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Report to the American Association of Acupuncture and Oriental Medicine

Impact of New Dietary Supplement CGMP Regulations on Asian Medicine Practitioners

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The enactment of Current Good Manufacturing Practice (“CGMP”) regulations for dietary supplements is neither surprising nor unusual. The process leading to the adoption of these regulations has been underway since 1994. The FDA has enacted CGMP codes for many of the other products that it regulates.

Background

The Dietary Supplement Health and Education Act (“DSHEA”) created and defined the category “Dietary Supplement” and authorized the Secretary of Health and Human Services (“the Secretary”) to establish Current Good Manufacturing Practice (“CGMP”) regulations for dietary supplements. DSHEA became law in 1994.¹

In 1997 the Secretary and the Food and Drug Administration (“FDA”) gave notice to the public of proposing the adoption of CGMP regulations for dietary supplements, attaching a draft proposed by the industry and posing various questions.

During 1999 the FDA conducted public meetings to discuss this subject, visited dietary supplement manufacturing facilities and continued evaluating the comments it receive on its proposal. In March 2003 proposed CGMP regulations for dietary supplements (“Proposed Rule”) were published together with an extensive preamble discussing the comments FDA received. In June 2007, FDA published its final CGMP regulations for dietary supplements (“Final Rule”).²

Establishing CGMP codes for regulated products is a part of FDA’s normal regulatory pattern. There is a CGMP for the manufacture of drugs, and a general CGMP for the manufacture of food, as well as several CGMP’s for the manufacture of subsets in the food category. DSHEA mandates that the CGMP for the dietary supplements be modeled on the CGMP for food.

FDA’s announcement of the Final Rule contains a lengthy preamble discussing the FDA’s approach to structuring of the rule and discussing the many comments on the proposed Rule and FDA’s response to them. The announcement also contains the 16-page text of the Final Rule.

The preamble to the Final Rule is organized into 27 sections. After 5 introductory sections on general topics, come 16 sections, one for each subpart of the Final Rule. These sections report the comments received on the subpart and FDA’s response. Next

¹ Public Law 103-417 (October 25, 1994).

² 72 FR 34752 (June 25, 2007).

comes a section on miscellaneous comments. Finally 5 sections respond to the requirements of other Federal statutes imposed on an agency issuing regulations like this and cover additional miscellaneous items. The text of the Final Rule follows the preamble.

To better understand the approach taken in drafting the Final Rule and the relationship between the preamble and the rule, consider the following remarks explaining why FDA rejected the suggestion that a definition of manufacturer be added:

“‘Manufacture’ is a broad term not limited to production, packaging or labelling activities. Consequently we prefer to explain our interpretation of the final rule in the preamble and to have codified provisions state general principles rather than attempt to capture subtleties in a definition of manufacturer”.³

The Final Rule is written in broad, general terms. Definitional and interpretive issues are discussed at length in the preamble.

Compliance with good manufacturing practice is important for manufacturing concerns to assure the integrity and safety of their products. However compliance with dietary supplement CGMP is costly, and perhaps prohibitively so for an Asian medicine practitioner.

For practitioners who employ fewer than 20 full-time equivalent employees, the compliance date is June 2010, which leaves ample time to study the Final Rule and seek any further guidance from FDA which may be desired.⁴

Scope

Why do Asian medicine practitioners need to concern themselves with Government regulations of manufacturing? There are two reasons for this. First, FDA employs an extremely broad definition of manufacture which includes the distribution of manufactured products. It is the case that many Asian medicine practitioners purchase products labeled as dietary supplements from manufacturers and sell these products to their patients. In this sense the practitioners are part of the distribution process. Second, FDA’s definition of manufacturer ignores the concept of scale. In other words even a single practitioner who prepares a formula from herbal ingredients is considered a manufacturer.

Although the Final Rule is directed at a manufacturing and the manufacturing process, FDA’s definition of these terms goes far beyond what is normally thought of as manufacturing. FDA explains that manufacturing and manufacturing process are used:

“...In the broad sense, i.e. the terms refer to those activities that may be done from receipt of raw ingredients through the distribution of a finished dietary supplement, including labelling, packaging and holding activities.”⁵

³ 72 FR 34752 at 34804.

⁴ 72 FR 34752 at 34752.

⁵ 72 FR 34752 at 34762, footnote 1.

FDA adds that it:

“...Sometimes uses the terms to apply to only part of the process, i.e. those operations other than labelling, packaging and holding.”⁶

The latter usage of the terms is closer to the dictionary definition, which defines “manufacture” as meaning “to make (as in raw material) into a product suitable for use” and “to produce in accordance with an organized plan with division of labor.” Furthermore, the second dictionary definition introduces the concept of scale; that a manufacturing enterprise means people working together with division of labor.⁷ Most persons would not characterize a single artisan working alone to produce a product suitable for use as a manufacturer. The broader definition, adding additional functions as well as sweeping in the solo practitioner, is an embellishment added by FDA.

Analysis

The Final Rule applies to you only if you “...manufacture, package, label or hold a dietary supplement...”.⁸ If you don’t engage in any of these activities, then you need not observe any of the Final Rule’s requirements. And if what you manufacture, package, label or hold is not a dietary supplement, the Final Rule doesn’t apply to you either. The definition of these terms is of paramount importance.

For the purpose of analysis, this paper takes three categories of Asian medicine practitioners and assesses the impact of the Final Rule on each.

- A. Practitioners who do not dispense herbal formulas or dietary supplements to their patients.
- B. Practitioners who dispense herbal formulas to their patients, but only packaged and labeled finished products obtained from manufacturers or distributors
- C. Practitioners who prepare formulas from herbs and dispense them to their patients.

A practitioner may fall into more than one category.

The Final Rule has no impact on a Category A practitioner.

The activities of the category B practitioner may be subject to the Final Rule. A typical Category B practitioner maintains a supply of finished products, most, if not all of which, are labeled as dietary supplements, and sells them to the practitioner’s patients. These activities subject the practitioner to the Final Rule’s holding and distribution requirements. As explained above, FDA defines manufacturing to include holding and distributing the product and any one engaging in these activities is subject to the Final Rule.

⁶ 72 FR 34752 at 34762, footnote 1.

⁷ Webster’s Third New International Dictionary.

⁸ 72 FR 34752 at 34943; 21 CFR S.III.I(a).

However, the very first section of the Final Rule contains an important exemption. The Final Rule exempts holding by retail establishments.

§. III.I (b) states:

“The requirements pertaining to holding dietary supplements do not apply to you if you are holding those dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers. A retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual customers.”⁹

While the language is very helpful, a few ambiguities remain which are addressed in the preamble.

First, the preamble frames the issue as whether the dietary supplement CGMP requirements apply to retailers or individuals who sell dietary supplements directly to individual consumers, meaning that the FDA is not just talking about what is commonly thought of as a retail store, but is also including an individual, such as an Asian medicine practitioner, who sells dietary supplements to the practitioner’s patients.¹⁰

Second, the text of the §. III.I (b) says the requirements pertaining to holding dietary supplements do not apply to a retail establishment. The preamble contains an important clarification. FDA explains that if all you do in the manufacturing/distribution process is sell to consumers in the manner described in §. III.I (b), you are not subject to the dietary supplement CGMP requirements.¹¹ For persons holding dietary supplements and not covered by this exemption, these would include the distribution requirements contained in § III.470, product complaints requirements contained in subpart O, personnel, physical plant and grounds requirements, and related record keeping and written procedure requirements.¹²

Category B practitioners may keep their supply of finished products in a separate room in their offices. I believe such a room is not a “storage facility” for the purpose of the exception in this section, for “warehouse or other storage facility.” This language means a storage facility similar to a warehouse where the products are stored in bulk. Of course if the practitioner does store the practitioner’s supply of finished products in a warehouse or sells directly from a warehouse, then this exemption is of no use to the practitioner.

Support for this interpretation is found in the preamble. FDA gives an example of a distributor subject to the dietary supplement CGMP regulations.

“In another example a distributor who purchases a packaged and labeled dietary supplement and who then holds the product in a warehouse for distribution to another physical location is subject to the requirements related to its operations. The codified (sic) uses the word “hold” since it is a broad term which encompasses the activities of a distributor. Thus, the distributor would be responsible for complying with requirements in subpart M, Holding and

⁹ 72 FR 34752 at 34943; 21 CFR § III.I (b).

¹⁰ 72 FR 34752 at 34792 (response to comment 31).

¹¹ 72 FR 34752 at 34792 (response to comment 31).

¹² 72 FR 34752 at 34790 (response to comment 27).

Distributing, in addition to other requirements relating to its operations (e.g. Personnel, Physical Plant and Grounds)”¹³

In constructing this example of a distributor that is subject to the Final Rule, FDA is careful to describe an operation that is outside of the retail establishment exemption. The differentiating characteristics are the product is held in a warehouse and the product is distributed from the warehouse to another physical location. This reinforces the conclusion that a practitioner otherwise entitled to the retail establishment exemption does not lose the exemption by storing a supply of dietary supplements in a separate room in the practitioner’s office.

Subpart M, which addresses Holding and Distribution, contains a section dealing with distribution. On the face of it this would apply to a Class B practitioner, but further analysis leads to a different conclusion. Recall that the Final Rule only applies to those engaged in manufacturing, packaging, labelling or holding, so if the class B practitioner qualifies for the retail establishment exemption, the entire CGMP for dietary supplements will not apply to the practitioner, including the distribution section.

The category C practitioner prepares formulas from herbs, stores the herbal ingredients and the formulas in the practitioner’s office and sells formulas to patients. To the extent that these formulas are dietary supplements, these activities involve “holding” and “manufacturing” requiring compliance with the Final Rule. In this example the practitioner can claim the retail establishment exemption to avoid compliance on account of the practitioner’s holding activities.

Turning to manufacturing, FDA was asked to exempt herbalists before the Proposed Rule was issued. The preamble to the Proposed Rule discussed whether herbalists should be exempted and concluded they should not. After giving this some further thought, the FDA decided to grant limited relief to “...herbalists, naturopaths and other related health care providers.” through the technique of an exercise of enforcement discretion. This means that FDA is not bound to enforce the Final Rule against every manufacturer. FDA can decide not to enforce for what it considers good and sufficient reasons. In this instance FDA was impressed by the amount of training received by these practitioners and that the dietary supplements were formulated following a one-on-one consultation with practitioner’s client.¹⁴

In the preamble to the Final Rule the FDA commented:

“We believe a one-on-one consultation by a practitioner who is adequately trained in their profession may not necessitate the same types of controls as we are establishing in this final rule for manufacturing activities that are on a larger scale. Such a practitioner may make the formulations in advance of consultation and still make some formulations in very limited quantities for individual clients. We believe that it would be appropriate to consider the exercise of our enforcement discretion, on a case-by-case basis, to determine whether to apply the requirements of this final rule to such persons.”¹⁵

¹³ 72 FR 34752 at 34790 (response to comment 27).

¹⁴ 72 FR 34752 at 34793 (response to comment 32).

¹⁵ 72 FR 34752 at 34793 (response to comment 32).

Finally, FDA cautioned that it is not considering exercise of its enforcement discretion in two situations. First, a practitioner who prepares and sells a dietary supplement to a consumer without assessing whether it is appropriate for the consumer's needs in a one-on-one consultation. Second, a practitioner who prepares dietary supplements for which there is a known or suspected safety concern.

In evaluating FDA's policy statement on exercising enforcement discretion, keep in mind that the text of the Final Rule does not contain any exemption for the practitioner who prepares formulas considered dietary supplements and sells them to the practitioner's patients.

FDA continued the discussion of its possible exercise of enforcement discretion by raising another important issue:

'We do not expect the number of those subject to the consideration of our enforcement discretion to be very large. Many products that are manufactured by practitioners would not necessarily be considered to be dietary supplements (e.g. certain products used by traditional Asian medicine practitioners).'¹⁶

The quoted language about Asian medicine practitioners raises an issue beyond the scope of the Final Rule. What this says is FDA does not believe that many herbalists, especially traditional Asian medicine practitioners, manufacture dietary supplements. To the extent that herbal formulas prepared by the practitioners are not dietary supplements, then the Final Rule does not apply to them. If certain products manufactured by Asian medicine practitioners are not dietary supplements what are they?

The FDA's recent Guidance on The Regulation of Complementary and Alternative Medicine Products ("Guidance") as well as the National Centre For Alternative and Complementary Medicine's Backgrounder on Whole Medical Systems ("Backgrounder") suggest that some of these products are medicines, used to treat disease.¹⁷ If this is the case these products could be drugs, as defined in the Food, Drug and Cosmetic Act ("FD&C Act").¹⁸ In the quoted language FDA describes the practitioners as practicing medicine, which almost by definition involves treating disease, a terminology which leads directly into the definition of drug and a terminology which is scrupulously avoided in marketing dietary supplements. This is another important instance where FDA has not exercised its enforcement powers, except in the case of perceived safety issues, such as *guang fang ji* and other herbs containing aristolochic acid.¹⁹

¹⁶ 72 FR 34752 at 34793 (response to comment 32).

¹⁷ The Backgrounder says that traditional Chinese medicine proposes that "natural products catalogued in Chinese Materia Medica or acupuncture can be used...to treat virtually any illness..." Backgrounder, p.2. The Backgrounder then goes on to discuss the effectiveness of herbs used in classic formulae and gives examples of herbs used to treat specific diseases. The Backgrounder may be found on the web at nccam.nih.gov/health/backgrounds/wholemead.htm. FDA's guidance may be found on FDA's website, FDA.gov, by clicking Dockets under Reference Room and entering the docket number (2006D - 0480)

¹⁸ 21 USC 321 (g) (I).

¹⁹ When FDA acted against products containing aristolochic acid, one of the agency's first moves was to write a warning letter to industry, addressed to the major manufacturer trade associations, which opened by citing reports that "aristolochic acid has been found in some dietary supplements or other products that may be marketed as traditional herbal medicines." Subsequently FDA issued an import alert authorizing

This is not a perfect situation for Asian medicine practitioners who make herbal formulas for their patients. To the extent that these formulas are dietary supplements, non-compliance with the Final Rule is dependant on FDA's exercise of its enforcement discretion. FDA's expression of intention on this point is written in very iffy language and FDA is always free to change its mind. To the extent that these herbal formulas may be drugs, as defined in the FD&C Act, continued non-compliance with this statute is also dependant on FDA's enforcement policy. This having been said, the current state of affairs has been in existence for a long time and appears to have worked fairly well.

FDA also considered the position of academic institutions which operate clinics where herbal formula are prepared and dispensed to patients. FDA explained it is not FDA's policy to inspect academic institutions that provide training "for therapeutic disciplines that use, for example, dietary supplements in their practices" and this is another instance in which FDA may exercise its enforcement discretion, provided the products are dispensed in a process that includes one-on-one consultation with the patient and a practitioner with adequate training.²⁰

Finally, FDA suggested there would be future guidance on how it intends to exercise its enforcement discretion in the case of practitioners who may be considered manufacturers under the Final Rule.²¹ This is an opportunity to continue to press for a rule amendment, confirming the exemption of Asian medicine practitioners who prepare their own herbal formulas from the burden of the Final Rule, conditioned, as stated in the preamble, on the herbal formulas being dispensed after a one-on-one consultation by an adequately trained practitioner and the absence of any known or suspected safety concerns.

In light of these developments my recommendation is that efforts be accelerated to achieve a legislative solution by establishing a separate regulated category for Asian Medicine herbal formulas.

Section by Section Review

The sections of this part of the paper correspond to sections of the Preamble which discuss each subpart of the Final Rule. This review is not intended to be a complete summary of the Final Rule. It is intended to give the reader an idea of extensive scope of what the Final Rule requires and the difficulty an Asian medicine practitioner would have meeting these requirements.

Section I – Background

detention without inspection of a list of herbs suspected of containing aristolochic acid. This import alert charged six violations of law, including that these products were either adulterated dietary supplements or new drugs without a new drug application. FDA explained that it was "...not aware of any uses for botanicals in the family except as drugs or dietary supplements." Import alert #54-10, "Detention Without Physical Examination of Bulk or Finished Dietary Supplements and Other Products That May Contain Aristolochic Acid." (July 6, 2000)

²⁰ 72 FR 34752 at 34793 (response to comment 33).

²¹ 72 FR 34752 at 34794 (response to comment 34).

The material covered in this section is discussed under “Background” at the beginning of this paper.

Section II – How is the Final Rule Organized?

This subject is discussed above under “Structure”.

Section III – What Does the Final Rule Do?

This section discusses the need for current good manufacturing practice in the manufacture of dietary supplements and the reasons for particular rules. The FDA’s expansive definition of “manufacture” is explained in this section. Finally this section lists the highlights of the Final Rule.²²

Section IV – What General Comments Did We Receive?

Discussion of the need for written procedures takes up the largest part of this section. Establishing written procedures is important but burdensome for a manufacturing enterprise to assure the consistency and quality of its products. One can readily see the difficulty of compliance with these written procedure requirements when the manufacturing enterprise consists of a single Asian medicine practitioner. FDA did reduce the burden somewhat by eliminating written procedure requirements for some subparts in the interest of avoiding redundancy.²³

Section V – What Legal Authority Comments Did We Receive?

DSHEA mandates that the CGMP for dietary supplements be “modeled after the current good manufacturing practice regulations for food”. Over half of this section is devoted to discussing whether the Final Rule is modeled on the food regulations and to discussing the meaning of “model”. This section also lays to rest any hope arising from a statement in the preamble to the Proposed Rule that there might be an exemption for practitioners who buy herbs originating in a foreign country or another state and sell dietary supplements made from these herbs only to patients in the state where the practitioner’s office is located, based on the notion that the transactions in dietary supplements only involve intrastate commerce. FDA says “the final rule covers not only finished products that have moved in interstate commerce but also products made from ingredients or components that have moved in interstate commerce. This is true regardless of the amount of ingredient or the component in the product....”²⁴

Section VI – What Comments Did We Get On The General Provisions? (Subpart A)

§ 111.1 of the Final Rule describes who is subject to its terms. The answer is given in broad terms. You are subject to the rule “...if you manufacture, package, label or hold a dietary supplement”.

²² 72 FR 34752 at 34761.

²³ 72 FR 34752 at 34765.

²⁴ 72 FR 34752 at 34776, 34787.

The preamble soon gets into a complicated discussion of who is responsible for compliance when more than one party is engaged in these activities for a particular dietary supplement. This is where the FDA's interpretation of "holding" to include the activities of distributors is found.

Next, the preamble discusses exemptions and FDA's decision to include the retail establishment exemption in the Final Rule. Further on FDA discusses its rejection of the requested exemption for herbalists. Both of these issues are explored under "Analysis".

The discussion then turns to the definitions contained in § 111.3. Here the FDA gives its reasons for declining to define "manufacture". This point is also discussed under "Analysis".²⁵

VII – Comments on Personnel (Subpart B)

This subpart applies to those who manufacture, package, label or hold dietary supplements, absent an exemption. The preamble explains that no minimum number of employees is specified. However the implication of the Final Rule is that at least two persons are required: "one to perform the work and the second to check the work performed". This requirement again emphasizes the importance for Asian medicine practitioners of an exemption from the Final Rule.²⁶

VIII – Comments On Physical Plant and Grounds (Subpart C)

Among this subpart's requirements are that the physical plant be kept in a clean and sanitary condition and that pests be effectively controlled. One or more employees must be appointed to supervise sanitation. Written procedures must be established for cleaning the plant and for pest control. Written records must be kept of carrying out cleaning and pest control procedures and confirming that water which may become a part of a dietary supplement meets the requirements of the subpart.²⁷

IX – Comments on Requirements Related To Equipment and Utensils (Subpart D)

This subpart contains requirements for equipment and utensils used to manufacture, package, label or hold dietary supplements. These requirements include calibration, maintenance, cleaning and sanitizing. Equipment includes measuring equipment, such as a scale. Specific rules govern refrigeration equipment. Quality control personnel must periodically review records of checks of automated, mechanical or electronic equipment. Written procedure and record keeping requirements apply to many of these mandates.²⁸

X – Comments on Requirements To Establish a Production and Process Control System (Subpart E)

A manufacturer of dietary supplements is required to establish a production process and control system which includes a master manufacturing record and specifications for the

²⁵ 72 FR 34752 at 34789, 34790 (distributor), 34792 (retail establishment exemption), 34793 (herbalists), 34804 (manufacturer).

²⁶ 72 FR 34752 at 34807, 34810 (two person requirement).

²⁷ 72 FR 34752 at 34812.

²⁸ 72 FR 34752 at 34822.

purity, strength and composition of the finished product. This subpart describes testing required for components, at intermediate stages of production and for the finished product. Also included are instructions on how to determine whether specifications have been met and what needs to be done if specifications are not met. Manufacturers are required to retain representative and reserve samples for each batch produced. Extensive record keeping and written procedure requirements are imposed here and in subsequent subparts, which deal with parts of the manufacturing process in greater detail.²⁹

XI – Comments on Requirements for Quality Control (Subpart F)

This subpart deals with one aspect of the production process and control system, quality control. This function is to be carried out by quality control personnel, who are expected to ensure that operations are conducted in a way that assures the quality of the product, and that the product is properly packaged and labeled, all as specified in the master manufacturing record. These extensive responsibilities are performed through checking and testing numerous specified items, or reviewing and approving the decisions of others and the results of checks and tests performed by others. These activities are to be carried out in accordance with written procedures and extensive documentation and record keeping is required.³⁰

XII – Comments on Requirements for Components, Packaging and Labels (Subpart G)

This subpart covers another aspect of the production and process control system, control of components, packaging and labelling. Detailed instructions are given on how to check each of these items upon receipt by the manufacturer. The process is protected by a quarantine system and requirements for a tracking system enabling the manufacturer to trace back the components in the finished product to particular suppliers. Written procedures and record keeping are required.³¹

XIII – Comments on Requirements for the Master Manufacturing Record (Subpart H)

This subpart describes the contents of the master manufacturing record, which is central to the production and process control system. Included in the instructions is a requirement that for manual operations two personal are required for weighing, measuring and adding a component; one to perform each of these acts and the other to check and verify.³²

XIV – Comments on Requirements for the Batch Production Record (Subpart I)

As part of the production and process control system the manufacturer is required to prepare a batch production record for each batch of dietary supplements produced documenting the performance of mandated tests, checks and verifications.³³

XV – Comments on Requirements for Laboratory Operations (Subpart J)

²⁹ 72 FR 34752 at 34833.

³⁰ 72 FR 34752 at 34861.

³¹ 72 FR 34752 at 34874.

³² 72 FR 34752 at 34881, 34885 (two person requirement).

³³ 72 FR 34752 at 34886.

This part of the production and process control system requires the manufacturer to use adequate laboratory facilities to perform the testing required by these rules. Some of these procedures can be outsourced, but the manufacturer remains responsible for the appropriateness of the tests and their compliance with designated procedures.³⁴

XVI – Comments on Requirements for Manufacturing (Subpart K)

The manufacturing system must be designed to ensure that product specifications are consistently met. Prior subparts also emphasize the importance of appropriate controls to support meeting specifications. Subpart K also describes the precautions that need to be taken to prevent contamination, including prevention of the growth of microorganisms and standards for the quality of water to be used in the manufacturing process. Protection against contamination of dietary supplements by metal or other foreign materials is also described.³⁵

XVII – Comments on Requirements for Packaging and Labelling Operations (Subpart L)

The objectives of the packaging and labelling requirements are to ensure the quality of the product and ensure that the product is packaged and labeled in accordance with the master manufacturing record. Protection against contamination, sanitary measures and avoidance of mix-ups are stressed.

A batch, lot or control number must be assigned to each lot of dietary supplements distributed, so that the manufacturer can determine the complete manufacturing history and control of the product through distribution. However, the Final Rule does not require this number to be affixed to the immediate container or product label. Nonetheless FDA believes these provisions are sufficient to permit a prompt and accurate trace back of a product in the event of an adverse event report.

This subpart also discusses questions raised about the content of the label. FDA responded that it is not proposing any specific statements in the Final Rule. As previously stated, FDA will judge voluntary statements on the label about the manufacturing process based on whether the statements are misleading. Simply saying a product is produced in compliance with CGMP without more is probably misleading unless it is explained that all dietary supplements must be so manufactured and that this does not guarantee that the dietary supplement is safe or effective.³⁶

XVIII – Comments on Holding and Distributing (Subpart M)

Many participants in the chain of distribution hold dietary supplements such as brokers, wholesalers and distributors. And if you do, unless you qualify for the retail establishment exemption discussed above, you are subject not just to the requirements of subpart M, but to all other applicable requirements, such as the requirements for

³⁴ 72 FR 34752 at 34891.

³⁵ 72 FR 34752 at 34894.

³⁶ 72 FR 34752 at 34898.

personnel, physical plant and grounds, equipment and utensils, quality control and others.

The objective of the holding and distributing requirements is to protect the identity, purity, strength and composition of the dietary supplement and protect against contamination and deterioration. These goals are accomplished by controlling temperature, humidity and light. The requirements cover dietary supplements as well as components, in-process materials, reserve samples, packaging and labels.³⁷

XIX – Comments on Returned Dietary Supplements (Subpart N)

The thrust of these requirements is that returned dietary supplements must be destroyed or suitably disposed of, unless quality control personnel, following a material review, approve salvage for redistribution or reprocessing. The dietary supplements may not always be returned to the manufacturer. At least in some instances suitable disposition includes returning the product to the manufacturer. In such a case, the manufacturer can then decide whether to destroy the product or explore the possibilities of salvage or reprocessing through a material review of the situation by quality control personnel. The role of quality control personnel in this process, including determination of what testing is necessary, is also discussed in subpart F, Requirements for Quality Control.³⁸

XX – Comments on Product Complaints (Subpart O)

All product complaints must be reviewed to determine whether a possible failure to meet specifications or other requirements of the Final Rule is implicated. If the reviewer determines that this is the case, then the complaint must be investigated. The review and any investigation must be carried out by qualified persons and the decision on whether to investigate, the findings and the steps taken in any follow up of an investigation must be approved by quality control personnel.

The Final Rule applies to everyone in the manufacturing process as well as the distribution chain. But a particular person in this group may not be in a position to fully respond to the requirements of this subpart. For example, a distributor receiving a complaint may not be aware of whether the complaint involves a failure at the manufacturer level, or be in a position to investigate this. FDA explains in the preamble that what the distributor should do is determine whether the complaint implicates the holding requirements and other requirements for which the distributor is responsible. If it does not, then the distributor should pass along the complaint to the manufacturer.³⁹

XXI – Comments on Records and Record keeping (Subpart P)

Most subparts of the Final Rule require creating written procedures and keeping written records of activities mandated by these regulations in accordance with Subpart P. Persons covered by these rules need to retain these written materials for a period of one year past the shelf life date of the product to which they relate, or if there is no shelf life given, for a period of two years after distribution. These procedures and records are useful tools for effective implementation and monitoring of the manufacturing process.

³⁷ 72 FR 34752 at 34903.

³⁸ 72 FR 34752 at 34905.

³⁹ 72 FR 34752 at 34908.

These materials are also a useful compliance check for FDA, which has the right to inspect these materials whenever it requests.⁴⁰

XII – Other Comments and Miscellaneous

In structuring the CGMP regulations for dietary supplements FDA considered whether to adopt just one rule or whether to have separate rules for subcategories of dietary supplements, as was done in the case of food. FDA opted for one broad rule. Here lies one basic cause of many of the problems for practitioners. One rule governs all, both large and small. Not surprisingly FDA admits that the controls being established are suitable for manufacturing activities on a larger scale than those performed by an individual practitioner.⁴¹

XXIII – XXVII

The concluding sections of the preamble discuss the impact of the Final Rule. FDA estimates that compliance will be costly, especially so for very small establishments, relative to their resources. A very small establishment is defined by the FDA as a business with less than 20 employees, a category having median annual revenue under \$1 million. Businesses with 20 to 499 employees, a category having median annual revenue of \$5 million to \$10 million, account for almost 90% of those affected by the Final Rule, according to FDA's estimate.

For the very small establishment FDA estimates setup costs of \$26,000 and annual costs of \$46,000. FDA's model predicts that 140 very small and 32 small manufacturers will be at risk of going out of business due to the impact of the Final Rule.⁴²

Although the point is not discussed in the preamble, I doubt whether the FDA's survey included many (if any) practitioners, either because FDA doubts that traditional Asian medicine practitioners manufacture dietary supplements or its enforcement policy.

The costs of implementing the Final Rule are offset by the benefits foreseen by the FDA from reducing the possibility of acute illness and from fewer product recalls.⁴³

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⁴⁰ 72 FR 34752 at 34911.

⁴¹ 72 FR 34752 at 34913, 34914 (single rule decision)

⁴² 72 FR 34752 at 34917, 34938

⁴³ 72 FR 34752 at 34936