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Affecting FDA-Regulated Products*

Premarket Notifications of New Dietary Ingredients—A Ten-Year Review

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I. “OLD” AND “NEW” UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

When the Federal Food, Drug, and Cosmetic Act (FDCA) was passed in 1938,¹ its drug approval provision was intended to respond to the tragic marketing of Elixir of Sulfanilamide—which mixed a safe and effective drug in a good tasting, but otherwise poisonous, ethylene glycol solution that led to over 100 fatalities. Nonetheless, the FDCA allowed drugs then on the market to remain on the market—and these existing drugs were referred to in the trade as “grandfathered” drugs. The products to be regulated under the law’s new requirement that safety be demonstrated and approval granted prior to marketing were referred to as “new drugs.” If a “grandfathered” drug was alleged to be harmful or mislabeled, the Food and Drug Administration (FDA) could proceed against it under the law’s adulteration and misbranding provisions.

Similarly, when the Food Additive Amendments of 1958² became law, ingredients then on the market were permitted to remain on the market if they were “generally recognized as safe (GRAS)” for use as food. This was accomplished in the definition of “food additive,”³ which excluded ingredients that met the definition of GRAS. If an additive was alleged not to be safe, it could be proceeded against under the law’s prohibition of unapproved food additives in food. The law also exempted ingredients that had received a prior sanction for use in food.

The Medical Device Amendments of 1976⁴ also contained a form of “grandfather” clause. That act required anyone first introducing a product after enactment to submit a premarket notification. Devices already on the market were reviewed in the context of a medical device classification process. Pre-Amendment devices that were alleged to be dangerous or mislabeled could be proceeded against under the FDCA adulteration or misbranding provisions.

II. “OLD” AND “NEW” UNDER DSHEA

In 1994, the newly-enacted Dietary Supplement Health and Education Act⁵ (DSHEA) adopted an approach that was consistent with these earlier laws with respect to “old” and “new” ingredients. DSHEA provided a statutory definition of a “new dietary ingredient” and imposed upon such ingredients the requirement that

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¹ Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended 21 U.S.C. §§ 301-397 (2000).

² Pub. L. No. 85-929, 72 Stat. 1784 (1958) (codified at 21 U.S.C. § 348 (1999)).

³ 21 U.S.C. § 321(s) (FDCA § 201(s)).

⁴ Pub. L. No. 94-295, 90 Stat. 539 (1976).

⁵ Pub. L. No. 103-417, 108 Stat. 4325 (1994).

a notification be submitted prior to their use in dietary supplements.⁶ As was the case with new drugs and postenactment medical devices, Congress “grandfathered” old dietary ingredients and any that were alleged to be unsafe or mislabeled could be proceeded against under the adulteration and misbranding provisions of the FDCA.

The difference between an old and a new dietary ingredient, according to DSHEA, is simply a matter of whether the particular ingredient was available for sale in the United States prior to the date of passage of the law. DSHEA defined a “new dietary ingredient” as follows:

The term “new dietary ingredient” means a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994.⁷

DSHEA controls the introduction of new dietary ingredients by defining as adulterated any dietary supplement product that contains a new dietary ingredient, including a known ingredient that has been “chemically altered,” *unless* FDA is notified prior to marketing such product. The requirement is stated in section 8 of DSHEA, which amended section 413(a) of the FDCA, as follows:

A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets one of the following requirements:

- (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.⁸
- (2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary [of Health and Human Services] with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.⁹

⁶ Pub. L. No. 103-417, § 8, 108 Stat. at 4331-32 (1994).

⁷ Pub. L. No. 103-417, § 8, 108 Stat. at 4331-32 (codified at 21 U.S.C. § 350(b)(c) (FDCA § 413(a))).

⁸ When DSHEA was enacted, the House and Senate sponsors of the legislation wanted to make sure that the legislative history of this new law would be minimal and controlled. Thus, a “Statement of Agreement” accompanied the law when it was enacted in both the Senate and House. One part of the Statement is pertinent to new dietary ingredients: “In Section 413(a)(1), added by section 8, the term ‘chemically altered’ does not include the following physical modifications: minor loss of volatile components, dehydration, lyophilization [sic], milling, tincture or solution in water, slurry, powder, or solid in suspension.” 140 CONG. REC. H11,179 (daily ed. Oct. 6, 1994).

⁹ Pub. L. No. 103-417, § 8, 108 Stat. at 4331-32 (codified at 21 U.S.C. § 350(b)(c) (FDCA § 413(a))).

Accordingly, there are two stated conditions that control the market entry of new dietary ingredients: 1) there must be an evidentiary basis that supports a reasonable expectation of safety for the marketed use, and 2) FDA must be provided with information to support this expectation 75 days prior to marketing (a “75-day notice” or “premarket notification”).

In actual practice, there is a third condition that controls the introduction of a new dietary ingredient: FDA must accept that the information provided is sufficient to ensure a reasonable expectation of safety. This acceptance is not addressed directly in either the law itself or the governing regulations; indeed, there is no legislative record that FDA ever sought premarket approval authority for new dietary ingredients. Instead, FDA sought notification only, probably on the theory that saying “no” is easy, saying nothing is neutral, and saying “yes” would become as burdensome and difficult—administratively—as it had become for food additives and new drugs. Thus, FDA has developed the practice of responding in various ways to notices it deems to be insufficient, while simply filing (usually without comment) those found to have met the statutory and regulatory requirements in the docket the agency has established for these notices.¹⁰

III. 75-DAY NOTICES TO DATE

FDA promulgated new dietary ingredient notifications that became effective in October 1997 and that were codified at 21 C.F.R. § 190.6.¹¹ These rules are quite straightforward in describing the process for submitting a 75-day premarket notification. The regulation identifies five specific information requirements that must be met:

- (1) the name and address of the distributor or manufacturer (either of the ingredient or of the supplement in which it will be included);
- (2) the name of the ingredient, which must include the Latin binomial, including the author of the name if the ingredient is a botanical;
- (3) a description of the supplement containing the ingredient, including the level of use and conditions of use;
- (4) the evidence on which a reasonable expectation of safety is based, including copies and, as necessary, English translations of references; and
- (5) a signature.

The rule also requires the submission to be in triplicate (one original and two copies). Table 1 provides a succinct summary of the specific details of the regulation.

¹⁰ See FDA Docket No. 95S-0316, 75-Day Premarket Notifications for New Dietary Ingredients, available at <http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s0316.htm> (last accessed May 11, 2004).

¹¹ 62 Fed. Reg. 49,886 (Sept. 23, 1997) (codified at 21 C.F.R. § 190.6).

TABLE 1: Specific Requirements in 21 C.F.R. § 190.6 for Submission of a 75-Day Notice

(a)	<ul style="list-style-type: none"> • Submit 75 days prior to marketing. • Submit in triplicate. • Submit to ONPLDS/CFSAN/FDA, College Park, MD.
(b)(1)	<ul style="list-style-type: none"> • Provide name and address of manufacturer or distributor of the new dietary ingredient (DI) or of the dietary supplement (DS) that contains the new DI.
(b)(2)	<ul style="list-style-type: none"> • Provide the name of the new DI. • If an herb/botanical, provide the Latin binomial and authority.
(b)(3)	<ul style="list-style-type: none"> • Provide a description of the DS that will contain the new DI. • State the level of the new DI that is contained in the DS. • Describe the conditions of use of the DS.
(b)(4)	<ul style="list-style-type: none"> • Provide information on the history of use or other evidence of safety to establish that the new DI, when used as described in (b)(3), will reasonably be expected to be safe. • Include citations to published articles or other such evidence. • Provide copies of references to published information that supports the notification. • Provide accurate and complete English translations of any such reference that is in a foreign language.
(b)(5)	<ul style="list-style-type: none"> • The notification must be signed.

DSHEA specified that information provided under the new dietary ingredient notification requirement should be kept confidential for 90 days after its receipt, and that all information except trade secrets and other confidential commercial information should be placed on public display at the expiration of the 90 days. FDA endeavors to submit 75-day notices to its Dockets Management Branch in accordance with this timeframe.

In March 2004, an examination of this docket revealed that FDA has filed 172 reports of premarket notifications in the nearly ten years since DSHEA was passed. Several of these are duplicates, where new numbers were assigned when revisions were made to original submission, and two notices were withdrawn. Also, FDA did not provide a response to two submissions and responses to three others could not be classified for purposes of this review. Taking these few duplicates and withdrawals into account, there have been 145 unique 75-day premarket notifications for which FDA has provided a classifiable response between September 1995, when the first notice was received by the agency, and November 12, 2003, the date of the last notice filed in the docket as of March 23, 2004.¹²

FDA's responses to the 145 unique new dietary ingredient notices can be broken down into several types of reply, which can be further organized into two broad classes. These two broad classes can be described as 1) notices to which FDA has objected, and 2) notices that the agency has acknowledged (i.e., "answers that say 'no'" and "answers that sound like 'yes.'").

A. Notices With Objections

FDA has objected to 68 of the unique notices that it has received thus far for new dietary ingredients. The agency has devised four separate replies to object to a notice.

¹² The authors were informed on January 5, 2004, that FDA had received 190 notices as of August 22, 2003—the last date on which FDA's files had been updated. FDA also stated that it updates its files every 90 days. This article addresses only those files available in the docket as of the date of its submission for publication.

These are:

- (1) identification by FDA of the ingredient (or the supplement that would contain the ingredient) as an unacceptable dietary ingredient (or supplement);
- (2) notices that the agency identified as incomplete in some technical detail;
- (3) notices that, while technically complete, did not provide adequate information to meet the statutory requirement for evidence of reasonable safety; and
- (4) identification of an ingredient by FDA as unsafe.

In some cases, FDA cited more than one of these reasons to object to a premarket notification. In counting the various replies, the sum of all of the responses, therefore, necessarily exceeds the number of unique submissions.

1. *Ingredients Deemed Not to Be Dietary Ingredients*

In 27 cases, FDA informed the submitting firm that it considered its products to be unacceptable dietary ingredients and, therefore, not allowed in dietary supplements. FDA's basis for this determination in 19 of these submissions referred to product claims that the agency viewed as drug claims that are not permitted for dietary supplements. Some examples of the claims that FDA identified as drug claims are provided in Table 2.

TABLE 2: Representative Claims/Conditions Identified by FDA as Drug Claims

• AIDS	• Cholesterol lowering	• Infections
• Arthritis	• Diabetes	• Malaria
• Cancer	• Flu (implied in name)	• Smoking cessation

In 10 of these 27 notices,¹³ FDA ruled the ingredient to be out of conformity with the legal definitions for a dietary ingredient or a dietary supplement. These included: 2 products that were represented in a form that is not for ingestion (1 gum or lozenge and 1 “acupoint patch for eye relaxing”)—thus failing to meet the statutory requirement that a supplement be “intended for ingestion;” 4 ingredients that did not meet the basic definition of a dietary ingredient (including 2 biologics, a hormone, and a desiccated medicinal leech); 3 ingredients that are the subject of drug investigations and are specifically excluded, therefore from being marketed as dietary supplements; and 1 ingredient that was identified as intended as a food sweetener and so classified as a conventional food ingredient. Table 3 provides specific information about the dietary ingredients that were the subjects of these 10 notices.

TABLE 3: Ingredients Identified by FDA as Not Dietary Ingredients

Ingredient	Reason Given
Acamprosate	Marketed as a new drug
<i>Heliopsis longipes</i> root extract	Not for ingestion (lozenge/gum)
Herbal eye patch	Not for ingestion (transdermal)
Hirudo (a medicinal leech)	Not a vitamin, mineral, amino acid, herb, or food or drink
Idebenone	Subject to new drug investigation
Pathogenic microbes (e.g., Streptococcus)	Defined as a biologic
Porcine relaxin	Defined as a hormone
<i>Siraitia grosvenorii</i>	Conventional food ingredient
<i>Trans-resveratrol</i>	Subject to new drug investigation

¹³ The total of 29 examples in this paragraph exceeds the number of cases because two of these submissions were cited both for drug claims and for nonconformity to the dietary ingredient definition.

2. *Incomplete Premarket Notifications*

In response to 33 of the premarket notifications submitted to date, FDA replied that the notice was incomplete. All of these replies stated that the notice did not meet one or more of the requirements of 21 C.F.R. § 190.6, and identified the information that was missing. Common faults cited by FDA in these responses have included missing copies (or English translations) of references on which safety determinations were based (in 22 of the notices, including 1 citing illegibility), and insufficient information on the product itself or on conditions of use, such as product form, serving size, or target populations (21 cases were cited for at least one of these use details). Other common concerns identified in the incomplete notices were of a more administrative nature, such as a missing signature or an unnamed manufacturer or distributor (1 case each), or failure of the submitter to provide submissions in triplicate (at least 7 notices). Of particular interest to companies that sell botanicals, is that FDA has refused to accept 8 submissions due to the absence of the full Latin name, including the author of the name as specified in 21 C.F.R. § 190.6(b)(4)—of these, only 6 actually were related to submissions of botanical ingredients.

3. *Premarket Notifications Deemed Inadequate*

The largest number of FDA objections to 75-day notices stated that the information presented did not provide an adequate basis to conclude that the new dietary ingredient will be reasonably expected to be safe for its intended use. That was the agency's reply to 45 unique submissions, including 24 for which it stated also that either the notice was incomplete or that the ingredient was improperly identified as a dietary ingredient.

4. *New Dietary Ingredients Deemed Unsafe*

In 6 instances, FDA's rationale for objection to a premarket notification was specific concerns about the safety of a new ingredient. These have included: pokeweed lectins from *Phytolacca americana*; *Montanoa tomentosa*; gamma-butyrolactone (GBL); *Echium plantagineum* seed oil; bio-geranium yeast; and extract of oleander (*Nerium oleander*).

Surprisingly, few of the notices to which FDA has objected have been resubmitted to address or cure the identified defects in the original filing. Of the 68 notices objected to by FDA, revised submissions have been made only 19 times. Two of these subsequently received communications that acknowledged that the submission standard had now been met and 8 were acknowledged as received by FDA. The other 9 notices were again subject to objections.

IV. SIGNIFICANCE OF FDA'S OBJECTION

An objection to a premarket notification for a new dietary ingredient by FDA has great significance. This response by the agency establishes a record that the identified new ingredient has failed to meet the statutory requirement for its marketing. The language included by FDA in each of these rejections, makes it clear that the agency is aware of the significance of this process and wants those who filed the notice to understand that significance. Accompanying their communication of objection to a submission, whether due to a failure to meet the definition of a dietary ingredient, through a technical fault, because the information was inadequate, or because FDA considered

the ingredient unsafe, is a statement that a product containing such objectionable ingredient:

[M]ay be adulterated under 21 U.S.C. § 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury ... [I]ntroduction of such a product into interstate commerce is prohibited under 21 U.S.C. § 331(a) and (v).

Objection to a notice does not necessarily mean that FDA has determined that an ingredient that has been identified by a company as a new dietary ingredient is unsafe, or even that the agency has agreed that the ingredient is “new,” as defined by the law. As discussed below, numerous ingredients that obviously are not new, such as red clover (*Trifolium pratense*) and reishi mushroom (*Ganoderma lucidum*), have been the subjects of filings to which FDA objected. Even common food ingredients, such as ginger (*Zingiber officinale*) and common black pepper (*Piper nigrum*), have been included as ingredients in dietary supplements that were submitted erroneously to this process and subsequently rejected by FDA. The agency did not state that these ingredients are unsafe; rather, it communicated that the filings were incomplete.

V. PREMARKET NOTIFICATIONS DEEMED ADEQUATE, OR NOT INADEQUATE

Of the 145 unique 75-day notices that are the subject of this article, only 12 received a response stating that the information provided did in fact provide an adequate basis to determine that the ingredient is reasonably expected to be safe under labeled or normal conditions of use. In 4 of these, FDA replied with an affirmative statement, such as “the agency concludes that [the submitted information] appears to meet the standard in 21 U.S.C. § 350b(a)(2),” or “FDA has determined that your notification meets the minimum requirements specified in 21 C.F.R. § 190.6.” In just 1 case, FDA stated simply that it “does not, at this time, object to the marketing of [the ingredient].” In the other 7 instances, the agency made a more passive statement—asserting that it had not found the submitted information to be *inadequate*. In some of these 12 acknowledged submissions, the agency identified conditions that would need to be addressed, such as specific labeling of “material” information or exclusion of use by children or by pregnant or lactating women. A detailed presentation of FDA’s comments in these 12 cases is presented in Table 4 and Table 5.

It is important to note that, in many of FDA’s responses to the few notices in which the agency acknowledged that a reasonable expectation of safety had been provided, FDA also sent two clear messages about the limitations of this “acknowledgement.” First, the agency asserted that it “is not precluded from taking action in the future against a dietary supplement containing [a new dietary ingredient] if it is found to be adulterated or misbranded.” Second, FDA made the point that “new dietary ingredients ... that FDA has reviewed through the premarket notification process are not ‘approved’ or ‘authorized’ by the agency.”

VI. PREMARKET NOTIFICATIONS FILED TO THE DOCKET (WITH OR WITHOUT FURTHER COMMENT)

All of the rest of the submissions, that is, those that were neither “objected to” nor “acknowledged,” were simply filed to the docket by FDA. There have been 65 unique

notices for which this has been the agency's response, including 8 notices that were resubmitted to address flaws that FDA had identified in an original submission.

Since early 1998, the agency's message to the notifying firm at the time that their submission is filed has consisted of an acknowledgement of receipt and a reminder that they must not market the product within the 75-day statutory period. Prior to that time, from the passage of DSHEA in 1994 to just after the regulations in 21 C.F.R. § 190.6 became effective in October 1997, the agency usually provided a simultaneous communication to the submitting company informing them that the agency considered their submission to be the required notification for a new dietary ingredient. In some of these earlier cases, FDA also expressed specific concerns regarding the content of the submission (e.g., references to drug-like uses), concerns that are similar to issues that were identified in later submissions as the basis for rejection. Some of the earliest submissions (e.g., for stevia and theobromine), also received communications from FDA regarding concern about the safety of the new ingredient even as the agency acknowledged receipt of these submissions and cleared the way for their marketing.

TABLE 4: Notices That FDA Acknowledged With an Affirmative Statement

Ingredient(s)	FDA's Statement	Conditions
<i>Tecoma mollis</i> ; <i>Tagetes tomentosa</i> ; <i>Loeselia mexicana</i> ; <i>Cecropia obtusifolia</i>	"[T]he agency concludes that [the submitted information] appears to meet the standard in 21 U.S.C. § 350b(a)(2) ..."	None stated.
Vincamine	The submission "appears to provide an adequate basis that a dietary supplement containing vincamine will reasonably be expected to be safe in healthy adults who would consume ... up to 20 milligrams of vincamine per day for up to 6 months."	Safety for use by children has not been established. Safety for chronic use (beyond 6 months) has not been established.
<i>Phaffia rhodozyma</i> yeast	"[T]he information in your submission ... appears to provide an adequate basis that a dietary supplement containing <i>Phaffia rhodozyma</i> will reasonably be expected to be safe in healthy adults who would consume ... no more than 250 milligrams of <i>Phaffia rhodozyma</i> per day (containing approximately 2 mg astaxanthin) for limited durations of time."	Safety for use by children has not been established. Safety for chronic, long-term use has not been established.
Kombu fucoidan (extract of <i>Kjellmaniella crassifolia</i> seaweed)	"FDA has determined that your notification meets the minimum requirements specified in 21 C.F.R. § 190.6. These requirements include providing FDA information on the basis of which you concluded that a dietary supplement containing Kombu Fucoidan is reasonably expected to be safe when used under the conditions recommended or suggested in the product's labeling."	None stated.
Conjugated linoleic acid (CLA)	"The agency does not, at this time, object to the marketing of the CLAs that were the subject of the June 2002 new dietary ingredient notification."	None stated.

TABLE 5: Notices That FDA Acknowledged With a Statement That the Notice Was Not *Inadequate*

Ingredient(s)	FDA's Statement	Conditions
Heme iron polypeptide	“Although the agency disagrees with some of the statements in your submission, we are not finding at this time that the basis on which you concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe is inadequate.”	None stated.
Astaxanthin (extract of <i>Haematococcus pluvialis</i>)	“[W]e are not finding at this time that the basis on which you concluded that a dietary supplement containing astaxanthin will reasonably be expected to be safe is inadequate.”	The submission stated that products would be labeled to warn pregnant and lactating women to consult a physician before use. FDA suggested that chronic use in children be excluded.
IronAid™ (Iron protein succinylate)	“[W]e are not finding at this time that the basis on which you concluded that a dietary supplement containing IronAid™ will reasonably be expected to be safe is inadequate.”	Limit dose to the upper limit (UL) set by the NAS. Use appropriate packaging and consumer warnings.
Neptune Krill Oil™ (Krill oil extract)	“[W]e are not finding at this time that the basis on which you concluded that a dietary supplement containing either Neptune Krill Oil™, Neptune Aquateine™, Neptune LyO-Krill™, and Neptune Euphausia™ will reasonably be expected to be safe is inadequate.”	Excluded subpopulations identified in the submissions are persons with seafood allergies and those taking anticoagulants.
Neptune Aquateine™ (Krill based protein concentrate)	As above.	As above.
Neptune LyO-Krill™ (Freeze-dried krill)	As above.	As above.
Neptune Euphausia™ (A blend of other products)	As above.	As above.

As with the responses in which FDA specifically acknowledged that the information required by 21 C.F.R. § 190.6 had been submitted, the agency usually has used the opportunity of informing companies that their notice was received to remind them of the limitation of this receipt, and that the product's marketer ultimately is responsible for its safety. The most recent communications include a statement that any failure by FDA to

respond to a notice, either within or after the established 75-day period, "does not constitute a finding by the agency that the ... ingredient ... is safe or is not adulterated" These communications also assert FDA's authority to take action in the future "against a dietary supplement containing [the new ingredient] if it is found to be unsafe, adulterated or misbranded." The agency has included the point made above, that "new dietary ingredients ... that FDA has reviewed through the premarket notification process are not 'approved' or 'authorized' by the agency."

VII. SUMMARY OF FDA RESPONSES

Over the past nine and one-half years, and especially since the implementing regulations were finalized in 1997, FDA has established a consistent response to premarket notifications that the agency has received from companies seeking to meet DSHEA's requirements. The agency has objected to any such notice if the ingredient did not comply with the statutory definition of a dietary ingredient or if the notice included a drug claim for the ingredient. Objections also were made if the notice was deficient in any regard, whether of a technical nature or in regard to substantive information that was submitted as the basis for demonstrating a reasonable expectation of the ingredient's safety. FDA also has objected to several notifications because of identified concerns regarding whether an ingredient can be consumed safely.

When FDA has considered a notice to have met all of the criteria required by 21 C.F.R. § 190.6, the agency occasionally has made a statement to that effect in its response to the submitter. Much more often, the agency simply has acknowledged receipt of the notice and filed it to the assigned docket. In corresponding with companies that have made complete submissions, FDA has used the opportunity to communicate reminders of certain aspects of dietary supplement regulations, such as the need to refrain from marketing a new dietary ingredient for 75 days from the date of notification and specific suggestions for inclusion of "material" labeling.

VIII. UNREQUIRED SUBMISSIONS

In reviewing the notices that have been filed to date under this regulatory scheme, it is evident that many of the filing companies do not understand clearly that their obligations are specific to dietary ingredients. Thus, there have been at least twelve 75-day notices filed for dietary *supplements* rather than for dietary *ingredients*. Many of these consisted only of common ingredients that do not require premarket notification as new ingredients, including such common food ingredients as black pepper (*Piper nigrum*) and ginger (*Zingiber officinale*), as well as broadly-sold herbs such as Asian ginseng (*Panax ginseng*) and honeysuckle (*Lonicera japonica*). FDA does not look to see whether these ingredients are "old"—the notice for the dietary supplement that included black pepper and ginger, for example, was objected to as incomplete.

In addition, there are numerous notifications for ingredients, especially botanical ingredients, which are not "new." For example, submissions have been filed for ganoderma spore powder and extract (*Ganoderma lucidum*), red clover extract (*Trifolium pratense*), and Thai kudzu root extract (*Pueraria mirifica*).¹⁴ Each of these plants has been broadly

¹⁴ A novel extract of a common ingredient arguably can be described as a "new dietary ingredient," and there have been submissions for new dietary ingredients that are identified as novel extracts of common plants (e.g., a polyphenolic extract of evening primrose (*Oenothera biennis*)). None of the examples identified here, however, provided any information to suggest that they were anything other than simple ethanolic extracts, traditionally prepared.

used as food ingredients or as teas, yet for each of these examples at least one marketer has received a letter from the U.S. Department of Health and Human Services informing them that *their* product containing these common ingredients “may be adulterated” under the FDCA.

IX. 75-DAY NOTICES FOR BOTANICAL INGREDIENTS

Nearly half of the submissions have included ingredients and extracts from the plant kingdom, including algae and fungi, and about 20 others have been for purified compounds that are obtained from plants. Several submissions have been for formulas containing multiple ingredients such that the total number of reported new ingredients exceeds the number of notices.

Lists of some of the over 100 herbs that have been the subject of one or more notices are provided in Tables 6 and 7. They are divided into those that have been the subject of an acknowledgement by FDA and those for which the agency has expressed objections. These tables also identify those plants for which FDA has stated acknowledgement in some cases and objections in others, depending on the quality of the submission and other factors. It also should be noted that some of the submissions were for an herbal ingredient itself or an extract of that ingredient, while others only identified the plant as the raw material from which a purified substance was obtained. The majority of herbs included in Table 7 were identified in submissions that were made for dietary *supplements* by persons apparently not sufficiently familiar with the regulation.

TABLE 6: Botanicals That Have Been the Subject of an Acknowledged Notice

As a dietary ingredient
<i>Amphipterygium adstringens</i>
<i>Brickellia cavanillesii</i>
<i>Buddleja americana</i>
<i>Casimiroa edulis</i>
<i>Castilleja canescens</i>
<i>Cecropia obtusifolia</i>
<i>Cordia boissieri</i>
<i>Cordyceps sinensis</i> (both as an extract and in a dietary supplement) [also rejected]
<i>Flourensia cernua</i>
<i>Ganoderma lucidum</i> [also rejected in some forms]
<i>Gnaphalium berlandieri</i>
<i>Haematococcus pluvialis</i> (both as an ingredient and as a source of astaxanthin)
<i>Laennecia filaginoides</i> (as <i>Conyza filaginoides</i>)
<i>Leucophyllum texanum</i>
<i>Loeselia mexicana</i>
<i>Rauwolfia vomitoria</i> root bark
<i>Solanum erratum</i> (as <i>S. verbascifolium</i>)
<i>Stevia rebaudiana</i> leaf
<i>Tagetes lucida</i>
<i>Tecoma stans</i> var. <i>velutina</i> (as <i>T. mollis</i>)
<i>Trigonella foenum-graecum</i> (decaffeinated)
As an extract
<i>Cordyceps sinensis</i> (both as an extract and in a dietary ingredient) [also rejected]
<i>Geissospermum vellosii</i> bark extract
<i>Siraitia grosvenorii</i> (fruit extract) [also rejected]

As a raw material source
<i>Haematococcus pluvialis</i> (both as an ingredient and as a source of astaxanthin)
<i>Huperzia serrata</i> (as source of Huperzine-A) [also rejected]
<i>Kjellmaniella crassifolia</i> (as source of fucoidan)
<i>Monascus pilosus</i> (as source of Monacolin J) [also rejected]
<i>Pinus</i> spp. (as source of pinitol)
<i>Schizochytrium</i> spp. (as source of fermented ingredient)
<i>Sesamum indicum</i> (as a source of a lignan)
<i>Vinca minor</i> (as source of vincamine)

TABLE 7: Botanicals That Have Been the Subject of a Rejected Notice

As a dietary ingredient
<i>Blumea balsamifera</i> leaf
<i>Cordyceps sinensis</i> [also acknowledged]
<i>Desmodium adscendens</i>
<i>Eurycoma longifolia</i> root
<i>Funtumia elastica</i> bark
<i>Hypoxis hemerocallidea</i>
<i>Kalanchoe pinnata</i> leaf
<i>Labisia pumila</i> whole plant
<i>Lagerstroemia speciosa</i> leaf
<i>Momordica charantia</i> leaf
<i>Montanoa tomentosa</i>
<i>Monascus pilosus</i> (source of Monacolin J) [also acknowledged]
<i>Nerium oleander</i> extract
<i>Ruta chalepensis</i>
<i>Salvia miltiorrhiza</i> root
<i>Siphonochilus aethiopicus</i>
<i>Sutherlandia frutescens</i>
<i>Vitex negundo</i> leaf
<i>Warburgia salutaris</i>
As an extract
<i>Agaricus blazei</i> extract (fungi)
<i>Heliopsis longipes</i> root extract
<i>Hordeum vulgare</i> extract
<i>Oenothera biennis</i> polyphenolic extract
<i>Padina pavonia</i> extract
<i>Persea americana</i> seed extract
<i>Pueraria mirifica</i> root extract
<i>Salacia oblonga</i> extract
<i>Siraitia grosvenorii</i> fruit extract [also acknowledged]
<i>Trifolium pratense</i> extract
As a raw material source
<i>Duboisia hopwoodii</i> (as source of cotinine)
<i>Echium plantagineum</i> (as source of seed oil)
<i>Huperzia serrata</i> (as source of Huperzine-A) [also acknowledged]

As a raw material source (con't)
<i>Phytolacca americana</i> (as source of lectins) <i>Polygonum cuspidatum</i> (as source of resveratrol)
... in a dietary supplement
<i>Abies spectabilis</i> (as <i>A. webbiana</i>) <i>Acicarpa tribuloides</i> aboveground parts <i>Aegle marmelos</i> <i>Alisma plantago-aquatica</i> <i>Amomum aromaticum</i> <i>Astragalus</i> spp. root <i>Boerhavia diffusa</i> <i>Bursera graveolens</i> stem <i>Chuquiraga spinosa</i> stem/leaf <i>Cinnamomum verum</i> (as <i>C. zeylanicum</i>) <i>Cornus officinalis</i> fruit <i>Crataegus pinnatifida</i> <i>Cuminum cyminum</i> <i>Curcuma aromatica</i> <i>Cuscuta epithimum</i> seed <i>Desmodium molliculum</i> stem/leaf <i>Equisetum bogotense</i> stem, leaf & flower [so stated] <i>Ferula sinkiangensis</i> <i>Forsythia suspensa</i> seed extract <i>Ganoderma lucidum</i> [also acknowledged] <i>Geranium filipes</i> stem, leaf & root <i>Hemidesmus indicus</i> <i>Imperata cylindrica</i> root <i>Isodon glaucocalyx</i> whole plant <i>Justicia adhatoda</i> (as <i>Adhatoda vasica</i>) <i>Lonicera japonica</i> flower extract <i>Lygodium japonicum</i> spore <i>Moringa oleifera</i> (as <i>M. pterygosperma</i>) <i>Mutisia acuminata</i> stem, leaf & flower <i>Oenothera rosea</i> stem, leaf & flower <i>Panax ginseng</i> <i>Perezia coerulescens</i> stem/leaf <i>Phyllanthus emblica</i> <i>Piper alveolatum</i> stem/leaf <i>Piper longum</i> <i>Piper nigrum</i> <i>Polygonum multiflorum</i> <i>Poria cocos</i> <i>Rehmannia glutinosa</i> root <i>Rheum palmatum</i> <i>Ricinus communis</i> <i>Salvia sagittata</i> stem/leaf <i>Sanguisorba minor</i> stem/leaf <i>Sargassum pallidum</i> (seaweed) <i>Satureja revoluta</i> branchlet/leaf

... in a dietary supplement (con't)
<i>Schkuhria pinnata</i> stem/leaf
<i>Scutellaria baicalensis</i> root/stem extract
<i>Stachys pusilla</i> whole plant
<i>Syzygium aromaticum</i>
<i>Terminalia bellerica</i>
<i>Terminalia chebula</i>
<i>Tessaria integrifolia</i> stem/leaf
<i>Tinospora cordifolia</i>
<i>Typha angustifolia</i>
<i>Wedelia calendulacea</i>
<i>Zingiber officinale</i>

X. A GUIDE TO FILING A 75-DAY NOTICE

Based on a detailed review of all of the notices for new dietary ingredients that have been filed since the passage of DSHEA, certain approaches can be identified as more likely to succeed than others in obtaining FDA's acknowledgement. Companies that are preparing to submit a 75-day notice should keep the following issues in mind:

- *Is it a dietary ingredient?* The statute clearly defines a dietary ingredient and FDA has consistently shown that it refers to that definition. It may be useful to identify which of the specific subdefinitions the ingredient fits into—vitamin; mineral, herb, or other botanical; amino acid; other dietary substance; or a concentrate, metabolite, constituent, or extract of one of the above—and also to ensure that the ingredient is not one of the excluded “drug” ingredients. Similarly, the identified dietary supplement in which the ingredient will be used should fit the statutory definition of a dietary supplement.

Although these points may seem obvious, the agency has, as discussed above, objected to 27 notifications because of the failure to meet one of these definitions. It is a waste of FDA's limited time and resources for the agency to respond to submissions for external-use products, for example, or ingredients that have been marketed previously as a new drug and, thus, are not eligible for marketing in a dietary supplement.

- *Is it a new dietary ingredient?* A firm should review records that predate October 15, 1994, to find evidence that an ingredient that might only recently have come to their attention is in fact “new” as defined by DSHEA. An ingredient that was marketed prior to that date is not subject to notification. Potential sources of information are dated manufacturing records and wholesale ingredient catalogues. Another consolidated reference is the American Herbal Products Association's *Herbs of Commerce*.¹⁵
- *Follow all of the instructions.* 21 C.F.R. § 190.6 is very specific in requiring certain information to be included in a 75-day notice. FDA has consistently objected to any submission that does not provide all of the required information, as listed in Table 1 above.

¹⁵ AMERICAN HERBAL PRODUCTS ASS'N, HERBS OF COMMERCE (2d ed. 2000). This document is a compilation of input received from herbal marketers and experts who were asked, in 1995, to identify all of the plants that were marketed in the United States prior to the passage of DSHEA. Because there was no effort to verify this input, however, the text disclaims any identity as a definitive reference to substantiate either presence in, or absence from, the market, and should be considered as only one source of information.

If a submission is missing any of the technical elements (i.e., any element other than the actual evidence), FDA's current policy is to contact the submitter to request that the notice be completed. Such a communication, while not particularly troublesome, will slow down the process and, thus, unnecessarily delay product introduction.

- *Consideration of special populations.* If a new dietary ingredient notification does not directly address use by children or by pregnant or lactating women, FDA is likely to note such an omission and object to its use by those populations. A firm either should state their intention to label products as "not for use" by these groups or provide information that is specific to establishing a reasonable expectation of safety when used by highly-protected populations.
- *Information to avoid.* FDA has consistently objected to any submission that makes a drug claim, whether direct or implied (e.g., by a product name). Except for the conditions of use (i.e., dosage, considerations of particular populations), a 75-day notice does not require the submitter to provide the name of the product in which the ingredient will be sold or any marketing claims that will be made for such products. The submitting firm should refrain, therefore, from providing such information or from making any claims.
- *Prior evaluation of the key information.* FDA's primary objection to a notice submitted in reference to a new dietary ingredient is the agency's determination that the information submitted to support a conclusion that the ingredient will reasonably be expected to be safe often is inadequate. Companies that wish to be successful in obtaining an acknowledgement of receipt of their notice would be well advised to have the submitted data reviewed in advance of submission by a qualified expert.

XI. ANDROSTENEDIONE

On March 11, 2004, FDA took its first regulatory action with respect to failure to file a premarket notification for a new dietary ingredient, and pumped enforcement life into DSHEA's premarket notification system. The ingredient was androstenedione, which first achieved prominence in the sports nutrition market when St. Louis Cardinal slugger, Mark McGwire, said he used it on his way to breaking Roger Maris' single-season home run record. That press, and the ingredient's reputation for helping build muscle mass, led the ingredient to become the supplement of choice for young athletes just emerging from puberty. While questions had been raised for some time about androsteneaction, FDA's action was not surprising after President Bush used his State of the Union address to call on professional sports to set an example for youth:

To help children make right choices, they need good examples. Athletics play such an important role in our society, but, unfortunately, some in professional sports are not setting much of an example. The use of performance-enhancing drugs like steroids in baseball, football, and other sports is dangerous, and it sends the wrong message—that there are shortcuts to accomplishment, and that performance is more important than character. So tonight I call on team owners, union representatives, coaches, and players to take the lead, to send the right signal, to get tough, and to get rid of steroids now.¹⁶

Androstenedione is widely touted as a steroid hormone precursor. FDA's action against products containing this ingredient proceeded on two fronts. First, FDA questioned whether, under the law, androstenedione is a dietary ingredient. A dietary ingre-

¹⁶ George W. Bush, State of the Union Address (Jan. 20, 2004), available at <http://www.whitehouse.gov/news/releases/2004/01/20040120-7.html> (last accessed June 21, 2004).

dient is defined as a vitamin, a mineral, an herb, or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, or extract of one of the preceding items.¹⁷ FDA seriously questioned whether androstenedione is any of these. Second, even if androstenedione could be considered a dietary ingredient, FDA stated it had received no new dietary ingredient notifications for this ingredient and that no one had shown that it was on the market prior to the enactment of DSHEA. Finally, FDA made clear in Warning Letters that if a required premarket notification were submitted, “based on what we know now, we know of no evidence that would establish that your product is not adulterated.” At the same time, FDA issued a White Paper entitled *Health Effects of Androstenedione*, which showed how the androgenic and estrogenic effects of androstenedione might endanger health.¹⁸

FDA’s action with respect to androstenedione plainly establishes the role of the new dietary ingredient provision under DSHEA, and the important role this provision can play as gatekeeper for new dietary ingredients. At the same time, it is clear that FDA needs to monitor dietary supplements to find new dietary ingredients that have not met DSHEA’s requirements before those ingredients become established in the marketplace.

XII. FROM THE PRESENT TO THE FUTURE

The premarket notification system for new dietary ingredients, in its current form and function, is working. FDA is receiving premarket notifications and generally is responding in a consistent manner, in accord with the published regulations. The agency is carrying out the intent of Congress to act as the gatekeeper with respect to new dietary ingredients that are brought to it.

At the same time, and as with any new system—even one almost ten years old—implementation has been less than perfect. For example, there is presently a lag between the closing of the file and its submission to the docket, so that the docket, which should provide useful guidance to firms that want to market a new dietary ingredient, is not as up to date as it should be. This is a simple issue that easily can be addressed.

More important, however, is the need for industry to learn to use this system. The fact that so many submissions have been made for dietary supplements, for which no submission is required, simply taxes the resources of companies and the agency. Failure to follow the instructions set forth in 21 C.F.R. § 190.6 similarly is wasteful, as are submissions of 75-day notices for ingredients that are not new dietary ingredients. The existing files provide a useful resource for identifying mistakes that others have made, and innovative firms will peruse these to learn what FDA has come to expect in terms of substantive information about new ingredients.

As is true in many consumer product categories, new and original products are an essential part of the dietary supplement marketplace. The law that governs new ingredients to support product innovation is clear and FDA’s implementation of this law is becoming more consistent. As the date of the passage of DSHEA continues to recede into the past, the relevance of the regulations for premarket notification of new dietary ingredients will become more important. Their understanding of this regulatory process, and their ability to provide the requisite information that is the basis for a legitimate conclusion that the ingredient will be reasonably expected to be safe may well differentiate successful, and unsuccessful, companies.

¹⁷ Pub. L. No. 103-417, § 3, 108 Stat. at 4327 (codified at 21 U.S.C. § 321(ff)(1)(A)-(F) (FDCA § 201(ff)(1)(A)-(F))).

¹⁸ Food and Drug Administration, White Paper, *Health Effects of Androstenedione* (Mar. 11, 2004), available at <http://www.fda.gov/oc/whitepapers/andro.html> (last accessed May 11, 2004).