BEFORE THE UNITED STATES FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE NANOTECHNOLOGY PANEL OF THE AMERICAN CHEMISTRY COUNCIL ON THE REQUEST FOR INFORMATION ON NEW AND EMERGING SCIENTIFIC ISSUES IN NANOTECHNOLOGY

Notice of public meeting; request for comments 71 Fed. Reg. 46232 (Aug.11, 2006)	FDA Docket No. 2006N-0107

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November 10, 2006

EXECUTIVE SUMMARY

The Nanotechnology Panel (Panel) of the American Chemistry Council submits these comments on the United States Food and Drug Administration's (FDA) August 11, 2006, *Federal Register* notice of meeting and request for comments on the new or emerging scientific issues involved in the development and utilization of nanotechnology materials in regulated products. The Panel consists of companies that are engaged in the manufacture, distribution, and/or use of chemicals and have a business interest in the products of nanotechnology.

The Panel compliments FDA on the initiative in meeting to further its understanding of nanotechnology and the opportunities and issues that the technology presents for FDA and the regulated industry. The Panel supports the formation of the Internal FDA Nanotechnology Task Force. The Task Force is charged with "determining regulatory approaches that encourage the continued development of innovative, safe and effective FDA-regulated products that use nanotechnology materials." The Panel hopes that the Task Force will play a pivotal role in the activities discussed herein. Finally, the Panel urges FDA to continue and expand its efforts to participate in all relevant aspects of the National Nanotechnology Initiative (NNI) and to coordinate efforts with foreign governments and voluntary standards setting organizations to seek to standardize testing protocols, risk/benefit approaches, and agreed upon nomenclature and terminology.

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INTRODUCTION

The Nanotechnology Panel (Panel) of the American Chemistry Council submits these comments on the United States Food and Drug Administration's (FDA) August 11, 2006, *Federal Register* notice of meeting and request for comments on the new or emerging scientific issues involved in the development and utilization of nanotechnology materials in regulated products.[1] The Panel consists of companies that are engaged in the manufacture, distribution, and/or use of chemicals and have a business interest in the products of nanotechnology.[2]

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1 71 Fed. Reg. 46232 (Aug. 11, 2006).

2 Panel member companies include: Air Products and Chemicals, Inc., Arkema Inc., BASF Corporation, Bayer Corporation, Ciba Specialty Chemicals Corporation, Cytec Industries, Inc., Degussa Corporation, The Dow Chemical Company, DuPont, Elementis Specialties, PPG Industries, Inc., Oxonica, Procter & Gamble, Rohm and Haas Company, Sasol North America, Inc., and Southern Clay Products, Inc.

3 FDA News, "FDA Forms Internal Nanotechnology Task Force" (Aug. 9, 2006), available at http://www.fda.gov/bbs/topics/NEWS/2006/NEW01426.html.

Initiative (NNI) and to coordinate efforts with foreign governments and voluntary standards setting organizations to seek to standardize testing protocols, risk/benefit approaches, and agreed upon nomenclature and terminology. The Panel was pleased to see that representatives of the European Commission and Health Canada were invited and participated in the first session of the October 10 meeting. The Panel hopes there will be many more such joint endeavors. The FDA financial situation is difficult, and FDA should take advantage of the ideas and efforts of other government agencies that are beginning to address the same issues FDA is confronting. The presentations at the meeting confirmed that the three governmental bodies are working on similar pathways, and cooperation among them can reduce duplicate effort and conserve scarce resources.

I. THE NANOTECHNOLOGY PANEL IS COMMITTED TO THE RESPONSIBLE DEVELOPMENT OF NANOTECHNOLOGY

The Panel was formed in 2004 to foster the responsible development and application of nanotechnology, to coordinate nanotechnology environmental, health, and safety research initiatives undertaken by member companies and other organizations, and to facilitate the exchange of information among member companies and other domestic and international organizations on issues related to the applications and implications of products of nanotechnology. The Panel supports nanotechnology products and applications consistent with the American Chemistry Council Responsible Care® Program to ensure that the commercialization of nanoscale materials proceeds in a way that protects workers, the public, and the environment.

The Panel recognizes that nanotechnology applications offer significant societal and sustainable development advancements, many of which could provide direct public health and environmental benefits that could greatly enhance the quality of life. The Panel shares FDA's goal, however, of identifying nanotechnology's potential risks to ensure protection of workers, human health, and the environment, and believes that the responsible development of nanotechnology will help assure the public that nanomaterials are being developed in a way that identifies and minimizes potential risks to human health and the environment.

In this regard, the Panel and Environmental Defense (ED) issued a Joint Statement of Principles[4] that reflects the parties' shared view of several core principles on which a governmental program for addressing potential risks of nanoscale materials should be premised. As many of the principles the Panel and ED jointly embrace are pertinent to the issues raised in the *Federal Register* notice, we restate them below:

- Some applications of nanomaterials are expected to offer significant societal and sustainable development benefits.
- The timely and responsible development and regulation of nanomaterials in an open and transparent process will best assure that nanomaterials are being developed in a way that identifies and minimizes potential risks to human health and the environment.
- A multi-stakeholder dialogue that includes all interested parties, including small businesses, labor, community organizations, and consumer advocates, as well as large businesses and environmental organizations, will best assure the development of an effective program for nanoscale materials.

[4] A copy of the Joint Statement of Principles is appended.

- A significant increase in government investment in research on the health and environmental implications of nanotechnology is essential.

- The development of an international effort to standardize testing protocols, hazard and exposure assessment approaches, and nomenclature and terminology is an important step to maximize resources and minimize inconsistent regulation of nanomaterials.

- Elements of safe and responsible development of nanotechnology should include appropriate protective measures while more is learned about potential human health or environmental hazards.

- A government program should address intentionally produced nanoscale materials produced in or imported into the U.S. and characterize hazard and exposure sufficiently to assess any risks of these materials. It should also assess the appropriateness of or need for modification of existing regulatory frameworks.

II. THE PANEL APPLAUDS FDA's EFFORTS TO ENCOURAGE DIALOGUE AND URGES FDA TO CONTINUE TO ACQUIRE MEANINGFUL INFORMATION ON THE APPLICATIONS AND IMPLICATIONS OF NANOTECHNOLOGY

The Panel supports multi-stakeholder dialogue of the type undertaken by FDA in sponsoring the nanotechnology public meeting. As a critically important member of the NNI, FDA is in the forefront in the consideration of the possible impact of the use of intentionally produced nanoscale materials on the public health and the environment. The lay and scientific press is replete with articles regarding varied uses of nanomaterials in the manufacture, assembly, or processing of drugs, drug delivery system combination products, medical devices and diagnostic products, cosmetics, foods, and food contact substances. The several FDA Centers responsible for the review of these products will be confronted over the near term with the issues that have been identified as possibly resulting from the properties of nanoscale materials, such as the altered magnetic properties, altered electrical or optical activity, increased

structural integrity, and increased chemical and biological activity cataloged by FDA in the *Federal Register* notice. It is appropriate for FDA to seek input from all sources as it evaluates what to require to be assured that the safety, efficacy, and compatibility with biological systems of the products has been established.

The task confronting FDA is a challenging one. Nanotechnology is in most respects in its formative stages. Many potential issues have been identified, but none has been resolved to the satisfaction of all concerned parties. The Panel believes that the resolution of these potential safety issues starts with the characterization of physical attributes, their *in vitro* biological properties, and their *in vivo* compatibility, considered in light of their modes of action and their function and compatibility with biological systems. The Panel urges FDA to use its Internal Nanotechnology Task Force and other available resources to collaborate with other governmental agencies, both foreign and domestic, academia, industry, and the general public to ensure that FDA has available to it the latest developments in testing, and employ those techniques in establishing any test requirements that may evolve for new regulated products employing nanotechnology.

In that regard, the Panel believes the recent *Federal Register* notice announcing the Memorandum of Understanding (MOU) between the FDA, the National Cancer Institute (NCI), and the National Institute of Standards and Technology (NIST)[5] is a step in the right direction. It is an acknowledgment that nanotechnology is a complex subject that requires the specific and disparate expertise of several agencies, and others, to capitalize fully on its potential.

[5] 71 Fed. Reg. 50072 (Aug. 24, 2006).

The Panel's specific recommendations for the immediate implementation of facets of the MOU are discussed below.

A best case scenario sees FDA stipulating that applicants for clearance of a regulated product manufactured using nanotechnology perform state-of-the-art tests, adapted as needed to account for the nanotechnology aspects, to establish the preclinical safety, compatibility, and effectiveness of their products in biological systems. The result will be an extensive body of current data relative to the safety, efficacy, and compatibility of nanomaterials. At that point, it is FDA's obligation to ensure that these unique data are made available to other agencies, scientists, and the general public to assist in the ongoing public dialogue about the opportunities and possible issues associated with nanotechnology. Present FDA regulations stipulate the release of summaries of safety information for various approved applications. Those summaries should be robust, and any claim of proprietary information should be thoroughly reviewed against applicable regulations and guidelines to ensure that any non-disclosure is appropriate in the circumstances and consistent with the regulations. Test results conducted by federal agencies on submitted nanomaterials should be made public. The information passing through FDA will provide direction for future inquiry, and seek to answer questions that will help move the technology beyond the speculative realm. This is plainly a situation where the public has a right, and a need, to know the effects of materials in the medication they take, or the products that are used on them.

The information garnered from the testing of new products by applicants can be equally important to FDA, beyond the application in which the information is presented. Since

the technology is in the development stage, the newly acquired information can be used to begin to standardize test procedures, establish protocols for future testing, and compose product standards. When the FDA makes the bulk of the information available to the public, it can then convene additional multi-stakeholder dialogues to discuss the significance of the developing database. FDA is in a unique position in the evolution of nanotechnology. It has shown in recent actions that it intends to be proactive, and it should use its position to further the development of a scientifically reliable body of information on the effects of nanomaterials on the public health and the environment.

The Panel has long maintained that a significant increase in government funding for nanotechnology related research is needed to identify the very kinds of information that FDA must have to fulfill its regulatory mission. The FDA speakers on October 10 urged members of the audience to support increased funding for the agency. The ideal would be for FDA to have sufficient additional funds to conduct its own research into these areas of potential significance. FDA does not receive any monies of significance from the NNI, because it is primarily a regulatory body and not a research organization. Even if more monies become available, the pressure of competing priorities on the funding provided to FDA means that FDA will not be able to conduct the full research program in-house it might like to conduct. That being the case, the Panel urges the FDA Task Force to take a leadership role in discussions within the framework of NNI to guide programs undertaken by the research agencies within NNI to ensure that information and data are generated that will assist FDA in regulating nanomaterials in a responsible manner. One program where such involvement and support is crucial is the work of the Nanotechnology Characterization Laboratory (NCL).

III. THE NANOTECHNOLOGY CHARACTERIZATION PROGRAM AT NCL SHOULD BE SUPPORTED AND ADVANCED BY FDA

The parties to the MOU state that they intend the document to be a framework for the effective risk identification, assessment, and evaluation of emerging cancer treatment products employing nanotechnology.[6] Under the MOU, the parties state that their activities will be addressed by the formation of working groups and steering committees to develop strategic plans, set priorities, and leverage resources.

The primary vehicle for accomplishing these tasks is claimed to be the NCL and activities directly related to it.[7] The parties hope to anticipate the impact of nanotechnology and standardize the approach for the evaluation of cancer treatment products produced using nanotechnology, and seek to facilitate the development of measurement methods and standard protocols appropriate to innovative and disruptive technologies.[8]

The NCL has addressed many of these same points in documents noted on its website. The Laboratory will provide infrastructure support to engineer and use nanoparticles for drug delivery, image contrast agents, and for diagnostic purposes. The nanoparticles are said to be central to the accomplishment of these goals because they can easily enter most

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6 *Id.* at 50073.

7 *Id.* at 50074.

8 *Id.* at 50075.

mammalian cells. The NCL will accelerate the transition from basic science to clinical applications.[9] While the NCL is denominated as a "characterization" laboratory, the implications of what it proposes to do go beyond mere characterization, and it is this facet of its mission that may be the most important contributor to the nanotechnology dialogue.

NCL states that one of the driving forces in setting up the program is the need for "'first principles' of understanding about nanomaterials' interactions with biological systems."[10] This is pivotal to a grounded, scientifically-based understanding of the effect of nanomaterials. It is essential to characterize nanomaterials, which is a fundamental and necessary first step. If the inquiry ends there, however, unwarranted inferences with a high probability of inaccuracy might be drawn from the characterizations, which would be detrimental to the sound development of nanotechnology. The work that NCL proposes to do is discussed below.

The Panel agrees with these broad objectives as they target many of the key issues. The concern that the Panel has is that the MOU is short on details and does not set any deadlines for accomplishing the laudable objectives set forth in the MOU. Establishing deadlines is essential when the need for the methods and protocols exists today, and will be more acute as new applications for products employing nanotechnology flow into the respective FDA Centers. The Panel believes the members signing the MOU need to act now, and an available and developing vehicle exists for doing just that -- the program set forth in the Business Plan

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9 Nanotechnology Characterization Laboratory, "NCL Business Plan" (Jan. 2005), available at http://ncl.cancer.gov/ncl_business_plan.pdf.

10 *Id.* at 5.

released by the NCL in January 2005. The parties to the MOU do not mention the Business Plan, except in a passing reference to one of the elements. Importantly, however, the Business Plan contains the framework upon which to build an effective means to evaluate the preclinical safety, compatibility, and utility of products using nanotechnology. The parties need to review the Business Plan, seek public input on any possible modifications that should be made, and then implement it forthwith. The purpose of the NCL is to support the development of cancer treatments and diagnostic procedures. The focus will properly be nanotechnologies intended for cancer therapies and diagnostics. As experience is gained, however, the program established at NCL can be the model for the investigation of the effects of nanotechnologies used in other regulated products, and the model can be employed by others outside the FDA areas of interest to probe the characterization and application of nanomaterials in unrelated settings.

A. The NCL and Its Business Plan

The NCL was established by the NCI, working in collaboration with FDA and NIST, specifically to perform preclinical efficacy and toxicity testing of nanoparticles in products intended to diagnose or treat cancer. As NCI states, to achieve its Mission, the NCL has established the following six objectives:

- Establish and standardize an analytical cascade for nanomaterial characterization.
- Facilitate clinical development and regulatory review of nanomaterials for cancer clinical trials.
- Identify and characterize critical parameters related to nanomaterials' absorption, distribution, metabolism, excretion, and acute toxicity (ADME/Tox) in animal models and cell lines.

- Examine the biological characteristics of multicomponent nanoscale platforms, including therapeutic, molecular and clinical diagnostic, and detection aspects.

- Engage and facilitate academic and industrial-based knowledge sharing of nanomaterial performance data and behavior resulting from pre-clinical testing (*i.e.*, physical characterization, in vitro testing, and in vivo pharmaco- and toxicokinetics).

- Interface with national nanotechnology planning and coordination efforts, such as the National Nanotechnology Initiative, in cancer research, nanoscience and nanotechnology research, and health, safety, and the environment.[11]

Even though the NCL is a relatively new endeavor, much thought and effort has gone into designing a very specific program to achieve the objectives. First, there are three elements that make up the "Analytical Cascade" for characterization. The first is the physical characterization. As stated in the Business Plan:

> The goal of this phase is to determine the particle's size, size distribution, molecular weight, density, surface area, porosity, hydrophilicity, surface charge density, purity, sterility, surface chemistry, and stability. The batch-to-batch reproducibility of material as provided by the sponsor/vendor will also be addressed during this stage.[12]

The second element is the *in vitro* characterization:

> Nanoparticles' binding, pharmacology, and uptake properties, for example, will be monitored by common cell and molecular biology methods, such as ELISA and fluorescence microscopy. Scanning electron microscopy (SEM) and transmission electron microscopy

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11 *Id.* at 3.

12 *Id.* at 11.

> (TEM) will also be used as tools to observe the particle's interaction with cellular-level components. Electron microscopy, chromatography, and electrophoresis protocols allow the NCL to characterize the nanomaterial's blood contact properties, such as opsonization and macrophage phagocytosis as well as pinocytosis and uptake by nonphagocytic cells.
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> Also included in the in vitro characterization is a thorough examination of the nanoparticle's therapeutic and/or diagnostic functionality. For example, particles with imaging modalities will be examined for their signal intensity (*i.e.*, signal-to-noise ratio); nanotechnology strategies that incorporate therapeutic or preventive agents will be characterized for their drug-release kinetics and ability to cross biological barriers. . . . In vitro models can also serve as a gross approximation of a nanomaterial's absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) properties.[13]

Finally, there is the *in vivo* characterization:

> Animal studies conducted under the in vivo phase for the study of nanoparticles will be in support of the FDA's Guidance for Industry, *Single Dose Acute Toxicity Testing for Pharmaceuticals* (http://www.fda.gov/cder/guidance/pt1.pdf). The nanoparticle will be administered to animals to identify (1) doses causing no adverse effect and (2) doses causing life-threatening toxicity. The information obtained from these tests will provide preliminary identification of target organs of acute toxicity and may aid in the selection of starting doses for Phase I human trials. Preliminary data on the nanoparticle ADME profile will also be obtained in this phase. In vivo studies will characterize the nanoparticle absorption, pharmacokinetics, serum half-life, protein binding, tissue distribution/accumulation, enzyme induction or inhibition, metabolism characteristics and metabolites, and excretion pattern.[14]

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13 *Id.* at 12-13.

14 *Id.* at 14.

On the NCL website, all of the specific protocols to be developed for the tests to accomplish the foregoing are set forth, and in the case of the *in vitro* testing, specific methods are already listed. In sum, over 50 tests are proposed.[15]

As set out above, characterization is the first step in the process. The next step that we will refer to as the "critical parameters" step is at least equally important. As discussed in the Business Plan, exploring critical parameters involves:

> research directed at elucidating the critical parameters that influence nanomaterials' compatibility and effectiveness in biological systems. For instance, a growing body of evidence implicates nanomaterials' size, surface chemistry, fluid dynamics, and hydrophilicity as key parameters contributing to their distribution and excretion. By determining the influence of each of these parameters (i.e., the partial derivative), the NCL will work toward a better understanding of structure activity relationships (i.e., total derivative). A systematic characterization of these parameters' influence on in vitro/in vivo ADME/Tox profiles will provide empirical data to engineering and predictive models. These modeling tools may predict and recommend functionalization and structural improvements, which can then be incorporated into the next iteration of nanomaterials submitted to the NCL.[16]

This is the type of investigation that can determine how the nanoparticles perform. While nanoparticles may be small enough to enter cells, their fate and disposition is not clear. There is speculation that an unexpected aggregation of substances with altered properties could have new effects. Studying where nanoparticles go and what they do when they get there is crucial to an

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15 *See* National Cancer Institute, Nanotechnology Characterization Laboratory, "Assay Cascade Protocols" (list of proposed tests), available at http://ncl.cancer.gov/working_assay-cascade.asp.

16 Business Plan at 17.

understanding of both the opportunities and potential risks of nanotechnology. For example, much is written about how nanoparticles might migrate through cell walls, aggregate, and inspire effects that conventionally-sized counterparts would not cause. Little work has been done, however, to determine whether normal macrophage clearance mechanisms would come into play and prevent any of the projected untoward events from happening.

There are additional elements of the proposed infrastructure support that should be reviewed by interested parties. A great deal of effort went into developing the plan. What is abundantly clear is that this is a resource that can be used to identify the best available testing protocol for nanoparticles. At the October 10, 2006, meeting, Scott E. McNeil, Ph.D., NCL Director, briefly described the activities of the Laboratory, and stated that the staff at NCL was already working with FDA staff to identify additional studies to perform. The Panel urges FDA to continue and expand this collaboration. The FDA Internal Task Force members should work with NCI, NIST, and the personnel of NCL to formalize the testing protocols, put them into effect, and start to accumulate data to determine the effectiveness of the program.

As a first step in the process, FDA should solicit comments and suggestions from members of industry, academia, and the public on the suitability of the proposed analytical cascade and the examination of the critical parameters. Recommendations for alternative or additional tests should be sought, as well as comments regarding any tests that might be dropped from further consideration. As good as the initial effort to develop the analytical cascade and the critical parameters is, it will benefit from another multi-stakeholder dialogue, this one more specific than that called for in the notice of meeting under consideration. For example, it is not

clear if NCL intends to evaluate solids (insoluble materials) in its testing or focus on soluble materials. There is a fine line between slightly soluble sources, leading to therapeutic levels of soluble species, and highly insoluble materials. Ideally, the purpose of the cascade should be to screen materials with false positive tests so that the expensive, more esoteric testing is focused on the more likely candidates for therapy and diagnosis.

The additional testing that NCL should consider focuses both on how NCL will perform the tests it lists, as well as on the addition of tests useful in determining migration possibilities. Solubility in simulated physiological fluids and temperatures should be conducted rather than the scientific conditions of distilled water at room temperature and 100^{o}C. Since many materials supplied by outsiders will be "as manufactured," there may need to be a common set of conditions for determining aggregation, meaning how much stirring before one takes the particle size measurement that is the basis of aggregation.

As indicated above, additional tests should focus on migration and binding effects, best summed up in the field of chromatography. An important benefit of employing the NCL cascade will be to correlate the physical characterization with later performance in toxicity testing. For example, if one fear of nanoparticles leading to the creation of reactive oxygen species (oxidants) could be correlated with the chromatographic profile of hydroquinone (an antioxidant), then one could use the results of the characterization tests to decide on further toxicological testing.

NCL may determine that wettability is a better parameter to follow than hydrophilicity. Wettability can be correlated with bioaccumulation and with the U.S. Environmental Protection Agency Office of Pollution Prevention and Toxics' (OPPT) octanol-water partition coefficient. Materials that bioaccumulate presumably favor fat cells and fatty tissues.

NCL implies that testing of adsorption and chromatographic properties will be conducted, but the Laboratory does not specify the testing to be done. Adsorption can characterize surface reactions, which are mentioned in the cascade, but not discussed.

Also, NCL should consider testing surface composition and resultant chemistry, not just surface chemistry. Surface chemistry is vague. All surfaces come into equilibrium with the species in a liquid. These are transitory species through to chemically bound species on the surface. Hence, the surface chemistry changes with the local chemical environment (acidic stomach versus alkaline intestine). There are techniques in surface chemistry used to determine the surface composition that leads to the resultant chemistry.

These are only a few examples of the kinds of issues that would arise if NCL conducted a multi-stakeholder discussion of its analytical cascade and critical parameters. NCL has taken the lead and produced a credible, useful document. Public comment should make it even better, and then all that will remain will be for FDA to utilize the document forthwith to begin the accumulation of information vital to its mission to protect the public health and the

environment, and critically important in the overall development of a competent database regarding nanotechnology.

IV. REVELEVANT DATA FROM NCL AND RELATED EFFORTS SHOULD BE MADE AVAILABLE

At the beginning of the Business Plan, NCl indicates that "[t]he goal of the NCL is to develop publicly available analytical data."[17] The preceding sections of these comments have demonstrated how the NCL data will be a key factor both in forming regulatory policy for FDA, and in contributing to the future study and development of nanomaterials. The analytical data must be made available to interested persons for any of this to occur. NCL makes it clear that it is the intention of the Laboratory to do just that:

> The NCL is intended to serve as a nexus for cross-disciplinary research, development, and clinical applications of nanotechnology. The NCL will disclose its findings to the scientific community and the public through full use of journal publications, scientific conferences, public forums, the Internet, and press releases. Care will be taken, however, to ensure that proprietary information and materials disclosed to the NCL by industry are protected in accordance with the terms of agreement (*e.g.*, Material Transfer Agreement).
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> The primary output of NCL's analytical cascade will be data and information related to nanomaterials' interaction and compatibility with biological systems. NCL's output will be provided to the originating investigator, and will include all aspects of the analytical cascade for support of an investigator-held IND application and subsequent clinical trials. Depending on the pre-negotiated agreement with the investigator, the NCL may wait up to 60 days prior to making NCL data available to the public

[17] *Id.* at Quick Guide for Prospective Applicants.

> domain. This delay allows for the submitting investigator/vendor to file the relevant patent application to further secure their intellectual property (IP). The emphasis of the NCL, however, is to serve as a nexus for transdisciplinary research, development, and clinical applications of nanotechnology. Information, knowledge, tools, and methods gleaned from the NCL's analytical cascade must therefore be made readily available to material scientists, engineers, modelers, regulatory bodies, and intramural and extramural cancer researchers.[18]

CONCLUSION

For all the reasons discussed above, the Panel urges FDA to consider the comments and suggestions offered by the Panel in implementing its program for the consideration of nanotechnology as used in regulated products. The Panel appreciates this opportunity to comment, and thanks FDA for it.

Attachment

[18] *Id.* at 18.