ANTIOXIDANTS & REDOX SIGNALING
Volume 16, Number 5, 2012
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DOI: 10.1089/ars.2011.4376

A False Sense of Security? The U.S. Food and Drug Administration's Framework for Evaluating New Supplement Ingredients

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Abstract

The evidence sufficient to establish the expectation of safety for new ingredients in dietary supplements is an area of considerable controversy. Recently, the U.S. Food and Drug Administration (FDA) proposed a sound scientific framework for evaluating the safety of new ingredients. The level of evidence the FDA requires (*i.e.*, *in vitro*, animal or human testing) hinges on three key factors: (1) documented history of use; (2) the dose and formulation of the new ingredient compared with the historically used ingredient; and (3) the supplement's recommended use (*i.e.*, daily or as needed). Despite its strengths, the framework requires four key modifications to ensure the expectation of safety: (1) historical use should rarely, if ever, be sufficient to replace experimental data; (2) entirely novel ingredients should undergo, at a minimum, a 90-day human testing; (3) manufacturers should be required to submit to the FDA all available data regarding new ingredients, both favorable and unfavorable; and (4) before assuming that consumers follow instructions on supplement labels, this assumption should be empirically confirmed. In the absence of significant modifications, the FDA's guidance may have the effect of providing a false sense of security to consumers seeking safe dietary supplements. *Antioxid. Redox Signal.* 16, 458–460.

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WHAT QUALIFIES as reasonable evidence of safety for new dietary supplements? What evidence of safety should be available to consumers, scientists, and regulators? These questions are at the core of the U.S. Food and Drug Administration's (FDA) draft guidance for new dietary ingredients (7). By law, all vitamins, minerals, botanical products, and amino acids consumed in the United States before 1994 are assumed to be safe, but this is not the case for the new ingredients introduced since 1994. Before marketing a new ingredient, manufacturers are required to submit to the FDA evidence that establishes the expectation of safety. The evidence sufficient to establish the expectation of safety has been an area of considerable controversy since 1994 when Congress enacted the Dietary Supplement Health and Education Act (DSHEA).

The draft guidance clarifies the FDA's framework for evaluating new ingredients, but without significant modifications, it will be inadequate to provide the expectation of safety for all new ingredients. The level of evidence required (*i.e.*, *in vitro*, animal or human testing) hinges on three key factors: (1) documented history of use; (2) the dose and formulation of the new ingredient compared with the historically used ingredients; and (3) the supplement's recommended use (*i.e.*, daily or as needed). As long as the manufacturer does not recommend dosages above, or formulations different than, those consumed historically, the FDA does not require any additional evidence of safety. If a new supplement either exceeds historical dosages or is formulated differently than the historically consumed ingredient, the manufacturer needs to provide additional experimental data, usually *in vitro*, animal and 30-day human testing. When no documented historical

Innovation

Currently, there is very limited oversight prior to the introduction of new ingredients in dietary supplements. The FDA has proposed a new guidance that clarifies the requirements for reasonable evidence of safety of new dietary ingredients. The author argues that the proposed FDA guidance does not adequately ensure the safety of new dietary ingredients and proposes four specific changes to the guidance prior to implementation.

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use exists, the FDA requires *in vitro* and more extensive animal testing; notably, human testing is not required.

This guidance, if enforced, will lead to a significant and important change in the available evidence of safety for new ingredients. To date, despite the legal requirements to the contrary, manufacturers usually introduce new dietary ingredients without submitting any safety data to the FDA. Critics of the supplement industry argue that manufacturers have ignored the legal requirements, while critics of the FDA have argued that the agency has failed to enforce a key aspect of DSHEA. Both critiques have merit. Manufacturers have only submitted adequate data on a very small fraction of new dietary ingredients, and the FDA has rarely, if ever, enforced the law. The combination of manufacturers' disregard for the law and the FDA's lack of enforcement has led to the marketing of countless new dietary ingredients without prior safety review. This *laissez faire* environment helps explain the ease with which some manufacturers and distributors have been able to introduce blatantly dangerous supplements, such as those adulterated with pharmaceutical products (2, 3).

The guidance provides a clear vision of how the FDA intends to apply the law. The overarching framework of the guidance is well conceived and has the potential to improve supplement safety. The concept that, for an individual ingredient, a combination of *in vitro*, animal and human testing may be necessary to provide an expectation of safety is scientifically sound. Furthermore, making this research widely available will provide essential data to clinicians, consumers, and others who wish to better understand the safety of new ingredients. However, the guidance does not require manufacturers to provide all available data in their possession, both favorable and unfavorable. This is particularly unfortunately, because it was a key recommendation of the Institute of Medicine and National Research Council's Committee on the Framework for Evaluating the Safety of Dietary Supplements 2004 report (4).

A welcome aspect of the guidance is that the FDA reaffirms that synthetic ingredients are not assumed to be identical to ingredients extracted from botanical sources. If an ingredient had been widely consumed before 1994 as a botanical extract and a manufacturer proposes to market a synthetic form, this product would require additional safety testing. Like most of the guidance, this is based on precedent established when the FDA responded to petitions for new products. For example, in response to a petition to approve homotaurine, a synthetically produced gamma-amino sulfonic acid found in seaweed dulse (*Rhodymenia palmate*), the FDA determined that it was not a botanical under DSHEA, because it was produced synthetically (6). Confronting the issue of synthetically produced ingredients is essential to provide the expectation of safety as well as to ensure that consumers are aware of the provenance of supplements.

Despite these sound principles, the guidance will not be sufficient to ensure that new ingredients can be expected to be safe. One problem is that human studies are not required for novel ingredients. Short-term human tolerability studies are required only when historically consumed ingredients are recommended at higher than historically consumed dosages. If limited human testing is required when a supplement is labeled to be consumed at dosages above historical levels, it should follow that entirely new ingredients, without documented historical use, should be subjected to additional human testing, not less. At a minimum, 90-day human studies (*e.g.*, repeat-dose tolerability, absorption, distribution, metabolism, and excretion studies) should be required for novel ingredients.

The presumption that ingredients previously consumed in food and traditional medicine are safe is similarly problematic. The FDA concludes that historical use, if the dose and formulation are the same, can negate the need for experimental data. DSHEA mandates that new ingredients may be marketed as supplements if "there is a history of use…establishing that the dietary ingredient…will reasonably be expected to be safe (5)." However, it is the FDA's responsibility to determine whether the documented history of use is adequate to provide the expectation of safety. The FDA appears to assume that if a documented history of safe use exists then no further animal or human testing is necessary. The Institute of Medicine and National Research Council committee tasked with developing a framework for supplement safety did not concur. When evaluating the safety of supplement ingredients, the committee found "significant scientific problems" with the concept that documented historical use is evidence of safety and that "even widespread historical use without documented ill effects, is no guarantor of long-term safety (4)." Documented use is only relevant to understand an ingredient's safety if consumers, clinicians, and public health experts could have detected an ingredient's adverse effects when consumed in food. There is broad consensus that dietary factors contribute to worldwide increases in diabetes mellitus, coronary heart disease, and obesity; however, the specific components of the modern diet that contribute to increased prevalence of these chronic diseases is still poorly understood. It should not be assumed that dietary ingredients even when they have been consumed in food for years can be expected to be safe.

A final concern is that the FDA assumes that consumers will follow instructions on the label. If experimental evidence suggests potential harm to certain vulnerable segments of the public, such as children or pregnant women, the FDA would still permit marketing of a new ingredient as long as it is labeled accordingly. However, once a supplement is available for self-medication, its use will not necessarily be restricted to the recommendations on the label. In an effort to avoid prescription medications, pregnant women may actually prefer natural treatments, and employees at retail outlets may recommend inappropriate supplements despite warnings on the label (1, 8). The FDA also assumes consumers will follow dosage suggestions on the label. However, if a customer believes the supplement is safe, then consuming a larger quantity might be an intuitive response if symptoms do not initially respond to the suggested dose.

The FDA's guidance, if aggressively enforced, will provide additional reassurance of safety for a subset of new dietary ingredients—specifically those supplements marketed for consumption at doses higher than used historically. Unfortunately, the guidance would not provide the same expectation of safety for the majority of new ingredients. Given the sound framework that the FDA has designed, this could easily be remedied. First, historical use, although essential to consider, should rarely be sufficient to replace experimental data. Even when products have a documented history of use, they should be approached with the same skepticism that is currently reserved for products marketed at higher dosages than historically consumed. Second, entirely novel ingredients should undergo, at a minimum, a 90-day human testing. Third, manufacturers should be required to submit to the FDA all

available data regarding new ingredients, both favorable and unfavorable. Finally, before assuming that consumers follow instructions on supplement labels, this assumption should be confirmed empirically. Absence significant modification, the guidance may have the effect of providing a false sense of security to consumers seeking safe dietary supplements.

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Date of first submission to ARS Central, October 31, 2011; date of acceptance, October 31, 2011.

Abbreviations Used

FDA = United States Food and Drug Administration
DSHEA = Dietary Supplement Health and Education Act