SENATE APPROPRIATIONS COMMITTEES SIGNIFICANT ITEMS

SENATE COMMITTEE REPORT (S. 114-82)

1. Active Pharmaceutical Ingredients

The Committee is concerned that the FDA has not yet approved a list of active pharmaceutical ingredients [APIs] for use by compounding pharmacists pursuant to the Federal Food, Drug, and Cosmetic Act [FDCA]. Within 90 days of the enactment of this act, the FDA is directed to provide a timeline for when the remaining substances will be considered, and in the meantime re-consider its policy with regard to enforcement of the bulk drug substances provisions under section 503A.

FDA Response:
FDA will provide the requested report.

2. Alcohol Based Hand Sanitizers

The Committee strongly supports the systematic review of healthcare antiseptic active ingredients used in alcohol based hand sanitizers [ABHS] products marketed under the over-the-counter [OTC] monograph to ensure the safety of healthcare workers and consumers, but is concerned about the potential impacts to public health that could occur if ABHS products containing healthcare antiseptic active ingredients are reclassified in a final monograph without full review of available, appropriate science based data and risk models. The FDA is requested not to issue a final monograph regarding OTC healthcare antiseptic active ingredients that are used in ABHS products, until full and fair consideration is given to existing evidence that has been provided to FDA that supports general recognition of safety and effectiveness of OTC ABHS products, and to potential costs associated with the final monograph.

FDA Response:
On May 1, 2015, FDA published a proposed rule in which the Agency proposed to establish conditions under which OTC antiseptic products intended for use by health care professionals in a hospital setting or other health care situations outside the hospital are generally recognized as safe and effective (GRASE). Alcohol based hand sanitizers (ABHS) fall under the category of antiseptic rubs, which are sometimes referred to as "leave-on products" and are not rinsed off after use. OTC products being considered under the health care antiseptic proposed rule include health care personnel hand washes, health care personal hand rubs, surgical hand scrubs, surgical hand rubs, and patient preoperative skin preparations.

The health care antiseptic proposed rule is part of a series of rulemakings for a monograph for OTC topical antimicrobial drug products. FDA first published an advanced notice of proposed rulemaking for a monograph for OTC topical antimicrobial drug products in 1974. In 1978, FDA issued a proposed rule in the form of a tentative final monograph or TFM for certain antimicrobial products. In 1994, FDA issued a proposed rule amending the 1978 TFM for certain antimicrobial products, including antiseptic hand washes (i.e, consumer hand washes), health care personnel handwashes, patient preoperative skin preparations, and surgical hand scrubs.

In addition, there have been three meetings of the Nonprescription Drugs Advisory Committee (NDAC) and two public feedback meetings with regulated industry that are relevant to the

discussion of health care antiseptic safety and effectiveness. One of the feedback meetings was specific to study designs for completing data gaps for ABHS products.[116]

Before issuing a final rule on a GRASE determination for health care antiseptic active ingredients used in OTC ABHS products, FDA will fully consider all the available evidence, including the recommendations of the NDAC, public comments on the agency's notices of proposed rulemaking, and all new data and information on OTC health care antiseptic products that have been submitted to the rulemaking docket or have other been made publicly available. In addition, FDA will assess the economic implications and the costs and benefits of the final rule under Executive Orders 12866, 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act of 1995.

3. Biosimilars

The Committee is concerned that FDA has failed to provide the public adequate opportunity to review and comment on regulatory standards for the approval and oversight of biosimilar drugs. Therefore, FDA is directed to provide the Committee with an estimated timeline by which the agency will: finalize all pending draft biosimilars guidance documents, publish draft biosimilar guidance documents included in its 2015 regulatory agenda, and finalize those draft guidance documents. The Committee expects to receive this report no later than 2 weeks after the Committee reports this legislation.

FDA Response:
FDA will provide the requested report.

4. Centers of Excellence in Regulatory Science and Innovation

The Committee is encouraged by the ongoing research and collaboration underway at the Centers of Excellence in Regulatory Science and Innovation program and commends the FDA for launching this program in 2011 and expanding it in 2014. As such, the Committee directs the Office of the Commissioner to use at least $2,000,000 within existing funds to provide additional funding opportunities for the existing CERSI Centers to allow for the capitalization of ongoing studies and research.

FDA Response:
FDA appreciates the recognition of the importance of the CERSIs, their contributions to regulatory science, and identification of support for them.

5. Comparative Oncology

The Committee recognizes the value in using data from cancers in companion animals to provide answers to important translational questions about cancer biology, diagnosis, and treatment. This research offers an important opportunity to study cancers in thousands of subjects to benefit both human patients and pets. The Committee requests FDA address the use of companion animals in diagnosis and treatment research and encourage the FDA to open grant opportunities in animal models to increase the study of the 1 million companion animals that naturally develop cancer each year.

FDA Response:
While FDA believes that a wealth of current information exists regarding companion animals with naturally occurring diseases that can be directly applies to drug approvals for both animal

[116] Available at: http://www.regulations.gov/#!documentDetail;D=FDA-2015-N-0101-1248

and human drugs without additional funding, FDA recognizes that additional research in oncology and studies in both companion animals and humans are needed to support future advancements in translational medicine. However, FDA believes that such efforts are more aligned with the National Cancer Institute's mission.

Currently information exists in companion animals with naturally occurring diseases that can be directly applied to drug development and review process for both humans and companion animals. This information can be utilized without additional funding by FDA. FDA recognizes that additional research in oncology and studies in both companion animals and humans are needed to support future advancements in translational medicine. However, these efforts are more aligned with the National Cancer Institute's mission.

6. Cord Blood Regulation

The Committee directs the FDA to undergo a review and seriously consider the potential need for revision of the current regulatory requirements for cord blood licensure, particularly those related to manufacturing and storage, to ensure the correct applicability to this industry since the current regulatory requirements being applied are the same ones that apply to pharmaceutical products. In addition, the Committee directs the FDA to create an advisory task force, comprised at a minimum of public and private cord blood bankers, transplanters and patients, to provide recommendations to the agency about the current licensing requirements and changes that may be necessary.

FDA Response:
FDA developed an innovative regulatory paradigm for minimally manipulated, unrelated allogeneic placental/umbilical cord blood (HPC, Cord Blood) through extensive outreach and collaboration with our stakeholders. This regulatory program has resulted in HPC, Cord Blood units that are manufactured more consistently without interfering with product availability.

The manufacturing and storage requirements, as well as other requirements, were developed in collaboration with our stakeholders through various means including:

- two meetings of the Cellular, Tissue, and Gene Therapy Advisory Committee
- development of the final guidance, ''Class II Special Controls Guidance Document: Cord Blood Processing System and Storage Container"
- two rounds of guidance development regarding recommendations for IND and Biologics License Application submissions for HPC, Cord Blood
- a cord blood licensure workshop; outreach to the Health Resources Services and Administration (HRSA)
- outreach to the National Marrow Donor Program (NMDP)
- outreach at professional meetings; more than 10 pre-BLA meetings with stakeholders and through participation as a liaison to the HHS Advisory Council on Blood Stem Cell Transplantation (ACBSCT).

The ACBSCT advises the Secretary of HHS and the Administrator of HRSA on the activities of the C.W. Bill Young Cell Transplantation Program and the National Cord Blood Inventory (NCBI) Program. Members of the ACBSCT include representatives of marrow donor centers, transplant centers, and cord blood banks, patient and patient family representatives, scientists, ethicists, and members of the general public.

In addition, FDA has met recently with the NMDP and representatives of licensed cord blood banks to discuss lessons learned and identify ways in which FDA and the industry may work

together to facilitate further development of HPC, Cord Blood products. Based on the input obtained, the manufacturing and storage requirements are considered appropriate for HPC, Cord Blood licensure, and FDA is committed to working with industry to improve best practices under the current regulations.

7. Cosmetics

The Committee provides not less than $11,700,000 for cosmetics activities, including not less than $7,200,000 for the Office of Colors and Cosmetics [OCAC]. Funding for OCAC is for the direct support of the operation, staffing, compliance, research and international activities performed by this office. The Committee notes that FDA's budget submission stated that FDA would meet a March 2015 deadline, set by this Committee, to respond to a citizen petition regarding trace amounts of lead in cosmetics. This has not occurred, and this unacceptable delay is indicative of longstanding issues with FDA's review of cosmetics. Since 1976, cosmetic ingredients have been reviewed by a private Cosmetic Ingredient Review program, established by the cosmetic industry, with nonvoting FDA participation. The Committee directs FDA to work with the industry to study the transfer of this program to a more formal public-private partnership, similar to the United States Pharmacopeia, if appropriate and beneficial for consumers, and to report back to the Committee on this effort.

FDA Response:
OCAC will use FY2016 funding for direct support of the operation, staffing, compliance, research, and international activities performed by this office. As noted in our response to the Committee last year, FDA sponsored and completed additional studies to address data gaps regarding trace amounts of lead in cosmetic products. FDA has evaluated data from these studies and other relevant information and has worked to respond fully to the citizen petition.

While FDA will prepare the requested report, the Committee's directive raises significant appearance concerns and resource issues that will be addressed in the report. The CIR is a private, industry-funded organization, and FDA believes that enhancing the authority and stature of a private organization is inappropriate for a Federal regulatory agency. In addition, charging a public-private partnership with determining the safety of cosmetic ingredients – an activity within the Agency's statutory purview – may create the appearance that the partnership's determinations represent formal FDA determinations.

8. Deeming Regulations

The Committee notes that the Family Smoking and Prevention and Tobacco Control Act, which became law in 2009, gave FDA immediate authority over certain tobacco products, and gave authority to the Secretary of Health and Human Services to deem other products subject to FDA regulation. On April 25, 2014, nearly 5 years after it had been granted the authority to do so, FDA issued those proposed deeming regulations, but has not yet finalized them. FDA is therefore directed to issue a final regulation addressing the deeming of other tobacco products under FDA's jurisdiction within 30 days and to act expediently to implement that regulation once finalized.

FDA Response:
Finalizing the tobacco deeming rule is of the highest priority for the Agency and the Administration. We share your sense of urgency on this important matter. FDA received over 135,000 comments to the docket and we are working diligently with the Administration to

finalize the rule as soon as possible. The rule has undergone extensive internal review within FDA and HHS, and is now under review at the Office of Management and Budget.

Once the proposed rule is finalized, some provisions – for example, establishment registration, product listing, ingredient listing, and the adulteration and misbranding provisions of the statute – in the Federal Food, Drug, and Cosmetic Act (FD&C Act) will automatically apply to all deemed tobacco products. In addition, other provisions of the proposed rule will apply to covered, newly deemed tobacco products such as:

- minimum age and identification restrictions to prevent sales to underage youth
- requirements to include health warnings
- a prohibition of vending machine sales, unless in a facility that never admits youth.

When the rule is final, FDA will prioritize implementation, including educating industry on how to comply with the requirements in the rule. In addition, FDA considers the deeming rule to be a foundational regulation, which, once finalized, will allow the Agency to take further actions regarding critical public health issues.

9. Duchenne Muscular Dystrophy

The Committee is aware that a patient-focused draft guidance for drug development on Duchenne Muscular Dystrophy was submitted to FDA in June 2014. The Committee supports this initiative and requests that FDA provide a detailed description of its plans to move forward with the development of a related guidance.

FDA Response:
FDA is committed to engaging with patient groups to receive their valuable input during the evaluation of the medical needs of patients with rare diseases whenever appropriate. We appreciate the guidance that members of the Duchenne muscular dystrophy (DMD) community submitted to FDA in June 2014. FDA announced the DMD community's guidance through a Federal Register notice (September 4, 2014) to seek additional guidance and public comment. FDA carefully considered the consortium's guidance and public comments received in response to it in writing the agency's own draft guidance.

The draft guidance for industry, "Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment," was released in June 2015, and a 60-day comment period was provided. We are currently reviewing the comments received and plan to issue a final guidance in 2016. The purpose of the guidance to industry is to assist sponsors in the clinical development of drugs for treating X-linked Duchenne muscular dystrophy and related dystrophinopathies, and to serve as a focus for continued discussions on this topic.

10. Farm Regulations

The Committee remains concerned about how the FDA will determine whether and to what degree a farm or food business is subject to regulation. It is important that FDA is careful to apply new rules appropriately for the size of the operation in accordance with congressional intent.

FDA Response:
FDA appreciates that the produce safety rule establishes, for the first time, federal regulatory requirements for on-farm growing, harvesting, packing, and holding of produce. We also appreciate that implementing the requirements of this rule will come with a cost, both in time

and resources. As such, the Final Rule does not cover farms that have an average annual value of produce sold during the previous three-year period of $25,000 or less.

The Final Rule also contains provision(s) for a qualified exemption and corresponding modified requirements for farms that meet certain requirements – including having food sales averaging less than $500,000 per year during the previous 3 years and the farm's sales to qualified end-users –either consumers or restaurants and retail food establishments in the same state or Indian reservation or within 275 miles – exceed sales to others.

In addition, FDA has provided extended compliance periods based, in part, on the size of the farm. We conclude that these provisions adequately address the concerns of small farms and are in compliance with our statutory mandate under section 419 of the FD&C Act.

FDA will work with partners to provide technical assistance to the farming community, especially small and very small farms, regarding compliance with the produce safety rule. We are developing guidance documents, including general guidance on the implementation of the rule, as well as a Small Entity Compliance Guide (SECG) in accordance with section 105(b) of FSMA (21 U.S.C. 350h note) and section 212 of the Small Business Regulatory Enforcement Fairness Act (Pub. L. 104-121). A SECG is a guidance that explains the actions a small entity must take to comply with a rule. We also plan to work closely with State, Territorial, tribal and local partners to develop education and training programs for the same purpose.

With respect to food businesses – both on and off farms – that are required to register with FDA and thus are potentially subject to the Preventive Controls for Human Food rule or the Preventive Controls for Animal Food rule (PC rules), we have provided modified requirements for qualified facilities – for example, very small businesses as defined in the PC rules – that exempt them from having to develop a written food safety plan. In addition, modified supplier verification activities apply when the supplier to be verified is a qualified facility under the PC rules or a farm that is not covered by the produce safety rule or that is subject to a qualified exemption under that rule.

11. Foreign High Risk Inspections

As the importation of drugs, food, and medical devices from China continue to increase, the Committee is concerned about the FDA's ability to keep pace with the exporter universe and volume of exports. For fiscal year 2015, an additional $2,000,000 was provided for foreign drug safety to address the growing number of human drugs produced overseas and the increasing number of imported drug shipments in order to ensure the continued safety and quality of these products. These funds have been provided to support the agency's overseas inspections, work with industry and other stakeholders in safety in manufacturing, strengthen agency relationships with foreign regulators, and analyze trends and events that might affect the safety of FDA regulated products exported to the United States. The Committee is supportive of FDA as it moves toward a more, targeted, risk-based, and efficient inspection model that incorporates commercially available information on high-risk establishments. As with other Federal agencies, such as CMS, better data has helped to make sure a company exists and is in good standing prior to an inspection and to help prioritize FDA's investigations and triage safety inspections. Within the funds provided for the China Safety Initiative the Committee directs the FDA to maintain robust funding for onsite verification support and integration of results in FDA inspection planning.

FDA Response:
FDA recognizes the concerns indicated in the Committee statements regarding the ability to keep pace with the importation of drugs, food, and medical devices from China, the exporter universe, and volume of exports. Globalization has increased the volume of imported products into the United States, and the complexity of supply chains poses challenges for ensuring the safety of FDA regulated products. FDA continues to implement risk-based decision making for field operations, including the efforts of the Foreign Offices to ensure the most efficient use of budget and human resources in protecting the U.S. public.

FDA will continue to fund and develop methods that enhance the data available and the quality of such data in order to continue to enhance a more targeted, risk-based and efficient system to oversee the safety of FDA regulated products.

FDA agrees that performing site verification is an important activity, given that it improves accuracy and completeness of firm manufacturing site data. That firm data leads to enhanced efficiencies when planning domestic and foreign firm inspections, and aids in proper identification of manufacturing firms. It also contributes to the FDA's ability to react swiftly to national emergencies involving food, drug and medical device supply chain problems, which ultimately improves the safety of the nation's food, drug, and medical device supply.

To that end, Dun & Bradstreet was contracted in FY 2014 for site verification services in China.

12. In Silico Clinical Trials

In Silico clinical trials use computer models and simulations to develop and assess devices and drugs, including their potential risk to the public, before being tested in live clinical trials. Advanced computer modeling may also prove useful in helping to predict how a drug or device will behave when deployed in the general population or when used in particular circumstances, thereby helping to protect the public from the unintended consequences of side effects and drug interactions. In Silico trials may potentially protect public health, advance personalized treatment, and be executed quickly and for a fraction of the cost of a full scale live trial. The FDA has advocated the use of such systems as an additional innovative research tool. Therefore, the Committee urges FDA to engage with device and drug sponsors to explore greater use, where appropriate, of In Silico trials for advancing new devices and drug therapy applications.

FDA Response:
FDA acknowledges the benefits to public health provided by in silico clinical trials, and has previously advocated for their use as one of many research tools. Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study design strategies, so that safe and effective new therapeutics can advance more efficiently, from preclinical studies through clinical trials to market. The efforts in modeling and simulation are enabled through multiple collaborations with external parties that provide additional expertize and infrastructure to advance the development of innovative state-of-the-art technologies.

FDA advises sponsors on the use of modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms. Some computational models are firmly embedded in the product review process and supported by guidances, while others are used as needed (fit-for-purpose) or in a research capacity to help inform regulatory decisions.

FDA is also collaborating, both internally and externally (with both Investigational New Drug applications sponsors and New Drug Application stakeholders, researchers, and other regulatory

bodies), to maximize the use of modeling and simulation to complement clinical trials or to improve their design and success, including – but not limited to – comparative predictions of Phase 3 responses across a novel therapeutic class and replacement of clinical studies with in silico modeling for cardiac safety testing.

In addition FDA is actively working to explore modeling approaches and enhance their regulatory impact through the Agency's Scientific Computing Board whose goal is to advance science, streamline operations, and strengthen FDA's overall effectiveness. FDA drug modeling reviewers have also actively engaged with device modeling efforts to build regulatory models for product design and evaluation, including the development of a digital library of models and a family of "virtual patients" for device testing.

13. In Vitro Clinical Trials

In Vitro clinical trials use specimens collected from patients to test how a particular cancer or disease will react to a specific therapy or combination of therapies. This personalized approach to treatment can improve a patient's quality of life by increasing the likelihood that physicians and researchers will find the proper combination of drugs uniquely suited to treat that individual's illness. An emerging new scientific methodology, In Vitro trials allow researchers to test therapeutics and treatment strategies on living human tissues without the risks posed by traditional whole patient clinical trials. Personalized treatment through In Vitro trials dismantles the ''one size fits all'' approach to care and enables medical professionals to diagnose and treat patients in a more efficient and effective way. While the Committee recognizes that In Vitro tests may not always predict clinical responses, it urges the FDA to continue to engage with drug sponsors to explore greater use, where appropriate, of In Vitro clinical trials for drug development programs under Investigational New Drug applications and general therapeutic indications, especially as it relates to complicated cancers and other common disease states.

FDA Response:
FDA acknowledges the benefits to public health provided by in vitro trials, and the potential to provide more personalized medical treatment options for patients. FDA recently launched the Critical Path Innovation Meeting program, which allows drug developers and other stakeholders to discuss new and emerging technologies with FDA. These meetings have included topics related to In Vitro trials to identify suitable combination therapies to take into clinical trials. FDA will continue to engage stakeholders through this mechanism to discuss such technologies. Where appropriate, companies may still discuss specific drug development proposals involving these technologies in the setting of FDA's formal meetings with industry under the Investigational New Drug application.

In addition, consortia and other stakeholders may interact with FDA via the Drug Development Tools Qualification Program to the extent that a particular technology platform is being formally developed to support regulatory decision-making. FDA has received submissions involving In Vitro trials, and will continue to engage with sponsors of drug development tools to advance In Vitro trials into drug development.

14. Mammography Quality Standards Act

The Committee recommendation includes full funding as requested for implementation of the Mammography Quality Standards Act. This program sets national quality standards for mammography facilities, equipment, personnel, and operating procedures, and has improved the quality of mammography and made mammograms a more reliable tool to detect breast cancers.

FDA Response:
FDA intends to fully fund the MQSA program.

15. Mammography Reports

The Food and Drug Administration is directed to revise its regulations regarding the summary mammography reports in lay language provided to patients to require the inclusion of information on the patient's breast tissue density; an explanation that dense tissue may mask the presence of breast cancer on mammograms; and advice that patients speak with their healthcare provider about whether they would benefit from additional tests, and about any other questions they may have. The FDA should also revise its regulations regarding the medical report provided to healthcare providers to require the inclusion of information on the patient's breast density and the masking effect such tissue may have on detecting breast cancer.

FDA Response:
FDA is working on proposed amendments intended to address the addition of breast density information to the content of reports required by the MQSA implementing regulations.

16. Medical Gases

The Committee is concerned that FDA has not initiated rulemaking to address numerous longstanding regulatory issues for medical gases despite the statutory requirement in FDASIA to issue a final rulemaking addressing all necessary changes for medical gases by July 9, 2016. Designated medical gases are a unique class of drugs that differ significantly from traditional pharmaceuticals and therefore must be addressed in the Federal drug regulations to prevent safety and enforcement issues caused by current regulations. The Committee disagrees with the FDA report to Congress sent on June 30, 2015 that despite decades of issues created by existing regulations ''the current regulatory framework is adequate and sufficiently flexible to appropriately regulate medical gases.''

FDA Response:
As required in FDASIA, FDA reviewed Federal drug regulations that apply to medical gases, and submitted the June 2015 Report to Congress. FDA sought public comments through meetings and a public docket.

As described in that report, FDA has determined that the current regulatory framework is adequate and flexible enough to appropriately regulate medical gases with regard to most issues. FDA can work within the existing regulatory to regulate the production and distribution of medical gases without rulemaking, through, for example, publication of revised guidance to industry and revisions to FDA's medical gas inspection program and related inspection training. FDA disagrees that these tools are inadequate to appropriately regulate medical gases, and specifically disagrees that the existing regulations have led to any significant safety issues in the provision of medical gases.

FDA is currently engaged in a number of activities intended to reduce regulatory uncertainty and clarify expectations for industry and other stakeholders including additional training of inspectors, implementing an updated inspection program, and updating the 2003 draft guidance for industry on current good manufacturing practices (CGMPs) for medical gases. In December 2015 FDA staff met with representatives of the medical gas industry regarding their views on the revision of the 2003 draft guidance on CGMPs.

As we stated in FDA's Report to Congress on the regulation review, FDA will continue to evaluate the need for regulatory changes on an ongoing basis. FDA expects to maintain open

communication with industry, members of Congress, and other stakeholders as appropriate, and we will continue to evaluate and address medical gas issues as needed.

The statutory deadline set in FDASIA to finalize any regulation changes that FDA has determined are necessary is July 9, 2016 (see FDASIA section 1112(b)). FDA will endeavor to meet that date for any such regulations.

17. Nanotechnology

The Committee recognizes the increased capabilities that FDA has developed to study environment, health, and safety of nanomaterials within FDA's Jefferson Laboratory Campus, including the National Center for Toxicological Research, and its consolidated headquarters at White Oak, Maryland. The Committee expects FDA to continue to support collaborative research with universities and industry on the toxicology of nanotechnology products and processes in accordance with the National Nanotechnology Initiative Environment, Health, and Safety Research Strategy as updated in October 2011.

FDA Response:
FDA has increased the capabilities to understand the health impact and safety of nanomaterials through increased training for FDA staff (lecture series, seminars, workgroups), increased research into the safety and disposition of nanomaterials in various products, increased collaboration with national and international agencies, and continued development of capabilities at the FDA's Jefferson Laboratory Campus in Arkansas and its consolidated headquarters at White Oak, Maryland.

The Collaborative Opportunities for Research Excellence in Science (CORES) Program is part of FDA's Nanotechnology Regulatory Science Research Plan and has funded 24 research projects since 2011. These projects align with the National Nanotechnology Initiative (NNI) Environment, Health, and Safety Research Strategy as well as the activities listed in Section 1126 of the Food and Drug Administration Safety and Innovation Act (Public Law 112–144).

To date, these projects have increased FDA knowledge on nanotechnology and provided essential baseline information that led to the development of regulatory science tools, including toxicity assays, assessment methodologies, and test protocols FDA uses to evaluate nanotechnology in FDA-regulated products.

Through these projects, FDA staff developed working knowledge of nanotechnology which they shared with FDA scientists and the scientific community through peer-reviewed journal articles and presentations at national and international scientific conferences. These projects increased collaboration across FDA and strengthened the agency's relationship with academia and across the U.S. government. The research findings from these projects proved vital in drafting regulatory guidance to industry and in providing sound and scientifically based responses to inquiries from stakeholders.

The continued development of the core-facilities at the Jefferson Laboratories and White Oak campuses have provided scientists at the FDA and other NNI agencies the appropriate tools to accurately detect and quantify nanomaterials in their research projects. Core-facility and other FDA scientists are participating in international efforts to develop standards and standard methodologies in support of regulatory science research and national and international development of regulatory guidance on nanotechnology-enabled products.

Together, the CORES program, development of core-facilities at Jefferson Laboratories and White Oak campuses, regulatory science-focused research projects within FDA, and training

through multiple modalities, has enhanced FDA's ability to understand and regulate nanotechnology-based products. FDA will continue to support collaborative research with universities and industry on the toxicology of nanotechnology products and processes in accordance with the National Nanotechnology Initiative Environment, Health, and Safety Research Strategy.

18. National Antimicrobial Resistance Monitoring System

The Committee recommendation includes $10,800,000 for the National Antimicrobial Resistance Monitoring System, equal to the level provided in fiscal year 2015.

FDA Response:
FDA will provide funding equal to FY 2015 levels as recommended by the Committee.

19. Nutrition Facts Label

The Committee is concerned that the FDA has not published in the Federal Register the results of FDA's ''Experimental Study on Consumer Responses to Nutrition Facts Labels with Various Footnote Formats and Declaration of Amount of Added Sugars'' (78 FR 32394, May 30, 2013). The purpose of the study, as described by the Agency, is ''to examine how consumers would comprehend and use this new information''. Given that sound science, peer review and transparency are essential to effective protection of public health, the Committee encourages the FDA to release this study for public review and comment prior to finalizing changes to the Nutrition Facts label.

FDA Response:
FDA provided the public the results of the "Experimental Study on Consumer Responses to the Nutrition Facts Labels with Declaration of Amount of Added Sugars" and the "Experimental Study on Consumer Responses to Nutrition Facts Labels with Various Footnote Formats" in the Federal Register of July 27, 2015 (80 FR 44303).

20. Opioid Overdose Prevention

The Committee notes that on June15, 2015, the CDC issued a report on ''Opioid Overdose Prevention Programs Providing Naloxone to Laypersons'', in which the CDC noted the benefits of expanding access to the life-saving drug naloxone, which reverses the effects of an opioid overdose. The Committee urges FDA to promote the development and widespread usage of naloxone products. The agency's efforts should include working closely with product sponsors interested in marketing naloxone for use without a prescription to expedite review and decision making.

FDA Response:
FDA continues to work to encourage the development of additional ways to administer naloxone and is supportive of appropriately broadening the use of naloxone, including discussions of over-the-counter (OTC) status and of studies that would appropriately assess its wider availability under appropriate circumstances. A little over three years ago, FDA partnered with other HHS agencies and laid out the pathway for the development and marketing of naloxone.

Naloxone has been a part of ONDCP's National Drug Control Strategy since 2012 and is a priority area in the recently announced initiative of the Secretary to address the complex problem of prescription opioid and heroin abuse. The Secretary's initiative emphasizes implementation strategies which include not only naloxone availability, such as Narcan nasal spray, the first FDA approved nasal naloxone product designed for administration by family members and caregivers

approved in November 2015, but better prescription practices and deployment of medication assisted treatment to treat opioid-use disorders. FDA has led two meetings with other HHS agencies that have explored the various issues around naloxone provision, including pharmacy availability, co-prescribing, use on ambulances and by other first responders, and over-the-counter status.

The availability of naloxone without a prescription would allow patients to obtain naloxone without contacting a physician for a prescription to bring to a pharmacy. If substantial data exist to support that consumers can appropriately select and safely use naloxone in an OTC setting without the assistance or training from a healthcare professional, the FDA encourages submission of these data to the Agency for review. Any application for OTC marketing of naloxone would be expected to meet FDA's criteria for priority review, which will help to expedite FDA's review of the data and a decision on the application.

FDA will continue to work to reduce the risks of opioid abuse and misuse, but we cannot solve this complex problem alone. A comprehensive and coordinated approach is needed; one that includes federal, state and local governments, public health experts, health care professionals, addiction experts, researchers, industry, and patient organizations.

21. Oversight Activities

The Committee notes that over the past 5 years FDA's responsibilities and resources have grown significantly. The Committee is concerned that oversight of FDA has not kept pace with the growth in the agency's regulatory authority or funding. Therefore, the Committee recommendation includes $1,500,000 for the HHS Office of Inspector General specifically for oversight of FDA activities. The funding provided under this appropriation is in addition to FDA oversight activities supported within the Inspector General's regular appropriation. The Committee instructs the Inspector General to submit a plan, within 60 days of the enactment of this act, on the additional oversight activities planned with this funding.

FDA Response:
HHS Office of Inspector General will provide the requested report.

22. Pediatric Device Consortia Grants

The Committee is pleased that the nine FDA-funded Pediatric Device Consortia have assisted in the development of more than 450 proposed pediatric medical devices since its inception in 2009, as well as promoting job-growth in the healthcare sector, and as such, continues to support this critical effort. The program funds consortia to assist innovators in developing medical and surgical devices designed for the unique needs of children that often go unmet by devices currently available on the market. The Committee directs FDA to fund this program at the highest possible level within available resources, and at no less than the level funded in the previous year.

FDA Response:
Since the program's inception in 2009, the pediatric device consortia have advised innovators on more than 620 potential pediatric devices – and assisted on more than 179 projects this past year. As a result of funding advice provided by the consortia, more than $ 90 million of additional funds have been raised to advance pediatric device projects affiliated with the consortia. Seven PDC-assisted pediatric medical devices are now being used in pediatric care, including Buzzy for relief of pain with needlesticks, Rhinoguard for assist in naso-tracheal intubation, and the Hypothermic Control Device head wrap for infants recovering from

hypothermia. Thus, the FDA intends to fund the Pediatric Device Consortia Grant Program at similar level as last year, with no less than $ 3 million dollars towards the program.

23. Repackaging for Long Term Care Pharmacies

In February the Food and Drug Administration released a draft guidance entitled, "Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities." The Committee is concerned that in issuing the draft guidance the agency failed to consider the unique nature of long term care pharmacies and the populations they serve. Before issuing a final guidance the Committee urges the agency to consider its implications on patient access to safe and effective medications from long term care pharmacies.

FDA Response:
FDA received 625 comments on the draft guidance, "Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities," mostly concerning long term care pharmacies and the facilities they serve. FDA also held a listening session in August 2015 with representatives of long term care facilities and the pharmacies that serve them to hear their views on FDA's proposed policies. FDA will consider all of the issues raised in the comments and input received during the listening session before finalizing the draft guidance.

24. Seafood Advisory

The Committee remains concerned that despite numerous commitments over many years, FDA has not published final advice on seafood consumption for pregnant women, mothers, and children. The Committee is pleased that FDA released draft advice in June 2014, however, pregnant women and healthcare providers still await clear, actionable and science-based final seafood advice. Based on the recommendation of the Dietary Guidelines Advisory Committee, the final FDA seafood advice shall re-evaluate the draft limit on albacore tuna to ensure it is consistent with the FDA net effects report and the Joint United Nations Food and Agriculture Organization/World Health Organization Expert Consultation on the Risks and Benefits of Fish Consumption, 2010. The Committee directs FDA to publish final advice to pregnant women on seafood consumption in conjunction with all applicable parties. Finally, FDA shall provide a progress report to the Committee 30 days after the enactment of this act and every 30 days thereafter until the final seafood advice is published.

FDA Response:
On June 10, 2014, FDA and EPA jointly issued a draft update to the seafood advice they last issued in 2004. The updated joint advice tracks the current recommendation in the Dietary Guidelines for Americans, issued by the Departments of Agriculture and Health and Human Services, in that it advises pregnant women, women who may become pregnant, and nursing women eat at least 8 and up to 12 ounces per week of a variety of fish lower in mercury in order to optimize the developmental benefits that fish could provide.

The two agencies announced that there would be at least one public meeting on the advice, to be held by the FDA Risk Communication Advisory Committee. For that reason, the public comment period, which opened on June 11, 2014, was indefinite until that meeting, and any other meeting, could be held. Specifically, FDA and EPA announced that the comment period would be open until 30 days after the last transcript from the advisory meeting and any other meetings that the agencies would hold on this subject became available.

The Risk Communication Advisory Committee met on the fish consumer advice on November 3-4, 2014 and the transcript from that meeting was subsequently made available. Since no other

public meetings are planned, FDA and EPA closed the comment period by publishing a notice in the Federal Register on February 24, 2015. The agencies have subsequently studied the public comments, made modifications to the advice where appropriate, and expect to publish the updated advice in 2016.

25. Seafood Economic Integrity

The Committee recognizes the importance of seafood to a healthy diet, but is concerned that the FDA does not focus sufficient attention on economic integrity issues, particularly with respect to mislabeling of species, weights, and treatment. The Committee encourages the FDA to work with States and the Department of Commerce to more aggressively combat fraud in parts of the seafood industry.

FDA Response:
FDA continues to invest in significant technical improvements to enhance our ability to identify seafood species using DNA sequencing. DNA sequencing capabilities greatly improve the Agency's ability to identify misbranded seafood products in interstate commerce. FDA is preparing to expand its DNA capabilities by releasing new test methodologies for detecting crustacean DNA, allowing for species substitution analysis of shrimp, crab and lobster.

FDA works toward implementing better-targeted and more efficient sampling strategies to identify seafood misbranding and adulteration and is currently conducting an evaluation of retail seafood counter substitution with the assistance of multiple states and their respective inspection agencies. FDA is currently a part of the new Presidential Task Force established to combat IUU Fishing and Seafood Fraud; and as such works closely with several agencies such as DOC-NOAA and DHS-CBP to help better target fraudulent activities.

26. Sodium

The Committee is concerned about FDA's continued focus on voluntary sodium reductions and the Institute of Medicine's [IOM] 2010 recommendation to modify the Generally Recognized as Safe [GRAS] status of sodium, particularly given the ongoing scientific discussion regarding appropriate sodium intake to maintain positive health. The IOM published a more recent study in 2013, which concluded additional research may provide further information with respect to the health effects of sodium intake on general and sub populations. The Committee recommends that a panel be convened, at the IOM or another leading Federal institution, which includes a representative array of research perspectives, including those who have raised concerns on the safety of low-sodium diets. The Committee does not believe any sodium reduction activities should be finalized until the disagreement between the impact of lower sodium on blood pressure (and an extrapolation to health) and direct research suggesting a negative impact of very low-sodium intakes is resolved.

FDA Response:
Americans are consuming excess sodium, which contributes to increased risk of hypertension, a primary contributor to stroke and heart disease. FDA and its federal partners have been focusing on voluntary reductions to move from a current sodium intake of about 3,400 milligrams (mg) in the U.S. to a value closer to 2,300 mg per day. About 75 percent of sodium in the diet is estimated to be added during the manufacturing of foods and preparation of restaurant foods, making it difficult for consumers to reduce their sodium intake (Anderson et al., 2010; Mattes and Donnelly, 1991). Encouraging industry to reduce sodium in products so consumers have

more options does not require bringing consumers into an excessively low sodium intake range. U.S. government efforts are not focused on reducing sodium to below 2,300 mg per day.

The 2013 IOM report entitled *Sodium Intake in Populations: Assessment of Evidence* reaffirmed that sodium intake levels are too high and should be reduced to 2,300 mg per day. This recommendation is also supported by the Scientific Report of the 2015 Dietary Guidelines Advisory Committee (DGAC), which thoroughly considered the 2013 IOM Sodium Report and other evidence in their review, and also the 2015-2020 Dietary Guidelines for Americans.

FDA is aware of recent observational studies (Stolarz-Skrzypek et al., 2011, O'Donnell et al., 2011; O'Donnell et al., 2014; Graudal et al., 2014) that are inconsistent with the large body of evidence that consistently shows a dose-response relationship between sodium intake and blood pressure (Aburto et al., 2013; Sacks et al., 2001; He et al., 2013, Mozaffarian et al., 2014; Eckel et al., 2014).

Results of these recent observational studies suggest low- and high-sodium intakes are associated with cardiovascular disease (CVD) events or deaths, and are inconsistent with other observational studies showing lower-sodium intake is associated with lower risk of CVD (Cook et al., 2014; Poggio et al., 2015).

Like other studies reviewed by IOM in 2013 and an American Heart Association Scientific Advisory Committee in 2014 (Cobb et al., 2014), these studies have major limitations in the selection of participants and/or measurement of sodium intake. Expert review of these studies by FDA and the Centers for Disease Control and Prevention indicate that these recent observational studies do not shift the weight of evidence.

High blood pressure is a leading risk factor for heart disease and stroke (Stamler et al., 1993; Kannel et al., 1996; van den Hoogen et al., 2000; O'Donnell et al., 1997, Prospective Studies Collaboration, 2002). Reducing average sodium intake in the U.S. population can reduce blood pressure and save tens of thousands of deaths and billions of health care dollars each year (Coxson et al., 2013; Bibbins and Domingo, 2010; Huang et al., 2014a).

27. Sunscreen

The Committee is aware that in July 2014, the U.S. Surgeon General issued A Call to Action to Prevent Skin Cancer, concluding nearly 5 million people are treated annually for all skin cancers combined, with an estimated cost of $8,100,000,000 per year. As a result, the Surgeon General called on the Federal Government to work with stakeholders to support skin cancer prevention. The Committee is pleased with the bipartisan reforms enacted in the Sunscreen Innovation Act [SIA] in 2014 to improve the process by which the FDA reviews sunscreen ingredients; however, the Committee is concerned that while skin cancer rates in the United States continue to climb, no new sunscreen ingredients have been generally recognized as safe and effective [GRASE] by the FDA since passage of the SIA. The Committee directs the FDA to provide a report that contains a detailed analysis of how FDA is balancing the Surgeon General's Call to Action, the known public health benefits that regular sunscreen use provides to prevent skin cancer and melanoma, and the long history of safe and effective use of sunscreens in comparable countries versus the hypothetical risk sunscreens posed to human health in FDA's generally recognized as safe and effective [GRASE] standard. Immediate action on sunscreen applications should be a priority. In addition, the Committee directs the FDA to work with stakeholders to ensure consumers in the United States have access to all sunscreen products that have been shown to be safe and effective; and therefore, requests that FDA, in finalizing the sunscreen

monograph consistent with the SIA, include provisions related to the maximum Sun Protection Factor [SPF] and to address spray dosage forms for sunscreens.

FDA Response:
The Sunscreen Innovation Act (SIA) imposes on FDA strict deadlines for making determinations about the generally recognized safe and effective (GRAS/E) status of these ingredients. It does not relax the scientific standards for evaluating safety and effectiveness or the requirement for sponsors to provide adequate data on which to base a GRAS/E determination.

A large increase in the amount and frequency of sunscreen usage, together with advances in scientific understanding and safety evaluation methods, has given rise to new questions about what information is necessary and available to support general recognition of safety and effectiveness of nonprescription sunscreen active ingredients. In particular, certain potential risks from long-term, regular exposure to sunscreen active ingredients cannot be detected or evaluated on the basis of commercial marketing experience.

FDA's expectations for safety and effectiveness data for nonprescription sunscreen active ingredients which are being considered through the SIA process are set to ensure consumers have access to sunscreens that are safe and effective, and are consistent with modern scientific thinking concerning safety and effectiveness of sunscreens.

As per the timelines in the SIA, FDA has completed reviews for all pending Time and Extent Applications for review of nonprescription sunscreen active ingredients and has tentatively determined that the pending sunscreen active ingredients are not GRAS/E for use in OTC sunscreens because the data are insufficient. FDA described certain data the Agency needs to determine that a nonprescription sunscreen active ingredient is GRAS/E and not misbranded in the proposed sunscreen orders it has issued under the SIA for each of the pending requests regarding nonprescription sunscreen active ingredients. The data described are in line with the safety data FDA is currently seeking for other topical nonprescription active ingredients under the OTC drug monograph system and for both topical prescription and nonprescription drugs seeking approval under the new drug application (NDA) process.

In addition, FDA has held public meetings with sponsors of pending requests for nonprescription sunscreen active ingredients to discuss data requirements and has issued draft guidance, as required by the SIA, to further delineate safety and effectiveness data needed to make a GRAS/E determination for a nonprescription sunscreen active ingredient. No data have been received, and there are no timelines imposed by the SIA for industry to submit this data. FDA looks forward to receiving and reviewing necessary industry data on which to base a (GRAS/E) determination.

FDA is committed to doing its part to provide American consumers with additional options for safe and effective nonprescription sunscreen active ingredients. However, FDA relies on industry to submit the data needed for review in order to support a GRAS/E determination. Americans deserve sunscreen products that are shown to be safe and effective. FDA has proposed data requirements that will allow us to determine that active sunscreen ingredients are generally recognized as safe and effective for use in nonprescription sunscreens. These data requirements were unanimously supported by a panel of scientific experts at a September 2014 public Advisory Committee meeting on sunscreens.

28. Vibrio

The Committee is aware of the public health challenge related to the naturally occurring bacteria called Vibrio parahaemolyticus (V.p.) that can accumulate in shellfish and believes that more scientific research is necessary to developing proper controls that will reduce the risk to consumers and sustain a healthy domestic shellfish industry. The Committee encourages the Food and Drug Administration [FDA] to increase funding for research into Vibrio illnesses associated with the consumption of raw molluscan shellfish, improve risk assessment models, and develop improved rapid detection methods for virulent Vibrio strains.

FDA Response:
FDA is aware of, and actively engaged in activities aimed at reducing, the risk that *Vibrio parahaemolyticus* (*V.p.*) poses to consumers of raw oysters and clams. Through participation in the Interstate Shellfish Sanitation Conference (ISSC), the FDA has been able to, over time, incorporate increasingly stringent time and temperature controls within the National Shellfish Sanitation Program (NSSP) Model Ordinance, which sets the standards and controls for implementation by state health authorities and the shellfish industry for controlling the safety of raw molluscan shellfish safety, including *V.p*.

By reducing time from harvest to temperature control and then the time from temperature control to an internal product temperature of 50°F, the post-harvest growth of *V.p.* can be limited, resulting in reduced risk in the final product. However, the cost of time/temperature control can be a significant challenge to the industry. To help develop the most effective time/temperature controls, FDA continues to participate in a number of collaborative efforts with state health authorities and the shellfish industry.

Each year FDA awards a grant to the ISSC. The grant serves to ensure that, in the U.S., the safety net for molluscan shellfish is consistently and uniformly managed at the state and industry level with administrative oversight from FDA. The grant also supports ongoing ISSC efforts to examine the science of *V.p.* and develop control measures aimed at reducing the risk of *V.p*. This is done through a collaborative effort among federal, state and industry partners to establish *V.p.* control standards in the NSSP Model Ordinance.

Recognizing the need for ongoing research to define effective and reasonable industry practices for controlling *V.p.*, FDA has awarded additional funding to the ISSC to support independent studies conducted by state shellfish authorities. The first round of funding, awarded in 2014, is supporting studies by three states (WA, NJ, CT) aimed at defining science-based industry practices to reduce the risk of *V.p.* in raw molluscan shellfish. Completion of those studies is expected in 2016. In further support of this effort, FDA again awarded funding to the ISSC in 2015 to support continued research intended to enhance our understanding of *V.p.* and how current and innovative industry practices impact and may reduce risk.

FDA works directly with the ISSC *Vibrio* Management Committee and the CDC to examine the incidence of *V.p.* illness and to engage the ISSC to adopt improved controls into the NSSP.

FDA works directly with state shellfish industry members to develop and implement shipboard controls to reduce risk through rapid onboard cooling techniques. Through this effort, FDA has seen a number of industry members implement controls that exceed those currently established in the NSSP and which have achieved significant additional illness reduction.

FDA has established a Workgroup on Ecological Forecasting for *Vibrio*. The goal for establishing the workgroup is to coordinate, plan, prioritize, and communicate ecological

forecasting activities related to *Vibrio* within and beyond FDA. Specifically, FDA is collaborating with NOAA under their Ecological Forecasting Roadmap to develop experimental *Vibrio* forecast products (among others) using FDA's risk models and NOAA's environmental data and hydrodynamic models. It is anticipated that the FDA-NOAA collaboration, with the engagement of other key federal, state, industry, and academic partners, will result in enhanced and regionally-specific forecasting tools for *Vibrio* risk assessments.

FDA continues to offer a program to extend research and technical assistance on *Vibrio* to states and industry through the *Vibrio* Assessment Review Board (VARB). States and industry can submit to FDA's VARB requests for research and technical assistance aimed at improving the science and control of *Vibrio* in molluscan shellfish. Through the VARB, FDA offers, as resources allow, assistance such as laboratory support, technical expertise, and statistical application to aid states and industry as they undertake independent *Vibrio* projects.