Rec'd in DMB
8/11/03

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8/7/03

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on Proposed Rule- Current Manufacturing, Packaging, or Holding Dietary Ingredients and Dietary Supplements (49 F.R. 12158)

Dear Karen Strauss and FDA Committee:

J.R. Carlson Laboratories, Inc. is a family owned business with about 80 full time employees, which has been in operation since 1965. We formulate and market approximately 260 dietary supplements to consumers, pharmacies, physicians, and international accounts.

While we agree that a Good Manufacturing Practice regulation should be implemented for dietary supplement products, we are confounded by several proposed provisions that we believe need clarification and disagree with other provisions.

Impact of Proposed Regulation on Small Businesses

In the proposed regulation the Agency states that, "Our intent is to provide the proper balance of regulation so that dietary ingredients and dietary supplements are manufactured in a manner to prevent adulteration using recognized scientific principles and both industry and consumer expectations that are reasonable and appropriate."(49 F.R. 12161). As discussed below, we believe that certain provisions of the proposed regulation are not balanced and based on reasonable and appropriate expectations. The impact of regulations that are not reasonable and based on an appropriate cost/benefit analysis will have a devastating effect on small businesses. For example, the cost of testing incoming material and finished product is the same regardless of the quantity received and/or produced. A company producing five million tablets of a product will spend the same amount in testing as a company producing ten thousand tablets. Of course, the cost per tablet will be far greater for small businesses that produce less and can result in the destruction of the ability of small businesses to effectively compete in the marketplace. Thus, it is extremely important for the Agency to provide a thorough cost/benefit analysis of all proposed provisions.

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The Law

Pursuant to Section 402(g)(2) of the Federal Food, Drug and Cosmetic Act (FDC Act), any regulation prescribing good manufacturing practices for dietary supplements must be "modeled after current good manufacturing practice regulations for food and may not impose standards for which there is no current and generally available analytical methodology." We do not believe that the Agency has complied with either of these requisites, and thus, has exceeded the authority provided by Congress.

Pursuant to 402(g)(2) of the FDC Act, whatever GMPs are established for dietary supplements must be modeled after food GMPs. To determine what Congress meant by the term "modeled", the Agency looked at Webster's II New Riverside University Dictionary. It appears the FDA had exhausted all other available resources in relying on the Riverside University Dictionary to support its overly broad interpretation of the word "modeled." According to the Agency, the term "modeled" should be interpreted as "[a] preliminary pattern serving as the plan from which an item not yet constructed will be produced."(49 F.R. 12165). Therefore, according to the FDA, Congress intended that the Agency use the food GMPs as a "preliminary pattern" for the dietary supplement regulations. The Agency then proceeds to liken dietary supplements to drugs and concludes that, because dietary supplements are more like drugs then foods, it must include GMP provisions that appear in the drug GMPs even though no parallel provision exists in the food GMPs.

We believe the FDA has adopted an overly broad definition of the term "modeled" in an effort to justify the legality of imposing dietary supplement GMP provisions that do not exist in the food GMPs. Widely used and authoritative dictionaries yield different meanings to the term "modeled". For example, the New Oxford American Dictionary, defines the term "modeled" as "an example to follow or imitate...an example to copy"(2001, p. 1097). The Merriam-Webster's Collegiate Dictionary, 11th Edition, defines the term "modeled" as "to plan or form after a pattern...to produce a representation or simulation of."(2003, p.798).

In the preamble to the proposed regulation the Agency states that GMP regulations for dietary supplements may include provisions that were not in food GMPs at the time DSHEA was enacted.(49 F.R. 12167). We disagree with the Agency's interpretation. If we were to accept the FDA's interpretation, there would be no limits on what GMP provisions the Agency could impose for dietary supplements. For example, records are not required under the food GMPs, various production and process controls that appear in the proposed regulation do not appear in the food GMPs, and consumer complaints are not required to be maintained under food CGMPs. By including the language "modeled after current good manufacturing practice regulations for food" Congress obviously intended that the Agency not impose overbearing Good Manufacturing Practices that

exist for drugs, but rather that good manufacturing practices for dietary supplements closely resemble those that exist for foods.

In the preamble to the proposed regulation the Agency states, "[i]n developing proposed GMPs for dietary supplements, we relied on the basic concept underlying the food CGMPs and the proposed dietary supplement CGMPs is the same: To establish regulations that will help ensure that your practices for preparing, packaging, and holding dietary ingredients and dietary supplements do not result in an adulterated food entering interstate commerce."(49 F.R. 12167). Under the FDC Act, however, the Agency is required to "model" GMPs for dietary supplements after food GMPs, and simply relying on the "basic concept underlying food CGMPs" does not comply with congressional mandate.

The Need for the Rule

We welcome and encourage the FDA's issuing GMP regulations for dietary supplements that are based on reasonable needs and an appropriate cost/benefit analysis of their usefulness. Appropriate GMPs will better ensure that a product has been manufactured in a clean and sanitary facility using Good Manufacturing Practices that will, in turn, increase both consumer confidence and possibly consumer safety. Consumers will be able to purchase a dietary supplement and know that the product contains the ingredients as listed on the label.

However, it is imperative, especially from the standpoint of small businesses, that any regulations imposed be reasonable and based on appropriate cost/benefit analysis. The benefits of the regulation must justify the cost. Extremely overbearing regulations ultimately result in significant additional finished product costs, particularly for small businesses, with sometimes little or no benefit to the consumer. Only regulations that benefit the consumer, while concomitantly outweighing resulting increases in production and finished product cost, should be mandated.

Also, it is imperative that any rule that is adopted is followed by the industry and equitably enforced. If certain companies chose to ignore the finalized GMPs, or chose only to comply with certain GMP requirements but not others, then companies that comply with the regulation will be at a severe economic disadvantage due to the increase in cost of production. This is particularly true for small businesses whose cost of production per tablet will be significantly greater than large companies that produce a greater number of tablets. Moreover, the final rule that is adopted must clearly set forth GMP requirements. Ambiguities in interpretation may also result in a tremendous economic disadvantage for small businesses, thereby affecting their ability to compete. Large companies with in-house legal counsel and/or large legal budgets may be more liberal in interpreting ambiguous provisions because they can afford to defend their positions if challenged by the FDA. Small businesses, on the other hand, must be more

conservative with their resources, and therefore, more conservative in interpreting ambiguous provisions of the regulations.

Dietary Supplements are Safe

From 1983-2001 only 106 deaths were attributed to dietary supplements, and most of these were caused by one company that improperly manufactured L-tryptophan. During this same period, 11,861 died from consuming prescription and OTC drugs. While the Agency provides numerous examples of dietary supplement adulteration that has taken place over the years, the fact remains that dietary supplements rarely cause bodily injury or harm, and the Agency must take that into consideration when engaging in cost/benefit analysis of the proposed rule. In the preamble to the proposed regulation the FDA likens dietary supplements to drugs, stating that "[d]ietary supplements...contain ingredients that are consumed in very small quantities", and that "[s]uch ingredients are more "drug-like" than "food-like"...because very small changes in strength, purity, or quality of the ingredient can have significant, and possibly adverse, health consequences to those who ingest it."(49 F.R. 12166). We disagree. Dietary supplements contain dietary ingredients such as vitamins, minerals, and amino acid and are not drugs.

While certain dietary ingredients, such as certain plant products or certain animal products, may raise particular purity or composition issues, this certainly does not justify the imposition of overbearing GMP regulations for the entire industry. Where particular problems or issues exist for particular ingredients or types of ingredients, then the FDA may be justified in imposing more stringent GMP regulations for those ingredients. However, it is not reasonable, nor an appropriate application of cost/benefit analysis principles, to identify limited problem areas and use those to justify the imposition of excessively stringent requirements industry-wide.

In the preamble to the proposed regulation the Agency expresses its support for a broad GMP regulation as opposed to multiple regulations focused on particular segments of the industry.(49 F.R. 12174). The FDA should reconsider whether such a broad approach satisfies reasonable and appropriate cost/benefit analysis.

Costs of the Rule

The proposed dietary supplement GMPs will have a profound economic impact on every company in the industry. Proposed GMPs estimate an average cost of analysis of around $110 per product. This figure is grossly underestimated. Our company's average costs per product are about four times as much. Actual product analysis tests often cost $2,000-$3,000 per batch for multiple-ingredient supplements.

The model estimates a first year increase in costs (per small establishment) of $99,000 and $66,000 each additional year thereafter. A company with over 250 products, and

multiple batches per year, would see an increase in laboratory costs alone that grossly exceed these figures.

Unreasonable and redundant product testing will likely result in a price increase for raw materials (since supplier must test) and an increase in the cost of producing finished products. This increased cost of production will have particular detrimental effect on small businesses that produce fewer pills per batch. The increased cost of production may force some small dietary supplement companies to go out of business, while others will have to increase their prices to stay in business. Small businesses may no longer be able to compete with larger companies that can better absorb the costs due to their greater output.

Requiring testing of all incoming material as well as testing in-process or finished batch testing is a commendable endeavor. However, if testing for every batch of every product is to be done for each established specification (as provided in §111.35 and §111.40), at all three control points (receipt, in-process, and finished product), the cost to each sector of the dietary supplement industry would be prohibitive. The costs could not be absorbed by the firms affected and would have to be passed on from firm to firm starting with the supplier and ending with the distributor and finally the consumer. Also, as discussed herein, consumers would benefit very little if at all from such redundant testing. Therefore, cost/benefit analysis would dictate that such redundant testing not be required.

Of particular concern are the costs that would be incurred by firms, especially small firms, that market many dietary supplements with multiple ingredients, each of which would have to be tested for each ingredient. For example, Carlson markets approximately 260 products, of which about 15% have multiple (5 or more) ingredients. Of these, about 10% have 10 ingredients or more and about 5% have 25 ingredients or more. Some of these products are produced as often as once a month. Currently, Carlson conducts extensive testing of finished product and raw material upon receipt as well as long-term stability testing, well in excess of $100,000 per year. This testing includes comprehensive testing of every ingredient of every new product shipment received, every ingredient of every product received from a new supplier, every raw material shipment received, every shipment of vitamin E products for potency and natural-source vitamin E, skip lot testing of fish oil shipments for potency and absence of contaminants and heavy metals, lead tests of all products containing significant amounts of calcium for compliance with California Proposition 65 as well as spot checks, as needed, for the remaining products. Some of these tests can cost as much as $3,000 per test, especially for multiple vitamin-mineral ingredient products and fish oils.

If the proposed rule were adopted, the volume of testing required would increase significantly, even though we already test extensively, as would the testing costs. The testing costs for each batch of each finished product plus raw material products would be, according to our calculations, well in excess of $600,000 per year.

Also, if certain suppliers are put out of business, some products will no longer be available. In such a case, not only will companies lose product sales, but consumers will no longer be able to purchase products that are beneficial to their health.

Also, there is a possibility that suppliers/vendors will no longer be able to manufacture products or raw materials as required. This will result in packagers, distributors and manufacturers having to find new vendors and incurring the cost for new packaging and label materials. Also, some suppliers may have longer lead times for their products due to the requirements imposed by the regulation. This may result in unavailable products, backorders, and ultimately, lost sales.

It does not appear that the FDA has fully evaluated the total cost impact on the dietary supplement industry, particularly small businesses. Loss of suppliers and loss of consumer products and product sales are not clearly addressed.

Comments concerning proposed §111.35- What production and process controls must you use?

Pursuant to proposed §111.35(e), manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements (but not labelers, which are not included in the definition of "You") are required to establish "specifications" for identity, purity, quality, strength, and composition of: (1) dietary ingredients, dietary supplements and components received, (2) in-process controls, where necessary, (3) the finished product, and (4) labels and packaging.

Pursuant to proposed §111.35(g), manufacturers, packagers, and persons who hold dietary ingredients and dietary supplements must test or examine dietary ingredients or dietary supplements to ensure that each of the specifications established under §111.35(e) are met. According to the Agency, there is some flexibility here. Manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements are required to test each finished batch for identity, purity, quality, strength, and composition if there is a scientifically valid analytical method available to conduct such testing. If there is no scientifically valid analytical method available to conduct such testing, then manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements must test each shipment lot of components, dietary ingredients, and dietary supplements received, as well as perform in-process testing where control is deemed necessary. Testing simply the finished product, or alternatively, testing incoming material and in-process, does not satisfy the requisite that compliance with "each specification" must be ensured through testing or examination. The term "each specification" would mean testing must take place on material received, in-process, and on finished product. The Agency should clarify its position.

We believe that testing for all components, including excipients, is unnecessary. Any ingredient that is not a dietary ingredient is subject to the food additive provisions and may only be added if it is GRAS on the subject of a food additive regulation. Further, the function of excipients is for physical properties during processing such as flowability, and they generally present no safety or efficacy concern in the finished product. Testing of such components would confer no benefit to the consumer, and therefore, testing such ingredients fails the cost/benefit analysis.

If the Agency disagrees, we believe that manufacturers should only have to test for one or two ingredients in the finished product. If those ingredient tests meet specifications then it is reasonable to infer that the product as a whole meets specifications. In an ideal world, for consumer confidence one would test for every single ingredient. However, this ignores cost/benefit analysis.

Pursuant to §111.35(h), manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements are required to use an appropriate test (scientifically valid analytical method) or examination to determine whether specifications are met. The same comment discussed above would be applicable to this section. The Agency must clarify whether it is requiring testing on all material received, in-process controls, the finished product, and labels and packaging, or whether it is only requiring finished product testing, or alternatively, incoming material testing and in-process testing.

Another issue is raised by §111.35 that requires clarification on the part of the Agency. Suppose a packager/labeler receives a multi-ingredient finished dietary supplement product for which there is no scientifically valid analytical method for chemical analysis testing for the identity, purity, quality, strength, and/or composition. The packager/labeler cannot test (other than perhaps organoleptic analysis) either the "finished batch" or the incoming material. In other words, it is unclear from the proposed regulation how a packager, labeler/distributor could conduct testing of component ingredients if all the firm receives is the finished product which cannot be tested if a valid method is not available. Complicating matters further is the fact the Agency has stated that it will not accept the supplier's certification in lieu of testing for each shipment. We can only assume that under 402(g)(2) of the FDC Act, no testing would be required (other than perhaps organoleptic analysis) on the part of the packager/labeler. We request clarification from the Agency on this point.

It should be noted that while a specific scientifically valid method may be available to perform a test, that test may not be feasible for use in all cases. For example, there is a scientifically valid analytical method for testing chondroitin sulfate. However, a method has not been published, to the best of our knowledge, for extracting chondroitin sulfate from bovine cartilage. As a result, chondroitin sulfate cannot be tested in bovine cartilage products. We assume that under 402(g)(2) of the FDC Act no testing would be required in this instance. We request clarification on this point.

In the preamble to the proposed regulation the Agency expresses its position that manufacturers may not rely on supplier's certification to determine that an ingredient is what it purports to be and is not adulterated in lieu of performing testing on each shipment lot of components, dietary ingredients or dietary supplements. In explaining its position the Agency simply states that, "it is possible that a supplier's certification or guarantee may not ensure the identity, purity, quality, strength, or composition of a component, dietary ingredient or dietary supplement."(49 F.R. 12198). While we do not deny that it may be possible that a supplier's certification may be inaccurate, the FDA has provided no evidence that this is a prevalent problem in the industry. The FDA instead cites to the *D. lanata* contamination case. As previously stated, if the FDA identifies a specific problem with a specific dietary ingredient or type of dietary ingredient then imposition of more stringent GMP requirements may be justified. However, to cite to one example of contamination to justify the imposition of overbearing testing requirements and rejection of a reasonable request for the FDA to accept supplier's certification in lieu of testing is unreasonable and ignores appropriate cost/benefit analysis. In Carlson's personal experience Certificates of Analysis' from validated vendors are consistently accurate. We request that the FDA reconsider accepting supplier's certification. Alternatively, we request that the FDA accept supplier's certification, and perhaps, require testing of every n^{th} batch to assure that the supplier's C of A is accurate.

It should be noted that a suppliers guarantee or certificate of analysis is considered acceptable for complying with §110.80 which generally requires that food raw materials not be contaminated. It is unclear why perishable foods require little or no testing to verify a lack of adulteration, while food-based dietary supplements will be deemed adulterated unless scientifically proven otherwise. The level of product testing in the proposed rule is excessive.

Comments concerning proposed §111.40- What requirements apply to components, dietary ingredients, dietary supplements, packaging, and labels you receive?

Pursuant to proposed §111.40(a)(2), manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements (but not labelers, which are not included in the definition of "You") must "perform testing, as needed, to determine whether specifications are met" for all components, dietary ingredients, or dietary supplements received. It is not clear how this provision should be interpreted in relation to §111.35(g) that only requires testing of incoming materials if finished product testing cannot be performed.

If this provision is interpreted by the FDA to mean that testing is required on both incoming material as well as in-process or finished batch material, then we believe such redundant testing is unwarranted. If incoming material is tested then other provisions

contained in the proposed regulation (e.g., calibration, batch records, etc.) would adequately ensure that the in-process and finished product will meet identity, purity, quality, strength, and composition specifications. In other words, manufacturers know what they are putting into the product and to require redundant testing is unwarranted and unreasonable. If the FDA can identify particular instances where what the manufacturer puts into the product is not what comes out in the finished batch due to certain anomalies in product composition or manufacturing methods, then perhaps redundant testing should be required in that instance. Otherwise, redundant testing is of little or no benefit to consumers, and imposes tremendous costs to industry, particularly small businesses.

At the very least, FDA should only require in-process or finished product testing only for one or two components of the finished batch. Testing of one or to components would ensure the blend and final potency of the finished product. To require full product testing would be to costly, of little or no benefit to consumers, and unreasonable.

If proposed §111.35 and §111.40 are interpreted to mean that testing is required by raw material suppliers, manufacturers, packagers and distributors, then we believe that testing is unnecessarily redundant. For manufacturers to retest material already tested by a supplier and store duplicate copies of laboratory data and reports is unnecessary. When components, dietary ingredients and dietary supplements are transferred from one facility to the next we understand that under certain detrimental conditions, the product may be contaminated. However, if precautions are taken (e.g., temperature and humidity are monitored, the truck is clean, the material is properly sealed in an airtight container, a significant amount of time is not permitted to elapse, etc.), as required under the proposed rule then it is unlikely that contamination will take place and redundant testing would be inappropriate. Consumers would not benefit from the imposition of such redundant testing. If FDA can identify particular ingredients or supplements, or types of ingredients or supplements, that raise particular issues regarding purity and potency during shipment, then perhaps the imposition of such redundant testing would be justified under appropriate cost benefit analysis.

Comments concerning proposed §111.60- What requirements apply to laboratory operations?

If the rule requires laboratory data to be stored at the facility doing the testing as well as the manufacturer's facility and the packager/distributor's facility, additional and substantial costs may be incurred for copying and storing the data. This duplicate documentation is unjustified and will be of no benefit to consumer health and safety.

Pursuant to §111.60, manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements are required to establish criteria for selecting appropriate examination and testing methods, verify that laboratory testing methodologies are appropriate for their intended use, and identify and use appropriate validated testing

methods for each established specification for which testing is required. Where chemical analysis is required for meeting testing specifications (which is most often the case), this section will result in tremendous financial burden for small companies that do not have in-house chemists, but rather contract outside laboratories to conduct such testing. If the laboratory contracted is assessed to have facilities that are adequate to perform the necessary testing using validated methods, then it should be at the discretion of the laboratory to decide which specific type of chemical test is most appropriate. Unqualified, untrained personnel should not be making these types of decisions and selecting testing criteria, and the cost of hiring qualified chemists to conduct such tasks in-house would be prohibitive for small businesses. Further, requiring that such decisions be made in-house, rather than permitting them to be made by qualified persons at a contracted laboratory, would not further benefit consumer health and safety. It should not matter who makes testing decisions, so long as that person is qualified to do so.

The final rule should require that the laboratory conducting the testing document, in writing, all testing that is performed. Without such documentation there would be no assurance that appropriate testing was indeed performed and that the product's identity, purity, quality, strength and composition are as claimed.

Comments concerning proposed §111.70- What requirements apply to packaging and label operations?

Pursuant to proposed §111.70(a)(7), manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements (but not labelers, which are not included in the definition of "You") must examine a representative sample of each batch of the packaged and labeled dietary ingredient or dietary supplement to ensure that the product meets specifications and that the label specified in the master manufacturing record has been applied. We request clarification as to what specifications the Agency is referring to. If it is referring to specifications required by §111.35(e) then the FDA should indicate so in the final regulation.

If the FDA intends this provision to mean that persons who simply package, label and store dietary supplements must conduct full product testing, this is unwarranted and unreasonable. As stated above, in route contamination from the supplier/manufacturer's facility to the packager/labeler/distributor's facility is unlikely to occur provided that certain environmental conditions are maintained as required by other provisions of the proposed rule. Also, testing would already be mandated upon the supplier/manufacturer, and if the supplier/manufacturer complies with the rule and adequately performs the required testing, reasonable cost/benefit analysis would dictate that redundant testing not be performed. It is the duty of the FDA to ensure that the industry is complying with regulations it enacts, not the duty of certain segments of the industry to ensure that other segments of the industry are complying. Since in route contamination is unlikely and

rare, consumers would enjoy little or no benefit from redundant testing at a tremendous cost to the industry, particularly small businesses.

Full product testing should not be mandated for companies that merely package, label and store finished product. The responsibility for raw material and finished product testing should lie soiely with those companies who handle the raw materials and dietary ingredients and who perform manufacturing duties. As previously stated, in general, the likelihood of contamination in route is low. Therefore, the packager should be required only to test those areas of contamination that are likely to occur during the shipment, or in the receipt, identification, packaging and holding areas of production operations (e.g., surface contamination). Product purity, potency, quality and consistency are not likely to be affected during shipping and packaging operations when adequate quality assurance measures are followed, as required under other provisions of the proposed regulation.

If the product manufacturer complies with dietary supplement GMPs, and the manufacturer's compliance is periodically verified by FDA audit, it would be reasonable to assume that the product is not adulterated upon receipt by the packager unless unusual shipping circumstances have occurred. It is not clear why a product should be assumed adulterated by the packager until proven otherwise when the product was manufactured in an FDA GMP compliant facility. The manufacturer's certificate of analysis should be considered sufficient if the manufacturer has performed all proposed required testing.

Pursuant to §111.70(e) manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements (but not labelers, which are not included in the definition of "You") must retest or reexamine any repackaged or relabeled dietary ingredients or dietary supplements, and such products must meet all specifications and the quality control unit must approve or reject their release for distribution. It is unclear what type of testing would be required. Potency testing (testing of all or some components) is not warranted for all repackaged or relabeled supplements. If a packager repackages a mineral tablet or multiple vitamin softgel from a 500-count bottle to a 60-count bottle, it would be costly to retest such product, and such testing would not benefit consumer health and safety. The ingredients would not lose potency during this process, and taking the average weight of tablets or softgels and a visual appearance examination would be sufficient.

Comments concerning proposed §111.85- What requirements apply to returned dietary ingredients or dietary supplements?

Pursuant to this section manufacturers, packagers, and persons who hold dietary ingredients or dietary supplements may not salvage returned dietary ingredients and dietary supplements unless tests demonstrate that such products meet all specifications for identity, purity, quality, strength and composition. This is unnecessary. Miss-shipped product that is returned unopened is safe for resale, and testing is unwarranted.

It is unclear whether returned products must be retested or simply examined before they are released for redistribution. No more than organoleptic testing should be required.

Conclusion

In summary, we believe standardized GMPs for dietary supplement products that are reasonable and based on appropriate cost/benefit analysis would benefit both the industry and consumers.

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