Kyowa Hakko U.S.A., Inc.
767 Third Avenue, 19th Fl.
New York, NY 10017

Telephone: 212 319-5353
Facsimile: 212 421-1283

KYOWA

US Food and Drug Administration
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

August 8, 2003

Re: 21 CFR Parts 111 and 112
Docket No. 96N-0417
Current Good Manufacturing Practice in Manufacturing Packing, or Holding Dietary Ingredients and Dietary Supplements; Proposed Rule
(68 FR 12158, March 13, 2003)

To whom it may concern:
Enclosed please find Kyowa Hakko U.S.A., Inc.'s comments on the above proposed rule. Our comments are submitted in response to 68 FR 12158.

111.3 (4) "Must"
Change "Must is used to state mandatory requirements" to "Must is used to state mandatory requirements unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance"

Rational:
Although this cGMP states many "HOW TO" in detail, there may be inapplicable or unachievable wording for some manufacturing system. cGMP must be established base on rational (i.e. scientific, industry practicality etc.), so alternative way based on rational must be permitted.

111.3 (4) "Sanitize"
Delete "that when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction."

Rational:
This paragraph is not based on scientific basis

111.15 (d) (2)
Change "must at a minimum comply with the National Primary Drinking Water regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any state and local government requirements" to one of following candidate;
"must at a minimum comply with the National Primary Drinking Water regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any state and local government requirements or equivalent quality water that is ensured by foreign public agency."

Rational:
There are many dietary supplement, dietary ingredient manufactured out of USA.

96N-0417

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111.15 (d) (2)

Change "must at a minimum comply with the National Primary Drinking Water regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any state and local government requirements" to "must have suitable quality for intended for use."

Rational:

Many highly processed dietary ingredients undergo extensive purification 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 (i) (1)

Delete this section

Rational:

This is out of GMP

111.25 (a) (2) (i)

Delete this section

Rational:

There is contradiction to 21CFR111.25 (a) (2) (i) and 21CFR73.1646 (a) (i), 21CFR73.1647 (a) (i). 21CFR73.1646 (a) (i) stated oleic acid is used as lubricant.

111.25 (b) (1)

Change "instruments and controls" to "critical instruments and critical controls"

Rational:

It is not necessary to calibrate all instruments and controls.

111.35 (c)

Change "You must use a quality control unit in your manufacturing, packaging, and label operations for producing the dietary ingredient or dietary supplement to ensure that these operations are performed in a manner that prevents adulteration and ensures that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition" to "You must use a quality control unit to ensures that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition"

Rational:

This sentence is too much verbose. It must be clearer.

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111.35 (i) (4) (iii)

Delete this paragraph

Rational:

In some case of manufacturing dietary ingredients (i.e. amino acids), it is possible to remove contaminants by performing reprocess.

111.37 (b)

Change "Your quality control unit must do the following" to "Your quality control unit must do the following or personnel/organization qualified by quality control unit must do and record it, and quality control unit review/approve the following"

Rational:

Even if quality control unit do not all of things, it's enough to review/approve record, because there is some case to perform quality test partially at contract laboratory.

111.37 (b) (11) and 111.37 (b) (11) (i)

Change "Each shipment" to "Each shipment/manufacturing"

Rational:

There is a case that same manufacturing lot is split into several shipments. In such a case, it makes no sense to collect representative sample by each shipments.

111.45 (b) (6)

Change "maximum and minimum percentage" to "normal range" or "pre-decided range"

Rational:

There are some controls methods.

111.50 (f)

Delete this paragraph.

Rational:

In some case of manufacturing for dietary ingredients (i.e. amino acids), it is possible to remove contaminants performing reprocess.

111.65 (c) (3)

Change "water that meets the National Primary Drinking Water regulations" to "water that meets the National Primary Drinking Water regulations or equivalent quality water"

Rational:

As some dietary ingredients consumed in the USA are manufactured at oversea facility, the situation should be reflected to the guideline.

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111.125 (b)

Delete this sentence "All electronic records must comply with part 11 of this chapter"

Rational:

Now FDA CDER withdraw guidelines of part 11, so it is earlier to describe part 11 matter on this cGMP.

These comments have been submitted by Kyowa Hakko's manufacturing and Quality Assurance professionals. We value this unique opportunity and welcome further discussion.

Respectfully yours,
Neil C. Sullivan, Director
Kyowa Hakko USA, Inc.
767 Third Avenue
New York, NY 10017
Tel: 212 319 5353