Elusive answers

FDA's latest NDI guidance falls short of goal

By Steve Mister, President & CEO, Council for Responsible Nutrition

Will the FDA ever take the intellectual property rights of the dietary supplement industry seriously? If the FDA's recent release of guidances relating the New Dietary Ingredients (NDIs) and its previous responses toward companies in the industry are any indication, the answer is a resounding "no." That's a lost opportunity not only for supplement manufacturers and marketers but also for the safety of our consumers.

Thirty years is a long time to live under uncertainty and indecision, but that's exactly what the dietary supplement industry has endured since 1994 with respect to its ingredient pipeline. While today we are debating which aspects of the Dietary Supplement Health & Education Act (DSHEA) may need to be modernized to keep pace with the growing industry, the NDI provision and related incentives to protect innovation embedded in that seminal law have languished without proper clarification or enforcement since the start.

As the FDA is fond of reminding the industry, it has received far fewer NDI notifications than the agency would expect, given the number of dietary supplements in the marketplace. And it's quick to mention that the NDI notification process is the only opportunity the FDA has to monitor a new ingredient about to enter the market and to evaluate the safety of such products. Yet, despite the FDA's feigned admiration of the NDI requirements, it certainly hasn't fully utilized this gatekeeping opportunity.

Consider that it took four years to adopt final regulations (21 CFR 190) intended to interpret the brief statutory provision on NDIs (codified at 21 USC 350b), and they are essentially a repetition of the statute itself, with some administrative housekeeping details sprinkled in. For the first 17 years of the law, industry was pretty much in the dark as to when changes in an old ingredient would transform it into an NDI, what were the operational criteria for "reasonably expected to be safe," and whether multiple companies marketing the same NDI would have to file duplicative notifications.

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Creeping toward clarity

We finally got some answers in 2011 with the issuance of the first Draft Guidance on NDIs, but industry respectfully disagreed with the tentative answers it contained. Since the first Draft Guidance was issued, CRN has advocated for clarity, fairness, and efficiency. CRN has consistently emphasized the need for a regulatory environment that supports innovation while ensuring consumer safety. In 2011, and again in 2016, we submitted comments on the FDA's revised NDI Draft Guidance, acknowledging the effort to clarify legal requirements and expectations and voicing our concerns over some of the more burdensome specifics.

In 2022, the FDA announced a proposed amnesty program intended to entice derelict companies that were marketing new ingredients without the benefit of having notified the agency with a chance to come in from the rain and submit an NDI without fear of being penalized for already having marketed the ingredient. CRN commented

then that the problem was *not* that companies were afraid of being slapped for not filing previously—the problem is a combination of: 1. companies that legitimately believe they are not required to file at all, and 2. other companies that believe there is no consequence for ignoring the law; so why bother? A real solution will require two things that amnesty can't provide: clarity in the Guidance for when an NDI notification is necessary and actual enforcement of the law against obvious NDIs that are being sold without a notification.

It is worth noting that while there may be uncertainty in some aspects of the law, there is no lack of clarity about two items. First, it is a prohibited act to introduce into interstate commerce a dietary supplement that is unsafe under the NDI provisions of the law (*see* 21 USC 331(v)) or one that is "adulterated" (*see* 21 USC 331(a)). Second, a dietary supplement is adulterated if it 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" (*see* 21 USC 342(f)(1)(B)).

Checking the small boxes

The FDA's recent Final Guidance, which focuses solely on timelines and procedures, is a significant stride towards demystifying the New Dietary Ingredient (NDI) notification process—but it's only a start. It addresses operational issues and provides a structured framework for submissions, which is a commendable step towards streamlining regulatory compliance. But now, the industry needs clarity on more than timeframes and deadlines.

CRN has long championed the importance of protecting intellectual property within our industry, which led us to welcome the FDA's plan to allow confidential NDI master files. This initiative fosters innovation by securing the competitive edge of dietary supplement companies, encouraging them to invest in new and beneficial ingredients. On April 3, the FDA released a guidance related to these master files.

The problem is that the FDA has exhibited no more commitment today to enforcing the master file concept than it has since the first draft guidance 13 years ago. When CRN met with the FDA in 2020, we stressed that protecting intellectual property through a master file would only succeed if the FDA was willing to prosecute companies that would illegitimately piggyback on another company's research. A "carrot and stick" approach doesn't work without a "stick." In the ensuing four years, we know of no enforcement actions to protect legitimate NDI notifications against copycat ingredients.

It's not just a matter of aiding innovator companies in their competitive battles with freeloaders. It's a public safety concern, too. When a follow-on company begins selling an ingredient and insinuates it relies on the original innovator's safety profile, how does the FDA know the ingredient is the same? Is it made using the same processes? Does it involve different solvents or reagents? Are environmental contaminants removed? Are strength and purity achieved in the same manner? Without any NDI notification for each ingredient manufacturer, the FDA has no way of knowing. While the FDA insists that each finished product utilizing the innovator's ingredient must file their own NDI notification using a similar rationale, the agency has done nothing to enforce the NDI requirements on copycat ingredient suppliers, particularly ones importing their substances from other countries that may pose unique risks.

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Eyes off the ball

The FDA has asserted that these disputes are motivated more by competitive quarrels over IP than safety and refused to take sides in those disagreements. By contrast, the agency has been more than willing to protect the supposed IP interests of pharmaceutical firms vis-à-vis supplements. When one considers the proactive manner in which the FDA has invoked drug preclusion against ingredients like NAC and NMN to protect the financial incentives for drug companies, it seems the agency is more than willing to protect IP rights if the ingredient is a drug. Supplements deserve equal treatment.

As the industry waits for a final guidance on more substantive issues, other incentives for innovation also languish. For example, the earlier draft guidance foreclosed the possibility of using synthetic copies of botanical constituents as dietary ingredients. CRN believes that the FDA's across-the-board exclusion of synthetic versions of botanical constituents is not supported by law and contradicts Congress's intent. From a practical standpoint, it also discourages innovative companies from developing synthetic versions of botanicals to be more environmentally sustainable, easier to deliver precise levels of bioactive constituents without impurities, and more affordable to produce. CRN has advocated for a broad interpretation of "dietary ingredient" to ensure a diverse and innovative dietary supplement market. We argue for equal treatment of synthetically and naturally derived ingredients,

as long as they are chemically and biologically equivalent, to foster innovation while ensuring consumer safety.

CRN has also criticized the FDA's broad interpretation of "chemically altered" when determining the need for an NDI notification. We still call for a narrower interpretation that only considers changes significantly altering a dietary ingredient's identity or safety profile. Minor manufacturing changes or processes that do not fundamentally change the ingredient's identity or safety should not trigger the need for a new NDI notification. The FDA's earlier interpretation unnecessarily complicates the regulatory process for dietary supplements, potentially stifling innovation and placing undue burdens on the industry without meaningfully enhancing consumer protection.

Staying pure

Finally, we have discussed how manufacturing changes to dietary ingredients should be evaluated regarding their impact on the ingredient's regulatory status and the need for an NDI notification. We propose that changes improving an ingredient's purity—without affecting its identity or safety—should not require a new NDI notification. This includes advancements in manufacturing that result in lower levels of impurities or contaminants. We suggest the FDA adopt a case-by-case evaluation approach for manufacturing changes, emphasizing that not all changes significantly impact an ingredient's safety or identity. This approach would align more closely with FDA policies on other food products and ingredients, promoting regulatory efficiency and effectiveness while supporting public safety and industry innovation.

Our goal is to finally clarify the NDI notification process, ensuring it not only promotes a thriving, innovative dietary supplement market but also protects consumers. Our vision for NDIs is one where the regulatory process is transparent, efficient, and conducive to the shared goal of delivering safe, effective nutritional products to consumers.

It is a matter of public health.