Docket No. 96N-0417

BEFORE
THE UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

COMMENTS BY
Herb Pharm, Inc.

ON THE PROPOSED RULE FOR
Current Good Manufacturing Practice
In Manufacturing, Packing, Or Holding
Dietary Ingredients and Dietary Supplements

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Introduction: Herb Pharm, Inc. is a small manufacturer and marketer of dietary supplements, predominantly liquid herbal extracts. We have been manufacturing herbal products for over 20 years and distribute primarily throughout the United States. Our manufacturing facility is complemented by our own certified organic farm that supplies most of the herbs that we use in our manufacturing process. Herb Pharm hereby submits comments to the U.S. Food and Drug Administration (FDA or Agency) in duplicate on docket number 96N-0417, Current Good Manufacturing Practice In Manufacturing, Packing, Or Holding Dietary Ingredients And Dietary Supplements (Proposed Rule) for consideration in drafting the final regulation (Final Rule).

Preamble to the Proposed Rule: Questions from the Advanced Notice of Proposed Rule Making (ANPRM) appeared in the preamble. Several of these questions warranted response, as did several statements from the preamble text.

Question 2 from the ANPRM in the preamble: We agree with the Agency's statement that organoleptic tests are appropriate for positive identification of herbs or plant parts.

Question 3 from the ANPRM in the preamble: Just as validated certificates of analysis are allowed in the manufacture of drug products under 21 CFR 211.84(d)(2), they should be allowed for the manufacture of dietary supplements with the same requirements for periodic evaluation.

Question 5 from the ANPRM in the preamble: We agree that it is a manufacturer's responsibility to identify certain types of injury or illness that may be associated with dietary supplement use. We maintain that a manufacturer's quality control unit is capable of initial review of adverse event reports because only serious adverse event (SAE) reports need to be passed on to medical

authorities. For example, a theoretical dietary supplement may be capable of producing a mild, self-limited upset stomach in some individuals. Reporting such events to medical authorities will create a burden on the manufacturer and a distraction for medical authorities by diluting SAE reports with reports of minor events. It should also be noted that the Board of Trustees of the American Herbal Products Association (AHPA) has filed a citizens petition requesting FDA to make all SAE reporting mandatory as a "serious adverse dietary supplement experience." Additionally, we believe that a definition for "serious adverse dietary supplement experience" should be added to the definition section of the Final Rule. We recommend that the definition be that stated in the AHPA petition:

"Serious adverse dietary supplement experience. Any adverse dietary supplement experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse dietary supplement experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse dietary supplement experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

Concerning the preamble relating to §111.35(k):

1) The preamble states (page 12199) that, "it is highly likely or certain that botanical components would be contaminated with filth and undesirable microorganisms of public health significance based on areas in which they are harvested." This would then imply there are other areas that produce botanicals that are likely not to be contaminated. This is particularly true in circumstances such as our own farming operation, where we grow most of the herbs we use. Because we control the entire farming operation, we are able to exercise a high degree of sanitary practice from the field

through the manufacturing process. Testing for microbiological contamination should therefore not be required in every circumstance.

2) The requirements for testing for toxic substances addressed in the preamble would be more reasonable if phrased, "If a toxic substance is a type of contamination that may reasonably be expected to adulterate or lead to adulteration of the dietary ingredient or dietary supplement, you must perform an appropriate test to detect the toxic substance." Without such a distinction, testing for unknown toxins of every description could be expected.

3) We also propose that in the case of microbial testing, herbal products that contain a minimum of 20% absolute ethanol should have more relaxed testing requirements than other types of products. Ethanol is bacteriostatic and inhibits any further development of bacteria at the start of the process.

Preamble Concerning Utensil Sanitation: FDA has invited comment in the preamble (page 12187) regarding documentation of utensil cleaning. Proper cleaning of utensils is obviously critical to GMP, but documentation of cleaning utensils is unnecessary and inappropriate. We agree with the appropriateness for documentation for cleaning large equipment. However, any requirement in the Final Rule that would obligate manufacturers to uniquely identify each spoon, spatula, container and hose in order to document each cleaning is inappropriate and would create an enormous burden on the manufacturer. Such a requirement would slow the cleaning process, making proper sanitation more cumbersome. The documents and document maintenance generated from this requirement would create an undue financial burden for small business and complicate the otherwise simple process of repeated cleaning of utensils. We request that the language concerning utensil cleaning in the Final Rule not include any requirement for documentation of such cleaning. We contend that it is adequate simply to require that utensils be properly cleaned.

Subpart A – General Provisions

Subpart A §111.3: A definition for "serious adverse dietary supplement experience" should be added to the definition section of the Final Rule (see above).

Concerning the definition of "sanitize": We request that the quantitative standard for the sanitizing process be stricken from the Proposed Rule. Excessive and specific requirements for sanitizing and sanitizing agents will impose an undue burden on the manufacturer, and the quantitative standard may be especially difficult to achieve in cases where the contact surfaces are already in a clean state. The definition would most appropriately be modeled after food GMPs. We suggest that the definition be changed to read, "Sanitize means to adequately treat surfaces that contact dietary supplement ingredients and finished product by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer." Ingredient and/or product testing required in other portions of the Proposed Rule will help to verify that surfaces did not contaminate dietary supplement ingredients or dietary supplement products at the time of processing.

Subpart A §111.6: The exclusion pertaining to harvesting, storage and distribution of raw agricultural commodities should be broadened to include other common and basic raw botanical processing such as drying (dehydration), chopping, cutting and milling. These processes are usually required in the preliminary preparation of raw botanicals to facilitate packaging and shipping, and result in botanicals that will require further processing before consumption.

Subpart B – Personnel, §111.12(b): The personnel requirement in the Proposed Rule, stating that employees must have a combination of training and education reads to be restrictive of employees who do not have previous training and experience and should be reworded to read "Each person engaged in

manufacturing, packaging, or holding must have the education, training or experience, or any combination thereof, to perform the person's duties."

Subpart C – Physical Plant, §111.20: Overly specific requirements that will not necessarily ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements or that may place an undue burden on small business appear in this section. While an inventory system of some kind is needed, it does not need to be computerized to be effective. Requirements for ceilings and walls in §111.20(d)(1) should be directed only towards those of a type that can be adequately cleaned, striking the phrase "smooth and hard." Eliminating all texture eliminates the use of any type of sound baffling in production areas. Similarly, §111.20(d)(4) and §111.20(d)(5) require fans and humidity controls to be used. If these are not applicable to a particular situation and do not play a role in reducing microbial contamination, there should be no requirement for them. Equipment should only be required to be in place "as necessary" to prevent microbial contamination.

Subpart D – Equipment and Utensils, §111.25: Target temperatures are not required where freezing is used only to enhance the milling properties (fracturing) of dried botanicals and not to prevent microbial contamination.

The equipment calibration requirements in this section are overly broad. Calibration of equipment should be required only when the calibration of manufacturing equipment is critical to achieving specifications or for analytical equipment where the calibration is critical in testing for specification conformity.

Subpart E – Production and Process Controls

§111.35(d): This section is already mandated by Federal law (the Dietary Supplement Health and Education Act or DSHEA) and should not be part of cGMP. This subparagraph should be stricken in its entirety.

§111.35(f): The requirements for in-process testing are overly broad and have the potential to impose an undue burden on small business. At the least, this testing should only be required "as necessary" to meet specifications. Properly monitoring critical points in the process will avoid "unanticipated occurrences

that may result in adulteration" and by its nature, monitoring and process control is a much more practical, effective and affordable mode of preventing adulterated product from reaching the market. As the Agency has recognized (FDA Outreach meeting, 6 May 2003, Oakland California), testing cannot assure that product is not adulterated. In the case of in process testing for adulteration from "unanticipated occurrences", there would be no direction or idea of what to test for since the theoretical adulteration is not anticipated.

§111.35(g) and §111.35(k): We agree that identity testing should be performed for ingredients, but disagree with the provision that disallows use and acceptance of certificate of analysis (C of A) from a vendor in all cases.

1) The proposed GMP for dietary supplements is, in general, overly dependent upon testing to determine compliance. While there is certainly a time and place for testing, the proposed GMPs would require redundant tests to be performed at every transaction of dietary ingredients or dietary products in the pre-consumer supply chain. This over-emphasis on testing seems to diminish the purpose and goal of the body of GMPs. GMP suppliers and manufacturers will be required to comply with the numerous other controls mandated by cGMP, therefore their properly prepared and audited C of A should be acceptable for chemicals, botanicals and botanical extracts, just as they are for drugs under 21 CFR 211.84(d)(2). Any required testing performed once on a botanical by a supplier, manufacturer or packager should suffice, as long as other GMP, certification and chain of custody standards are met.

2) Non-botanical components such as USP ethanol that have been produced by a GMP manufacturer, that arrive properly sealed and bear lot tracking numbers matching the attending documentation should not require any further identity testing.

3) Certificates of analysis generated by qualified and audited GMP ingredient suppliers using adequate process controls should be allowable for dietary supplement ingredients. The same ability to use validated certificates of analysis should be allowed for dietary supplements as they are for drugs

under 21 CFR 211.84(d)(2), wherein it is stated:

"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."

After establishing the acceptable performance of a GMP compliant ingredient supplier, auditing periodically to assure specification conformity and accuracy of their certificate of analysis will adequately ensure that specifications for dietary ingredients and dietary products are met.

4) Disallowing the use of a validated certificate of analysis at least comparable to that used in the manufacture of drugs under 21 CFR 211.84(d)(2) puts an unfair burden on all manufacturers, and an especially unfair financial burden on small manufacturers. This aspect of the GMPs will probably be the most costly and burdensome for small business, and because the goal and intent of the GMPs can be met through more practical, efficient and affordable means, we view this approach as undesirable and the burden to be unnecessary.

§111.35(g)(1): Identity testing using organoleptic, macroscopic, microscopic and morphological examination of whole botanicals is a valid and acceptable practice. Just as it is not necessary for a food manufacturer to perform HPLC to properly identify the chicken or the tomato used as soup ingredients, so it is not necessary for experienced botanical manufacturers to use HPLC to properly identify botanicals such as echinacea root or saw palmetto berry, for example. Once we have used these botanicals to manufacture our liquid extracts, identification through chemical means may be theoretically possible, but it is not practical in a real world scenario, especially for small businesses. In such cases,

the regulatory specifications mandated under §111.35(f) would ensure that the originally identified ingredient is the same ingredient contained in the finished product. To require chemical identity testing of finished product simply because it is scientifically feasible (rather than practical) would impose an inordinate and unnecessary burden on small manufacturers. This is especially true when §111.35(f) and other provisions of the regulation are specifically designed to and will adequately ensure the identity of dietary ingredients and finished dietary supplements, thus achieving the goal and intent of the regulation.

§111.35(g)(2) and §111.35(h): The Agency's Proposed Rule contradicts itself by stating that organolepsis may be an acceptable test method (for identity testing) and at the same time claims that organolepsis probably cannot, as required by the proposed GMPs, be scientifically validated (FDA Outreach meeting, 6 May 2003, Oakland California).
It is imperative for the financial survival of small businesses that organolepsis, coupled as necessary with macroscopic and morphological examination and comparison with voucher specimen(s) or voucher photograph(s) (macroscopic and microscopic photographs of voucher specimens), be deemed an acceptable test method for identification and we request that this be made clear and obvious in the Final Rule.

§111.35(k)(3): In this section the Agency states, "You must test or examine compounds, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration."

1) We find the use of the word "may" in both cases to be overly broad and wide reaching. Testing for adulterants should be required only in cases where a dietary ingredient is "liable" to be adulterated, similar to the requirements for drugs in 21 CFR 211.84(d)(5) of the drug GMPs. Without this qualifier, there is no recognizable limit to the testing required on any given botanical.

2) Based upon the wide-reaching language in this part of the Proposed Rule, testing of each material becomes an endless, cost prohibitive and scientifically unachievable endeavor.

3) Consumption levels are critical and must always be factored into the toxicity equation. In many cases, the total equivalent of botanical material consumed in a day is 1 gram or less. The most effective way to address public health concerns is the total daily intake from a product. It is not rational to impose the same unit weight of adulterant limits for dietary supplements as for foods, because foods are consumed at a rate hundreds of times the level of most botanical dietary supplements.

4) There is an implication that this is a zero tolerance policy for any number of compounds that could be considered toxic at some level. It should be recognized that toxic chemicals such as lead are ubiquitous and may be detected at some level in nearly all plant material. Similarly, aflatoxin is detectable in many common foods in the U.S. food supply.

5) We are concerned that the proposed requirements for dietary supplements exceed those in food GMP. Given the large difference in consumption levels between foods and most dietary supplements, where foods are consumed in far larger quantities, it is concerning that proposed testing of dietary supplements would greatly exceed testing required for food. In many cases, the same botanical material may be used for a food and a dietary supplement, but there would be no testing requirements when used as food (e.g. garlic and ginger). We ask the Agency to explain why there is such a blatant discrepancy between these two classes of products that, in many cases, deliver the exact same botanical material to the consumer.

6) The testing requirements posed in §111.35(k) would be better stated as testing for toxic substances that "are reasonably expected or liable to be present in quantities that may be of public health significance."

§111.50(f): We agree with the intention to prohibit reprocessing to blend out contamination. However, reprocessing botanicals received by the manufacturer is a critical step in quality and should be clearly allowed under the rule. This may be a matter of defining "other contamination" more clearly so as not to confuse it with cleaning botanical material. A simple example is a manufacturer who receives whole, dried root with stem levels that exceed their specifications, and the botanical is thereby rejected pending rework. In this case, the stem can be cut off and separated out by the manufacturer before further processing. We believe that this type of "contamination" is not meant to be included in the rule, but the language should be clarified to make this point obvious.

§111.85(b)(2): We agree with the need to examine and carefully control returned product. We believe that two situations warrant further consideration for flexibility. This is especially true given the acknowledgement by FDA that in some cases finished product testing is not possible.

1) Products returned undelivered by the shipper should be given special consideration for return to usable inventory. If, upon inspection by the QC unit, it is found that all outer packaging, including the safety seal, is intact, this product should be allowed to return as is to usable finished goods inventory.
2) It is very common for numerous products to be returned by large retailers after a short period, for reasons such as shelf space adjustments. Being unable to use these returned products would be a significant financial burden for small manufacturers, especially those making a large number of products. If, upon inspection by the QC unit, it is found that all outer packaging, including the safety seal, is intact, this product should be allowed to return as is to usable finished goods inventory.

Concerning the Financial Impact Report.

We disagree with the estimates of cost to industry proposed by the Agency. As a small business that produces over 300 batches per year, our cost increases will be tied to final testing required. Some of the language in the Proposed Rule is overly

vague, and we have asked for clarification on specific issues in other sections of our comments.

For example, if heavy metal screening, microbiological testing, pesticide residue screening and chemical identity testing were all required, this would double the cost of materials for many products. This would be particularly true where we manufacture very small annual batch sizes, some comprising one hundred finished units or less. The undefined toxic screening would add substantially more to the cost. Together, the proposed level of testing would require us to eliminate a number of otherwise compliant products that are currently on the market.

We have estimated a general staffing increase of six full time employees, costing approximately $192,192 annually plus two analytical chemists, costing approximately $112,000 annually.

We find the Agency's estimate of 250 dietary supplement companies (about 16% of the entire dietary supplement industry) going out of business due to the cost of GMP implementation to be unacceptable. We request that the Agency consider the above recommendations to make the rule more practical and affordable for manufacturers while realizing the intent and goal of protecting the consumer.

Conclusion: Herb Pharm appreciates this opportunity to comment on docket number 96N-0417, Current Good Manufacturing Practice In Manufacturing, Packing, Or Holding Dietary Ingredients And Dietary Supplements. We ask that you consider these comments in earnest and give them due consideration in drafting the Final Rule.