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REGULATORY REPORT
FDA Regulation of Food Packaging Produced Using Nanotechnology

By Michael F. Cole and Lynn L. Bergeson

Food packaging is a target opportunity for the commercialization of nanotechnology. One respected industry analyst has reported that there are already 250 packaging products on the market incorporating substances manufactured using nanotechnology (nanopackaging). These products generated over $860 million in sales worldwide last year, and the same analyst projects that within10 years, nanopackaging will be a $30 billion market.[1]

Food packaging materials must comply with the provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA).[2] Nanopackaging for the most part involves the use of materials that are not intended to have any effect on the food in the package, but may contact the food if the material migrates from the packaging. Such materials are regulated as indirect food additives or food contact substances. There are precedents that permit the marketing of indirect food additives without the need for clearance, and there is a regulatory process in place to review additives that require approval. The critical question in the food packaging area, as in every regulated industry, is whether existing precedents and process will be sufficient to address any issues that arise as the application of nanotechnology matures.[3]

Regulation of Food Packaging Using Nanotechnology

As the result of past regulatory decisions, there is a large body of published approvals for the use of chemicals as indirect additives in food packaging. The decisions are published in the form of regulations, or are listed on the website of the Center for Food Safety and Applied Nutrition (CFSAN), the unit of FDA charged with the responsibility for reviewing indirect food additives that require review. With the exception of effective Food Contact Notifications (FCN), discussed in more detail below, the decisions permitting the marketing of the listed chemicals are generic. Any manufacturer can rely on those past decisions to go to market without involving FDA, if the chemical it proposes to market is the same as the listed chemical, it is sold for the same intended purpose, and the product complies with any specifications and limitations placed on the intended use when the decision was made to permit marketing.

In addition to conforming to an existing approval or clearance, a manufacturer can go to market without consulting FDA if it makes a determination that the substance is not regulated as a food additive. Generally Recognized As Safe (GRAS) substances are excluded from the definition of a food additive, so a manufacturer can make a determination that the material proposed for use is GRAS for the intended purpose. A substance is GRAS if publicly available scientific information demonstrates that the substance is safe for the specified use, and if qualified experts confirm that view in one of a number of specified ways. Also, a manufacturer can make a self determination that the substance being incorporated into the packaging will not migrate to the food. If that is the case, there is no reasonable certainty that the substance will become a component of food, so it does not meet the definition of a food additive.[4] As a result of a suit filed against FDA, there is a court ruling that “no migration” can mean an insignificant amount of migration as well as no migration at all.[5]

If the manufacturer cannot satisfy one of the above criteria for going to market, it has to interact with CFSAN to get clearance. The CFSAN review is limited by law to issues concerning safety. “Safety” means that “there is a reasonable certainly in the minds of competent scientists that the substance is not harmful under the intended conditions of use,” taking into account both the probable consumption of the substance that migrates to the food from the package and the cumulative effect of the consumption of the substance from all sources in a person’s diet.[6]

At the present time, the procedure used almost exclusively for the consideration of new indirect additives by CFSAN is the FCN.[7] To have an FCN declared effective, a manufacturer has to submit an application with extensive data on the identity of the

chemical in question. This information must be accompanied by proscribed toxicological data. A cornerstone of the process is comprised of data from migration studies or calculations, detailing how much of the substance might migrate when used as specified. CFSAN has published broad guidance documents explaining the chemistry and toxicological data required, that will vary from chemical to chemical.[8] The question that regulatory agencies are now beginning to ask is whether the processes described above are sufficient for considering the risks and benefits of new materials produced using nanotechnology in manufacturing.

Nanopackaging

Nanoparticles are under investigation to improve the mechanical and heat resistance properties of packaging to prolong shelf life, and to increase the barrier properties of packaging by affecting gas and water vapor permeability.[9a-d] "Active packaging" is being developed to facilitate antimicrobial and antifungal surfaces to decontaminate packaging and protect the food contents. "Smart packaging" is under investigation. Sensors would be incorporated into packaging materials to signal microbiological and biochemical changes. Other smart packages would be used to track and trace food products.[9a/9d]

The first products into the commercial market are a variety of organo clay fillers used primarily in a nylon matrix resin. Foils or membranes are also available that offer adjustable gas permeability. Materials exhibiting antimicrobial properties imparted by nanoparticles of silver, zinc oxide, and magnesium oxide are in distribution, and dirt repellent coatings are being developed to prevent the invasion of microorganisms.[9a]

Nanotechnology in food packaging involves the manipulation of particles at the molecular level to develop materials with novel, unique properties that address vexing packaging problems. For example, polymers are not inherently impermeable to gases such as oxygen, carbon dioxide, or water vapor. Often, multilayer films composed of different plastic materials have to be developed to provide both oxygen and water impermeability, while providing barrier properties. Nanoclays and other nanoparticles engineered at the molecular level have been developed that will greatly reduce both oxygen and water vapor release, while at the same time providing barrier protection. The new material will be only one layer thick, while still meeting the needed performance specifications.[10]

Manipulation of particle size at the molecular level can cause physical and chemical changes compared to the substance at the macroparticle level. The reduction in the size of the particles means that their small mass makes gravitational forces negligible. Instead, electromagnetic forces are dominant in determining the behavior of atoms and molecules. Second, particles at the nanoscale express quantum mechanical phenomena, rather than classical behaviors. Third, size of the nanoparticle further creates a very large surface area to volume ratio, which makes nanoparticles "staggeringly reactive" in comparison to their macroscale counterparts.[11] The bandgap—or distance between electron energy levels in an atom—also morphs at the nanoscale, changing the electrical resistance and chemical reactivity of a nanoparticle (e.g., the nanoparticle could become a conductor, an insulator or a semiconductor).[12] Lastly, nanoparticles are affected far more than macroscale particles by random molecular motion. These changes combine to produce at the nanoscale properties which can differ fundamentally from those same particles at the macroscale.[13] These changes include color and related interactions with light, electrical conductivity, magnetization and polarity, melting points, hardness, resistance, and strength.[11] Any or all of the foregoing properties can differ fundamentally from the same properties at the macroscale.

A chemical comprised of nanoparticles can behave differently than its macro counterpart. Whether this in and of itself makes the chemical a "new" chemical for regulatory purposes is unclear. There is very little FDA precedent to rely upon in deciding this question. To date, CFSAN has issued no guidance documents or proposed any modification to the rules governing submissions to account for any nanotechnology-related issues. In response to inquiries, CFSAN spokespeople state that CFSAN has a great deal of experience working with substances at the molecular level and believes its present regulations and guidance documents will be sufficient for the review of products of the new technology.[14] This is, of course, the refrain of all federal agencies, the National Nanotechnology Initiative (NNI), the federal progam established to coordinate multi-agency efforts in nanoscale science, engineering, and technology, and NNI's National Science and Technology Council, Committee on Technology, Subcommittee on Nanotechnology Science, Engineering and Technology (NSET).

There is at present only one published precedent that might be applied to help resolve the question of the status of a nanoparticle as a "new" chemical. That is the decision made by the Center for Drug Research and Evaluation (CDER) in its Final Rule for Sunscreen Products for Over the Counter Human Use in response to a comment filed. When the rule was published for comment, a comment was submitted stating that the micronized titanium dioxide used by some manufacturers was a new ingredient, a new

chemical that differed from the titanium dioxide listed in the monograph. The comment went on to say that the differences in the chemical raised several unresolved safety and efficacy issues.[15] CDER stated that data filed in support of monograph status included acute animal toxicity, irritation, sensitization, photoirritation, photosensitization, and human repeat insult patch and skin penetration studies. The several studies showed no deleterious effects, and CDER said that it was unaware of any evidence that demonstrated a safety concern. It therefore indicated that it considered micronized titanium dioxide to be a specific grade of the substance originally reviewed by the OTC panel. The absence of safety concerns, therefore, served as the basis for finding that the nanotechnology produced version of the substance was the same chemical.[16] This is a sensible resolution of the issue of "old" versus "new." If the testing done shows that the chemical presents no new safety issues, then it can be expected that the chemical will have the same effect as the macro version, i.e., that it will be safe in the intended use, and there is no need to engage in a protected academic exercise as to the sameness of the particle.

A question going forward will be whether the technology will be readily available to develop the necessary data on toxicity and migration to answer the question of whether or not a chemical should be treated as new. As one FDA spokesperson put it, characterization concerns include the crucial physical and chemical properties, including residual solvents, processing variables, impurities, and excipients, and what are the standard tools that can be used for this characterization. Validated assays are not readily available in all cases.[3]

This will be an ongoing process, but that has always been the case with the refinement of testing techniques and the discussion of their applicability. The FCN process described above is flexible, and the tests utilized, and the information gathered, can, and will, vary from application to application. CFSAN can supplement the present chemistry and toxicology guidelines it has regarding FCNs when new tests are developed that it thinks should be utilized to generate data to support an FCN submission. Manufacturers can comment if they think the tests are not appropriate, or they can submit alternate tests and data and justify their use to CFSAN. Two areas of ongoing interest will be the publication of ongoing research into the migration patterns of nanoparticles, and their toxicity compared to comparable macroparticles.

Going Forward

Manufacturers make the first determination regarding the regulatory status of chemicals used as indirect additives for a specified purpose. At present, as mentioned above, the only relevant decision by FDA on how to approach the question of the status of a nanoparticle is the sunscreen ruling by CDER in its Final Rule for Sunscreen Products for Over the Counter Human Use. The rationale for the ruling should be of value to the manufacturer in the food packaging context. The issue is whether the substance is safe. It is not presumed to be safe unless it has been approved or declared effective, or unless it is GRAS, meets the TOR criteria, or does not migrate to the food.

So the manufacturer is attempting to demonstrate that the substance produced using nanotechnology is safe because it is the "same" chemical as one previously considered in one of the above ways. That was the issue with the sunscreen. Was the titanium dioxide the same titanium dioxide that had previously been found safe for over the counter use? CDER said it was, albeit a specific grade of the chemical, because it was a refinement of particle size distribution that raised no safety concerns.16 That logic may apply equally well in considering the status of indirect food additives. Commentators in the environmental area, however, have urged caution in using such a regulatory strategy, since to their minds it is unclear that such judgments can be made without the intervention of the regulator. They urge the regulator to be proactive, and require submissions, in no small part because of confusion as to how the requirements of statutes such as the Toxic Substances Control Act (TSCA) apply to nanomaterials.[17]

Manufacturers will also have to address whether the use of the nanoparticles complies with any specifications or limitations that apply to existing approvals. Again, the rule of reason as set forth in the sunscreen example may suffice. If a manufacturer completes its battery of tests, and there appear to be unresolved toxicological issues, or different migration patterns that appear to be possibly significant, the manufacturer can either file an FCN, or pre-meet with CFSAN to discuss whether a filing might be appropriate.

Speculation is rife that nanotechnology may be creating strange new substances that should not be commercialized until further research is completed. What is known today does not support such a view. With regard to food packaging, the review of a substance at the molecular level has been going on for some time, and FDA has considerable experience with the sort of issues presented by the particles being used to achieve a desired result in answering packaging questions. At least two FCNs have been declared effective for nanopackaging products, and there is no indication that those notifications posed any unique problems for the companies involved or CFSAN. The present attitude of CFSAN seems reasonable in the circumstance.

It believes its procedures can be used effectively to assure that nanopackaging is safe.

If the procedures need to be modified, CFSAN will do that as needed, and manufacturers will object if they do not feel the modifications are necessary. Such a protocol is preferable to trying to enact rules to an-ticipate as-yet unverified issues. CFSAN is now devoting substantial resources to improving the FCN process in general. That would appear to be the best use of limited staffing resources and funds until future information proves otherwise.

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2. FFDCA §§ 401-411d, 21 U.S.C. §§ 341-350d.

3. Some FDA representatives are beginning to raise questions in presentations about the sufficiency of existing regulations and test methodologies to address nanotechnology driven issues. See, e.g., "FDA Perspective on Nanomaterial-Containing Products." Nakissa Sadrieh, Ph.D. NanoBusiness/Conference. May 2005. www.fda.gov/nanotechnology. The dialogue in environmental law has progressed further, with active discussions in publications and meetings regarding the sufficiency of specific statutory provisions to address risk issues identified. See, e.g., Environmental Law Institute, "Securing the Promise of Nanotechnology: Is U.S. Environmental Law Up to the Job?" www2.eli.org/pdf/research/nanotech/d15-10.pdf; and "Getting Nanotechnology Right the First Time." March 25, 2005. www.environmentaldefense.org/documents/4444_DenisonNRCPanelslides25Mar05c.pdf.

4. FFDCA § 201(s), 21 U.S.C. § 321(s).

5. Monsanto v. Kennedy, 613 F.2d 947 (D.C. Cir. 1979).

6. 21 Code of Federal Regulations § 170.3(i).

7. FFDCA § 409(h), 21 U.S.C. § 348(h); see also 21 C.F.R. § 170.100.

8. "Guidance for Industry: Preparation of Food Contact Notifications: Administrative Final Guidance." May 2002. www.cfsan.fda.gov/~dms/opa2pmna.html.

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13. Nanosense.org. "Lesson 3: Unique Properties at the Nanoscale." May-June 2005. nanosense.sri.com/activities/sizematters/properties/SM_Lesson3Teacher.pdf.

14. This is a prevailing view, though not unanimously held, among those studying the broad implications of nanotechnology. See "Responsible Development of Nanotechnology," E. Clayton Teague, Director, National Nanotechnology Coordinating Office (Apr. 2, 2004). www.nano.gov/html/res/CTInfocast%202004%20PresentationB.pdf.

15. In the Federal Register, CDER summarized the objections raised in the comment: (1) it does not meet the definition of a sunscreen opaque sunblock; (2) there is no control of particles to agglomerate, which is critical to effectiveness; (3) no standards exist to ensure integrity of coatings; (4) there are no performance-based standards of identity; micronized titanium dioxide is not included in the USP; (5) its photocatalyst potential; and (6) the potential for the smaller particle size to accumulate under the skin. 64 FR 27666, 27671. May 21, 1999.

16. 64 Federal Register at 27671.

17. Environmental Defense Fund. Letter from EDF to Susan B. Hazen, U.S. EPA. Sept. 2, 2004. www.environmentaldefense.org/documents/4457_NanotechLetterToEPA.pdf.

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