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By Electronic Delivery

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

ATTN: FDA-2011-D-0490, Comment on Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives

To whom it may concern,

On behalf of The Pew Charitable Trusts, I am writing to express our general support for the U.S. Food and Drug Administration's (FDA) draft "Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives." The guidance helps address this important emerging technology. Pew strongly agrees with the FDA's draft decision to deny "generally recognized as safe" (GRAS) status to nanoengineered chemicals and review them as food additives. However, as is detailed in these comments, we have concerns with certain aspects of the document and question the agency's claim that it has not reviewed GRAS notifications sanctioning the use of nanoengineered chemicals.

We believe it is important that FDA address the concerns we raise to ensure the safety of the nanoengineered particles, maintain public confidence in the process, and avoid costly product changes and recalls if problems arise once the chemicals are on the market. These suggestions should assure that the decision is:

- Made by the agency, not a food manufacturer;
- Made in a transparent, scientifically sound manner that considers how the chemicals could be changed when consumed and digested; and
- Considers the impact on absorption or release of other chemicals in the food.

FDA properly excluded from GRAS nanoengineered chemicals

We applaud the FDA's statement on page 14 of the draft guidance that it is "not aware of any food ingredient or FCS [food contact substance] intentionally engineered on the nanometer scale for which there are generally available safety data sufficient to serve as the foundation for a determination that the use of a food ingredient or FCS is GRAS." We also agree with the agency's conclusion on page 19 that "[a]t present, for nanotechnology applications in food substances, there are questions related to the

technical evidence of safety as well as the general recognition of that safety, that are likely to be sufficient to warrant formal premarket review and approval by FDA, rather than to satisfy criteria for GRAS status." Taken together, the agency makes clear for nanoengineered chemicals or products that industry must not use the GRAS exemption from the definition of food additive or seek to employ the GRAS notification program.

Thus, before any nanoengineered substance is allowed in the food supply, the agency must take formal action to approve its use. We agree with this approach, and believe it is essential that FDA make the final decision[1] on the safety of these products in their nanoengineered form.

As with all GRAS substances, we are concerned that FDA relies on non-binding guidance to establish expectations. Since the law allows food manufacturers to self-affirm that chemicals can be GRAS and use them in food without notifying FDA of the decision, there is no practical way for the agency to know when a company has chosen to disregard FDA's recommendation.

FDA should require petitions for prior GRAS decisions of nanoengineered products

We were surprised by FDA's statement on page 14 of the draft guidance that "[t]o date, we have not, to our knowledge, received food or color additive petitions, or GRAS affirmation petitions or notices, for any uses of food ingredients with a particle size distribution fully in the nanometer range." We reviewed the 410 GRAS notifications (GRNs) that the FDA received between 1997 and 2011 and identified four notices, GRN #202, GRN #248, GRN #298, and GRN #321, which explicitly refer to nanoengineered chemicals. FDA issued "no questions" letters for all but GRN 298 (which was withdrawn by the notifier) effectively sanctioning their use in food. Table 1 provides details on each of these notices.

TABLE 1. GRAS NOTICES EXPLICITLY REFERRING TO NANOENGINEERING IN DESIGN OR PREPARATION

Description	Substance and intended use	Comment
GRN 202 filed on June 5, 2006. FDA said it had no questions about the notice on December 6, 2006.[2]	Polyoxyethanyl-alpha-tocopheryl sebacate "as a solubilizer for the dietary ingredient coenzyme Q10 (CoQ_{10}) in dietary supplements."[3] In essence it overcomes fats' normal tendency to float on water so that they can be dissolved in water.	While FDA's memo does not use the word "nano," the GRAS Notification (GRN) refers to the technology as using "[p]articles size analysis has measured such nanomicelles at 20nm. Such complexation facilitates ease of addition of the dietary supplement ingredient into water matrices."[4]

[1] The decision must be a final agency action consistent with the Administrative Procedure Act. 5 U.S.C. §551 et seq.

[2] FDA, Letter to Edward A. Steele of AAC Consulting Group, 2006. See http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm153708.htm.

[3] Id.

[4] AAC Consulting Group, Submission of GRAS Notification – Polyoxyethanyl-a-tocopheryl sebacate (PTS) for use as a solubilizer, 2006. See http://www.accessdata.fda.gov/scripts/fcn/gras_notices/612858A.PDF.

GRN 248 filed on April 10, 2008. FDA said it had no questions about the notice on October 24, 2008.[5]	Sucrose fatty acid esters "as emulsifiers in fruit-flavored beverages and beverage concentrates, at levels up to 50 milligrams per Liter (mg/L) as consumed."[6] In essence, it overcomes fats' normal tendency to float on water so that they can be dissolved in water.	While FDA's memo does not use the word "nano," the GRN states that the "size of the emulsion particles resulting from formulations containing sucrose monolaurate, monopalmitate or monostearate are generally in the range of 20 nm that are considered to be in the range of nanotechnology products (0 to 100 nm in diameter). This size of the fruit beverage emulsion particles overlaps with the size of the micelles formed in the digestion of fat and therefore [these particles] are not expected to affect the digestion and absorption of the sucrose monoesters to a large extent."[7]
GRN 321 filed on February 18, 2010 after the firm withdrew a previous notice (GRN 298 submitted on July 14, 2009). FDA said it had no questions about the notice on August 18, 2010.[8]	Synthetic amorphous silica "as an anticaking agent, defoaming agent, stabilizer, adsorbent, carrier, conditioning agent, chill proofing agent, filter aid, emulsifying agent, viscosity control agent, and anti-settling agent" in 33 types of food "at levels up to 2.0 percent weight/weight (w/w), and as an indirect additive in the manufacturing of adhesives, coatings, defoaming agents, greases and lubricants, paper and paperboard, and polymers that are then used as components of food-packaging material."[9]	FDA's letter states that the company "notes that most solid SAS particles range from 0.1 [100 nm] to 1 micrometer [1000 nm] and do not exist as easily dispersible nanoparticles." The earlier notice that was withdrawn states that the product was "Colloidal silica" and was described as "a stable aqueous dispersion or sol of discrete amorphous silica particles having diameters of 1 to 100 nm."[10] Comparing the notices, only the description of the product and not the product itself changed. The health and safety studies appear to have been conducted on silica many years before using a manufacturing process that did not involve nanotechnology. Also note that while not all of the particles are in nanometer range, the firm states that some are.

There may be other notices that dealt with chemicals containing particles in the nanoscale range where the firms did not use term "nano."

For these three GRNs, FDA should require the firm to submit a petition for formal FDA review.

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[5] FDA, Letter to Bob Comstock of Compass Foods Pte Ltd, 2008. See http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm154444.htm.

[6] Id.

[7] Compass Foods Pte Ltd, The generally recognized as safe (GRAS) status of sucrose monoesters of lauric acid, palmitic acid and stearic acid as emulsifying agents for flavors used in fruit flavored beverages, 2008. See http://www.accessdata.fda.gov/scripts/fcn/gras_notices/804897A.PDF.

[8] FDA, Letter to Elliot Harrison of Lewis & Harrison, LLC, 2010. See http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm225016.htm.

[9] Id.

[10] Lewis & Harrison, Letter to FDA, 2009. See http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn0298.pdf.

FDA should explicitly call for safety reassessments for changes that alter nanoscale particles

The draft guidance does not explicitly state that food manufacturers should seek FDA approval when changes in the manufacturing process either increases the proportion of the particles in the nanoscale range or alter the structure of particles in that range. The document recommends that a safety assessment be conducted when it changes the identity of the food substance and describes that these changes include "characteristic properties such as physicochemical structure and properties, purity, impurities, bioavailability, or toxicity."[11] Physicochemical is not defined but generally means that it relates to both its physical and chemical properties or to physical chemistry. Since particle size and structure is central to nanoengineering, it seems inappropriate to not to be explicit in the guidance.

Rather than use such an abstract term as physicochemical to define a change in the manufacturing process, FDA should explicitly state that a safety assessment is needed whenever there is a change in manufacturing process that alters the size or structure of nanoscale particles.

To eliminate conflicting approaches, FDA should delete footnote 9 which puts FDA in the untenable position of regulating based on the intent of a manufacturer, which is often difficult or impossible for FDA to know

In footnote 4 of the draft guidance, the agency discusses its Nanotechnology Task Force report and acknowledges that "[t]he term is perhaps most commonly used to refer to the intentional manipulation, manufacture or selection of materials that have at least one dimension in the size range of approximately 1 to 100 nanometers." The footnote goes on to explain the FDA-wide approach as follows.

> "In the absence of a formal definition, when considering whether a FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, FDA will ask: (1) whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or (2) whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer."

These statements use the term "engineered" to evaluate whether the end product was manufactured or processed. Each of the two questions can be objectively answered by an analysis of the final product. It is not dependent on the source of the raw materials (natural or chemical production) or the primary purpose of the engineering.

Unfortunately, the draft guidance in footnote 9 appears to significantly alter the agency-wide approach. It indicates that the agency is only focused on products that are "engineered to contain nanoscale materials or involve the application of nanotechnology" for food additives. The document states that the agency guidance does not question the regulatory status of conventionally manufactured food substances or naturally occurring substances even if they are in the nanoscale range. In essence, the guidance takes a narrower view of the term by focusing on the intended purpose of the engineering. This purpose cannot be assessed objectively.

How will FDA discern the intent if compliance questions arise? While nanotechnology is an emerging technology, often the changes in the manufacturing process are relatively subtle involving alterations in

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[11] The guidance uses this language on each of the four sections from page 16 to 19.

the oxidation state, temperature, or mixing. They may also have benefits on energy efficiency, conversion rates, and process capacity beyond altering the particle size of the chemical. Rather than focus on the intent of the engineering change, the agency should rely on the approach used by the agency as a whole, namely whether it has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or whether it exhibits properties or phenomena that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.

Rather than create ambiguity with differing approaches, FDA should delete footnote 9.

FDA should address three important scientific questions

If there is a change in the manufacturing process that alters the particle size or structure, FDA needs to use scientific procedures to assess the safety of the chemical. If the chemical is being considered for GRAS status, the pivotal toxicological study must be published. The statutory allowance for GRAS substances based on common use before 1958 would not apply.

The draft guidance does not explain how the safety assessment for the altered particle should be conducted. Since manufacturers are expected to conduct the evaluation and submit it to FDA, the guidance should address the how the evaluation should be prepared.

We think that the safety assessment should focus on three crucial questions presented by nanoengineered particles.

1. Were the scientific toxicological studies conducted using chemicals with the same particle size and structure as the substance being considered? If the studies were conducted on substances different in size or structure from the nanoengineered chemical, then they may have limited relevance to the agency's determination that an intended use is reasonably certain not to be harmful. Without affirmative safety information, the agency cannot be confident that the use is safe. In the case of GRNs 298 and 321 (discussed above), FDA does not appear to have investigated whether the original safety studies for the silica were based on the same material covered by the GRAS notification. However a presentation by Dr. Prabir Dutta at the Institute of Food Technologists' 2012 annual meeting[12] suggests that the nanoengineered chemical may behave quite differently in the small intestine than the original particle.
2. How does the altered particle in the nanoscale range affect the absorption, distribution, metabolism and excretion (ADME) of the chemical? To our knowledge, there are no published and validated methods to evaluate ADME of nanomaterials. Despite this lack of validated methods, FDA has essentially cleared (through "no objections" letters) approved a number of food contact substances that appear to involve nanotechology.[13]
3. Does the nanoparticle increase dietary exposure to a chemical beyond what was already anticipated by FDA? The nanomicelles cleared by the agency in its decisions on GRNs 202 and 248 enable fats to be used in water-based beverages where they could not be used previously. If the dietary exposure assessment of the fats delivered by the nanomicelle did not consider these uses, it is conceivable that this technology will increase exposure and warrant a reassessment. It is not clear from the documentation that FDA considered this issue. Nanotechnologies may

[12] Detection and Safety Evaluation of Engineered Nanoparticles in Foods, presented at Safety Evaluation of Nanodelivery Systems and Nanoparticles in Foods session on June 27, 2012.

[13] For that reason, Pew has funded the ILSI Research Foundation to manage a multi-stakeholder program to identify potential methods and evaluate their effectiveness through an interlaboratory testing process.

effectively override the traditional self-limiting levels of use that the agency relies on as described on page 11.

We believe that the guidance should explain how food manufacturers should address these questions.

In conclusion, Pew appreciates the opportunity to comment on the draft guidance and encourages FDA to make the recommended changes and quickly finalize the document.

Thank you for reviewing our comments.

Sincerely,

Tom Neltner
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Pew Health Group
The Pew Charitable Trusts