

Analysis & Perspective

TOXIC SUBSTANCES

NANOTECHNOLOGY

The Food and Drug Administration is considering further implementation of the recommendations made by its Nanotechnology Task Force in July 2007. The authors of this article note that nanotechnology will be a fact of life for FDA-regulated products for years to come. They say nanotechnology is an important issue, but only one among many that FDA must address, and FDA's limited resources must be allocated sensibly. The authors suggest FDA build on existing databases and correlate the information from submissions required for certain products. When the facts clearly warrant it, the authors recommend FDA issue guidance documents that set forth the issues to address in making filing determinations, but the need for such filings should follow the established, existing framework unless and until that framework is proven inadequate.

Food and Drug Administration's Regulation of Nanotechnology

By LYNN L. BERGESON AND MICHAEL F. COLE

The Food and Drug Administration's recent public meeting to consider regulated products that may contain nanoscale material has renewed discussion regarding FDA's policy and regulatory approaches to all things nano.¹ To date, FDA has taken a measured

¹ The public meeting was Sept. 8, 2008. FDA is accepting written comments until Oct. 24, 2008, at <http://www.regulations.gov>. See 73 Fed. Reg. 46022 (Aug. 7, 2008).

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The opinions expressed here do not represent those of BNA, which welcomes other points of view.

approach to the health, safety, and environmental concerns voiced by public interest groups and others regarding the use of nanomaterials in medical and other products FDA regulates. Some critics have urged FDA to do more to assess the potential for biological interaction involving nanoparticles and enhance regulatory scrutiny accordingly. Other commentators have expressed the view that FDA's current and historic approach to nanoscale materials is well-informed and sensible.² In the face of increasingly strident calls for action, FDA has stated that the important goal at this stage in nanotechnology's evolution is to address knowledge gaps and assess the current state of the science.³ No regulatory action is presently warranted, according to FDA, since it has no knowledge of any instances of adverse reactions related to the nanosize of resorbable drugs or devices,⁴ and reports that it is cur-

² A plethora of articles and comments have been published pro and con on the role of FDA in regulating nanotechnology. A broad sampling of such material is posted to Docket 2006N-0107: FDA-Regulated Products Containing Nanotechnology Materials, available at <http://www.fda.gov/ohrms/dockets/default.htm>.

³ See FDA, "Nanotechnology, A Report of the U.S. Food and Drug Administration Nanotechnology Task Force" (Task Force Report) (July 25, 2007) at 14 and 15, available at <http://www.fda.gov/nanotechnology/taskforce/report2007.html>.

⁴ "To date, FDA has no knowledge of reports of adverse reactions related to the 'nano' size of resorbable drug or medical device products. If new risks are identified, arising from new materials or manufacturing techniques for example, new tests

rently unaware of any safety concerns. FDA has been more circumspect regarding the safety of sunscreen products, likely because of the impact that the pending petition filed by the International Center for Technology Assessment (ICTA) (ICTA Citizen Petition) seeking to halt the use of nanoparticle titanium dioxide in sunscreen drug products would have on the continued marketing of sunscreens.⁵

FDA has become involved in a variety of activities regarding nanotechnology that are designed to expand its information base. FDA is participating in the efforts of the National Nanotechnology Initiative. FDA spokespersons have presented at many public seminars, discussing how FDA views the challenges and opportunities presented by the use of nanoscale materials in products regulated by FDA, and soliciting comments from attendees. FDA is conducting research at several of its centers to understand the characteristics of nanomaterials and processes, while reminding all that the Federal Food, Drug and Cosmetic Act provides it jurisdiction over products, and not over technology, except to the extent that FDA needs to consider some element of technology in deciding the safety and effectiveness of a regulated product.⁶ FDA has nominated various materials for testing by the National Toxicology Program as part of NTP's Nanotechnology Safety Initiative.⁷ FDA participates in several other collaborative efforts, such as the Nanotechnology Characterization Laboratory, which it co-sponsors with the National Cancer Institute and the National Institute for Standards and Technology.⁸

In August 2006, FDA formed a Nanotechnology Task Force (Task Force) to assist in "determining regulatory approaches that encourage the continued development of innovative, safe and effective FDA-regulated products that use nanotechnology materials."⁹ The Task Force was charged with "identify[ing] and recommend[ing] ways to address any knowledge or

or other requirements may be needed." FDA, "FDA and Nanotechnology Products," available at <http://www.fda.gov/nanotechnology/faqs.html>.

⁵ See International Center for Technology Assessment, "Petition Requesting FDA Amend Its Regulation for Product Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically" (ICTA Citizen Petition) (May 16, 2006) (FDA Docket No. 2006P-0210), available at <http://www.fda.gov/ohrms/DOCKETS/dockets/06p0210/06p0210.htm>.

⁶ "FDA regulates products, not technology." FDA, "FDA Regulation of Nanotechnology Products," available at <http://www.fda.gov/nanotechnology/regulation.html>.

⁷ Some examples of the projects underway can be found in a presentation by Nakissa Sadrieh, Ph.D., associate director for research policy and implementation, Office of Pharmaceutical Science, CDER, FDA, at the International Life Science Institute-Health and Environmental Sciences Institute (ILSI-HESI) annual meeting (Jan. 17, 2005) at 18-24, available at http://www.fda.gov/nanotechnology/powerpoint_conversions/ilsi-hesi-ann-mtg_files/800x600/index.html. Information on studies undertaken for FDA by NTP can be found on the NTP Nanotechnology Safety Initiative webpage at <http://ntp.niehs.nih.gov/index.cfm?objectid=7E6B19D0-BDB5-82F8-FAE73011304F542A>.

⁸ Information on the Nanotechnology Characterization Laboratory is available at <http://ncl.cancer.gov/>.

⁹ NCI, Nanotech News, "FDA Forms Internal Nanotechnology Task Force" (Aug. 14, 2006), available at http://nano.cancer.gov/news_center/nanotech_news_2006-08-14e.asp.

policy gaps that exist so as to better enable [FDA] to evaluate possible adverse health effects from FDA-regulated products that use nanoscale materials."¹⁰ The Task Force issued its initial report in July 2007,¹¹ a report that represents the first major statement by FDA on its role in regulating the use of nanoscale materials.

The balance of this article is devoted to FDA's consideration of the Task Force recommendations and other actions FDA is taking in regulating nanotechnology products, and whether those actions are likely to provide effective management of nanotechnology in regulated products.

Issues Raised by the Task Force Report

The Task Force Report is organized into discussions of science and regulatory issues. A recurrent theme throughout the science issues discussion is the emerging and uncertain nature of this fast-evolving area of science.¹² According to the Task Force Report, substantial differences in the characteristics of the nanomaterials in use suggest that the most sensible approach at this time is to conduct a case-by-case analysis of the interaction of nanoscale materials with biological systems for each new application of nanotechnology.¹³ The Task Force states that this approach is preferred because there is a need for substantial additional basic research and specific data before action can be taken on applications on the basis of general knowledge.¹⁴ The Task Force Report acknowledges that there are interesting efforts underway to generalize from the available specific data, but concludes that these efforts have not yet progressed to the point where such generalizations could be a credible basis for regulatory decisions.¹⁵ The Task Force Report notes that the development of a comprehensive database would provide a wealth of material to aid FDA, but again, it is difficult to generalize from such information, given the different disciplines and laboratories employing different methods and standards to generate data reported in the literature.¹⁶

The Task Force next examined whether existing authority provided under the Federal Food, Drug and Cosmetic Act is adequate to permit the case-by-case analysis that the Task Force believes is the most effective means to regulate the use of nanotechnology. The Task Force concluded that FDA's authority would be adequate in any instance where a manufacturer was compelled by the language of the Federal Food, Drug and Cosmetic Act to obtain pre-market authorization for a product. Since Congress traditionally has required pre-market authorization for products thought to be more likely to present a safety hazard, FDA would get the desired case-by-case review where it is most likely needed. For the remainder of regulated products, the Task Force believes that it should be sufficient for FDA to wait and seek information if a problem develops as a result of the incorporation of nanotechnology in the process.

¹⁰ FDA, "FDA Nanotechnology Task Force," available at http://www.fda.gov/nanotechnology/nano_tf.html.

¹¹ The Task Force Report is available at http://www.fda.gov/nanotechnology/nano_tf.html.

¹² *Id.* at ii.

¹³ *Id.* at 9.

¹⁴ *Id.* at 8-10 and 12-14.

¹⁵ *Id.* at 9-11.

¹⁶ *Id.* at 14.

FDA Authority to Regulate Nanotechnology

The pre-authorization group of regulated products described by the Task Force is a broader group than many will be used to considering. The Task Force describes it as including the traditional products that require FDA signoff on a Pre-Market Approval Application, a New Drug Application, or some similar document relating to a single product by a single manufacturer. The Task Force goes on, however, to include products that do not require approval of an individual application, but simply must comply with requirements extending to an entire class of products as defined. This subgroup includes products subject to Over-the-Counter Drug Monographs and food and color additives that are the subject of regulations set forth in the Code of Federal Regulations. All such products must meet applicable identity and quality specifications. An application for pre-authorization is plainly required for new substances or ingredients not already included in a Monograph or regulation, and to that extent, the inclusion of these products by the Task Force in the group requiring pre-authorization makes sense. The issue usually faced by a manufacturer, however, is whether the ingredient or substance it proposes to use is the same as the substance in a Monograph or regulation, or whether it is "new." As the Task Force notes, there is precedent helping to define the information needed to establish whether a particular macroscale material can be regarded as the same as the substance already listed. Based on such precedent, manufacturer decisions to market without a filing seldom lead to health risks or other safety concerns.

The situation is different for nanoscale materials, at least at this time. There is no precedent of the type the Task Force describes to guide a decision whether a nanoscale version of an ingredient or substance can be considered as having the same identity as the macroscale version of the ingredient or substance for purposes of making a filing decision.

FDA states that it has the authority to require information, including particle size information, for any of the products that require pre-authorization, either on a case-by-case or a product category basis. To examine more specifically the Task Force's position that FDA has the authority to require the pre-market submission of information and data on a case-by-case basis, it is useful to list the regulated products on the basis of when the manufacturer is permitted to make a unilateral filing decision. Such a list would result in two groups:

■ Group I: Products requiring pre-authorization

- ▶ New drugs;
- ▶ OTC drugs where an active ingredient not in a Monograph is proposed for inclusion;
- ▶ Class III medical devices;
- ▶ Class I and II devices not exempt from the filing of a 510(k);
- ▶ New food additive substances not included in a regulation in the C.F.R.;
- ▶ New color additives not contained in a regulation in the C.F.R.; and
- ▶ Dietary supplements that contain a new dietary ingredient not previously marketed.

■ Group II: Products requiring conformance with a standard of identity or quality

- ▶ OTC drugs where the ingredient proposed is considered the same as the ingredient identified in a Monograph;
- ▶ Class I and II devices exempt from 510(k);
- ▶ Food additive substances already listed in a C.F.R. regulation or determined to be Generally Recognized as Safe (GRAS);
- ▶ Color additive substances already listed in a C.F.R. regulation;
- ▶ Cosmetics; and
- ▶ Dietary supplements that do not contain any new dietary ingredients.

The Task Force assertion that FDA has the authority to require data needed to regulate the use of nanotechnology for products in Group I is accurate because manufacturers do not have the option of making a determination that a filing is not necessary. For Group II products, however, a manufacturer may make a determination that a change to a nanoscale material is not a change to a different substance. A filing may not be needed if the manufacturer determines that the use of a new material does not put the product outside the scope of a 510(k) filing exemption, that the nanoscale material is not a new dietary ingredient, or that the nanoscale material is the same as an active ingredient listed in a Monograph. The recurring problem is that there is little data and even less agreement on exactly when a nanoscale material meets the identity requirements of a macroscale material. The nanoscale material may interact differently with biological systems, enter cells that a macroscale material does not, cause irritation due to increased surface area, agglomerate in tissue to a greater degree, or migrate more freely within the human body. Until nano-specific information is developed similar to the information available for the comparison of various macromaterials in determining their similarity, there may arguably be a greater risk in allowing manufacturers to make self determinations. The Task Force does not discuss the effect of manufacturer self determinations. That will be an issue that will have to be resolved as the body of information on nanomaterials grows.

Task Force Recommendations

The Task Force makes recommendations intended to increase the knowledge base of both industry and FDA regarding nanomaterials used in regulated products. These recommendations include the need to ensure that manufacturers disclose that nanomaterials have been used in the manufacture of a product or are contained in the final product itself. A second recommendation describes different guidance documents that FDA should issue to assist industry in deciding when a filing is needed for the products placed in Group II. Finally, the Task Force details information requests intended to expand the FDA database on nanotechnology.

The Task Force's recommendation that any nanoscale material used in a product that is the subject of a filing be identified as such is a straightforward matter that addresses a problem FDA states it has had with past submissions. Manufacturers have not routinely disclosed that they have used nanomaterials in a product or a manufacturing process. Without having that infor-

mation available, FDA did not know to ask questions about that use during its review of submissions. While FDA may learn more about the use of nanomaterials through plant inspections, inspectors might not review the particular product lines where the materials are being used, and there is no assurance that an inspection at a given facility will take place in any relevant time frame.

The Task Force also made recommendations regarding the development of guidance documents that are intended to address situations where a manufacturer might otherwise make a unilateral filing decision when a change is made from a conventionally sized material to a nanomaterial, or an increase is made in the amount of the material used. The Task Force recommends that separate guidance be written to address when a manufacturer should submit, or at least generate, information on new food and color additives using nanoscale materials, or previously cleared additives now incorporating nanoscale materials.¹⁷ The Task Force Report suggests that guidance be prepared for exemptions from 510(k) devices that incorporate new nanoscale materials. This guidance would address when to file for the use of a new material. It would also address when to file for changes to a previously cleared 510(k). Additional guidance that the Task Force describes in its Report would contain information on when a manufacturer might need to file because a nanoscale material constituted a new dietary ingredient.

Finally, the Task Force Report makes recommendations for the development of guidance describing when data should be generated or submitted in cases where nanoscale materials are used in food ingredients for which a Generally Recognized As Safe (GRAS) notification has been submitted, or where the particle size of substances described in a previously submitted Food Contact Notification (FCN) are reduced to the nanoscale range. A last product group guidance document would describe safety issues that manufacturers should consider to ensure that cosmetics made with nanoscale materials are not adulterated.¹⁸ Such adulteration could occur if nanomaterials are used in containers and the nanomaterials have some deleterious substance that could make the contents injurious to humans. The adulteration could result from the use of any nanomaterial that affects the strength, quality, or purity of any component of the cosmetic.

The language the Task Force uses in describing each of these guidance documents is instructive. Only the guidance pertaining to devices speaks directly to the need to file in the event of changes to nanomaterials in medical devices. The other guidance materials describe data to be submitted or generated, in the latter instance presumably to support a no-filing decision. At this stage in the development of nanotechnology, it is not possible to set forth all the particular situations where a supplemental filing would be needed, and it is prudent for the FDA not to speculate. FDA is wise to proceed on a case-by-case basis. As long as that is the first option, there is no need for guidance describing when a filing might not be needed.

The Task Force also makes recommendations not tethered to particular products. These recommendations seem to be intended to increase FDA's database

on nanotechnology. One such recommendation would be for FDA to "[i]ssue a notice in the Federal Register requesting submission of data and other information addressing the effects on product safety of nanoscale materials in products not subject to premarket authorization. The notice would address both new products made with nanoscale materials and existing products that are changed to include or include greater proportions of nanoscale materials."¹⁹

Another recommendation addresses the effect of nanotechnology on the manufacturing process. Manufacturers would gather information and submit it in any filings to demonstrate how the presence of nanoscale materials might affect the manufacturing process for products subject to pre-market authorization. Similar information would be gathered by the manufacturer where a filing is not required, presumably so that information could be submitted if requested. Relevant information would address situations when the product contains nanoscale materials and when any part of the manufacturing process involves nanoscale materials, even if those materials do not become part of the finished product.²⁰

Assessment of Recommendation for Guidance

A strong argument can be made that the development of FDA guidance documents is premature. Traditionally, such documents evolve when a considerable amount of information has been developed on a given subject, and that information can be utilized to describe the data a manufacturer could develop so that it can prove a point relating to safety or efficacy. As information on the issue of the identity, migration, and interaction of nanoscale materials with biological systems becomes available, it may be prudent to provide guidance to industry on the data needed to establish safety and efficacy, if it is clear that the use of some nanotechnologies could present safety concerns. For now, however, FDA can monitor developments, act on particular applications, and gain information that may be sufficiently focused to provide the basis for standardizing filing requirements. The acquisition of the information will take time, and additional work. As suggested by Dr. Sadrieh of FDA's Center for Drug Evaluation and Research (CDER):

CDER/FDA's current requirements for safety testing of products is very rigorous. However if research identifies toxicological risks that are unique to nanomaterials, additional testing requirements may become necessary.²¹

On the subject of guidance, Dr. Sadrieh further states:

Guidances are built on precedence from review and on extensive literature data. Because nanotechnology is an evolving field and we are still learning, CDER is not anticipating any new preclinical or [chemistry, manufac-

¹⁷ *Id.* at 32-33.

¹⁸ *Id.* at 33-34.

¹⁹ *Id.* at 33.

²⁰ *Id.* at 33-34.

²¹ See Presentation by Nakissa Sadrieh, Ph.D., Associate Director for Research Policy and Implementation, Office of Pharmaceutical Science, CDER, FDA, "Nanotechnology: Issues and Future Directions" (Oct. 2006) at Slide 14, available at http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4241s2_7.ppt.

turing, and control] guidance documents regarding nanomaterials in the near future.²²

There may be merit in the development of one form of guidance. FDA has considerable knowledge about the issues posed by nanotechnology, and on those issues that may be relevant to particular product lines. As conditions warrant, FDA could issue guidance documents that describe the questions raised by the use of nanotechnology, and manufacturers could be encouraged to address those issues in any testing they undertake to determine whether a filing is necessary. It would be the manufacturer's responsibility to develop pertinent data and have them on file should FDA raise a question about why no filing was made. Many believe that it is the manufacturer's burden to establish the prudence of a change to some aspect of nanotechnology in a new version of a product covered by a Monograph, a food additive regulation, a change in materials in a product covered by a 510(k), or a product previously exempt. Time will determine if a more proactive stance is needed.

Assessment of Recommended Data Collection

The Task Force suggests building the FDA nanotechnology database through the submission of two kinds of data. The first category includes data and other information addressing the effect on product safety of nanoscale materials in products, regardless of whether the products are subject to pre-market authorization. The *Federal Register* or other notice that FDA would issue requesting submission of this type of data would address "both new products made with nanoscale materials and existing products that are changed to include or include greater proportions of nanoscale materials."²³ The second category includes data concerning the effect of nanotechnology on the manufacturing process. Manufacturers would submit information on how the presence of nanoscale materials affects the manufacturing process.

It does not appear to be useful to call for the submission of any and all information on the effect of the use of nanotechnology in any regulated product. For confidentiality reasons, manufacturers are unlikely to submit the most useful information, and will likely submit general data. Many companies may submit the same information. FDA will have difficulty reviewing and processing the information that is submitted, and it would be challenging to identify the types of product for which information should be submitted. Much of the information would not be relevant to any particular product FDA is required to review, and there is no telling whether the information submitted could be used to prepare the guidance documents recommended in the Task Force Report. A more orderly submission of targeted materials on the basis of identified and specific issues would likely lead to the generation of more useful information.

Assessment of FDA Testing Program

FDA is involved in the testing of nanoscale materials in several of its centers and in collaboration with other

²² *Id.* at Slide 15.

²³ Task Force Report at 33.

federal government agencies and private parties. In some instances, the FDA testing program appears to be designed to develop basic information to characterize relevant materials, such as fullerenes.²⁴ Some question whether this use of funds is appropriate in view of the scarce resources available to FDA. A more appropriate question to ask may be whether the FDA/NTP efforts will add sufficient information to the existing database on such materials. A more effective option FDA might consider is first to obtain pertinent available information.²⁵ If FDA determines that the use of a particular nanoscale material poses a hazard, it can require the submission of additional information when considering pre-market authorization applications. FDA can issue guidance to manufacturers addressing the safety and health issues that the nanoscale material poses, and ask that manufacturers address these issues, if relevant, in future submissions or in internal testing done to determine if a filing is needed.

Another type of testing underway appears to be intended to obtain information to make sound regulatory decisions. The testing of nanoscale titanium dioxide and nanoscale silver are examples. The desire to test titanium dioxide is likely in response to the ICTA Citizen Petition filed regarding the use of a nanoscale version of the ingredient in sunscreen products.²⁶ The need to test nanoscale silver may be derivative of the fact that nanoscale silver is used in a variety of medical devices, as well as in other applications.²⁷

It is not clear in all cases what FDA hopes to accomplish by this testing. The testing of nanoscale titanium dioxide at NTP does not appear to utilize the material as it is used in sunscreen products.²⁸ The results would most likely be limited in applicability, thus diminishing the value such testing may offer. Also, the testing duplicates work that is already underway or was completed, some of which was presented at the public meeting the

²⁴ In this category would be the fullerenes studies being conducted at NTP. See NTP, "Nanoscale material (Fullerene-C60 1 micron)," available at <http://ntp.niehs.nih.gov/?objectid=BD5B6EF5-123F-7908-7B411D954ACC3B7E>; NTP, "Nanoscale material (Fullerene-C60 50 nanometers)," available at <http://ntp.niehs.nih.gov/?objectid=BD5B54D6-123F-7908-7B261814FD3A16FF>. FDA states that nominating materials under study by NTP indicate only that fullerenes are used as a platform for the transport of other molecules. See FDA Chemical Selection Working Group, "Nanoscale Materials [no specified CAS]: Nomination and Review of Toxicological Literature" (Dec. 8, 2006) (Nomination and Review of Toxicological Literature), available at http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Nanoscale_materials.pdf.

²⁵ See, e.g., Thomas, K. and P. Sayre (2005). Research Strategies for Safety Evaluation of Nanomaterials, Part I: Evaluating Human Health Implications for Exposure to Nanomaterials. *Toxicol. Sci.* 87(2):316-321, available at <http://toxsci.oxfordjournals.org/cgi/content/full/87/2/316>.

²⁶ See ICTA Citizen Petition.

²⁷ Nomination and Review of Toxicological Literature, *supra* note 25 at 4.

²⁸ Report of William T. Allaben, Ph.D., Associate Director of Scientific Coordination, NIEHS/FDA National Toxicological Program Liaison, National Institute of Environmental Health Sciences/National Toxicology Program Interagency Agreement (undated) at 117, available at http://www.fda.gov/nctr/science/06-07_Research_Plans/pdf/NTP.pdf.

Task Force held on October 10, 2006.²⁹ As the Task Force acknowledged, FDA has the authority to call for data on whether nanoscale titanium dioxide used in sunscreen drug products is non-Monograph, and FDA can reopen the Monograph to make that determination. Given the difficulties the testing could pose, and the fact that the results will not be significant in light of other work underway, some believe that FDA would be wise to take a more traditional position and limit its role to that of the evaluator of information submitted by interested parties. The resources could be better used to help develop a database, something that FDA readily admits is sorely needed.

Next Steps

FDA announced on Aug. 7, 2008, that it would host a public meeting on Sept. 8, and accept written comments until Oct. 24, to consider further implementation of the recommendations made a year or more ago by the Task Force.³⁰ The announcement noted that FDA is considering drafting the guidances recommended by the Task Force, and is interested in securing data, information, and testimony that would assist FDA in that task, particularly data on the effects of nanoscale material on the quality, safety, and effectiveness of products. FDA also noted that such information would be essential as FDA considers the development of guidance documents addressing chemical manufacturing issues and quality

²⁹ Information on the meeting, including a transcript of the proceedings, is available at <http://www.fda.gov/nanotechnology/meeting1010.html>.

³⁰ 73 Fed. Reg. at 46,022.

controls as they relate to characteristics unique to nanoscale materials.

From the notice, it appears that FDA intends to explore further the guidance issue. Other recent information FDA will have to consider is the fact that its Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (Manufacturing Section) split 50/50 when asked whether FDA should give industry guidance for the development of nanotechnology-derived drug applications.³¹

Conclusion

Nanotechnology will be a fact of life for FDA-regulated products for years to come, and will present opportunities to improve the quality of health care in many ways. Nanotechnology is an important issue, but only one among many that FDA must address, and FDA's limited resources must be allocated sensibly. The issues raised by the use of nanotechnology are important issues to consider. The more difficult question is *how* FDA should consider them. FDA would be wise to build on existing databases and correlate the information from submissions required for certain products. When the facts clearly warrant it, FDA should issue guidance documents that set forth the issues to address in making filing determinations, but the need for such filings should follow the established, existing framework unless and until that framework is proven inadequate.

³¹ Nanotechnology Industries Association Press Release, "Tie vote on guidance at the FDA" (July 25, 2008), available at <http://www.nanotechia.co.uk/news/global>. No official committee report had issued as of this writing.