Submitted by: The Arkansas Research Alliance to
U.S. Senate Committee on Appropriations
FY15 Hearing: Driving Innovation through Federal Investments

Tuesday, April 29th, 2:30 pm
Dirksen Senate Office Building, SD-G50

We write to describe some activities in which investments at FDA's National Center for Toxicological Research (NCTR) are indeed driving innovation. The Arkansas Research Alliance (ARA) signed a Partnership Intermediary Agreement (PIA) with Commissioner Hamburg in September of 2013 that relates directly to this issue of innovation. We believe it is important to show the effectiveness and impact of the federal investment in rural states such as Arkansas, realizing that in addition to local impact, there is also national and global impact.

First, some background on NCTR. NCTR is the only FDA center outside of the Washington, D.C. metropolitan area. NCTR's mission includes the: conduct of peer-reviewed research to assess safety of FDA-regulated products; development of new scientific tools to speed scientific development; provision of multidisciplinary training in regulatory science; and fostering of national and international collaborations between scientists in government, academia, and industry.

NCTR's 500 plus acre campus has well-equipped facilities utilizing 123 experimental laboratories occupying portions of the available 1,000,000 square feet of floor space. Combined resident staff and postdoctoral fellows account for 183 doctoral level researchers working with approximately 400 other staff. The space includes a 14,000 sq. ft. neurotoxicology primate facility with superb imaging and surgical capabilities; equipment for sophisticated genomic, proteomic, metabolomic, and related research; with phototoxicity, genetic, carcinogenic, microbiologic, bioinformatics, biostatistics and many other specialized capabilities needed to support modern toxicological research. In addition, the Nanotechnology Core Facility, a collaborative venture between NCTR and Arkansas Regional Laboratories (an FDA inspection laboratory co-located on the Jefferson Labs campus) is the most extensive laboratory focused on Nanotechnology within FDA.

It is further characterized by: scientific excellence and superb publication record in prestigious journals; a multi-disciplinary approach to finding inter- and intra-cellular mechanisms associated with adverse events; a focus on finding markers of these events at the time of exposure that would predict adverse effects later in life; and upholding a gold-standard for assessing the toxicity of widely used products already in commerce, one based on good science in well-controlled experiments. With these assets, NCTR has enormous capability for innovation.

Academic relationships: Since its beginning, NCTR has been a collaborating scientific resource for Arkansas universities. That relationship has been strongest with Arkansas's medical school, the University of Arkansas for Medical Sciences (UAMS.) Over 100 UAMS doctoral students in toxicology and related fields have been trained on the NCTR campus, and many UAMS researchers have worked collaboratively on many projects with NCTR. Many NCTR staff have held adjunct faculty positions at UAMS. As research capabilities have grown across the state, similar collaborations have developed with the University of Arkansas-Fayetteville,

the University of Arkansas at Little Rock, the University of Arkansas at Pine Bluff, and Arkansas State University. We have no direct measure of the innovation provided by these students and the collaborative research. It is however axiomatic that the value has been quite large and important for this rural area.

Other training is deeply woven into the fabric of NCTR. Over 1,000 students and staff from the State of Arkansas, the U.S. and over 47 countries worldwide have received training at NCTR. This training has great value as is demonstrated through the very large distribution of international and national postdoctoral fellows who are alumni of NCTR training programs. Several international officials responsible for FDA-related safety issues around the globe were trained at NCTR. At a time when the complexities and critical importance of regulatory science need to be better understood, defined, explained, and expanded, this capability and interest by NCTR staff and leadership represent a valuable asset. The innovative impact of this federal investment has global ramifications. It is also significant in helping to assure the safety and effectiveness of products now produced globally and distributed to U.S. consumers.

Among areas of scientific strength in Arkansas, nanotechnology emerges as a primary set of capabilities. At NCTR, the Nanotechnology Core Facility, the expertise, and the impressive record of accomplishments and publications is a key factor. However, Arkansas universities also have distinguished programs. In Fayetteville, the University of Arkansas Institute for Nanoscience and Engineering is at the forefront of research in nanoscience and nanotechnology. At the University of Arkansas at Little Rock, the Center for Integrative Nanotechnology Sciences has a strong record in synthesis and nanomedicine. There is a very strong program in nanomedicine research at the Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences where the Arkansas Nanomedicine Center resides in the College of Medicine. This set of strengths has emerged as an obvious asset for Arkansas and was influential in Arkansas Governor Mike Beebe's strong interest and investment in an Arkansas/FDA partnership in regulatory science, particularly as it relates to nanomaterials.

Memorandum of Understanding (MOU): Recognizing the capability resident at NCTR, Arkansas Governor Mike Beebe and FDA Commissioner Margaret Hamburg signed a Memorandum of Understanding (MOU) between Arkansas and FDA in August of 2011. The MOU established an Arkansas Center of Excellence in Regulatory Science (ACERS). A major strength of the ACERS is the development of a strong collaboration between the Arkansas research universities NCTR, and other State entities. This relationship has resulted in a very positive capability to leverage resources to the benefit of FDA.

Several major accomplishments have flowed from that effort:

Regulatory Science Curriculum: One component of the ACERS is a Regulatory Science curriculum at UAMS. Within one year of signing the MOU, that program was begun with 22 students. One year after that, 18 students (many postdoctoral fellows) were graduated with certificates in Regulatory Science. The program is continuing and is moving forward with a Master's program and online instruction so that students in remote locations can participate. There is a strong interest within UAMS and Arkansas to support FDA/NCTR in extending this training function to include others who need and desire training in regulatory science, including domestic and international scientists. A thorough understanding of regulatory science is essential for successful innovation of products associated with FDA.

Nanosafety Research: The ACERS instituted a program of research investigating the public health impact of nanomaterials. After reviewing national assessments of nanotoxicology research, understanding which nanomaterials are being studied elsewhere, and assessing future trends, the group chose to focus initial efforts on carbon-based nanomaterials with emphasis on graphene. In part, these materials were chosen because they are both challenging to detect in our carbon-rich bodies and environment and likely to present significant exposures and regulatory approval challenges. In addition to their use in areas such as electronics, body armor, and construction materials, they are being proposed in products regulated by FDA. It is not possible at this time to accurately predict how many graphenic-nanomaterials will be included in products proposed to FDA as either drug, device, or food contact materials. We know that many companies are exploring uses of these materials in biological sensing and imaging, drug delivery systems, cancer treatment, disease detection, scaffolding for cell culture, inclusion in prosthetics and other medical devices, antibacterial materials, antimicrobial food contact materials, night vision contact lenses, implantable sensors and many other applications that are expected to result in products that will require FDA approval. The importance of this research is to generate key data and understand the graphenic-platform that will pose considerable difficulty for FDA in order to (i) understand the difficulties in analyzing the purity, size and shape of graphenic materials, (ii) provide a quantitative measure of the toxicity of these materials in a variety of toxicity assays, and (iii) provide some measure of the difficulty in quantifying these materials *in vitro* and *in vivo*.

Because of the federal investment at NCTR, there is a very strong core of biological capability that when combined with the capabilities of the five area universities, provide a powerful consortium with a full range of needed capabilities. The universities bring the disciplines of engineering, physics, biomedicine, aquatic disposition, plant uptake and metabolism to the capabilities within FDA. In addition, the work is preparing scientists and students for additional work in this area, all with added innovative potential.

The ARA is managing the research program between researchers at the five Arkansas universities and NCTR. Governor Beebe provided a $1,000,000 grant to support this research, and the ARA team has successfully competed for a $289,000 contract from FDA supporting research at the universities that is closely coordinated with the current and future needs of FDA. The work is progressing very well with impressive results and demonstrates how federal funds are being leveraged for the public benefit. Thus far the team has: developed novel methods for detecting carbon-based nanomaterials in cells and tissues; shown that commercial products contain large amounts of impurities that could have a tremendous impact on potential environmental and health impacts; produced graphenes that contain metallic markers to enhance the potential for tracking them in cells organisms and the environment; used advanced imaging techniques to accurately and rapidly characterize the shape and size of individual graphene "flakes;" received and reviewed research proposals from Arkansas universities that will extend current research to detect graphenes in biological and other environmental substrates; and established an advisory board of individuals who are international leaders in the field of environmental and health safety of nanomaterials.

Partnership Intermediary Agreement (PIA): As stated earlier, in September, 2013, Commissioner Hamburg signed a PIA with the Arkansas Research Alliance (ARA). That PIA is indeed relevant to this issue of driving innovation. ARA is a 501 c) 3) public/private partnership

created by the Arkansas legislature in 2007 with the mission of supporting the development and extension of job-creating research in Arkansas. The ARA has the full respect of Arkansas's leaders in academia, government and industry and has been chosen to coordinate all of the activities of the MOU. ARA is supported by a Board of Trustees comprised of the chancellors of Arkansas's five research universities and senior management of fifteen of Arkansas' most significant industries, notable among them—Walmart and Tyson Foods, Inc. The value of ARA is that it is established as a trusted partner by all sectors. It is a critical link between industry, government, and academia, forging alliances, partnerships, and significant collaboration. With a phone call, ARA can bring key leaders to the table and effect needed action. Being a small state, Arkansas leaders from all sectors know each other and are eager to join together to solve problems and implement both change and positive action.

Working together with others, this public/private partnership has become an important and effective facilitator of efforts to advance regulatory science. It is working within the guidelines of the PIA to extend the intellectual and technical resources of NCTR into commercially viable innovations so that they may be translated into patient/consumer benefit. In addition to the more obvious needs of publicizing existing intellectual property, ARA has worked to increase training and awareness on the part of researchers of the need for intellectual property protection as a prerequisite for achieving public health benefits. In addition, ARA is working to develop more opportunities for Cooperative Research and Development Agreements (CRADAs) with NCTR in order to leverage the existing federal investment with academic and private resources. The extensive collaborative relationships NCTR has established with regional academia enhances the opportunity for more successful endeavors.

A good example of successful innovation is the spin out of a CRADA-produced technology to rapidly identify and quantify pathogenic micro-organisms within a few hours as opposed to days with other technology. This company, Vivione Biosciences, is now publicly traded and providing a product with a huge public health impact. There is other technology at NCTR that ARA believes has similar if not even better potential. The successful spin-out of these technologies will help protect the public health and provide an opportunity for commercial development. These successes are directly related to the federal investment at NCTR.

Without the federal investment at NCTR, the entire ARA effort would look very different and would have a different scale of effectiveness. Recognizing this, ARA has established an external advisory group to help shape its future efforts and to become more entrepreneurial in promoting innovation. Along those lines, there are efforts in development for the graduate program in regulatory sciences at UAMS to provide scholarly reviews of how these programs can be revised to optimize their public benefit.

Other Opportunities: The MOU brings Arkansas into a closer relationship with FDA/NCTR. There are other examples of collaboration that will lead to increased innovation. For example, ARA is now establishing an Arkansas Bioinformatics Consortium to bring the strengths of our universities to bear on problems faced by FDA. This is another example of how federal funds are being leveraged to the benefit of consumer protection. ARA will continue to explore with our advisory group, ways in which the impressive innovative capacity at NCTR might be increased to even greater levels to optimize this investment.