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**NEW DIETARY INGREDIENTS AND FOOD ADDITIVES:  
WHAT THEY HAVE IN COMMON**

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## **BACKGROUND**

The purpose of this presentation is to make industry aware of the enormity of the task that the Food and Drug Administration (FDA) has posed in its request for comments on numerous new dietary ingredient (NDI) issues, and to alert industry to the critical importance of the policies and interpretations of law that might result. Through ten years of implementation, FDA has interpreted the law and created policies with respect to NDIs with no formal input and little resistance from industry. Industry is now being given its first opportunity to provide the necessary formal input, but the wide array of issues on which FDA has requested comment, and the minimal time allowed for filing comments, makes any real impact on FDA's policy impossible.

First and foremost, if FDA has a real interest in informed comment, the comment period for the October 20, 2004 notice should be extended for a minimum of six months, or until June 3, 2005. The two-month extension that the industry trade associations have requested is entirely inadequate given the scope and importance of the issues FDA has raised, FDA's recent release of an important strategy document and draft substantiation guidance (which provides an inadequate 60 days for comment), and FDA's impending release of the final rule for good manufacturing practices.

FDA has requested comments on interpretations of the Federal Food, Drug, and Cosmetic Act (FDC Act), as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA), that will impact the continued vitality of the dietary supplement industry. Industry must understand that, given FDA's assigned mission to protect the public health, the agency will, over time, develop policies and legal interpretations that make FDA's job easier, not harder. Given this basic truth, industry should not be surprised that FDA, lacking explicit premarket approval authority over dietary supplements, will interpret the law in ways that give FDA implicit premarket approval authority, and that limit the numbers and types of ingredients that may be introduced into the dietary supplement market. This is what happened in the 1980s and is what will happen again if industry permits.

Some of the critical issues in FDA's recent NDI notice are:

1. Whether the term "dietary ingredient" should be interpreted narrowly to exclude many potential dietary ingredients that FDA does not view as meeting the "dietary substance" provision of 21 U.S.C. § 321(ff)(1)(E).
2. Whether the phrase "marketed in the United States before October 15, 1994" in the FDC Act's definition of "new dietary ingredient," 21 U.S.C. § 350b(c) should be changed by inserting the word "lawfully" before "marketed," and thus excluding many "old" ingredients now on the market that FDA had alleged or would now allege were "food additives" pre-DSHEA – forcing ingredients such as evening primrose oil, black currant

oil, borage seed oil, linseed/flaxseed oil, chlorella, lobelia, St. John's Wort, glucosamine, chondroitin sulfate and coenzyme Q10, to name a few, either off the market or into the NDI notification process.

3. Whether § 350b(a)(1), which excludes from the NDI notification and review process "dietary ingredients which have been present in the food supply," should be narrowly interpreted, as FDA has already done, to exclude many potential dietary ingredients that are "inherent components" of food, such as vitamins, proteins, carbohydrates, or other prominent food "components" that can be separated from the foods and sold as dietary ingredients.
4. Whether the safety standard used in § 350b, "reasonably expected to be safe," means a full-blown safety review under the FDC Act's "food additive" provisions, which would drastically limit market access for NDIs and would be contrary to the intent of DSHEA.
5. Whether the "risk/benefit" analysis that FDA derived from the "unreasonable risk" standard of 21 U.S.C. § 342(f)(1)(A) requires NDI notifications to prove benefits, since NDIs are subject to the same "unreasonable risk" standard through § 342(f)(1)(B).

By developing interpretations and policies surrounding the issues listed above, FDA is moving to minimize the number of ingredients that qualify as "dietary ingredients," maximize the number of ingredients that require NDI notification prior to market, and expanding the data requirements to make NDI reviews similar or the same as food additive reviews. If FDA is allowed to move unhindered in its current direction, all of these factors will have a substantial and negative impact on innovation and future marketing of products for the dietary supplement industry.

The following discussion of these issues is intended to illustrate the problems that FDA's direction will cause for industry, and to serve as a basis for thought in the filing of comprehensive comments. Since FDA has not engaged industry on most if any of these issues, time will be needed to research and develop the arguments to support DSHEA's intent to keep the market open for innovation, and to counter FDA's natural tendency to interpret the law in novel ways that result in serious market limitations.

### **FDA'S NARROWING OF THE DEFINITION OF "DIETARY INGREDIENT"**

FDA has asked "[w]hat should FDA consider to determine whether a substance falls within a particular category of the statutory definition of 'dietary ingredients' under sections [321](ff)(1)(A) through (F) of the [FDC Act]?" 69 Fed. Reg. 61680, 61682 (October 20, 2004)(column 1, question 1). While this request pertains to all of the relevant listed categories of dietary ingredients, the greatest danger lies in FDA's interpretation of 21 U.S.C. § 321(ff)(1)(E). This section states that a "dietary ingredient" includes "a dietary substance for use by man to supplement the diet by increasing the

total dietary intake.” Read in conjunction with DSHEA as a whole and the rest of § 321(ff), it is clear that this section was added to make the definition of “dietary ingredient” as broad as possible, and to capture virtually any “substance” that is suitable for consumption, other than ingredients that are excluded from the definition of “dietary ingredient” under § 321(ff)(3) because they were studied or approved as “drugs” prior to being marketed in dietary supplements.

Predictably, FDA has rejected NDI notifications, and will reject more in the future, based on an unacceptably narrow reading of § 321(ff)(1)(E). FDA’s theory is that, if a “substance” submitted for NDI review is not a vitamin, mineral, herb, or amino acid, in order for that “substance” to fall within § 321(ff)(1)(E), the substance must be “part of man’s usual food or drink.” FDA has not explained why it adopted this “part of man’s usual food or drink” standard, or what the basis for this standard is.

Unless industry challenges FDA’s interpretation of § 321(ff)(1)(E), this section, which was intended to include within the definition of “dietary ingredient” virtually any substance that is suitable for consumption, in addition to the specifically listed categories of vitamins, minerals, herbs, and amino acids, will be applicable to nothing that industry might want to market as dietary supplement. The number of potential ingredients that the industry would lose by capitulation is difficult to estimate, but could be in the thousands.

#### **“MARKETED” OR “LAWFULLY MARKETED”?**

FDA has asked “[w]hat should FDA consider to determine whether a dietary ingredient was not marketed in the United States before October 15, 1994, and is therefore an NDI?” 69 Fed. Reg. at 61682 (column 1, question 3). The FDC Act defines the term “new dietary ingredient” to mean “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.” 21 U.S.C. § 350b(c). In FDA warning letters and in NDI correspondence relating to stevia and other NDIs, FDA has changed the statutory language – “marketed in the United States before October 15, 1994” – to “lawfully marketed in the United States before October 15, 1994.” This one-word change to the statutory language has enormous implications.

Before DSHEA was enacted, FDA had pursued regulatory actions based on allegations of “unapproved food additive” status against many once-popular dietary supplement ingredients – including evening primrose oil, black currant oil, borage seed oil, linseed/flaxseed oil, chlorella, lobelia, St. John’s Wort, and coenzyme Q10. Industry has assumed for more than ten years that these ingredients are legally marketed dietary supplement ingredients that had been “grandfathered” by DSHEA pursuant to 21 U.S.C. § 350b(c), and that these ingredients were thus not subject to the FDC Act’s NDI notification provisions. However, FDA appears to be developing a policy that would render all of the above ingredients, as well as many other widely marketed ingredients,

including glucosamine and chondroitin sulfate, as well as most herbs and herbal extracts, illegal under DSHEA unless there is proof of “lawful” marketing or they are first reviewed by FDA under the NDI notification process.

## **NARROWING THE EXEMPTION FOR NDIs “PRESENT IN THE FOOD SUPPLY”**

In answer to FDA’s own question as to why the agency is holding this meeting, FDA states that “[t]he agency is seeking public comment on several issues that need to be addressed to clarify the requirements of [§ 350b(a)(2)] for NDIs that have not been present in the food supply as an article used for food in a form in which the food has not been chemically altered.” 69 Fed. Reg. at 61681 (column 2)(emphasis added). The underlined text is quoted from § 350b(a)(1), where the FDC Act provides that certain NDIs do not require notification because they are presumed to meet the “reasonably expected to be safe” standard of § 350b(a)(2).

The meaning of § 350b(a)(1) is, like many statutory provisions, open to interpretation. The underlying concept, however, is clear. If an ingredient that meets the definition of an NDI has historically been consumed as food, there is no point in forcing industry to submit a notification to FDA, and there is no point in wasting the agency’s limited resources through the review of such notices.

Interpreting § 350b(a)(1) broadly, but still in a way that adequately assures safety, it would be reasonable to conclude that the exemption from NDI notification would apply to foods and the significant components that make up foods, including proteins, fiber, carbohydrates and vitamins, to which humans are routinely exposed. Components of food that are found in de minimus quantities would, presumably, not qualify for a presumption of safety and should go through the NDI notification process in order to meet the “reasonably expected to be safe” standard. Components of food that are not de minimus should not go through the NDI notification process.

In correspondence to industry, FDA has given § 350b(a)(1) the most narrow construction possible, excluding any ingredient that has not been sold on its own as an article of food from this exemption and, therefore, excluding potentially thousands of dietary ingredients, such as proteins, vitamins, carbohydrates, fiber and other “inherent components” of food from this exemption. This FDA interpretation of § 350b(a)(1), consistent with FDA’s “lawfully marketed” standard, will force many more ingredients into the NDI process, leading to more NDI rejections and giving FDA tighter control over the dietary supplement market.

## **WHAT QUANTITY OF DATA IS REQUIRED TO MEET THE “REASONABLY EXPECTED TO BE SAFE” STANDARD?**

This question actually has two parts: 1) what does the standard mean, and 2) what quantity of data is required to meet the standard? Curiously, even though the first part appears more important, FDA did not ask for an answer in its request for comments. Nonetheless, industry should provide a complete and thorough answer by submitting comments.

Clearly, the words “reasonably expected to be safe” imply a standard that is less than actual “safety.” DSHEA clearly was intended to replace the “food additive” approval process, which FDA used to prohibit the marketing of virtually all dietary supplements except traditional vitamins and minerals, with a more lenient market-friendly standard. Exactly how lenient this standard should be is unclear. It would be unreasonable and unwise for industry to leave FDA to its own devices to establish the meaning of “reasonably expected to be safe.” To be fair to the agency, if FDA is to protect the public from unsafe NDIs, more data will always be better than less data. However, FDA, if left to act on its own, will turn the NDI process into a safety review that is as close to the safety review for food additives as possible.

The question then becomes, what can and should industry do? There appear to be only two answers. First, industry could permit FDA to exercise control and apply a strict safety standard, which will limit innovation but likely not provide much public perception benefit (remember, FDA does not “approve” NDIs, FDA just files them – there is no positive FDA message and FDA will state that it is free to change its mind based on new information – no positive press statement there). In the alternative, industry could work with FDA to develop a self-regulatory, standardized process for reviewing the safety of NDIs similar to the expert panel method of the cosmetics and flavors industries. Industry would bear the expense of the initial review, and then FDA could determine whether the “reasonably expected to be safe” standard was met based on an expert panel report. FDA’s filing of the NDI would be a tacit concurrence in the expert panel’s finding of safety, a positive event that could be used to help bolster consumer confidence.

The other advantage to an FDA/industry safety review process is that it avoids the second part of the NDI safety question – as FDA puts it, “[w]hat quality and quantity of data and information are needed to establish a reasonable expectation of safety. . . .?” From FDA’s perspective, safe is safe, and the truthful answer is “the same amount required to approve a food additive petition.” Industry’s only avenue for avoiding the same type of bottlenecks that the industry experienced in the 1980s is to develop a safety review system of its own, with FDA participation and acquiescence.

## **SHOULD NDI REVIEWS BE “RISK/BENEFIT” REVIEWS?**

A scenario in which FDA requires NDI notifications not only to establish safety but also to prove benefits is a nightmare that industry does not care to contemplate. Nonetheless, now that FDA has established, and the trade associations have apparently accepted, a “risk/benefit” standard for adulteration, industry should anticipate that it will also have to agree to prove the benefits of ingredients in NDI notifications.

It is correct to view the “reasonably expected to be safe” standard as a safety standard, pure and simple. However, NDIs are also subject to the safety standard in 21 U.S.C. § 342(f)(1)(B), which provides that an NDI is “adulterated” if “there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.” FDA derived the “risk/benefit” standard from the “unreasonable risk” standard in § 342(f)(1)(A). Requiring NDIs to prove benefits as well as safety appears to be required by § 342(f)(1)(B), and would be entirely consistent with FDA’s arguments in the ephedra rule and the natural tendency of the agency to require more data rather than less to gain market access for supplements. It appears, once again, that industry’s best hope of avoiding this fate is to take steps toward self-regulation of safety with FDA cooperation.

## **CONCLUSIONS**

Industry is at a crossroads with respect to FDA regulation of dietary supplements. For years, FDA, lacking resources and unhappy with DSHEA, has done little or nothing to enforce even the most necessary legal requirements for these products, such as the need for products to actually contain the ingredients identified on the label in the amounts stated on the label. Industry, suffering from consistently biased and false press reports that supplements are unregulated, unsafe, and for the most part useless, has understandably begged for more regulation and more enforcement. Now industry is about to get just that – in an onslaught of FDA policies, legal interpretations and guidance that will set the stage for the dietary supplement market for years to come.

Industry should first ask for sufficient time to react, and should then should react in a constructive, thoughtful and unified way. This will be a difficult task, given the disparate interests of the varied trade associations. The issues raised in this discussion should help industry recognize the potential consequences of failure.