Rexall Sundown

901 Broken Sound Parkway NW
Boca Raton, FL 33487-3693
(561) 241-9400
Fax (561) 995-5188
E Mail Address: RSRegDpt@aol.com

June 5, 1997

BY UPS OVERNIGHT DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Docket No. 96N-0419: Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements

Dear Sir:

Enclosed please find four (4) copies of Rexall Sundown, Inc.'s Comments on the above-referenced Docket.

Very truly yours,

Debbie Trinker/mw

Deborah Shur Trinker
Director of Regulatory Affairs
and Corporate Counsel

DST/mw

Enclosures

96N-0419

COMENCVR DOC

C66

Rexall Sundown

901 Broken Sound Parkway NW
Boca Raton, FL 33487-3693
(561) 241-9400
Fax (561) 995-5188
E Mail Address: RSRegDpt@aol.com

June 6, 1997

VIA UPS OVERNIGHT DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

RE: Docket No. 96N-0419: Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements

I. INTRODUCTORY REMARKS

1. The following Comments are submitted by Rexall Sundown, Inc. ("Rexall Sundown" or the "Company") in response to the Food and Drug Administration ("FDA") Advance Notice of Proposed Rulemaking ("ANPRM"), Current Good Manufacturing Practice ("CGMP") in Manufacturing, Packing, or Holding Dietary Supplements, 62 *Fed. Reg.* 5700 (February 6, 1997). As a manufacturer and distributor of over 1900 stock keeping units (SKUs) of dietary supplements, this Docket is of the utmost significance to Rexall Sundown. To generally summarize Rexall Sundown's position, the Company believes that existing food GMPs under 21 CFR Part 110 need some refinement to assure that dietary supplements, which are typically formulated in solid oral dosage forms, are safe, quality foods. Accordingly, Rexall Sundown supports the FDA's proposal to develop and implement CGMP regulations that are specific for dietary supplements and dietary supplement ingredients. Rexall Sundown participated in the preparation of the industry

submission which is published in the ANPRM, and urges FDA to carefully consider the responsive comments on the industry proposal in formulating the proposed rule on dietary supplement GMPs.

2. However, in questions posed after the industry proposal, FDA appears to be suggesting potential GMP requirements that would exceed the statutory parameters of the Dietary Supplement, Health and Education Act ("DSHEA"), and in certain instances would exceed current GMPs required for finished pharmaceutical products under 21 CFR Part 211. For example, FDA has posed the question of whether consumer injury and illness complaints received by a dietary firm should be referred to competent medical authorities. DSHEA amends Section 402 (g)(2) of the Federal Food, Drug and Cosmetic Act ("the Act"), 21 U.S.C. 342 (g)(2) to provide that "[t]he Secretary may by regulation prescribe good manufacturing practices for dietary supplements and that [such] regulations shall be modeled after current good manufacturing practice regulations for foods and may not impose standards for which there is no current and generally available analytical methodology." Thus, imposing GMP requirements for dietary supplements which exceed the admittedly more stringent **drug** GMPs would not comply with Section 402 (g) (2) of the Act. In its review of this and other safety-related issues in this Docket, such as manufacturer review of the safety of a specific supplement, FDA should recognize that the product category of lawfully marketed dietary supplements, when used according to labeled directions, has a

history of safe use. Apart from these general comments, specific remarks on aspects of the industry proposal and the FDA questions are discussed below.

II. DISCUSSION ON THE INDUSTRY PROPOSAL

3. Rexall Sundown has comments on the portions of the Industry Proposal under the section, **Production and Process Controls**. At **Section (c) (7), Handling and storage of raw materials, in-process materials and rework**, Rexall Sundown supports the FDA position the each lot of raw material, in-process and reworked material that is liable to adulteration should be examined against specifications to ensure compliance with applicable FDA regulations. To further promote quality raw materials, the Company supports FDA's proposal that in lieu of such examination by the manufacturer, a guarantee or certification of examination may be accepted from the supplier of a component, provided that the manufacturer establishes the reliability of the supplier's examination. With respect to raw materials and other ingredients susceptible to adulteration with aflatoxin and other natural toxins, FDA should, in a proceeding outside this Docket, establish defect action levels (DALs) for specific natural contaminants that are identified with specific dietary ingredients. This practice is followed by FDA for conventional foods[1] and would be appropriate for dietary supplements.

[1] Consistent with FDA's approach with DALs for conventional foods, listed DALs for dietary ingredients could be periodically lowered as technology permits. See 21 CFR 110.110.

4. **Production and Process Controls, Section (d) (5) Manufacturing operations,** states that "[m]easures such as sterilizing, **irradiating,** pasteurizing, freezing, refrigerating, controlling pH, etc. shall be adequate under the conditions of manufacture, handling, and distribution to prevent dietary products from being adulterated within the meaning of the Act." 62 *Fed. Reg.* at 5705 (emphasis added). However, the irradiation of dietary supplement ingredients is disallowed under Section 402(a)(7) of the Act as an effective means of controlling microbiological contamination, because there is currently no authorizing regulation or exemption. Rexall Sundown requests FDA revisit and reevaluate the propriety of using irradiation, or other generally acceptable methods of sterilization, of certain dietary ingredients of plant origin when traditional manufacturing measures are insufficient to control microbiological contamination.[2]

5. Production and Process Controls, **Section (d) (9) Manufacturing Operations** proposes that "[e]ffective measures shall be taken as necessary to protect against the inclusion of metal or other extraneous material in product. Compliance with this requirement may be accomplished by using sieves, traps, magnets, electronic metal detectors, or other suitable means." *Id.* It is Rexall Sundown's experience that contamination of its dietary supplement product line with metal and other extraneous material that might be detected by

[2] Rexall Sundown understands that FDA would need to proceed by separate rulemaking to authorize use of irradiation. See generally, Part 179 - Irradiation in the Production, Processing and Handling of Food.

sieves, traps, magnets, electronic metal detectors and other suitable effective means is highly unusual. Moreover, manufacturers are typically able to identify the particular piece of equipment that is the source of the metal contamination. For these purposes, the use of a portable metal detector is an effective and suitable means to protect against the inclusion of metal in product. Given the rarity of metal contamination, the ability to isolate the source of contamination, the effective use of portable metal detectors and the high costs associated with use of stationary metal detectors on a plant-wide basis, Rexall Sundown respectfully requests that the first sentence of this provision should be modified as follows:

> "Effective measures shall be taken as necessary to protect against the inclusion of metal or other extraneous material in the product when there is reason to suspect that the product is contaminated by metal or other extraneous material."

III. RESPONSE TO FDA QUESTIONS

6. **Question 1 asks if there is a need to develop specific DALs for dietary ingredients.** Rexall Sundown refers to its response in paragraph 3 above supporting FDA issuance of DALs and notes that the need for DALs is most likely for botanical ingredients, which like spices and certain plant-derived foods, are susceptible to unavoidable defects. Rather than prohibit the dietary ingredient as an adulterated food, allowances should be made that would allow for reasonable use of the dietary ingredient while protecting the public

against natural or unavoidable defects that pose hazards to health. FDA's role in identifying botanicals at risk for defects is important because not all companies may have sufficient laboratory equipment and technical expertise to identify and quantify potential defects.

7. **Question 2 requests comments on appropriate testing requirements to provide positive identification of dietary ingredients, particularly plant materials, used in dietary supplements.** Rexall Sundown believes it is unnecessary for FDA to promulgate specific testing requirements for this purpose. Regulatory specification of dietary ingredients in e.g., herbals assumes that specific dietary ingredients should be qualified in all botanical-derived supplements--a premise which may not be appropriate for all botanicals. For example, the active constituent "of choice" in Echinacea purpurea has changed over time. Rexall Sundown has also experienced that laboratories of high repute "reasonably differ" over what constitutes an appropriate marker in certain plant materials. Moreover, analytical methodology to identify plant materials continues to evolve. DSHEA requires that dietary supplement GMPs may not impose standards for which there is no current and generally available analytical methodology. See Section 402 (g)(2) of the Act. Conversely, an FDA designation of specific testing requirements would have to be updated regularly as methodologies evolve. Rexall Sundown submits that the decision as to what constitutes adequate testing to identity different types of ingredients should be left to the scientific and technical expertise of the manufacturer. Also, testing requirements may attach to vendors asked to provide raw material guarantees to the manufacturer under the proposed Production

and Process Control provisions of the CGMP. For example, botanical vendors could develop plant reference standards and confirm botanical identity on Certificates of Analysis supplied to manufacturers.

8. **Question 3 requests comments on standards that should be met in certifying that a dietary ingredient or dietary supplement is not contaminated with filth; that it is free of harmful contaminants, pesticide residues, or other impurities; that it is microbiologically safe; and that it meets specified quality and identity standards.** Certification by the supplier is sufficient with appropriate steps taken to confirm reliability of the supplier's certification process. Confirmation of reliability can be accomplished by the manufacturer with a variety of measures, including e.g., "due diligence" review of vendors, additional independent analyses, audits conducted in-house by the supplement manufacturer, and vendor-supplied analysis from manufacturer-selected independent laboratories to confirm in-house results. With respect to the Agency's inquiries on standards to avoid microbiological contamination, there are currently in place general microbiological assays in the United States Pharmacopoeia ("USP") that Rexall Sundown has found beneficial in assuring that its products are free from unsafe microbiological agents. There are also monographs with standards of identity for many dietary ingredients in the USP which help assure specified quality and identity standards.

9. **At Question 4 the Agency asks for comments on whether the CGMP should include requirements for manufacturers to establish procedures to document that the procedures prescribed for the manufacture of a dietary supplement are followed on a continuing or day to day basis.** Rexall Sundown does not believe there is a need for GMPs to require a manufacturer to establish still further procedures to document that its standard operating procedures are followed on a continuing or day-to-day basis. This requirement would be redundant to actual practices and poses unnecessary administrative burdens on dietary supplement companies. As a practical matter, following SOPs is vital to assuring that products are safely and properly manufactured; deviations from SOPs result in faulty products that may be adulterated and/or misbranded, and thus subject to safety issues, regulatory action and recall.

10. **Question 5 asks for comments on whether dietary supplement CGMP should require that reports of injuries or illnesses to a firm be evaluated by competent medical authorities to determine whether follow-up action is necessary to protect the public health.** As mentioned at paragraph 3 above, Rexall Sundown opposes this suggestion on the legal grounds that it is outside the authority of DSHEA, and is not even required by Part 211, "Current Good Manufacturing Practice for Finished Pharmaceutical,"[3] as well as on practical considerations related to its experiences with

[3] 21 CFR 211.198 requires that written procedures for complaints include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be

consumer complaints. In those limited instances where injury or illness is reported to the company, the report generally related to minor complaints, and fortunately, not to serious illness. Also, the Company has found that in those limited instances of reported illness, the consumer has already been evaluated be a competent medical authority.

11. **Question 6 asks for comments on whether CGMP for dietary supplements should require manufacturers to establish procedures to identify, evaluate and respond to potential safety concerns with dietary ingredients. In addition, the FDA asks for comments on whether it should require that such an evaluation be documented in a firm's records, and, if so, what type of records would be adequate to document that such an evaluation had occurred.** Under the Act, dietary supplements, like all foods, must be safe. Moreover, DSHEA amended the Act by adding Section 402(f)(1)(A)(i)(ii) which states that "[a] food shall be deemed to be adulterated ... if it presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or, if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use." The Act effectively already requires the manufacturer to identify, evaluate and consider potential safety concerns for lawfully formulated and labeled dietary ingredients. To the extent that FDA is proposing formalized procedures and FDA review of the manufacturer's safety data that would be generated responsive to such

---

reported to the FDA. This section does not delegate investigation responsibility to outside "competent medical authorities."

procedures, the Agency would, as a practical matter, be imposing preclearance and post-surveillance requirements for supplements that exceed the statutory provisions of DSHEA.

12. **At Question (7), FDA has asked for comments on whether specific controls are necessary for computer controlled or assisted operations.** This is another instance where technology is rapidly evolving and a manufacturer electing to use software programs and equipment should be required to implement reasonable internal procedures to determine if computer controlled operations are functioning properly. FDA should also recognize that there are other "checks and balances" to confirm validity of computer controlled operations in the traditional assays that are performed on finished dietary supplements to ensure e.g., content uniformity, and qualitative and quantitative evaluation of dietary ingredients. Also, while dietary supplements must meet specified label claim, the USP recognizes minor deviations in amount of active dietary ingredients that are not allowed by USP for pharmaceutical entities with more narrow therapeutic and toxicity ranges. Thus, any minor variation in the amount of active ingredient that might be result from a computer-generated deviation and fall outside of product specifications would tend to be unlikely and not pose a safety issue.

13. **Questions (8) and (9) ask for comments on whether Hazard Analysis Critical Control Points (HAACP) principles would be preferable to broad CGMP regulations for the dietary supplement industry.** After reviewing HAACP, which is currently

required only for the seafood industry, Rexall Sundown rejects HAACP as being appropriate for dietary supplement manufacturing operations. Dietary supplements enjoy a safe history of use, and HAACP principles are utilized to identify and address hazards that are reasonably expected to occur with a particular product category, based on e.g., microbiological contamination that can result in food-borne illness. As a practical matter, CGMPs have well served the dietary supplement industry. The proposed broad-based industry CGMPs will further promote safe, quality supplements and assure the public that all lawfully marketed dietary supplements have been manufactured according to a baseline standard of quality.

IV. CONCLUSION

14. Rexall Sundown appreciates the opportunity to comment on the FDA's ANPRM to implement CGMPs specific to dietary ingredients and dietary supplements. As noted above, Rexall Sundown is in general support of the published industry proposal and appreciates the complexity of the Agency's task in this Docket. Certain aspects of the ANPRM, however, call for Agency action that goes beyond the statutory authority of the Act.

Respectfully submitted,

Rexall Sundown, Inc.:

By: Deborah Patane /DST
Deborah Patane, R.Ph.
Vice President of Operations

and
Richard Werber
Vice President and General Counsel

Deborah Shur Trinker
Deborah Shur Trinker
Director of Regulatory Affairs
and Corporate Counsel