a necessity and among the least costly of all the procedural requirements that FDA has proposed. Moreover, written quality assurance procedures are already in place throughout most of the industry. Therefore, we support the recommendations of the American Herbal Products Association regarding the need for written procedures.

111.3 Microorganisms

The issue of microorganisms raises significant issues with regards to botanical raw material quality but is not a significant issue regarding nutrients. Microorganisms are a natural part of the ecology of all natural products. Certain levels of microorganisms are to expected and many do not present a public health risk. This is acknowledged in the preamble of the proposals. However, it has been proposed that the presence of non-pathogenic microbes that do not present a public health risk represents a "sanitary"

concern that would render a dietary ingredient adulterated. This is inappropriate for a number of reasons. As noted by FDA in the preamble:"

> "…E. coli O157:H7 would be a ``microorganism" because it is a species that has public health significance. Other forms of E. coli, however, might not be of public health significance because not all forms of E. coli are pathogenic and present a public health risk. However, the presence of other forms of E. coli would be of sanitary concern."

It is clear that all food products (e.g. dietary supplements) must be free of pathogens to be sold. This is inherent in the definition of what constitutes a food. There should be little concern with the presence of microorganisms that present no public health consequence purely for "sanitary" reasons. These can be part of the plant naturally or be introduced through organic cultivation techniques. No restriction should be imposed if there is no health consequence there should be no requirement for a product to be "sanitary" as described.

Perhaps more importantly, dealing with unsanitary product within this context requires some type of sterilization technique. Currently, ethylene oxide (ETO), a known carcinogen and mutagen, autoclaving, and gamma-irradiation are the three primary techniques available for reducing microbial loads in plant material. Both ETO and irradiation cause considerable degradation of numerous compounds. Also, in some cases, botanicals exposed to ETO can absorb as much as 15% extra weight in gas. ETO is also a significant environmental concern whose use has been banned in most European countries. There have been similar proposals to prohibit its use domestically. This may eventually constitute a trade infringement under GATT as products treated with such sterilization techniques will not be acceptable to the European Union.

Gamma-irradiation is only allowed for those products that have been specifically approved for such treatments. Moreover, neither of these two options are considered desirable for the natural health product consumer. Autoclaving is safe but can cause

significant degradation of valuable compounds, especially those that are volatile and is therefore not appropriate for a large number of dietary ingredients.

As noted, FDA has cited USP as an official reference standard for supplements. USP currently proposes an upper limit of 10,000 cfu/g total plate count for botanical supplements. We believe this is reflective of USP's orientation of drug products which are generally sterile versus natural products which have naturally high microbial loads For a botanical ingredient, such a standard can only be attained through aggressive sterilization. Also, these requirements are not consistent with international standards established for botanicals by the European Pharmacopoeia and WHO. The standards of both organizations are more realistic and reflective of natural products (see below). We do not propose that these be established. We only present them as an example of more realistic standards that exist for plant products.

Table 1 Microbial standards of European Pharmacopoeia and World health Organization

Organization	**Euro Pharm**		**WHO**		
Plant Material	Boiling water is added before use	Boiling water is not added before use	Untreated crude	To be pretreated (tea)	For internal use
Total aerobic microbial count	10^7	10^5		10^7	10^5
Yeast & mold	10^5	10^4	10^5 (mold propgules)	10^4	10^3
enterobacteria		10^3		10^4	10^3
Bile tolerant gram negatives					
E. coli	10^2	absent in 1 gm	10^4	10^2	10
***Salmonella* spp**		absent in 10 gm		none	none
Staphylococcus aureus					

Also, a number of processes such as through alcohol or solvent extraction or application of heat, can result in a significant reduction in microorganisms. Therefore, a dietary ingredient may be considered not to be "sanitary" within the meaning of this rule but, with appropriate processing, the microorganisms can be reduced or eliminated completely from the end product.

The guiding principle regarding the presence of microrganisms and requirements for their reduction should be based on those that create a public health hazard or can result in a degradation of the product to a degree whereby the ability of it to fulfill its claimed use is compromised.

111.3 Sanitize

It is unrealistic to require a 5-log reduction in surfaces which are already clean in which a 5-log reduction is not attainable.

111.6 General Provisions—Exclusions

We understand that it is proposed that handlers of raw material ingredients be exempted from these GMPs. This requires some clarification of what constitutes a raw agricultural supplier. Every farmer and wildcrafter has to process the botanical in some manner, predominantly by washing, drying, and basic size reduction for shipping purposes. While we acknowledge that the entirety of the proposed GMP procedures are not applicable to farmers and wildcrafters, we disagree with the idea that there should be no requirement at all. We believe a modified set of GMPs or guidance documents that focus on those areas specific to the harvest, cultivation, identification, and handling of raw agricultural materials be required. It is at this point in botanical commerce where there is the greatest control over identity, purity, and quality and the greatest potential for problems to occur. It is also precisely at this point where the declaration of certificates of analyses is given greatest validity. If the identity, purity, and quality can be assured at the stage of harvest and initial processing then the potential for problems associated with adulterations, contaminations, and substandard quality in the supply chain is greatly reduced.

111.12, 111.13, 111.15, 111.50 Quality Assurance Personnel

In outlining the requirements for quality assurance supervisors and personnel it is stated that employees must be "qualified by training and experience. In the herbal products industry, there are no fields of academic study that train individuals to be herbal product manufacturers. Therefore, there is no appropriate training that would qualify someone for such a position. There is academic training that can partially serve for herbal products quality assurance personnel, such as graduates of biology or chemistry programs. However, academic training specific to herbal products manufacturing is lacking. Training of personnel by those experienced with herbal supplement manufacturing processes is the primary means for obtaining the training and experience. Perhaps more relevant, these proposals are more burdensome than the requirements for pharmaceuticals, the GMPs for which state:

> "Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, **or any combination thereof**, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess." (Part 211, Subpart B, §211.25(b))

The FDA should remember that the dietary supplement industry is predominantly dealing with substances such as Vitamin C and American ginseng, whereas the pharmaceutical industry is dealing with morphine and digoxin. We believe there is no justification to require more burdensome guidelines for dietary supplement personnel than is considered appropriate for pharmaceutical manufacturers. We would appreciate a response from FDA regarding this disparity. Throughout the GMP proposal, this requirement should be consistent with the drug requirement as follows: " must be qualified by training or experience, or any combination thereof…"

111.35

Under subsection (d) the proposals seem to imply that excipients cannot be used without prior sanction of the substance. There are numerous excipients that have been used in food, supplement, and drug products that do not meet the criteria listed but have generally been accepted for use in food products for decades. This requirement should be stricken.

111.35(e)(1) Subpart E—Production and Process Controls: Specifications

The proposals explicitly state that specifications must be established for the "identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive."

As noted, there is a fundamental flaw in this requirement. First and foremost is that it has no precedent in either food or drug GMPs as stated previously in which composition is not a requirement of either food or drug GMP. Secondly, from a very practical perspective, the composition of the 1200+ botanicals in trade will be impossible to determine in an economically feasible manner. Such testing will clearly distort FDA's economic impact estimates more than they are already as will be discussed.

Such requirements may be appropriate for single entity, purified drug compounds where the quality, strength, purity, and compositional standards are outlined in official compendia as the legally mandated "quality" which is required to be met in order for the drug to be sold. These requirements may also be appropriate for the majority of isolated nutrients which can easily be tested according to these same parameters. However, it is not appropriate for botanical dietary ingredients which consist of multiple compounds, for which there is no specifically defined "strength" or "composition", and for which "quality" is relatively subjective.

If all of these aspects (identity, purity, quality, strength, and composition of components) are required for all ingredients, more explicit guidance is needed. For example, it is clear that identity tests must be performed in order to ensure the claimed ingredient being marketed is in fact the authentic material. Similarly, objective standards for purity are realistic; there is already a legal mandate for the product to be free from pathogens or

adulterants that would render the product unsafe or ineffective for the intended use. However, a determination of what constitutes "quality", "strength" (unless a strength is declared), and composition will differ from product to product.

Regarding quality, what is the specific quality marker of a dietary ingredient of St. John's wort? For many years to present, hypericin has been categorized as a good qualitative marker for St. John's wort, despite the fact that it is not generally considered to be correlated with clinically relevant pharmacological activity. In reality it is still a good qualitative marker, in the opinion of many. Others have suggested hyperforin and a multiple of flavonoids to be more appropriate markers based on a demonstration of pharmacological activity for these compounds. Testing of all of these would be cost prohibitive and may not yield any more meaningful information regarding its quality than analysis of one of these.

Regarding composition, the St. John's wort monograph of the American Herbal Pharmacopoeia reports a total of approximately 40 different compounds making up the composition of St. John's wort not including the analysis of the essential oil which contains numerous other compounds. What composition profile is enough for FDA? Similarly, on which component is "strength" to be based?

Threshold Enterprises manufactures a range of products from single herbal ingredients with no claimed characterization to highly characterized products. In the case of single herb ingredients and ingredients used in multi-ingredient formulas, our specifications primarily focus on identity and relative quality based on organoleptic analysis, with additional requirements for microbial loads, heavy metals, etc. However, as no "composition", "quality", or "strength" of the ingredient is claimed, this is not part of the ingredient specification. We utilize more than 100 botanical ingredients in our products. Guidance will be needed as to what FDA expects in terms of establishing quality, strength, and composition criteria of these ingredients plus the other 1000+ on the market.

As guidance, the proposal cites the United States Pharmacopoeia and AOAC international as examples of officially accepted reference standards and methods. Neither source provides complete compositional information for St. John's wort, nor do they provide testing methodology for all of its components. USP has approximately 60 monographs encompassing only 20 botanical ingredients. To our knowledge, AOAC provides no such guidance and is rather focused on the validation of analytical methods. While AOAC may be a good source for methods, the analysis of a single compound, no matter how good the method, will not fulfill the criteria for determining identity, purity, strength, quality, and composition of a botanical ingredient, or the requirements of FDA. American Herbal Pharmacopoeia monographs contain detailed information about what constitutes a "quality" botanical. However, the lack of guidance by FDA in defining these parameters leaves manufacturers guessing as to how "quality", composition", and "strength" are to be discerned even when such information is available.

Therefore, we recommend for the language to be amended as follows: "that specifications must be established for the "identity, purity, quality, strength, **and/or** composition of components, dietary ingredients, or dietary supplements that you receive, **as are appropriate to meet the claimed specifications."** alternatively; because the terms "quality", "strength", and "composition" are completely subjective with respect to botanical ingredients for which no claimed potency is made, these should be stricken. This would leave identity and purity as the primary requirements for dietary supplements, a requirement that is consistent with GMPs for foods, from which these GMPs should have been modeled. Neither of these recommendations lessen the quality assurance requirements. If a strength is claimed as part of a specification or finished product, then the manufacturer is legally accountable for the statement to be true.

Additionally, we believe that further guidance as to what constitutes an official or scientifically valid standard is appropriate. We currently utilize a variety of official and non-official sources for the development of internal specifications including but not limited to:

American Herbal Pharmacopoeia
Ayurvedic Pharmacopoeia
British Pharmacopoeia
British Herbal Pharmacopoeia
European Pharmacopoeia
Japanese Herbal Medicine Codex
Japanese Pharmacopoeia
Pharmacopoeia of the People's Republic of China
United States Pharmacopeia
World Health Organization

There is a tremendous advantage of being able to utilize a variety of different sources of information for the development of quality control specifications. Each organization or monograph system has strengths and weaknesses, various bodies of information, and different areas of application. FDA has confirmed the validity of using internally developed analytical methods. We support the right to be able to utilize whatever methodology is deemed most appropriate for the analytical endpoint. However, complete non-specificity of what constitutes a scientifically valid standard leaves the appropriateness of our specifications open to question by inspectors. For purposes of macroscopic, organoleptic and chemical assessment, the monographs of the American Herbal Pharmacopoeia, European Pharmacopoeia, and United States Pharmacopeia have been most useful.

111.35(i)(4) Reprocessing

There are a number of cases in the manufacture of botanicals in which reprocessing procedures are appropriate. For botanical raw materials, a specification for foreign organic matter may be set at 5%. A received sample may be initially rejected if foreign organic matter is in excess of 5%. However, it is often very easy to sift the foreign material in a manner so as to meet the desired specifications. This may be the decision of the quality assurance unit and it is an appropriate decision as the quality of the material is not negatively affected in any manner. Similarly, there are some specifications, such as

with cranberry fruits, where there are US Department of Agriculture (USDA) standards for the number of "defective" fruits that can be used in a batch. Material initially rejected based on general QC standards can be subsequently sifted if it is determined that it is the most appropriate course of action.

California-based companies have a particular challenge in this area due to Proposition 65 requirements. Reprocessing techniques can be applied to reduce the heavy metal burden of raw material that is initially in excess of Prop 65 limits, which are much lower than most national and international standards. In these cases, reprocessing techniques can include extraction in which the relative percentage of heavy metals is reduced to acceptable limits. There may also be extraction processes that precipitate lead specifically, again bringing raw material in compliance. GMPs should allow for reprocessing when reprocessing is appropriate to bringing the ingredient into compliance.

111.35(k) Testing for Contaminants

This section requires that supplement ingredients be tested for any substance that "may (emphasis added) adulterate or lead to adulteration." The ability to control this with single chemical entities is relatively easy. However, this is almost impossible and unrealistic for natural products such as botanicals. With natural products that are obtained from virtually any sector of the world, by any number of individuals, under an infinite number of conditions, and then transported tens-of-thousands of miles across the world, appropriate guidance for doing so will be needed from FDA. An infinite number of substances may adulterate a botanical product and what they all may be is completely unpredictable and can not be tested for.

FDA has to also recognize that the presence of a toxin in certain amounts may not pose a health hazard. In the preamble, FDA made an example of mycotoxins as potential contaminants of botanical ingredients stating that these should be tested for. Ochratoxin is present in many common foods that are consumed at much greater levels on a daily

basis for extended periods of time than are botanical supplements. In this regard, the principles of renowned toxicologist Kingsbury should be used as a guiding post;

> "In order for a plant to be functionally poisonous, it must not only contain a toxic secondary compound, but must also possess effective means of presenting that compound to an animal in sufficient concentrations, and the compound must be capable of overcoming whatever physiological or biochemical defenses the animal may possess against it. Thus the presence of a known poison principle, even in toxicologically significant amounts, in a plant does not automatically mean that either man or a given species of animal will ever be effectively poisoned by the plant." Kingsbury JM, The Problem of Poisonous Plants (1979).

According to the Canadian Food Inspection Agency, it has been estimated that as much as 25% of the world's food production is contaminated with mycotoxins yet they do not always constitute functional toxins. Similar findings have been reported by European authorities (European Commission Regulation (EC) No. 472/2002. *Official Journal of the European Commission*. 16.3.2002; L75/18–L75/20.)

Maximum allowable levels of such commonly occurring food toxins have been established for numerous food and botanical ingredients. Should such contaminants be found to commonly occur in foods or dietary ingredients, then appropriate maximum allowable limits should be established for these. FDA should acknowledge that the presence of a small amounts of such contaminants may not be avoidable and may not pose a significant public health risk.

If there is a requirement to test for all substances, such as mycotoxins, that may adulterate dietary supplement ingredients or products then identical requirements will also need to be imposed on conventional food products, especially those known to commonly contain mycotoxins (coffee, wine, beer, soy beans, raisins).

A more appropriate requirement would be to test for contaminants that are likely to contaminate a botanical ingredient. For example, it has been reported that mycotoxins may be present in botanical ingredients such as licorice, turmeric, soy beans, and ginger. Therefore, if such a contamination is common or frequent , mycotoxin testing may be an appropriate requirement for these commodities. Similarly, there are common plant adulterations that occur on the market and are widely known, such as the adulteration of skullcap (Scutellaria lateriflora) with the potentially hepatotoxic substance germander (Teucrium spp); Siberian ginseng—Periploca sepium; Stephania—Aristolochia spp. Such adulterations are predictable and therefore appropriate as part of a specification. However, to require testing for any potential contaminant that may contaminate or lead to the adulteration of a product is a virtual impossibility and must be reconsidered within the context as discussed.

111.37(ii)170.35 In Process Controls

Subsection (f) discusses the need for in process controls to ensure specifications are met. Unless we are not understanding the meaning of this section, it is often impossible to establish in process controls to ensure finished product specifications are met. This is especially true for the manufacture of liquid extracts whose specifications are not met until the processing time is complete. It is possible and pertinent to require a manufacturing process that maintains the integrity of the process itself, but it is not relevant to have in process testing to ensure a specification is met for a product that is not yet done processing. There is similarly no reason to require that a retention sample of an unfinished product.

Subsection (g)(2)(i) states that every batch of components must be tested. In many cases, this is unnecessarily redundant and is also a more burdensome requirement than is applied to drugs in which skip lot testing according to specific parameters is allowed (see below; 21 CFR 211.84 of drug GMPs). As noted, the dietary supplement GMPs were to be modeled after food GMPs specifically so as to not impose unnecessary and inappropriate GMPs to the dietary supplement sector. Some consumers are dependent on their pharmaceutical medications for their very lives. Per the mandate of DSHEA, dietary

supplements are used to promote general well-being. If skip lot testing is appropriate for pharmaceuticals, they are more than appropriate for dietary supplement products. There appears to be no justification to impose standards for dietary supplements that are more restrictive than those required for drug products. Skip lot testing within specific guidelines should be allowed. Similarly, if adequate controls are in place including review of documentation that the dietary ingredient meets its claimed specification; or through supplier audits and random testing, this should be acceptable. Moreover, there is a tremendous amount of redundancy in these proposals as it appears that everyone along the chain of custody is expected to perform the same tests. Therefore, after implementation of GMPs and appropriate enforcement, there should be greater confidence in a manufacturer's or vendor's certificate of analysis. Notwithstanding, the manufacturer or marketer must be fully accountable for all statements made in the marketing of their dietary supplement whether such criteria are spelled out in the GMPs or not.

111.37(11)(ii): This section goes even further to suggest that in process retention samples should be taken. This is completely irrelevant for processes, such as the manufacture of liquid extracts and dry extracts in which the specifications are not met until the process is completed. Again, FDA is being redundant in its testing requirements.

Subsection (g)(2)(ii): Requires in process controls for meeting the specifications of master control records. Again, as discussed, in some processes this requirement is impossible to meet.

111.37(12): Reserve samples: The retention time requirements for samples should be based on the nature of the product. A 3-year retention requirement for a product with a relatively high level of instability, such as in a probiotic products is irrelevant.

11.40(2) Certificate of analyses: We believe that certificates of analyses can be relied upon if there are guidelines for ensuring the accuracy of the stated findings. We believe that processes by which the declaration contained within certificates of analysis can be

confirmed through random testing, vendor audits, and/or receipt of independent documentation of compliance. This is yet another area where FDA has chosen to impose more burdensome restrictions than those applied to food and pharmaceutical products as follows:

Section §211.84(d) of the drug CGMP states:

"(d) Samples shall be examined and tested as follows:

At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals." (emphasis added).

There appears to be no justification as to why a certificate of analysis is acceptable for a cardiovascular medication or potentially life-saving chemo-therapeutic drug but not ginseng. We would appreciate an FDA response regarding this disparity. In imposing more burdensome regulations to dietary supplements than are required for drugs, we believe FDA again has not followed the Congressional mandate of modeling these guidelines after food GMPs. Minimally, the same allowances for skip lot testing that is applied to drugs should be applied to dietary supplements.

111.45 Expiration Dating

We support the FDA's decision to remove the expiration dating requirement from the GMP proposal.

111.50 In past communications: FDA has asserted that all declared yields of dietary ingredients in a supplement product must be at 100% of the claimed amount. This is a physical impossibility with the majority of supplement products, especially for botanicals

which are inherently of uneven consistency, density, and particle size, and is not even a requirement for pharmaceutical products. FDA should allow for the same variabilities that are allowed for food and pharmaceutical products.

111.85 Returned products: if a returned product of intact and shows no sign of mishandling and is within the time limit established by the expiration or 3 years from the manufacturing date there should be no reason to perform additional testing.

111.90 Distribution of dietary supplements: All products are subject to a certain level of deterioration from the moment they are made. There is already a legal requirement for products to conform to label claims. Dietary supplement products are typically shipped through normal shipping channels as are other dry goods including foods and many pharmaceuticals. It is not practical to expect that all distribution channels can be controlled any more than is reasonable for other product categories. This paragraph should be stricken.