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Room 1061
Rockville, MD 20852

RE: Docket No. 96N-0417

To Whom It Concerns:

The following is presented before the United States of America, Department of Health and Human Services, Food and Drug Administration concerning the published Proposed Rule on **Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements** as it appeared in the *Federal Register: March 13, 2003 (Volume 68, Number 49)*. The commentary is provided exclusively on behalf of **ChromaDex, Inc.**, a California corporation.

ChromaDex is a manufacturer and supplier of reference standards and reference materials to the food, dietary supplement, and pharmaceutical industries. Our product line primarily consists of botanical reference materials and reference standards. ChromaDex is the only supplier of reference materials and reference standards that seeks independent verification from a knowledgeable source as to the quality and validity of standards. ChromaDex uses the American Herbal Pharmacopoeia (AHP) as that source. ChromaDex also develops scientifically valid analytical methods on behalf of our clients that utilize reference materials and reference standards for method evaluation and validation as well as for quantification of the materials presented. ChromaDex staff has participated in AOAC method validation and served as instructional sources concerning the AOAC practices employed in methods validation. This understanding of the substances and science necessary to ascertain accurate information concerning the identity, purity, quality, strength and composition of dietary ingredients and dietary supplements provides us with a unique perspective on specific aspects of the Proposed Rule. Not only do our customers include the manufacturers and distributors of dietary supplements and dietary ingredients, we serve as a resource for reference standards and reference materials to US government organizations inclusive of the National Institutes of Health (NIH), the Office of Dietary Supplements (ODS), the National Institute of Standards and Technology (NIST) and the Food and Drug Administration (FDA). This background and perspective allow us to offer specific commentary on specific areas of the Proposed Rule.

BACKGROUND AND COVERAGE

The background, experience and demonstrated capabilities of ChromaDex afford us the perspective necessary to comment appropriately on the primary issues discussed in this document. ChromaDex has long supported the development and application of codified cGMPs

specific to dietary supplements and we have awaited the issuance of the Proposed Rule with anticipation. Our primary areas of address concern the following:

- The *de facto* requirements for developing and applying "scientifically valid" test methods
- The matter of assessment and requirements for laboratories performing testing using such "scientifically valid" test methods
- The issue of identification of sources for methods and criteria that are essential in evaluating dietary supplements and dietary ingredients

These issues are particularly relevant to the stated purpose of the Proposed Rule insofar as they are the critical piece in meeting FDA's stated goal of what will become a Final Rule to:

"*. . . require manufacturers to evaluate the identity, purity, quality, strength, and composition of their dietary ingredients and dietary supplements.*"[I]

As cited within the Proposed Rule such evaluation must be performed using "scientifically valid methods[II]." This remains true regardless of whether the testing is performed on the finished form dietary ingredient or dietary supplement or on the incoming or inprocess materials[III]. The matter of mandating the use of scientifically valid methods in application (whether they are "official" or not) is the essential element.

There are requirements for developing, maintaining, and applying scientifically valid methods that are not cited in either the preamble to the Proposed Rule or within the body of the Proposed Rule itself. Moreover, there is limited identification of the sources of such methods and criteria noted in the Proposed Rule and preamble. Lastly, there is but a single notation within the Proposed Rule that identifies only reference standards with implicit assertion that these are useful[IV]. We find that these issues require address on a specific level in order to insure that FDA achieves the goals for the Final Rule concerning establishment of cGMPs for dietary supplements. To clarify the position that ChromaDex offers in its commentary two general sections:

- The need to clarify requirements for scientifically valid methods
- The need to clearly identify sources of scientifically valid methods and criteria that are not "official" within the meaning of the term as FDA applies it to compendia

REQUIREMENTS FOR SCIENTIFICALLY VALID METHODS

The evaluative process involves testing a host of parameters to achieve FDA's stated goal of assuring the "identity, purity, quality, strength and composition" of dietary ingredients and dietary supplements. Each of these evaluative parameters imposes requirements on the methods employed in order to insure the accuracy of the resultant data. Some point of reference must be used to insure that the methods are valid and that the data generated are accurate. These points of reference fall into two general categories (as defined and understood in the world of analytics.

Reference Materials

Reference material is defined as:

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"*Material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, assessment of a measurement method, or for assigning values to materials.*[vi]" [emphasis added]

Reference materials by their definition provide points of certainty concerning one or more of the property values associated with the method applied. This affords them service in calibrating apparati and validating methods. Reference materials are, therefore, essential to the determination of the validity of the method and by extension the validity of the results generated by application of the method. Their usefulness may be broad or narrow dependent on the number of property values that are "well established". Reference materials are particularly valuable when testing complex chemical mixtures such as those that naturally exist within botanical dietary ingredients and dietary supplements. As the simplest example, a voucher specimen serves as a reference material for determining the identity of a botanical material intended for incorporation in a dietary supplement or for transformation into a dietary ingredient. The fact that such specimens' identity are sufficiently well established to insure that they are the correct genus and species of plant "calibrates" the organoleptic evaluation of the botanical material in comparison.

Increasing in level of detail, a well-characterized reference material is necessary to evaluate the identity of processed botanicals in that they provide at a minimum macro and microscopic reference points for determining the identity of the material and, at a maximum level, afford validation of methods employed in determining the strength and composition of multifaceted chemical components in these botanicals. Reference materials are useful in these evaluations during and after processing. The fact that reference materials come with characterization not necessarily of a single entity but with characterization of a wide variety of indigenous phytochemicals in plant extracts assures the user that the method they employ is applicable to their conformance with the cGMP requirement.

The use of reference materials as part of a program that insures the scientific validity of the methods employed is mandatory. It is because of this mandate and further discussed misapplication of terms that formal citation for the use of reference materials in codified cGMPs for dietary supplements is necessary.

Reference Standards

Reference *standards* are frequently and inappropriately confused with reference *materials*. Reference standards may be used for some of the same purposes as reference materials but they are applicable with greater specificity. Reference standards are also potentially damaging as a sole criterion particularly as applied to testing botanical dietary ingredients and dietary supplements. As the definition of reference standard states:

"*A reference standard is a highly purified compound that is well characterized.*[vi]"

The simplicity of the definition arises from the fact that a reference standard is a single entity in highly purified form. The characterization aspect is the common element in comparing reference standards and reference materials. This similarity does not mean they are capable of complete substitution. Reference standards are particularly applicable (as noted in the source of the quotation) for validating methods that determine quantification of specific single chemical entities. Reference standards are designed to perform as tools for such assessments. They are also used as comparatives in the routine evaluation of single chemicals as often present in dietary supplements or dietary ingredients. According to FDA's own guidance (cited as a reference in the preamble to the Proposed Rule[vii]), the use of reference standards is a requirement in the determination of the validity of such scientific methods[viii]. Thus, the

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requirement should be more clearly stated in the context of the Final Rule on Dietary Supplement cGMPs.

The challenge in applying reference materials and reference standards comes when they are substituted one for the other. The misapplication of reference standards poses a significant challenge to the dietary supplement industry today. The FDA goal of assuring the identity, purity, quality, strength and composition of dietary ingredients and dietary supplements mandates the use of both reference materials and reference standards. The following example demonstrates this point:

The testing and evaluation of a St. Johns Wort extract becomes mandatory under the cGMPs for dietary supplements. Commonly only a single "marker" compound is used for such determinations. This marker compound (hypericin) is available as a reference standard useful in affirming the scientific validity of the method employed and in assuring the "strength" of the extract. However, synthetic hypericin is too readily available today and can be used as an added component to the St. Johns Wort "extract." Thus, while the hypericin reference standard is useful for determining the strength of one component of the St. Johns Wort extract it is not applicable to the determination to the determination of the identity, purity and composition and thus quality of the material. An independently verified reference material representative of St. Johns Wort extract serves this purpose. If applied from the beginning of the production of a dietary supplement of St. Johns Wort extract, the application of reference materials and reference standards affords conformance to the cGMP requirements as follows:

- The St. Johns Wort botanical is examined using a reference material (specifically a voucher specimen) to establish the validity of the examination of the plant used (identity).
- The dried and ground St. Johns Wort is prepared for extraction by a manufacturer of the extract and is compared to a reference material of specific characterization to insure that the ground material is St. Johns Wort (identity, purity, composition).
- The extract is produced and the methods used to determine the success of the extraction are demonstrated as valid using reference materials from known extracts and (possibly) reference standards for hypericin, hyperforin and possibly other components to determine if the desired levels of these single entities are achieved in the extract (quality, strength and composition).
- The extract is then used in the making of the dietary supplement capable of being tested in finished form using methods demonstrated as valid using reference materials for St. Johns Wort and reference standards for hypericin and hyperforin (since these levels are among the labeled claims). This testing and evaluation conforms to the requirements of proposed 21 CFR 111.65(g) but can only occur if appropriate reference materials and reference standards are employed (identity, purity, quality, strength and composition).

The application of reference materials and/or reference standards is not truly intuitive. While the application of these substances is mandatory (as inferred by proposed section 111.60(b)(1)(iv) the lack of inclusion of reference materials here and elsewhere in the Proposed Rule is an omission that requires correction. The designation of the use of reference materials and/or reference standards adds clarity to the testing requirements. If the dietary supplement were to offer but a single chemical entity (vitamin C for example) or a combination of single chemical entities (a multivitamin) the exclusive use of reference standards would make sense. However, the dietary supplement world includes botanicals and all their complexity. Thus, it is

imperative to mandate the application of reference materials as appropriate since there are instances where such application is fully appropriate and necessary to achieve the scientific validity requirement of the cGMPs.

RECOGNITION OF OTHER AUTHORITATIVE SOURCES

Throughout the preamble discussion of sections 111.35 and 111.60 of the Proposed Rule, FDA specifically cited the applicability of standard compendial methods and criteria for the identification and quality assessment of dietary ingredients and dietary supplements[IX]. These evaluations may include macroscopic, microscopic, and various types of chemical analyses[X]. The "official references and others[XI]" as noted are useful for a variety of test methods and criteria. However, ChromaDex has found that there are other authoritative sources for the criteria and methods necessary to determine the identity, purity, quality, strength and composition of dietary ingredients and dietary supplements. This is particularly true in the area of botanical dietary ingredients and dietary supplements. The monographs that exist in the American Herbal Pharmacopoeia (AHP), the European Pharmacopoeia (EP) the botanical monographs published by the World Health Organization (WHO) are specific sources of particular worthiness. While the USP and AOAC compendia present 19 total "official" monographs for botanical products, these other authoritative sources present hundreds. The real-world picture is that the dietary supplement market contains many more than 19 botanicals offered for supplemental consumption. Specifically identifying AHP, EP and WHO monographs as appropriate authoritative sources for methods and criteria allows the industry to source their methods from far more reliable sources more economically than if they developed them independently. While these sources do not carry the "official" status granted to USP or AOAC, they are authoritative and their methods validated to the same criteria as outlined in the preamble discussion offered in the preamble to the Proposed Rule[XII].

As noted earlier in this presentation, ChromaDex provides analytical methods development services to its clients as well as to government agencies, including the FDA. The reliance on authoritative sources such as AHP, EP and WHO serve us well in development and application of specific methods and to determine the identity, purity, quality and compositional characteristics of botanical products. The fact AHP references have demonstrated effectiveness not only to ChromaDex but also by extension to FDA through ChromaDex's work on their behalf should be reflected in the cGMPs for dietary supplements. While these authoritative sources are not cited within the Federal Food, Drug and Cosmetic Act (FFDCA), this should not be a deterrent to their citation within the cGMPs for dietary supplements. The American Herbal Pharmacopoeia is particularly useful and is a United States source of such vital information. The fact that AHP was not in existence at the time the FFDCA was written and passed does not diminish its validity as a source of methods and criteria useful in testing and evaluating botanical dietary supplements and dietary ingredients. The methods and criteria found in these other authoritative sources are demonstrably applicable in the real world of developing and applying appropriate scientifically valid methods and establishing criteria for assessing these materials. ChromaDex requests specifically that the Final Rule on cGMPs affirm these authoritative sources as applicable in identifying methods and criteria for the evaluation of dietary ingredients and dietary supplements.

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PROPOSAL

As demonstrated earlier in this document, the use of reference materials and/or reference standards is necessary to determine the scientific validity of methods applied in assessing the identity, purity, quality, strength, and composition of dietary supplements and dietary ingredients. It is because of this that ChromaDex proposes the following changes in the wording of the rule:

Section 111.3 What definitions apply to this part?

[Insert]

Reference Material means a substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, assessment of a measurement method, or for assigning values to materials.

Reference Standard means a highly purified compound that is well characterized to be used for the calibration of an apparatus, assessment of a measurement method or for assigning values to materials.

Section 111.35 What production and process controls must you use?

[Change]

(g) You must ensure, through testing or examination employing appropriate reference materials and/or reference standards, that each specification you established under paragraph (e) of this section is met. Specific testing requirements are as follows:

(1) You must test each finished batch of the dietary ingredient or dietary supplement produced before releasing for distribution to determine whether established specifications for identity, purity, quality, strength, and composition are met, provided that there are scientifically valid analytical methods employing appropriate reference materials and/or reference standards available to conduct such testing.

(2) For any specification for identity, purity, quality, strength, or composition for which you document cannot be tested on the finished batch of a dietary ingredient or dietary supplement, because there is no scientifically valid analytical method available for such testing, then you must:

(i) Perform testing on each shipment lot of components, dietary ingredients or dietary supplements received to determine whether such specification is met; and

(ii) Perform testing in-process in accordance with the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements

(3) Testing performed in accordance with paragraph (g)(2) must use scientifically valid analytical methods employing appropriate reference materials and/or reference standards available to conduct such testing.

(h) You must use a scientifically valid test or examination employing appropriate reference materials and/or reference standards to determine whether your specifications are met.

. . .

(k) You must test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration. You must use

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a scientifically valid method that employs appropriate reference materials and/or reference standards for the test or examination.

. . .

[Insert]

(m) Tests in accordance with this section must be performed as follows:

(1) For official components, dietary ingredients or dietary supplements the official compendial analytical methods employing appropriate reference materials and/or reference standards applying official criteria are to be used.

(2) For non-official components, dietary ingredients or dietary supplements the analytical methods and criteria found in authoritative sources such as AHP, EP, or WHO monographs employing appropriate reference materials and/or reference standards are to be used.

(3) For non-official dietary ingredients or dietary supplements without compenidally or other authoritatively sourced analytical methods and criteria, the scientifically valid methods you use as part of your standard operating procedures employing appropriate reference materials and/or reference standards applying appropriate criteria are to be used.

[Renumber Sections 111.35(m) through (o) as (n) through (p)

Section 111.60 What requirements apply to laboratory operations?

[Change]

(b)(1) You must establish and follow laboratory control processes that are approved by the quality control unit. Laboratory control processes must include, but are not limited to, the following:

. . .

(iv) Use of criteria for selecting reference materials and reference standards used in performing tests and examinations;

(v) Use of appropriate test method validations employing appropriate reference materials and/or reference standards and procedures; and

(vi) Use of test methods and examinations employing appropriate reference materials and/or reference standards in accordance with established criteria

. . .

(c) You must verify that the laboratory examination, testing methodologies, reference materials and/or reference standards are appropriate for their intended use.

(d) You must identify and use the appropriate scientifically valid testing method employing appropriate reference materials and/or reference standards as required for each established specification for which testing is required to determine whether the specification is met.

In the preamble to the Proposed Rule, FDA discussed means by which scientific validity can be established but neglected to mention the requirements for application of reference materials and/or reference standards[xiii]. This omission requires correction in order for a legitimate explanation of the phrase "scientifically valid method" to exist. Insertion of the definitions and application of the terms later within the rule corrects this oversight. The insertions in the definitions section of the rule (111.3) provide clarity of the changed sections later on in the rule. As originally presented, the Proposed Rule in Section 111.60(b)(1)(iv) cites

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only the acceptability of "reference standards" as being determined by the Quality Control Unit. As discussed previously, reference standards are not always appropriate or sufficient for testing and examination as an exclusive criterion. The St. John's Wort example noted earlier on is useful in understanding the need to include reference materials as part of the determination of the scientific validity of the method and the appropriateness of the specifications established for the identity, purity, quality, strength and composition of dietary ingredients and dietary supplements. Thus, the changed language throughout Section 111.35(g) and (h) insists on the utilization of appropriate reference materials and/or reference standards. Reference materials and reference standards are also applicable in evaluation and testing of components other than dietary ingredients and therefore the changes made to 111.35(k) are appropriate.

Moreover, should FDA deem necessary it could issue guidance on the matter of establishing scientific validity through multiple testing potentially involving multiple sites and the incorporation of reference materials and/or reference standards as part of this validation program. FDA has issued guidance for establishing the validity of scientific methods in the past for other categories of products and such guidance for the testing and examination of dietary ingredients and dietary supplements would be welcome. However, the fundamental differences between dietary ingredient and dietary supplement materials and other products require separate address rather than application of the current guidance documents.

The dietary supplement industry holds a wealth of information concerning the materials it uses accompanied by in depth understanding of some of the complex ingredients (primarily botanical) employed. ChromaDex as part of this industry holds some of this knowledge, particularly as it relates to analytical methods, reference materials and reference standards. The American Herbal Pharmacopoeia is another authoritative source within the US for information concerning botanical dietary ingredients particularly. This greater understanding from within the industry at large should be acknowledged and used in development of the Final Rule on cGMPs. The most shining example in support for this knowledge differential and in support of the proposed changes to the Proposed Rule comes from the preamble to the Proposed Rule where FDA states:

". . . we are not aware of a situation where an appropriate scientifically valid analytical method is not available.[xiv]

The dietary supplement industry has repeatedly explained to FDA that there is in reality a shortfall of such methods. As early as July 20, 1999, at an FDA outreach meeting in Oakland, CA, representatives of the dietary supplement industry specifically explained that this "methods gap" exists. The recognition and acceptance of other authoritative sources beyond recognized "official" compendia begins to address this matter. The direction of the manufacturers to the scientifically valid analytical methods and criteria as found in these other authoritative sources (such as AHP, EP and WHO monographs) as shown in new paragraph 111.35(m)(2) is vital to allowing conformance while insisting that manufacturers employ methods that have been appropriately reviewed for validity. Further, while the analytical methods situation has improved since 1999, it still requires additional allowance. The FFDCA as amended by DSHEA allows for the sale of dietary ingredients present in dietary supplements in the US prior to October of 1994. In order for some of these products to be sold while complying with the requirements of proposed cGMPs, allowance must be given to manufacturers concerning their internally developed analytical methods. The insertion of new paragraph 111.35(m)(3) covers this. The acceptance of methods employed by manufacturers as part of their standard operating procedures (naturally subject to verification by FDA upon inspection) recognizes the reality of the analytical method shortfall while affording conformance to the statute. The model for these

insertions comes from the FDA in its *Compliance Guidance Document 7152.01*. Placing these requirements for testing and criteria into the cGMPs accomplishes the goal of insuring the scientific validity of the methods used by industry while avoiding conflict between the regulation and the statute.

CONCLUSION

The Proposed Rule on cGMPs for dietary supplements is a good first step in addressing the matters of concern to FDA concerning the manufacture of dietary ingredients and dietary supplements. ChromaDex is grateful for the opportunity to provide comment and insight to the FDA on these matters. The solicitation of input from those stakeholders with best knowledge of the industry and its challenges mandates our participation in our area of greatest knowledge. FDA has relied on ChromaDex in the past to assist in determinations of the identity, purity, quality, strength and composition of dietary ingredients and dietary supplements. Accepting the input from ChromaDex and the suggested alterations to the Proposed Rule accompiishes the following:

- Clarifies requirements for application of appropriate scientifically valid methods
- Directs the dietary supplement industry to utilize authoritative sources of criteria and methods that are valuable albeit not specifically cited in the FFDCA
- Affords FDA the opportunity to assess the performance of the testing requirements out of the cGMPs
- Prevents FDA from issuing regulations that are in conflict with the statute

We hope you find the commentary provided here useful, applicable, and supportive of the concepts behind establishing these cGMPs.

Respectfully submitted:

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[I] United States Food and Drug Administration. *Federal Register Volume 68, Number 49*. March 13, 2003. Page 12158.

[II] United States Food and Drug Administration. *Proposed 21CFR Section 111.35*. Paragraphs (g), (h) and (k). March 13, 2003.

[III] Loc. Cit.

[iv] United States Food and Drug Administration. *Proposed 21CFR Section 111.60(b)(1)(iv)* March 13, 2003.

[v] National Institute of Standards and Technology. *NIST Technology Services Website.* http://patapsco.nist.gov/srmcatalog/about/Definitions htm

[vi] United States Food and Drug Administration. *Reviewer Guidance, Validation of Chromatographic Methods.* November 1994. Page 5.

[vii] United States Food and Drug Administration. *Federal Register Volume 68, Number 49.* March 13, 2003. Page 12209.

[viii] United States Food and Drug Administration. *Reviewer Guidance, Validation of Chromatographic Methods.* November 1994. Pages 5-6.

[ix] Op Cit. *68 FR No. 49.* Pages 12169 and 12209.

[x] United States Food and Drug Administration. *Proposed 21CFR Section 111.35(k).* March 13, 2003.

[xi] United States Food and Drug Administration. *Federal Register Volume 68, Number 49* March 13, 2003. Page 12209.

[xii] Loc. Cit.

[xiii] Loc. Cit

[xiv] Ibid. Page 12198.

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