Docket No. 96N-0417

Before the United States of America
Department of Health and Human Services
Food and Drug Administration

Comments of Select Supplements, Inc.

On the proposed rule for
current good manufacturing practices
in the manufacture, packing, or holding of
dietary ingredients and dietary supplements

August 11, 2003

Select Supplements, Inc. (SSI) is a contract manufacturer of hardshell capsules, softgel capsules, acidified food, and form-fill-seal pouches. SSI is a subsidiary of Kyowa Hakko USA, an importer and distributor of dietary ingredients and dietary supplements manufactured in the USA and Japan.

General Comments to the Proposed Rule.

1. SSI is generally in favor of the proposed regulations. SSI believes the proposed regulations will benefit both the dietary supplement industry and consumers, by fostering an environment in which ingredients and products are required to adhere to appropriate standards of identity, purity, strength, and composition. The rule will benefit consumers by helping to ensure the integrity of the products they buy. The rule will benefit industry by enhancing public confidence in dietary supplement products and by providing a more level playing field for all industry participants.

2. SSI believes that the rule should cover both dietary supplements and dietary ingredients.

Rationale:(a) In many cases, the presence of substandard dietary supplements in the marketplace is due to the use of substandard dietary ingredients. And yet, most dietary supplement manufacturers – especially contract manufacturers - are not in a position to dictate the quality of the ingredients they use. They either (i) are instructed by their customers which ingredients to purchase, from what source, and/or what price to pay; and/or (ii) have purchasing volumes that are too small to exert a significant influence on the actions of dietary ingredient vendors. For example, dietary supplement manufacturers individually can be too small to demand disclosure of their vendors' analytical methods, or to demand that certain standards of quality be met. Therefore it requires the influence of a powerful third party – i.e. the federal government – to effect an overall improvement in the quality of the dietary ingredient supply.

(b) It is necessary to distribute the burden of compliance with the proposed GMPs over the largest possible number of companies. It will not be economically feasible for supplement manufacturers alone to bear the entire cost of compliance. We estimate that the proposed regulations, as currently written, may require up to several hundred dollars worth of testing for each shipment of each ingredient; and up to several thousand dollars worth of testing for the more complicated types of dietary supplements (e.g. multivitamin/mineral formulas). This cost will be compounded many times over, if ingredient manufacturers escape regulation and supplement manufacturers are left to sort through an inconsistent ingredient supply in order to find those which meet their standards.

(c) We agree with the agency that in some instances, proper regulation of dietary ingredients and dietary supplements is necessary to protect the public health.

3. SSI believes that written standard operating procedures should be required for all GMP functions, not just calibrations.

Rationale: (a) The agency is incorrect in its assumption that eliminating requirements for written procedures in some way eases the burden on small businesses. The use of written procedures saves time and other resources since it greatly facilitates the training of employees. (b) In fact many companies both large and small already have written procedures. A review of established standard operating procedures is usually an important part of any vendor audit program. (c) Without written procedures it is impossible for the quality unit to ensure products are unadulterated; in particular, it is impossible to "approve or reject all processes....and deviations from or modifications to them" unless it is clearly established in writing what those processes are intended to be.

4. SSI believes that the American Herbal Pharmacopoeia (AHP) should be recognized as a source of scientifically valid information and quality standards for botanical dietary ingredients and botanical dietary supplements. In our experience the AHP monographs are the most comprehensive and the most useful monographs available for botanicals.

Comments to Specific Sections of the Proposed Rule.

111.3 Definitions.

Batch: We agree with this definition.

Consumer complaint: We agree with this definition.

Lot: We agree with this definition.

Reprocessing: Delete "clean, unadulterated" and "for reasons other than insanitary conditions". Rationale: See discussion of section 111.15(g)(4)(iii) below.

Sanitize: Split the definition into "sanitize" and "sanitizing agent" as follows:

* "Sanitize means to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying a sanitizing agent to cleaned food contact surfaces."
* "Sanitizing agent means a treatment, such as heat or chemicals, which when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganism of public health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer."

Rationale: Combining the definitions into one creates the impression that the person performing the sanitization is also responsible for validating the performance of the sanitizing agent. We believe it is unnecessary and inappropriate to require cleaning validations for dietary ingredients and supplements.

111.6 Exclusions. Add "dehydration" and "cutting into smaller pieces to facilitate shipment (such pieces to average at least 0.5 cm)."

Rationale: Many agricultural products are dried on the farm before shipment.

111.10(a)(1) Add "from working in any operations involving direct contact with components, dietary supplements, or sanitized product contact surfaces until the condition is corrected....

Rationale: Persons who may be a potential source of microbial contamination may still be suitable to work in other operations, such as office or warehouse work.

111.12(b), 111.13(b) Add "training and experience, or any combination thereof, to perform...."

Rationale: It is not necessary to require both training and experience.

111.12, 111.13 Add section (c) requiring training to be documented.

Rationale: It is not possible for the QC unit to ensure training is appropriate and current unless the training is documented.

111.15(a) Separate the requirements for the manufacture of dietary ingredients from those for the manufacture of dietary supplements. The proposed sections (a)(1) and (a)(2) are appropriate for the manufacture of dietary supplements but may be more extensive than is required for dietary ingredients. For the manufacture of dietary ingredients the requirement should be "You must maintain your physical plant in a condition adequately clean, sanitary, and repaired to ensure dietary ingredients manufactured or processed at the site meet established purity specifications."

Rationale: The manufacture of synthetic or highly processed dietary ingredients often includes extensive purification steps, especially toward the end of the manufacturing process. These purification steps serve to remove contaminants that may have been introduced at earlier stages in the manufacturing process. Therefore not every stage of the ingredient manufacturing process needs to occur under the same strict controls as those used for finished dietary supplements.

111.15(b) Add "Compliance with this requirement may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification, or examination of these substances for contamination."

Rationale: This explanation of the means of verification is included in food GMPs and it is appropriate for dietary supplements as well.

111.15(c)(1) and (c)(2) We propose adding [in (c)(1)] "You must not allow

animals or pests in any interior area of your physical plant"; and [in (c)(2)] "You must take effective measures to exclude pests from the interior of your physical plant, and to...."

Rationale: Synthetic or highly processed dietary ingredients are often manufactured in extensive facilities in which large tanks and vessels are interconnected via piping. In some cases portions of the tanks and/or piping may not be enclosed inside a separate structure. The existing language would seem to require enclosure in a separate structure in order to prevent animals and pests from contacting the outside of the sealed equipment. In fact, such an enclosure is not necessary to prevent adulteration as long as the exposed portions of the facility are properly sealed. The proposed language clarifies that it is the interior of the structures that must be protected.

111.15(d)(2) and (d)(3) Separate the requirements for the manufacture of dietary ingredients from those for the manufacture of dietary supplements. The proposed sections (d)(2) and (d)(3) are appropriate for the manufacture of dietary supplements but may be more extensive than is required for dietary ingredients. For the manufacture of dietary ingredients the requirement in (d)(2) should be "Water used in the manufacture of dietary ingredients must be adequately pure to ensure the finished dietary ingredients meet established purity specifications." The requirement in (d)(3) should not apply to water used in the manufacture of dietary ingredients.

Rationale: Many synthetic or highly processed dietary ingredients undergo extensive purification near the end of the manufacturing process, which serves to remove contaminants that may have been introduced at earlier stages in the manufacturing process. Therefore not every stage of the ingredient manufacturing process needs to be performed using water that is as pure as that used for finished dietary supplements.

111.15(j) Add "training and experience, or any combination thereof, to develop...."

Rationale: It is not necessary to require both training and experience.

111.20(d)(1) Change to read "Floors, walls, and ceilings must be constructed to facilitate adequate cleaning and repair, and should preferably constructed of smooth, hard materials."

Rationale: In some operations, such as grinding, soundproofing may be necessary to comply with OSHA regulations.

111.20(d)(4) Add "Fans and other air-blowing equipment, where used, must be located and operated...."

Rationale: The existing language implies that the use of fans and other air-blowing equipment is required. Their use should not be required but allowed.

111.20(d)(5) Add "Equipment that controls temperature and humidity, where necessary to protect ingredients or products;"

Rationale: (a) Not all dietary ingredients or products are adversely affected by fluctuations in temperature and humidity. For example, calcium carbonate is non-hygroscopic and is not affected by temperature fluctuations. (b) Not all manufacturing processes require control of environmental temperature and humidity. For example, the ambient temperature and humidity are largely irrelevant during the maceration of a botanical, since the conditions to which the herb is exposed are determined by the composition and temperature of the extraction solvent, not by the ambient environment in the facility.

111.20(h) Delete this section.

Rationale: Redundant; the requirement to exclude pests from the facility is established above under 111.15(c).

111.25(b)(1) Change to read, "Instruments and controls used in manufacturing or testing a component, dietary ingredient, or dietary supplement must be calibrated if they are critical to achieving specifications."

Rationale: (a) The sentence should be changed from the active to the passive voice because use of "You" requires the dietary ingredient or supplement manufacturer to perform the calibration, when in fact such calibrations are often performed by an outside service. (b) The requirement should be limited to instruments and controls that are critical to achieving specifiations. Equipment may feature instruments and controls that are not used, or that serve as a convenience but are not critical (e.g. the speed control on a conveyer belt).

111.25(b)(2) Change to read, "Such equipment must be calibrated before first use."

Rationale: (a) Calibrations are often performed by the equipment manufacturer or vendor or other outside service, rather than by the dietary ingredient or supplement manufacturer. (b) The existing language implies that the calibration must be performed on-site (i.e. at the plant manufacturing the dietary ingredient or supplement) when in fact many calibrations can, or even must, be performed off-site. For example, most dietary ingredient or supplement manufacturers lack the facilities and/or expertise to perform calibrations of timers, mass standards, etc.

111.25(c) Change to read, "When you perform calibrations, you must:"

Rationale: The dietary ingredient or supplement manufacturer should not be required to establish written procedures for calibrating equipment when the calibration is performed by an outside service, because (a) such a requirement would be unduly burdensome,

and (b) the dietary ingredient or supplement manufacturer usually lacks the expertise to evaluate the adequacy of the procedures used by the outside service.

111.25(d) Change to read, "The following must be identified..."

Rationale: (a) Calibrations and re-calibrations are often performed by the equipment manufacturer or vendor or other outside service, rather than by the dietary ingredient or supplement manufacturer. (b) The existing language implies that the calibration or re-calibration must be performed on-site (i.e. at the plant manufacturing the dietary ingredient or supplement) when in fact many calibrations can, or even must, be performed off-site.

111.25(e)(6) Delete this section.

Rationale: Redundant; the safety and adequacy of cleaning and sanitizing agents is addressed above under 111.15(b).

111.30(a) Change to read, "When you use automatic, mechanical, or electronic equipment to manufacture, package, label, or hold a dietary ingredient or dietary supplement, and when the function of such equipment is critical to the established specifications, you must:"

Rationale: (a) "Or" is more appropriate than "and" because the same piece of equipment will not serve to manufacture, package, label, and hold the items. (b) Not all automatic, mechanical, or electronic equipment has a critical effect on the outcome of the manufacturing process; for example, the speed of conveyer belts may not be critical.

111.30(a)(1) Change to read, "Use appropriate equipment to ensure..."

Rationale: The existing language "Design or select" implies that a formal, prospective study (similar to a pharmaceutical IQ/OQ/PQ) must be performed; such a requirement would be unduly burdensome. It might even be impossible, because in many instances, dietary supplement manufacturers cannot predict at the time of purchase the entire range of ingredients and products for which a particular piece of equipment will be used. Rather, the suitability of a particular piece of equipment for a particular ingredient or product must be evaluated at the time the need arises.

111.30 (a)(2) Change to read, "...equipment operates satisfactorily..."

Rationale: The existing language "is capable of operating" implies that a formal, prospective study (similar to a pharmaceutical IQ/OQ/PQ) must be performed; such a requirement would be unduly burdensome. It might even be impossible, because in many instances, dietary supplement manufacturers cannot predict at the time of purchase the entire range of ingredients and products for which a particular piece of equipment will be used. Rather, the suitability of a particular piece of equipment for a particular ingredient or product must be evaluated at the time the need arises.

111.30(b) Change to read, "For any automatic, mechanical, or electronic equipment used to manufacture, package, label, or hold a dietary ingredient or dietary supplement, and when the function of such equipment is critical to the established specifications, you must:"

Rationale: The requirement should apply not to ALL automatic, mechanical, or electronic equipment, but only to equipment which is used in regulated operations and which has a critical effect on the outcome of the manufacturing process.

111.30(b)(5) Move this section and/or otherwise clarify that backup data files are necessary for any computerized data that is relied upon to meet the requirements of these good manufacturing practices.

Rationale: (a) Many types of data are critical to ensuring compliance with good manufacturing practices but are not stored in equipment used directly in the manufacture, packaging, labeling, testing, or holding of ingredients or supplements. For example, computerized systems may be used to control inventory status or track calibration schedules. (b) Some types of data may be stored in a computer system for convenience, but are not relied upon for GMP compliance. For example, inventory data may be stored in a computer for the convenience of the purchasing department, while the production and quality units rely upon written documents. In such a case the computer data is not critical to meeting GMP requirements and therefore no backup should be required.

111.30(b)(5) Delete the requirement for backup files of software programs used in automatic or electronic equipment.

Rationale: Many equipment vendors consider their software programs proprietary and are unwilling to share them. This is particularly true, for example, for the programs that run PLCs embedded in larger pieces of equipment (e.g. high speed encapsulators). In practice it is unnecessary for dietary ingredient or supplement manufacturer to have the software, since if problems with the function of the machine arise they contact the equipment manufacturer or vendor to resolve the problem.

111.35(a) Add, "...that covers all stages of manufacturing, packaging, labeling, and holding of dietary ingredients and dietary supplements that occur in your facility or for which you otherwise have responsibility."

Rationale: The production of dietary supplements is often broken up into several stages which are under the control of different entities. For example, it is often the case that a marketing company will create a formula, deciding the labeled types and amounts of dietary ingredients, and the type of packaging and labeling. The marketing company may manufacture and package the product itself; or it may contract with one company to manufacture and package the product; or it may contract with one company to

manufacture the product and another company to package the product. In turn, contract manufacturers and packagers may subcontract portions of the manufacturing or packaging.

Furthermore, the marketing company may go so far as to specify details such as the types and quantities of excipients; the approved sources of ingredients; the manufacturing overages to be used; the shelf life of the product; etc. In other cases, the contract manufacturer decides the source the ingredients, the overages to be used, the shelf life, etc. The permutations are endless.

In summary, it may not be possible for any one company to implement a system that covers "all stages of manufacturing, packaging, labeling, and holding" the dietary supplement. Rather, each company must be responsible for its own portion of the process.

Insofar as ultimate responsibility must be assigned to one entity, this must be the marketing company, since that is the only entity involved in the entire process from inception to consumer sale, and it is often that company which dictates what the other companies do.

111.35(b) Change to read, "...control system must ensure that...."

Rationale: The existing language "designed to ensure" implies that formal, prospective studies (similar to a process validation) must be performed; such a requirement would be unduly burdensome.

111.35(c) Change to read, "meets specifications for identity; purity as appropriate to protect the public health; and quality, strength, and composition as appropriate for the ingredient or product."

Rationale: It is confusing and unnecessary to require that all five of these attributes be addressed for all dietary ingredients and supplements. For example, it would be burdensome and confusing to require the establishment of formal specifications for the chemical composition of peppermint leaf, given that (a) it contains thousands of biochemicals, and (b) the usual or desirable levels of any one of them - or even of any group of them, such as proteins - may not be known. Furthermore, the term "purity" requires explanation since not all ingredients or supplements are subject to the same types of contamination, and it would be unduly burdensome to require that all ingredients and supplements be tested for all possible contaminants (as opposed to all likely contaminants).

111.35(d) Delete this section.

Rationale: (a) Limitations on the types of items which may be used in manufacturing of food and dietary supplements is not part of good manufacturing practices. (b) These limitations are covered by other existing laws and regulations.

111.35(e) Change to read, "...in your manufacturing or packaging process...."

Rationale: (a) Manufacturers and packagers should be responsible to establish specifications only for the processes occurring in their own facility or for which they are otherwise responsible (e.g. subcontracted operations), not for upstream or downstream processes over which they may not have any control. (b) Packaging processes should be included to be consistent with the other requirements in this section.

111.35(e)(1) Change to read, "For components, dietary ingredients, or dietary supplements that you purchase, specifications must be established for the identity; purity as appropriate to protect the public health; and quality, strength, and composition as appropriate for the ingredient or product."

Rationale: (a) See discussion under 111.35(c). (b) "Purchase" is more appropriate than "receive" because many manufacturers and packagers operate on a tolling basis, in which their customer provides the ingredients or product to be processed or packaged. In such a case the customer, not the manufacturer or packager, establishes the specifications.

111.35(e)(3) Change to read, "For dietary ingredients or dietary supplements that you manufacture, specifications must be established for the identity; purity as appropriate to protect the public health; and quality, strength, and composition as appropriate for the ingredient or product."

Rationale: See discussion under 111.35(c).

111.35(f) Change to read, "You must monitor the in-process control points, steps, or stages to ensure that specifications established under section (e)(2) are met and to detect any unanticipated occurrence that may result in adulteration;"

Rationale: The existing language appears to state that attributes must be tested that no longer exist (i.e. specifications for the raw material) or do not yet exist (i.e. specifications for the finished product).

111.35(g)(1) Change to read, "You must test or have tested each finished batch...identity, purity, quality, strength, and/or composition are met, provided that there are generally available, scientifically valid...."

Rationale: (a) The manufacturers and purchasers of finished batches should be allowed to delegate the necessary testing to an appropriate party, such as a competent outside laboratory or the manufacturer or vendor who processed the material or product. (b) As discussed above under 111.35(c) and 111.35(e)(3), not all five of these attributes should or will be specified for every ingredient or supplement. (c) The statute prohibits the agency from imposing testing requirements for which scientifically valid methods are not generally available.

Comment: We note and support the use of the phrase "scientifically valid analytical method." The method used must yield suitably accurate results. This is distinct from the

requirement for the method to be "validated" in the sense that its linearity, accuracy, precision, ruggedness, robustness, etc. be formally demonstrated in each laboratory in which the method is used. We believe that the latter requirement would be unduly burdensome, especially insofar as many of the methods used (e.g. AOAC methods) have already undergone extensive interlaboratory validation. We would support a requirement for validated methods to be "qualified" for use in individual laboratories, with "qualification" consisting of a brief series of precision and accuracy tests designed to ensure the method has been implemented properly.

111.35(g)(2) Add "...method generally available..."

Rationale: The statute prohibits the agency from imposing testing requirements for which scientifically valid methods are not generally available.

111.35(g)(2)(i) Add, "Perform or have performed testing...whether each specification is met, unless the shipment was previously tested by a qualified manufacturer or vendor and arrives with the manufacturer's or vendor's unique tamper-evident seals intact;"

Rationale: (a) The purchaser should be allowed to delegate testing to an appropriate party such as an outside laboratory or the toll manufacturer that will receive the material for further processing. (b) With appropriate controls, it should be possible to eliminate redundant testing and still ensure the ingredients meet the necessary specifications. If the ingredient is tested by an honest and competent vendor or manufacturer and then sealed with unique, tamper-evident seals, it should be possible for the purchaser of the material to rely on the vendor's or manufacturer's test results, as presented in a certificate of analysis, rather than repeat all the testing again. At most, the purchaser should need only to test or examine the material to ensure it has not been damaged by exposure to excessive heat. (d) The vendor or manufacturer could be "qualified" through auditing by an outside party, either a third-party certifying organization (e.g. NSF, USP) or the purchaser. (e) Tamper-evident seals are necessary to prevent intentional adulteration of the material between the time it is sampled and tested by the vendor or manufacturer and the time it is received by the purchaser. The seals should be unique to prevent their being broken and replaced by a third party.

111.15(g)(2)(ii) Delete this section.

Rationale: Redundant; in-process testing requirements are already established in 111.15(f).

111.15(g)(4)(iii) Delete; or add "...such as heavy metals, unless the reprocessing is demonstrated to remove the contaminant."

Rationale: In many instances it is possible to process or reprocess materials in order to remove contaminants. For example, heavy metals and pesticides can be removed from botanical extracts using appropriate purification processes.

111.15(k) Move to 111.35(e)(5) and change to read "Purity specifications for purchased or manufactured components, dietary ingredients, and dietary supplements must be established for those types of contamination which can reasonably be expected to affect the component, ingredient, or supplement in question. These types of contamination may include, but may not be limited to, the following...."

Rationale: (a) It is more clear to discuss this at the first point where the subject of purity comes up, i.e. under the topic of "establishing specifications" rather than under the topic of "testing." The purity specifications, once established, are subject to the same testing requirements as any other specification.(b) Not all ingredients or supplements are subject to the same types of contamination, and it would be unduly burdensome to require that all ingredients and supplements be tested for all possible contaminants (as opposed to all likely contaminants).

111.15(l) Delete this section; or at least move to 111.15(h).

Rationale: (a) This list is neither exhaustive nor sufficient to cover the various types of testing that will be required for compliance with 111.15(g). (b) If it must be included, this list of testing types belongs more appropriately with the other section that discusses what types of tests to use, namely 111.15(h).

111.15(n) Delete the section.

Rationale: Redundant; the requirement for material review and disposition is already established under 111.15(i)(2) and (i)(3).

111.37(a) Add, "...meet established specifications...strength and/or composition."

Rationale: As discussed above under 111.35(c) and 111.35(e)(3), not all five of these attributes should or will be specified for every ingredient or supplement.

111.37(b)(1) Change to read, "...strength, or composition...."

Rationale: Anything that may affect any one of these attributes (not all of the attributes) should be approved or rejected by the quality unit.

111.37(11)(ii) We agree that the quality unit must be responsible for sample collection. Production operators may have a strong incentive to submit biased or non-representative samples.

111.37(b)(12) Change to read, "...three years from the date of manufacture or 1 year past the expiration date, whichever is less...."

Rationale: Some dietary ingredients and supplements have a shelf life of 1 year or less, so there is no reason the manufacturer should keep the reserve samples for 3 years.

111.37(b)(13) Change to read, "Perform appropriate tests and examinations of labels and other components, dietary ingredients, and dietary supplements, as established in 111.15(g)."

Rationale: Redundant; the testing requirements have already been set forth in 111.15(g) in more detail than is given here.

111.40(b)(3) We agree that shipments of labels and packaging components should be assigned lot numbers.

SSI appreciates the opportunity to submit comments with respect to the proposed rule. We encourage the agency to promulgate a final rule as soon as practicable.

Respectfully submitted,

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