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MEMORANDUM

Via E-Mail

DATE: October 23, 2009

TO: Clients and Friends

FROM: The Acta Group, L.L.C.

RE: FDA Research Involving Nanoscale Materials

This memorandum outlines research being sponsored, conducted, or planned by the U.S. Food and Drug Administration (FDA) regarding nanoscale materials. FDA has indicated repeatedly that it needs additional information on the characterization of such materials to make informal decisions regarding the safety of regulated products that incorporate nanotechnology.[1] While those decisions are for the most part in the future, there is at least one use of nanotechnology in drug and cosmetic products that has already been challenged. That issue involves a Citizen's Petition filed more than two years ago to ban the use of nanoscale titanium dioxide in sunscreen products.[2] FDA has commenced testing to determine whether such nanoscale materials differ from macroscale versions of the same substance or material, and, if so, whether those differences raise new safety issues that must be addressed by manufacturers in applications submitted to the U.S. Environmental Protection Agency (EPA).

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1 *See* generally, remarks at the FDA Press Conference on the Nanotechnology Task Force Report (July 25, 2007), *available at* http://www.fda.gov/downloads/NewsEvents/Newsroom/mediaTranscripts/ucm123593.pd.

2 *Available at* http://www.fda.gov/ohrms/dockets/dockets/06p0210/06p0210.htm.

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FDA Involvement in Nanoscale Material Research

FDA research is being conducted at the facilities of the National Center for Toxicological Research (NCTR),[3] the laboratories at the National Toxicology Program (NTP) campus,[4] and at facilities such as the National Institute of Environmental Health Sciences (NIEHS), a component of the National Institutes of Health (NIH). NCTR is one of the eight coordinate centers at FDA. NTP is a part of the Department of Health and Human Services (HHS). The FDA, through NCTR, manages and oversees the work of NTP, in conjunction with NIH and the Centers for Disease Control and Prevention (CDC).

NCTR

FDA states the mission of NCTR in succinct terms: "The National Center for Toxicological Research (NCTR) conducts FDA mission-critical, peer-reviewed, critical path (translational) research targeted to develop a scientifically sound basis for regulatory decisions and reduce risks associated with FDA-regulated products." With respect to nanomaterials, the bulk of the investigation being conducted directly by FDA is being done at the recently established NCTR/Office of Regulatory Affairs (ORA) Nanotechnology Core Facility (Core Facility) located in Jefferson, Arkansas.[5] FDA characterizes the Core Facility as a major undertaking designed to move FDA to the center of nanoscale materials research.[6] ORA,

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[3] The homepage for NCTR can be found at http://www.fda.gov/AboutFDA/CentersOffices/NCTR/WhatWeDo/default.htm.

[4] The homepage for NTP is located at http://ntp.niehs.nih.gov/index.cfm.

[5] NCTR is also working with NTP at the NCTR Center for Phototoxicology on projects involving nanoscale silver and titanium dioxide, both topically and orally applied. Those projects are discussed below.

[6] "NCTR/ORA Nanotechnology Core Facility," available at http://www.fda.gov/AboutFDA/CentersOffices/NCTR/WhatWeDo/NCTRResearchPriorities/ucm083172.htm.

through its Arkansas Regional Laboratory (ORA/ARL), is involved because it is a regulatory center that "monitors nanoscale materials in FDA regulated products"[7]

On its website, NCTR describes ongoing research projects involving titanium dioxide, manganese, and silver nanoparticles, which include:

- "Skin Penetration, Phototoxicity, and Photocarcinogenicity of Nanoscale Oxides of Titanium and Zinc." QUANTUM DOT (E0215611).
- Tumorigenicity of Photoactive Nanoscale Titanium Dioxide in Tg.AC Transgenic Mice (E0215801).
- Neurotoxicity Assessment of Manganese Nanoparticles in PC 12 Cells and in Mice (E0725701).
- Neurotoxicity Assessment of Silver (Ag) Nanoparticles in PC-12 Cells and in Rats (E0728201).

The Center also discusses these studies and other milestones in the operation of the Core Facility, and the ambitious plans for 2009, 2010, and 2011:

NCTR/ORA Nanotechnology Core Facility Milestones Achieved FY06 and earlier

- In collaboration with NTP, initiated studies on dermal penetration of nanoscale quantum dots and TiO_2 in mouse model (Gopee, Howard).
- In collaboration with CDER, initiated studies on dermal penetration of TiO_2 in minipig model (Gopee, Howard).
- FDA nominated nanoscale silver and nanoscale gold to NTP for toxicological studies.

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[7] *See* http://www.fda.gov/AboutFDA/CentersOffices/NCTR/WhatWeDo/NCTRResearchPriorities/ucm083162.htm. The web materials do not explain the nature of this monitoring, whether it is proactive, or only done after a referral from one of the FDA Centers.

FY08 Milestones

- ORA's Division of Field Sciences contacted NCTR regarding collaboration on developing methodology for nanotechnology that will enable ORA/ARL to detect nanomaterials in FDA-regulated products.

- Formulated research plan on toxicology of nanosilver with FDA Centers (Boudreau).

NCTR/ORA Nanotechnology Core Facility Proposed Milestones, FY09-FY11

- Initiate studies on ADME and toxicology of nanoscale silver (Boudreau);

- Develop research plan and protocol for detection of nanoscale silver in food and drug matrices;

- Develop research plan and protocol for detection of nanoscale TiO_2 and ZnO in food, drug, and cosmetic matrices;

- Identify food safety issues regarding nanoscale materials;

- Begin studies on detection of nanoscale silver in food and drug matrices;

- Develop research plan on nanoscale gold (Boudreau);

- Initiate ADME and toxicology studies on nanoscale gold (Boudreau);

- Develop SOPs for use of X-ray fluorescence spectrometer for routine surveillance of elements in food, drug, and cosmetic samples;

- Test/validate SOPs for the detection of nanoscale silver in food and drug matrices;

- Test/validate SOPs for the detection of nanoscale TiO2 and ZnO in food, drug, and cosmetic matrices;

- Develop/validate SOPs for food safety research plan regarding detection of adulterated or contaminated foods;
- Develop research plan and protocol for detection of nanoscale materials in dietary supplements;
- Develop protocol for routine use of electron microscopy for support of ADME studies on nanoscale materials;
- Continue ADME and toxicology studies on nanoscale silver;
- Continue ADME and toxicology studies on nanoscale gold; and
- Continue protocol and development/validation of SOPs for detection of nanoscale materials in dietary supplements, food, drugs, and cosmetics (ORA/ARL).[8]

From an examination of the several links on the site, it does not appear that any of the research conducted to date has been reduced to publicly-available printed study results, abstracts, or reports.

NTP

Research at NTP is being conducted as an element of the Nanotechnology Safety Initiative.[9] NTP lists a wide variety of nanoscale materials either being tested presently, or planned for testing in the short term:

- Metal oxides

[8] *See* "NCTR/ORA Nanotechnology Core Facility," *available at* http://www.fda.gov/AboutFDA/CentersOffices/NCTR/WhatWeDo/NCTRResearchPriorities/ucm083172.htm.

[9] The Initiative goals and objectives are described at http://ntp.niehs.nih.gov/?objectid=7E6B19D0-BDB5-82F8-FAE73011304F542A.

The focus of these projects is to evaluate nanoscale titanium dioxide and zinc oxide due to their presence in cosmetics.

- Characterization of size, crystallinity, and coating of these metal oxides in representative commercial sunscreens.
- Evaluation of photoactivation of titanium dioxide in *in vitro*, *ex vivo*, and *in vivo* models.
- Dermal penetration of titanium dioxide in *in vivo* and *in vitro* model.
- Phototoxicology of titanium dioxide in mice.
- Photocarcinogenicity of titanium dioxide in mice.

■ Fluorescent Crystalline Semiconductors (Quantum Dots)

The focus of these projects is to evaluate cadmium selenide/zinc sulfide spheres and rods of varying sizes and surface chemistry as a model system to test hypotheses about role of size and surface chemistry on tissue distribution.

- Synthesis and characterization of specific materials.
- Development of quantitative fluorescent microscopy system and IPC-mass spectroscopy approach for evaluating tissue levels.
- Quantitative evaluation of the tissue distribution following dermal and systemic routes of exposure.

■ Carbon-based Fullerenes

The focus of these projects is to evaluate carbon-based fullerenes of varying particle size, fullerene cage size, and surface derivatisation.

- Physical and chemical characterization of procured materials and formulation development.
- *In vivo* subchronic repeat dose toxicity studies following inhalation and oral exposure.
- Tissue distribution and half life evaluation after subchronic inhalation exposure.
- Pulmonary toxicity and evaluations following a single intratracheal instillation.
- Immunotoxicological evaluation following inhalation exposure.

■ Carbon Nanotubes

The focus of these projects is to evaluate the impact of variation in length, and diameter on the toxicity of single and multi-walled carbon nanotubes.

- Physical and chemical characterization of commercially available nanotubes.
- *In vivo* subchronic repeat dose toxicity studies following inhalation exposure.
- Tissue distribution and half life evaluation after subchronic inhalation exposure.
- Pulmonary toxicity and evaluations following intratracheal instillation.
- Immunotoxicological evaluation following inhalation exposure.

■ Nanoscale Silver (NTP Research Concept)

The focus of these projects is to evaluate the impact of particle size on comparative toxicity of nanoscale metallic silver compared to ionic silver. Nanoscale silver is increasingly being used in a variety of consumer products based on its antibacterial properties.

- Characterize the relationship between nanoscale silver particle size and degree of ionization to Ag+.
- Evaluate the effect of particle size and ionization state on the pharmacokinetic profile of nanoscale silver.
- Evaluate the effect of particle size and ionization state on the toxicological profile of nanoscale silver *in vivo*.

■ Nanoscale Gold (NTP Research Concept)

Nanoscale gold is being used as a potential platform for nanoscale-based therapeutic applications. The focus of these projects is to understand how physiochemical properties impact on the disposition, metabolism, elimination, and toxicity of nanoscale gold.

- Evaluate the effect of particle size and particle coatings on the pharmacokinetic profile of nanoscale gold.
- Evaluate the effect of particle size and particle coatings on the toxicological profile of nanoscale gold *in vivo*.[10]

Conclusion

FDA has embarked on a testing program for various forms of nanoscale material. The testing program may not be a top priority, given the many challenges that have arisen in the recent past (*e.g.*, food safety, swine flu) and resource and budgetary constraints. That said, the various tests being conducted need to be monitored, since any initial results could have a

[10] "Nanotechnology Safety Initiative-Projects" at http://ntp.niehs.nih.gov/?objectid=303069A0-F1F6-975E-72D33ECBD3E11363.

substantial impact on the FDA regulation of products produced using nanotechnology or containing nanoscale materials.

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We hope this information is helpful. As always, please let us know if you have any questions.