SENATE APPROPRIATIONS COMMITTEES SIGNIFICANT ITEMS

SENATE COMMITTEE REPORT (S. 115-131)

1. Atypical Actives

The Committee requests that the FDA provide an update on how it regulates ''atypical actives.''

FDA Response:

FDA does not have an official definition for the term "atypical actives;" however, an atypical active is generally understood to mean an excipient, food additive, or cosmetic ingredient used as an active ingredient in pharmaceutical products.

The safety and quality of atypical actives are covered by the same policies applicable to all active pharmaceutical ingredients (API) in marketed drugs, including those with approved drug applications or those conforming to an over-the-counter (OTC) drug monograph. The definition of a "drug" under section 201(g)(1)(D) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) includes "articles intended for use as a component" of a drug. Section 501(a)(2)(B) of the FD&C Act states that a drug shall be deemed to be adulterated if a drug's "manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice [CGMP] to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." Section 501 further states that the meaning of CGMP "includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."

The agency has not promulgated CGMP regulations specifically for APIs or excipients; however, with the International Conference on Harmonisation (ICH), the agency has published a guidance document regarding good manufacturing practices (GMP) for the manufacturing of APIs entitled ICH Q7 *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.*[112] The guidance is "intended to help ensure that APIs meet the quality and purity characteristics that they purport, or are represented, to possess." As stated in the guidance document, firms may use alternative approaches if they satisfy the requirements of applicable statutes and regulations. Accordingly, firms may employ other approaches for atypical actives if they can demonstrate they meet the requirements of 501(a)(2)(B).

2. Autoantibody Qualification

The appearance of certain islet autoantibodies in the serum of individuals increases the chance of developing type 1 diabetes at some point in the future. Therefore the Committee encourages the FDA to work with the Type 1 diabetes community on the assessment of potential diabetes biomarkers related to islet autoimmunity, which might help inform the design of clinical studies.

FDA Response:

Biomarkers of islet autoimmunity that can be shown to accurately and reliably predict an individual's future risk of Type 1 diabetes would be valuable. Such biomarkers could enhance clinical care by enabling healthcare professionals to potentially identify at-risk individuals,

[112] www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf.

prevent or delay disease onset, and manage the disease. Such biomarkers could also inform the planning and design of clinical studies, and the evaluation of Type 1 diabetes therapeutics.

The FDA is committed to working with stakeholders to make safe and effective drugs to treat diabetes available to patients with this condition and last year sponsored a workshop in collaboration with diabetes professional organizations, healthcare providers, researchers and other advocates of patients with diabetes. The purpose of the workshop was to have a forum for dialogue with the public, patients, patient advocacy groups and industry to gain greater appreciation of the extent to which the current regulatory paradigm for antidiabetic drug therapies addresses the needs of patients with diabetes.[113]

In addition, the 21st Century Cures Act established a statutory framework for the qualification of drug development tools (DDTs), including biomarkers. This authority allows the agency to work with submitters as they develop or refine a DDT that, once qualified for a context of use, can be used by anyone to develop new drugs in a particular area. FDA hopes that this will be a useful tool in many areas in need of improved treatments, including diabetes.

3. Botanical Dietary Supplements Research

The Committee appreciates the work CFSAN has done to ensure the safety of botanical dietary supplements. Existing work to develop authentication and identification tools for evaluation of botanical supplements is promising, and the Committee directs the Center to invest further in this important research.

FDA Response:

In 2001, CFSAN established a highly successful cooperative agreement with the National Center for Natural Products Research (NCNPR) at the University of Mississippi to promote the efficient development and dissemination of natural products research and science. The programs developed under this agreement, which relate to FDA-regulated commodities such as dietary supplements and cosmetics, complement the diverse activities of both public and private sectors. The cooperative research, education, and outreach programs developed by NCNPR address scientific issues related to the identity and safety of botanical dietary ingredients. FDA values NCNPR's contributions and intends to continue to work closely with the principal investigators at NCNPR on the development of additional projects.

Additionally, CFSAN's Office of Dietary Supplement Programs, the Office of Regulatory Science, and Office of Applied Research and Safety Assessment, and the Department of Health and Human Services work together on research focused on identity and safety concerns with botanical dietary supplements.

4. Botanical Drug and Drug Interactions

The Committee commends CDER for its work to ensure that botanical drugs available to the public are safe and effective. However, little is known about potential drug interactions caused by botanical drugs, and given the recent publication of the Botanical Drug Development Guidance for Industry, the Committee is concerned that this will likely catalyze additional applications for approval of botanical drugs. Therefore, the Committee directs the FDA to invest in this research

[113] www.fda.gov/AdvisoryCommittees/Calendar/ucm499281.htm

by working with its Center of Excellence network partners with expertise in developing analytical methods and reference standards for botanical formulations.

FDA Response:

Botanical drugs have a number of unique characteristics that may pose challenges during drug development. The goal of the Botanical Drug Development Guidance for Industry is to provide a practical and feasible approach to support sponsors who are working to develop botanical drugs and ensure the safety, efficacy, and quality of these drugs. The guidance describes CDER's current thinking on appropriate development plans to be submitted in new drug applications (NDAs) and includes specific recommendations on submitting investigational new drug applications in support of future NDA submissions.

The guidance also includes analytical methods and reference standards for quality control of botanical drug products. In addition, raw material control, manufacturing process control, bioassays, as well as in vitro and in vivo drug-drug interaction studies will play important roles to ensure batch-to-batch consistency and reduce the potential risks of drug-drug interactions. The guidance specifically recommends that sponsors evaluate the potential for interactions with drugs or other botanicals.

Currently, two botanical prescription drugs are approved: Veregen (sinecatechins) for the treatment of genital warts; and Fulyzaq (now known as Mytesi, crofelemer) for the treatment of HIV/AIDS related diarrhea. Numerous other botanical products are currently being investigated in various phases of clinical trials with the eventual goal of seeking FDA approval and providing additional options for disease management.

Since 2001, the Center of Excellence for Botanical Dietary Supplement Research at the National Center for Natural Products Research (NCNPR) at the University of Mississippi has worked with FDA to develop analytical methods and reference standards for botanical formulations sold as dietary supplements in the U.S. CFSAN is the lead liaison for FDA, while CDER interacts with CFSAN and the Center of Excellence for Botanical Dietary Supplement Research at the National Center for Natural Products Research (COE) on botanical drug quality related issues. In addition, the newly established FDA-wide Botanical Natural Products Special Interest Group will work closely with the COE in order to leverage their botanical expertise and laboratory resources.

5. Caloric Content

The Committee is concerned that the FDA Nutrition Facts Label final rule does not include specific requirements for certain carbohydrates that may have insignificant or no caloric content. Consumers generally rely on the caloric information provided on food and beverage labels. The Committee is aware that the FDA is working to provide additional information for food manufacturers clarifying how certain carbohydrates, as appropriate, that may have insignificant or no caloric content should be labeled. The Committee urges the FDA to provide clarity to food manufacturers on the labeling of such carbohydrates, as appropriate.

FDA Response:

FDA has issued draft guidance documents on dietary fibers, added sugars, and Reference Amounts Customarily Consumed (RACCs) to assist industry in complying with the Nutrition Facts Label (NFL) final rule and is working to finalize these guidance documents

expeditiously.[114] FDA is also actively working on additional guidance documents on other NFL topics. The agency plans to issue additional information to clarify for industry the labeling of carbohydrates that may have insignificant or no caloric content.

On October 2, 2017, FDA proposed to extend the compliance dates for the NFL/SFL (Supplement Facts Label) and serving size final rules to provide additional time for implementation.[115] The proposed rule would extend the compliance dates from July 26, 2018, to January 1, 2020, for manufacturers with $10 million or more in annual food sales. Manufacturers with less than $10 million in annual food sales would have until January 1, 2021, to comply.

The comment period on the proposed rule closed on November 1, 2017.[116] FDA is considering all comments received concerning the compliance date and is working expeditiously to finalize the rule on the compliance date extension. The agency is committed to issuing final guidance on NFL-related topics noted above on a timeline that will ensure industry has sufficient time to comply with the new requirements. FDA may consider whether, under some circumstances, it should consider exercising enforcement discretion pending further rulemaking.

6. Center for Safety and Nutrition Centers of Excellence

The Committee is aware of the important contribution of the FDA Center for Food Safety and Applied Nutrition's Centers of Excellence [COEs] program in supporting critical basic research as well as facilitating the implementation of the FDA Food Safety Modernization Act. The Committee encourages the Agency to continue to fully utilize the COEs to accomplish these goals, and instructs that it enhance its level of support for FDA Food Safety Modernization Act activities.

FDA Response:

FDA appreciates the recognition of the importance of the agency's Centers of Excellence (COEs), their contributions to critical basic research, and their role in facilitating the FDA Food Safety Modernization Act (FSMA) implementation. FDA plans to continue utilizing COEs, including supporting their contribution to FSMA implementation activities.

7. 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. The Committee believes that these programs will help the Agency improve public health, address scientific challenges presented by revolutions in medical product development, and improve food safety and quality. The

[114] Draft Guidance for Industry: Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30): https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm528532.htm, Draft Guidance for Industry: Questions and Answers on the Nutrition and Supplement Facts Labels Related to the Compliance Date, Added Sugars, and Declaration of Quantitative Amounts of Vitamins and Minerals: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm535371.htm Draft Guidance for Industry: Reference Amounts Customarily Consumed: List of Products for Each Product Category: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm535368.htm

[115] https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm385663.htm

[116] Food Labeling: Revision of the Nutrition and Supplement Facts Labels and Serving Sizes of Foods That Can Reasonably Be Consumed at One Eating Occasion; Dual-Column Labeling; Updating, Modifying, and Establishing Certain Reference Amounts Customarily Consumed; Serving Size for Breath Mints; and Technical Amendments; Proposed Extension of Compliance Dates: https://www.federalregister.gov/documents/2017/10/02/2017-21019/food-labeling-revision-of-the-nutrition-and-supplement-facts-labels-and-serving-sizes-of-foods-that

Committee commends the Agency for launching this program in 2011 and expanding it in 2014. For this reason, the Committee believes that the Agency should continue to invest in the existing locations in the CERSI network at their original funding level for a period of at least 5 years to ensure their efficacy and to capitalize on existing studies.

FDA Response:

FDA appreciates the recognition of the importance of the Centers of Excellence in Regulatory Science and Innovation, and their contributions to regulatory science. FDA plans to support four CERSIs in the future within the parameters of their existing or new grant awards.

8. Cotton Ginning

The Committee is concerned about the impact of the ''Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Food for Animals'' final rule (80 FR 56170; September 17, 2015) on the cotton industry. The Committee notes post-harvest activity of ginning cotton does not transform the resulting cottonseed into a ''processed food,'' and thus, cottonseed should fall within the definition of a ''raw agricultural commodity'' for purposes of rules promulgated pursuant to the FSMA. In addition, the Committee is concerned about the rationale for the definitions of ''primary production farm'' and ''secondary activities farm'' and how these definitions factor into the determination of operations either being exempt from or covered by certain requirements of the final rule. Therefore, the Committee directs the FDA to provide outreach and technical assistance to cotton ginning operations to assist them in complying with the final rule or subsequent guidance documents.

FDA Response:

FDA is aware of the cotton ginning industry's concerns regarding whether certain entities are classified as farms or facilities. The agency also is aware of their concern related to whether ginning results in a "processed food." FDA is examining the farm definition and will consider the concerns of the cotton ginning industry in that evaluation. To facilitate this effort, the agency extended the compliance dates for cotton ginners to January 28, 2019, or later depending on business size to provide FDA time to consider the issues raised by the industry. Please see the following webpage for more information about the compliance date extensions: www.fda.gov/Food/GuidanceRegulation/FSMA/ucm517545.htm.

FDA has had multiple meetings with the cotton ginning industry on this topic. FDA representatives met with them in August 2017. FDA staff subsequently participated in an educational tour with representatives from the cotton ginning industry, cotton farmers, the Alabama Department of Agriculture and Industries, and Rep. Robert Aderholt's office.[117] During the meetings and the educational tour, FDA reiterated its commitment to resolve the cotton ginning industry's concerns about the applicability of the PCAF rule to ginning operations prior to the extended compliance date. In the meantime, FDA has committed to a continuing dialogue with the cotton ginning industry as the agency works to address these concerns. FDA will continue to provide outreach and technical assistance, such as through meetings, to the cotton ginning industry to assist them in complying with the PCAF rule.

[117] https://blogs.fda.gov/fdavoice/index.php/2017/11/talking-fsma-in-the-land-of-cotton-and-looking-for-middle-ground/

9. Dietary Fiber

The Committee is concerned that the FDA has not issued final guidance regarding the definition of dietary fiber, and encourages the FDA to issue these final guidance documents and provide sufficient time for food manufacturers to comply.

FDA Response: FDA is committed to working with manufacturers covered by the Nutrition and Supplement Facts Labels (NFL/SFL) and serving size final rules, published on May 27, 2016, to understand the time needed to complete and print updated NFLs/SFLs for their products before they are expected to be in compliance.
FDA defined dietary fiber to ensure that the amount of non-digestible carbohydrates declared as dietary fiber on the NFL/SFL will assist consumers in maintaining healthy dietary practices. A non-digestible carbohydrate must provide a beneficial physiological effect to be declared as a dietary fiber on the NFL/SFL. The definition does not prevent companies from continuing to add a non-digestible carbohydrate to a food product, even if the ingredient does not meet the new definition of dietary fiber; in that circumstance, the added non-digestible carbohydrate would be declared as Total Carbohydrate only.

FDA received 12 citizen petitions asking the agency to amend the definition of "dietary fiber" to include specified ingredients in the definition as dietary fibers. FDA is reviewing these petitions as expeditiously as possible. After FDA completes its scientific review, it will notify the petitioners concerning the agency's decision. For those non-digestible carbohydrates for which FDA's determination is that they meet the new "dietary fiber" definition, the agency intends to amend the regulatory definition by adding those non-digestible carbohydrates to the existing list of dietary fibers.

As FDA works to complete the petition review process, stakeholders who use isolated or synthetic non-digestible carbohydrates have expressed a need for clarity from FDA, and the need for clarity has also resulted in requests to extend the NFL/SFL compliance dates.

On October 2, 2017, FDA proposed to extend the compliance dates for the NFL/SFL and serving size final rules to provide additional time for implementation. The proposed rule would extend the compliance dates from July 26, 2018, to January 1, 2020, for manufacturers with $10 million or more in annual food sales. Manufacturers with less than $10 million in annual food sales would have until January 1, 2021, to comply.

The comment period on the proposed rule to extend the compliance date closed on November 1, 2017. FDA is considering all comments received concerning the compliance date. FDA's goal is to complete the rulemaking as quickly as possible. The agency is committed to issuing final guidance on NFL-related topics, including dietary fiber, on a timeline that will ensure industry has sufficient time to comply with the new requirements. FDA intends to consider whether, under some circumstances, it should consider exercising enforcement discretion pending further rulemaking.

10. Dietary Ingredients Guidance

The Committee encourages FDA to meet with representatives of the supplement industry as well as consumer groups and to review all comments received regarding the ''Dietary Supplements: New Dietary Ingredient [NDI] Notifications and Related Issues'' guidance.

FDA Response:

On August 11, 2016, FDA published a revised draft guidance entitled "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" (FDA-2011-D-0376).[118] The purpose of this revised draft guidance is to help companies decide whether to submit a premarket safety notification to FDA for a product that is, or contains, a new dietary ingredient (NDI). The revised draft guidance is also intended to provide recommendations on how to conduct a safety assessment for an NDI and to help companies improve the quality of their NDI notifications. In response to stakeholder requests, FDA extended the initial comment period to December 2016. FDA currently is reviewing more than 300 comments on the revised draft guidance. As with any draft or final guidance document, FDA will accept comments at any time; the agency suggests a comment period for draft guidance documents to encourage stakeholders to respond in a time frame that allows the agency to most efficiently and effectively review and consider the information submitted. FDA does not implement draft guidance; the final guidance may vary from the draft, depending on the comments and information submitted.

FDA is committed to addressing issues raised in comments and during stakeholder meetings and continues to devote significant resources to stakeholder engagement. FDA has met with representatives from the dietary supplement industry, including firms and trade associations, as well as representatives from consumer groups, to discuss specific issues relating to the revised draft NDI guidance. The agency also is examining whether there are specific issues for which additional stakeholder engagement might enable us to more effectively work towards finalizing the guidance. For example, on October 3, 2017, FDA held a public meeting to discuss development of a list of pre-Dietary Supplement Health and Education Act dietary ingredients, a topic that was mentioned in a number of comments on the revised draft guidance. The agency also has planned stakeholder meetings to discuss implementing a system for accepting master file submissions, another topic that was raised in the comments.

11. Fatal and Debilitating Diseases

The Committee directs the FDA to exercise its current law authorities, as provided under the FDA Safety and Innovation Act and the 21st Century Cures Act, when reviewing new drug applications for patients with 100 percent fatal and debilitating diseases. The Committee further encourages the FDA to afford patients, caregivers and treating physicians the opportunity to participate in the drug review process.

FDA Response:

FDA agrees that patient experience data can play an important role in the development of new drugs. The agency agreed to a systematic effort to learn more about patient experience under PDUFA V and has been able to commit more staff to expand its activities dedicated to providing review divisions with greater patient input. FDA has held a number of public meetings as part of its Patient Focused Drug Development Initiative (PFDDI) and found them very informative. The agency believes that, in addition to these meetings, it is important to develop validated methods and standards that will facilitate the incorporation of patient input in the drug development and review process.

[118] https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/dietarysupplements/ucm257563.htm

The agency is also working to implement the patient-focused drug development provisions included in the 21st Century Cures Act. In May 2017 FDA published a 5-year plan for the issuance of draft and final patient-focused drug development guidances and workshops, including one held on December 18, 2017, "Public Workshop on Patient-Focused Drug Development: Guidance 1 - Collecting Comprehensive and Representative Input."[119] At this workshop, FDA obtained feedback from stakeholders including patients, caregivers, patients' advocates, researchers, practitioners, drug developers and others, on considerations for: (1) standardized nomenclature and terminologies for patient-focused drug development; (2) methods to collect meaningful patient input throughout the drug development process; and (3) methodological considerations for data collection, reporting, management, and analysis of patient input.

FDA believes that methods and approaches to the collection of relevant and objective patient data should be developed; that the guidance process is an appropriate means of developing and disseminating such information to drug developers, patients and their advocates; and that public meetings are an effective means for gathering information from varied stakeholders.

Regarding patients with 100 percent fatal and debilitating diseases, many factors may be considered in the drug approval process, including the nature and severity of disease for which a drug would be indicated and whether other safe and effective treatments are available. The provisions in the FDA Safety and Innovation Act and the 21st Century Cures Act reinforce the agency's longstanding commitment to regulatory flexibility regarding the evidence required to support product approval for the treatment of serious or life-threatening diseases with limited therapeutic options.

The Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) published a guidance in 2014 on Expedited Programs for Serious Conditions – Drugs and Biologics. This guidance addresses the various expedited development and review programs available to drugs and biologics intended for serious or life-threatening conditions, including accelerated approval (and the use of surrogate and intermediate endpoints to support accelerated approval), fast track designation, priority review, and breakthrough designation, a very successful program that was established in the FDA Safety and Innovation Act in 2012.

FDASIA created section 506(a) of the FD&C Act, which enables FDA to designate certain drugs as "breakthrough therapies" if (1) the drug is intended to treat a serious or life-threatening disease or condition AND (2) preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Breakthrough therapy designation enables sponsors to receive intensive FDA guidance on an efficient drug development program, an organizational commitment to intensively involving senior managers and experienced review staff, and rolling review of its application, as well as any other expedited programs (e.g., priority review) for which the drug might qualify.

Building on the FDA's existing expedited programs, which have always been available to eligible regenerative medicine products for serious conditions, the Regenerative Medicine Advanced Therapy (RMAT) Designation was established though the 21st Century Cures Act in December 2016. In November 2017, CBER published a draft guidance (Expedited Programs for

[119] www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf

Regenerative Medicine Therapies for Serious Conditions), which supplements the 2014 Expedited Programs guidance and provides information about all of the expedited programs available for regenerative medicine therapies, including the new RMAT designation program.

The agency has been applying its expedited programs, including breakthrough therapy designation and RMAT designation, as well as its fast track, priority review, and accelerated approval authority, to all applications meeting the criteria, including any such applications for drugs to treat 100 percent fatal and debilitating diseases.

In addition, in 2016, FDA took a number of actions to streamline expanded access, also known as "compassionate use," which provides a pathway for patients to gain access to certain investigational drugs, biologics and medical devices for serious diseases or conditions.

12. Food Safety Mission

The Committee directs the FDA Foods Program to report to the Committee all activities and resources spent on nutrition-related activities for the Center for Food Safety and Applied Nutrition [CFSAN], associated field offices [ORA], and support components.

FDA Response:

The FDA Foods Program works to ensure that the nation's food supply is safe, sanitary, wholesome, and honestly labeled, and that nutrition labeling is informative and accurate. Nutrition information obtained through the labeling of food is a key tool for advancing public health by allowing consumers to build healthy dietary patterns and avoid obesity and diet-related chronic diseases such as heart disease and diabetes. In September 2017, FDA Foods Program leadership met with Senate Committee staff to discuss activities and resources related to nutrition. If the Committee would like additional information, the Foods Program, including Center and Field components, would be happy to offer another briefing.

13. Food Safety Modernization Act

The Committee is aware that some states that have entered into cooperative agreements under the State Produce Implementation Cooperative Agreement Program to provide education, outreach, and technical assistance are considering changing the state agency responsible for implementing these agreements. The Food and Drug Administration is directed to work with any state that designates a new implementing agency to ensure it can continue to receive funding under existing cooperative agreements without delay or loss of funding.

FDA Response:

FDA is aware of several states that are considering changing the grantee (funded) state agency under the State Produce Implementation Cooperative Agreement Program. FDA has been in discussions with both current and potential grantee state agencies. As of October 2017, FDA has not received formal requests to change the grantee state agency. If received, FDA will follow the appropriate grants policies and procedures to change the grantee state agency without delay or loss of funding.

14. Foreign High Risk Inspections

The Committee has provided robust funding for this initiative over the last several years and directs the FDA to provide an update on these efforts, including estimated efficiencies and concerns, and plans to continue or expand this effort in the future.

FDA Response:

The Committee provided robust funding for foreign site verifications of high risk facilities which provided FDA with additional data on entities of interest. This funding enabled FDA to better identify foreign food facilities, with a goal of reducing "washout" inspections. The funding is also of value in the medical device space, which has seen a boom in manufacturing of devices and device components in emerging economies. FDA does, however, face obstacles in expanding the program. To identify data that best expands FDA's coverage of pharmaceutical products, FDA needs to seek a Paperwork Reduction Act waiver. In addition, many of the sites identified for in-person verification are in China, where it is difficult to perform this work.

15. FSMA Clarification for Small Farms

The Committee directs the FDA to provide further clarification to small farms on the requirements for compliance with the Food Safety Modernization Act, including information on the qualified exemptions available to small and very small farms and the actions required to achieve compliance under these exemptions. The Committee also urges the Food and Drug Administration to communicate with (including through appropriate guidance) and offer technical assistance to assist small farms with compliance.

FDA Response:

FDA is committed to ensuring that farms, in particular small and very small farms, have the assistance they need to understand and comply with the rules issued under the FDA Food Safety Modernization Act (FSMA). In September 2017, FDA issued a small entity compliance guide on the FSMA Produce Safety Rule, intended to assist small and very small farms to better understand the rule. The guidance provides the definitions for small and very small businesses and explains the qualified exemption provision. Thus, the small entity compliance guide can help farmers determine whether they are eligible for a qualified exemption, which would modify the requirements they are subject to under the Produce Safety Rule[120]. In addition, FDA has issued small entity compliance guides for the current good manufacturing practice, hazard analysis, and risk-based preventive controls regulations for both human food and animal food that can help small and very small farms that also engage in on-farm manufacturing and processing.

FDA has engaged in other activities intended to provide technical assistance to farmers on the requirements of the Produce Safety Rule and how to comply. For example, the FSMA Technical Assistance Network is a central source of information for questions related to FSMA rules, programs, and implementation strategies, including for small and very small farmers, who have questions on complying with the Produce Safety Rule. FDA - along with USDA and Cornell University - created a Produce Safety Alliance (PSA) to develop and deliver training on the produce safety regulation requirements that would be of particular assistance to small and very small farms. PSA training courses have been available since Fall 2016. FDA also awarded a cooperative agreement, called the Local Food Producer Outreach, Education, and Training to Enhance Food Safety and FSMA Compliance Cooperative Agreement, intended to address small entities, in August 2016. The cooperative agreement is intended to develop and provide science-based, culturally specific food safety training, education, and outreach for local food producers and processors.

[120] https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm574281.htm

16. Grape Varietals

The Committee is aware that the FDA has excluded certain produce that is rarely consumed raw from having to comply with the FSMA Produce Safety Final Rule entitled ''Standards for Growing, Harvesting, Packing, and Holding of Produce for Human Consumption.'' There is concern that the FDA did not distinguish between grape varietals that are consumed raw and those that are grown, harvested and used for wine and further processing. The Committee directs the FDA to consider any relevant distinctions between grape varietals, including grape varietals from different regions, that may provide additional flexibility to wine grape growers in demonstrating a product is eligible for exemption or exclusion from the produce safety regulation, including through listing as a produce that is rarely consumed raw.

FDA Response:

The characterization of fruits and vegetables as "rarely consumed raw" in the Food Safety Modernization Act (FSMA) Produce Safety Final Rule was based on consumption patterns reported in the National Health and Nutrition Examination Survey[121], which is the most comprehensive and robust, nationally-representative dataset currently available on dietary intake in the U.S. The reported consumption of uncooked wine grapes – by 18.6 percent of consumers and on 1.9 percent of eating occasions in two days of dietary intake data, and by 11.4 percent of consumers and on 1.5 percent of eating occasions in a single day of dietary intake data – was high enough to exclude them from the rarely consumed raw list (and, therefore, wine grapes are covered produce subject to the rule). Furthermore, according to the National Grape Registry, some grapes used to make wine can be used for other purposes as well. For example, the Malaysia Bianca grape cultivar can be used as wine grapes and table grapes, and the Muscat of Alexandria grape cultivar can be used to make wine or raisins or as table grapes. For these reasons, FDA concluded that ''wine grapes'' are not rarely consumed raw.

In the FSMA Produce Safety Final Rule, FDA stated that it did not have information on the specific grape cultivars or varieties that are solely and exclusively grown for use in winemaking that would allow the agency to establish a category covering only "wine grapes" and evaluate their eligibility for the rarely consumed raw list, using currently available dietary consumption data. FDA also indicated its intent to consider updating the list of rarely consumed raw commodities in the future, as appropriate, such as if new data become available. FDA encourages interested stakeholders to identify or submit data that are sufficiently robust and representative to allow FDA to draw scientifically valid conclusions that the criteria are met for including the commodities on the rarely consumed raw list. The criteria for inclusion are that the commodity is consumed raw by less than 0.1 percent of population; is consumed raw on less than 0.1 percent of eating occasions; and that consumption in any form – raw, processed, or other – was reported by at least one percent of a weighted number of survey respondents. FDA has discussed this with interested stakeholders that have contacted FDA about adding wine grapes to the list of rarely consumed raw commodities.

Although grapes used in the production of wine currently are not considered "rarely consumed raw," grapes used to produce wine are eligible for an exemption provided certain documentation requirements are met. FDA determined that winemaking adequately reduces the presence of microorganisms of public health significance and, therefore, added "wine" to the list of examples

[121] Available at: https://www.cdc.gov/nchs/nhanes/index.htm

of products of commercial processing. FDA has extended the compliance dates for some of the documentation needed to qualify for the commercial processing exemption while the agency considers the best approach to address feasibility concerns – see 81 FR 57784, August 24, 2016. FDA remains committed to working with the food industry throughout FSMA implementation to ensure that requirements are as practical as possible while still protecting public health.

17. Improving Diversity in Clinical Trials and Safety Studies

The Committee supports FDA's efforts, including the FDASIA 907 Action Plan, to promote inclusion of racially and ethnically diverse populations into clinical trials. The Committee encourages FDA to address the specific lack of racial and ethnic diversity in genome wide association studies, precision medicine studies, and post-market surveillance safety monitoring for drugs, biological products, and devices. The Committee further encourages FDA to also include data for Hispanics in the Clinical Trials Drug Snapshots, including stating when no data is available based on the study design of the clinical trial. The Committee also directs FDA's to help ensure that public-facing resources are available in Spanish, including MedWatch reporting forms and online portal, and consumer information materials.

FDA Response:

FDA has implemented 26 of 27 action items in the "FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data" and posted "Questions and Answers" about the Plan. In 2016, FDA hosted a meeting "Enhancing the Collection, Analysis, and Availability on Demographic Subgroup Data," to update the public about progress in implementing the Plan. Progress includes:

- Issuing two guidance documents: "Collection of Race and Ethnicity Data in Clinical Trials" and "Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies." Both provide clear and detailed guidance for regulated industry on matters related to clinical trial inclusion data. FDA released its "Women's Health Research Roadmap" to better coordinate women's health research across the agency.
- Updating MedWatch forms for adverse event reporting to include fields for race and ethnicity. Portions of the MedWatch portal are now available in Spanish as well as 14 other languages and language assistance is available for those wishing to access the portal.
- Conducting meetings/workshops and making the information publicly available:
    - The Institute of Medicine and FDA joint meeting (2015), "Strategies for Ensuring Diversity, Inclusion, and Meaningful Participation in Clinical Trials: A Workshop." More than 100 participants attended and a publication detailing the proceedings was released.
    - FDA and Johns Hopkins University joint workshop (2015), Clinical Trials: Assessing Safety and Efficacy for a Diverse Population.
    - FDA public meeting (2016), Progress on Enhancing the Collection, Analysis and Availability of Demographic Subgroup Data.
- Launching Drug Trials Snapshots to inform consumers about demographic data indicating who participated in clinical trials that supported FDA approval of new drugs and biologics. Drug Trials Snapshots also highlight whether there were any differences in the

benefits and side effects among sex, race and age groups, when such data are available. The agency has published more than 100 Drug Trials Snapshots, which are written in clear, consumer-friendly plain language.

- Developing tools to support clinical trial participation. FDA's Office of Minority Health collaborated with the National Library of Medicine to help consumers and patients find clinical trials, and conducted an ongoing multi-media Minorities in Clinical Trials Campaign which encompasses public service announcements, educational materials, webinars, and print/digital outreach that highlights the importance of clinical trial participation. FDA's Office of Women's Health developed and disseminated, through collaboration with Association of Clinical Research Professionals, a national training webinar series titled "Engagement, Recruitment and Retention of Diverse Women in Clinical Trials". As part of FDA's Language Access Plan, the agency released multiple consumer information materials and updates in Spanish that describe why representation of minorities in clinical trials is important and how FDA is working to increase participation.
- FDA's Office of Women's Health launched its Diverse Women in Clinical Trials initiative. Developed in collaboration with the National Institute of Health's Office of Research on Women's Health, this multipronged effort includes a national awareness campaign, scientific dialogues and webinars/ workshops designed to raise awareness and share best practices about clinical research design, recruitment, and subpopulation analyses. Since January 2016, OWH has mobilized a network of 275 partners to disseminate FDA clinical trials educational materials, host workshops for health professionals, and conduct digital and community-based outreach.

18. In Silico Clinical Trials

The Committee appreciates FDA's interest in in silico medicine and directs the Office of the Chief Scientist to enter into an affiliation agreement with an academic institution with expertise in physiological modeling for the purpose of bridging the gaps between genetics and clinical practice with in silico clinical trials, allowing the development of personalized medicine and optimizing the regulatory process, pursuant to the goals set forth in the Critical Path Initiative.

FDA Response:

FDA appreciates the Committee's interest in advancing the goals of the Critical Path Initiative and developing tools to support personalized medicine. FDA currently partners with the University of Mississippi Medical Center (UMMC), using its sophisticated computer models to predict in silico how drugs and devices may affect the human body. This partnership is currently focused on the kidney, but UMMC's model may also be used to evaluate drugs and devices across the entire body, project the long-term effects of an intervention, and study ways in which drugs might impact populations differently.

In addition, FDA has a Memorandum of Understanding with the Avicenna Alliance, an association comprised of industry and academic partners, to seek actionable ways to harness in silico clinical trials. The existing grant from the Office of the Chief Scientist to the Stanford/UCSF Center of Excellence in Regulatory Science and Innovation, provides another opportunity to pursue physiological modeling in conjunction with the Precision Medicine Initiative-focused projects.

19. Misleading Maple Marketing

The Committee is concerned about the explosion of products marketed using the word maple and related iconography, which intentionally misleads consumers who perceive the use of the word maple and related iconography to mean that a food product contains some measurable quantity of maple syrup to flavor or sweeten the product, which consumers identify as a characterizing ingredient. The Committee directs the FDA to perform a detailed analysis of consumer perception of foods marketed with the word maple or related iconography.

FDA Response:

FDA shares your concern for the truthful labeling of food products and intends to continue to monitor the marketplace for potentially false and misleading labeling. If a food does not contain the ingredient maple syrup, the label cannot include the term "maple syrup" in the ingredient statement or as a part of the statement of identity. FDA will consider taking action, as appropriate, consistent with our food safety priorities and resources, against products that are misbranded.

Further, FDA shares your concern to avoid consumer confusion. In September 2016, FDA developed an FDA Consumer Update to help educate consumers about the differences in the ways that ingredients and flavors are declared on product labels; this update included "maple" and "maple syrup." The update is available at: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm521518.htm. FDA may develop additional educational materials if further needs are identified.

FDA has worked with representatives of the maple syrup industry and is happy to meet with them to discuss available data and other industry information on consumer perceptions regarding maple and maple syrup. This information would be valuable in assessing and analyzing the impact that the use of the term "maple" and related iconography have on consumer perceptions. FDA also would welcome the opportunity to meet with Committee staff to discuss the labeling regulations regarding the use of the terms "maple syrup" and "maple" and the Committee's directive to perform a detailed analysis of consumer perceptions of foods marketed using these terms.

20. Opioids

The Committee is deeply concerned about the opioid abuse epidemic that took the lives of more than 33,000 Americans in 2015. As the Agency that oversees the approval of these drugs, the FDA has a responsibility to consider the public health impact of opioid misuse, abuse, diversion and overdose death. The Committee supports FDA's commitment to addressing this crisis through all available authorities, and encourages them to work with other Federal Agencies in their efforts.

The Committee continues its directive for FDA to refer any new drug application for an opioid submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act to an advisory committee for their recommendations prior to approval, unless the FDA finds that holding such advisory committee is not in the interest of protecting and promoting the public health.

The Committee notes that the vast majority of patients prescribed opioids are dispensed a substantially larger amount of pills than what is effective for pain management, and that 8 percent of patients who receive a week's supply of opioids continue to use them 1 year later.

Additionally, despite promotion of abuse deterrent varieties of opioid medication, FDA has itself recognized that these drugs are still misunderstood as being abuse-proof by prescribers.

Therefore, the Committee believes that it is imperative that FDA, consistent with its own Advisory Committee recommendations, take any and all steps necessary to require continuing medical education, aligned with the most recent Center for Disease Control and Prevention's Guidelines for Prescribing Opioids for Chronic Pain, for providers who write opioid prescriptions, including through the Risk Evaluations and Mitigation Strategy. The Committee directs FDA to establish authoritative opioid labeling guidelines that align prescribing and dispensing volumes with the lowest number of pills needed to be effective for pain management. Additionally, the Committee believes that FDA should develop messaging to mitigate the risk that healthcare practitioners will confuse the term ''abuse-deterrent'' for ''abuse-proof''.

The Committee is also concerned that the Drug Enforcement Administration's approved annual aggregate production quota for opioids, which are established through engagement with the FDA, have increased dramatically in the last two decades. The Committee directs the FDA to account for changes in the currently accepted medical use of opioids and the downstream public health impact when informing DEA's quota-setting process, and provide public justification for any future recommended changes to the DEA's aggregate production quote for opioids.

FDA Response:

FDA will continue to implement its opioid action plan announced in February 2016, and will continue to follow section 106 of the Comprehensive Addiction and Recovery Act (CARA) concerning this action plan. Specifically, FDA will convene an expert advisory committee before approving any New Drug Application for an opioid unless FDA determines that such referral is not required, as provided in CARA section 106(a)(1)(B) ("Public health exemption").

FDA remains committed to increasing the number of prescribers who receive training on pain management and safe prescribing of opioid analgesics to decrease inappropriate opioid prescribing. FDA continues to explore potential methods to increase prescriber training, bearing in mind that clinicians may be receiving opioid analgesic prescribing education from sources other than training provided under the existing REMS.

Accordingly, the agency held a public workshop on May 9-10, 2017, "Training Health Care Providers on Pain Management and Safe Use of Opioid Analgesics – Exploring the Path Forward," to obtain input on issues and challenges associated with Federal efforts to support training on pain management and the safe prescribing, dispensing, and patient use of opioids (safe use of opioids) for health care providers. During the workshop, the agency discussed how FDA might best use Risk Evaluation and Mitigation Strategy (REMS) to ensure training of prescribers, including adequate training in the appropriate management of pain. This training would help prescribers make the best treatment decisions, including the careful use of opioids under appropriate circumstances.

In a related action, on September 28, 2017, FDA notified sponsors that it was requiring updates and modifications to the existing Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting (ER/LA) opioid analgesics, and for the first time, the agency's decision to require immediate-release (IR) opioid analgesic products be subject to the same REMS requirements. The modified REMS will include revisions to the existing FDA Blueprint for

prescriber education, which describes the content that must be covered in an educational program for it to be considered REMS-compliant. As one part of the education, FDA intends to broaden information on pain management, including the principles of acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic).

The Blueprint will also enhance the information about the safe use of opioid analgesics, basic elements of addiction medicine, and opioid use disorders, and the new REMS will require that training be made available to other health care providers involved in the management of patients with pain, including nurses and pharmacists. FDA believes that all healthcare providers involved in the management of pain should be educated about the safe use of opioids. The new training will also be aimed at making sure providers are prescribing opioids only for properly-indicated patients, and only under appropriate clinical circumstances. This is part of a broader effort to take new steps to make sure providers are properly informed about suitable prescribing and the risks and benefits associated with opioid drugs.

One approach to reducing the rate of new addiction is to reduce exposure to prescription opioid analgesics. To accomplish this, FDA is exploring ways to use our regulatory authorities to influence how opioid analgesics are prescribed to make sure that only appropriately indicated patients are prescribed opioids, and that the prescriptions are written for durations and doses that properly match the clinical reason for which the drug is being prescribed in the first place. FDA is also exploring whether the agency should take additional steps to make sure that prescribing practices, and the number of opioid doses that an individual patient can be dispensed, are more closely tailored to the patient's medical need. Among other steps, FDA is soliciting public input on these questions in the form of a public docket that was established the week of September 25, 2017.

Abuse-deterrent (AD) technology is still evolving and epidemiological studies are in progress to assess AD products' effectiveness in reducing abuse in the real world. While the FDA recognizes that the AD formulations are not failsafe and more data are needed, AD opioids are expected to reduce abuse compared to non-AD opioids, which make them an important part of a much larger strategy to combat opioid abuse. FDA held a public meeting in July 2016 to discuss ways to improve the science of evaluating the postmarketing impact of AD formulations, both by improving use of existing data and methods and developing new data streams and methods. FDA has since awarded several contracts to support cutting edge research to facilitate evaluation of AD products, despite the limitations of currently available data.

FDA provides DEA an annual estimate of medical, scientific, and reserve stock needs for Schedule I and II substances, including opioids, based in significant part on prescribing data. It is FDA's understanding that these estimates are used by DEA to determine the amount of controlled substances (Aggregate Production Quota (APQ)) that is appropriate to set as an upper limit on the amount of that substance that can be manufactured in the coming year, as outlined in the Controlled Substances Act and 21 CFR Part 1303. However, DEA relies on data and information to which FDA does not have access, such as diversion data and data on international need, to determine the final published APQ. The exact methods DEA uses to determine quotas, including opioid quotas, are not known to FDA. Over time, FDA has observed significant differences between our estimates of projected trends for medical need of certain drugs and the actual aggregate quotas DEA establishes.

21. Orphan Products Development

The Committee is encouraged by the Office of Orphan Products Development and recognizes the importance of the work being supported by Orphan Product Grants. The Committee requests for the FDA to provide a review of the indication for which the drug is intended to treat and for the number of pediatric clinical trials that have received a grant since fiscal year 2015.

FDA Response:

FDA's Orphan Products Clinical Trials Grants Program provides grants for clinical studies of products (drugs, biologics, medical devices, or medical foods) for use in rare diseases or conditions where no current therapy exists or where the proposed product has a plausible hypothesis that it will be superior to the existing therapy. Since the program's inception in 1983, OOPD has funded over 600 studies and the program has contributed to bringing nearly 60 products to marketing approval.

In FY 2015-2017, the Orphan Products Clinical Trials Grants Program supported 48 clinical trials that included pediatric (

Pediatric Only Trials:

Phase 1 Study of Ursodeoxycholic Acid Therapy for Pediatric Primary Sclerosing Cholangitis

Phase 2 Study of rhCC10 to Prevent Neonatal Bronchopulmonary Dysplasia

Phase 2 Study of Levetiracetam in the Treatment of Neonatal Seizures

Phase 2 Study of Dextromethorphan in the Treatment of Rett Syndrome

Phase 3 Study of Triiodothyronine Supplementation for the Treatment of Young Infants After Cardiopulmonary Bypass

Phase 1/2 Study of Aerosolized Survanta for the Treatment of Neonatal Respiratory Distress Syndrome

Phase 2 Study of Imatinib for the Treatment of Airway Tumors in Children with Neurofibromatosis Type 1

Phase 1 Study of Omigapil for the Treatment of Congenital Muscular Dystrophy (CMD)

Phase 3 Study of Standard vs Reduced IV Fat for the Prevention of Parenteral Nutrition-Associated Cholestasis (PNAC)

Phase 2 Study of Selective Cytopheretic Device for the Treatment of Pediatric Patients w/ Acute Kidney Injury

Phase 2 Study of EDI200 for the Treatment of X-Linked Hypohidrotic Ectodermal Dysplasia

Phase 2 Study of Furosemide for the Prevention of Bronchopulmonary Dysplasia in Premature Infants

Phase 2 Study of Oxytocin for the Treatment of Hyperphagia in Prader-Willi Syndrome

Phase 1 Study of HSV G207 & Radiation for the Treatment of Pediatric Brain Tumors

Phase 2 Study of Inhaled Activase for the Treatment of Acute Plastic Bronchitis

Phase 3 Study of Dichloroacetate (DCA) for the Treatment of Pyruvate Dehyrugenase Complex Deficiency

Phase 3 Study of Magnetic Alteration of Pectus Excavatum

Phase 2 Study of Radioactive Iodide Therapy for Pediatric Graves Disease

Phase 2A Study of Exendin for the Treatment of Congenital Hyperinsulinism

Pediatrics and Adult Trials:

Phase 2 Study of High TC Susceptometer to monitor Transfusional Iron Overload

Phase 2 Study of Vitamin D for Prevention of Respiratory Complications from Sickle Cell Disease

Phase 3 Study of Cheatham Platinum Stent for Prevention or Treatment of Aortic Wall Injury Associated with Aortic Coarctation

Phase 2 Study of T-Cell Depleted Familial Haploidentical SCT for the Treatment of High-Risk Sickle Cell Anemia

Phase 2 of Defibrotide for the Prevention of Complications in High-Risk Sickle Cell Disease Patients Following AlloSCT

Phase 2 Study of the HemiBridge System for the Treatment of Idiopathic Scoliosis

Phase 2 Study of Etanercept for Children with Kawasaki Disease

Phase 2/3 Study of Sitagliptin in the Prevention of Cystic Fibrosis Diabetes

Phase 3 Study of Anacoral (Coralmyn) Antivenom for Emergency Treatment of Coral Snake Envenomation

Phase 2 Study of Glycomacropeptide vs. Amino Acid Diet for Management of PKU

Phase 2 Study of Mexiletine in Treatment of Myotonic Dystrophy Type 1

Phase 1 Study of HSV1716 in Patients with Non-CNS Solid Tumors

Phase 2 Study of [18F] FLT for PET Imaging of Brain Tumors in Children

Phase 1/2 Study of Taurine for the Treatment of Cystathionine Beta-Synthase Deficient Homocystinuria

Phase 2 Study of Esophageal String Test in Diagnosing Eosinophilic Esophagitis

Phase 1 Study of IL-2 for the Treatment of Wiskott-Aldrich Syndrome

Phase 1 Study of ALK001 for the Treatment of Stargardt Disease

Phase 2 Study of Abatacept combined with Calcineurin Inhibition and Methotrexate for Prophylaxis of Graft Vs Host Disease

Phase 2 Study of Deferiprone in the Treatment of Neurodegeneration with Brain Iron Accumulation

Phase 2 Study of Vincristine vs. Sirolimus for the Treatment of High Risk Kaposiform Hemangioendothelioma

Phase 1 Study of Quercetin for the Treatment of Fanconi Anemia

Phase 2 Study of Carbidopa for the Treatment of Familial Dysautonomia

Phase 2 Study of L-Arginine Therapy for the Treatment of Pediatric Sickle Cell Disease Pain

Phase 2 Study of the Melanocortin 4 Receptor Agonist RM-493 for the Treatment of Prader Willi Syndrome

Phase 2 Study of Gamunex (Intravenous Gammaglobulin) for the Treatment of Sickle Cell Acute Pain

Phase 1 Study of Viralym-A for the Treatment of Adenovirus Disease

Phase 2 Study of a Networked Neuroprosthesis (NNP) for Grasp, Reach, and Trunk Function in Cervical Spinal Cord Injury

Phase 1 Study of Humanized 3F8 MoAb and NK cells for the Treatment of Neuroblastoma

Phase 1 Study of Dual PI3K/BRD4 Inhibitor SF1126 for the Treatment of Neuroblastoma

22. Pediatric Cancer Drug Approvals

The Committee is encouraged by the enactment of the RACE for Children Act as part of the reauthorization of the Prescription Drug User Fee Authorization Act. RACE for Children could improve the treatment options for children battling cancer and close the divide between adult and pediatric oncology therapies. The Committee encourages the FDA to fully implement the provisions specific to the lists of molecular targets and FDA guidance on pediatric study plans under the Pediatric Research Equity Act and the Best Pharmaceutical Practices for Children Act.

FDA Response:

FDA appreciates the Committee's support for the development of oncology drugs for cancers affecting pediatric patients, and is committed to fully implementing the provisions specific to the lists of molecular targets included in the FDA Reauthorization Act (FDARA), and issuing FDA guidance on pediatric study plans under section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA is working internally and with external stakeholders to solicit input regarding the molecular targets that are substantially relevant to the growth or progression of a pediatric cancer and the process for updating the list of molecular targets that may impact the application of the requirements of the FDA Reauthorization Act of 2017 (FDARA).

Consistent with the requirements of FDARA, FDA intends to publish a list of molecular targets considered to be substantially relevant to the growth and progression of a pediatric cancer and that may be subject to the requirements of section 505B of the FD&C Act, as well as a list of molecular targets of new cancer drugs and biological products that will be granted automatic waivers by August 2018. FDA also intends to issue a final guidance regarding the implementation of the new section 505B requirements regarding molecularly targeted cancer drugs for pediatric patients by August 2019.

23. Seafood Advisory

The Committee is concerned that the FDA published final seafood advice for pregnant and nursing women on January 18, 2017, without going through necessary interagency review, consumer focus group testing, or the opportunity for the public to comment on the scientific peer review. Therefore, the Committee directs the FDA to review its final seafood advice and to make

such technical corrections as are necessary to ensure the advice is consistent with the FDA's scientific review of the net effects of seafood consumption. In addition, the Committee directs the FDA to follow the Administration's review process prior to publishing the updated seafood advice.

FDA Response:

The 2017 final fish advice, entitled "Fish: What Pregnant Women and Parents Should Know,[122]" is based on extensive scientific research and expertise across a range of disciplines as well as multiple opportunities for public comment and stakeholder input. The 2017 advice reflects the work of experts in a range of disciplines within both FDA and the Environmental Protection Agency (EPA), with assistance and input from the National Institutes of Health and other operating divisions within the Department of Health and Human Services. The 2017 advice went through an extensive interagency review process as well as an external peer review process. The agency posted a peer review plan for "Technical Information on Development of Fish Consumption Advice" as part of the agency's peer review agenda. Documentation of the technical information and external scientific peer review process is available on FDA's website.[123]

Furthermore, FDA and EPA received and considered more than 220 public comments on the 2014 draft version of the advice; these comments came from academia, industry, nongovernmental organizations, and consumers. In light of these comments and updated research and technical information, FDA and EPA developed a revised method for categorizing fish and conducted an external peer review of the information and method used.

In November 2014, the FDA's Risk Communications Advisory Committee held a meeting that addressed the draft updated fish advice in great detail and included presentations by FDA and EPA on the substance and presentation of the draft advice as well as presentations by invited experts in risk communications. Members of the public were given an opportunity to express their views to the Risk Communications Advisory Committee and to the agency officials in attendance. Documentation of the public and expert input is available at FDA's website. FDA believes this additional information demonstrates the rigor of our process for reviewing and updating the fish advice.

On October 13, 2017, FDA issued a denial letter in response to a citizen petition requesting that FDA withdraw and reissue the 2017 seafood advice. FDA's response letter, which includes information about FDA's consideration of the FDA Net Effects Assessment, is available in Docket No. FDA-2017-P-3296 at https://www.regulations.gov/document?D=FDA-2017-P-3196-0071.

24. Sunscreen Labeling Regulations

The Committee remains significantly concerned that the FDA has not approved a new over-the-counter [OTC] sunscreen ingredient since the 1990s, despite having a number of ingredients pending approval for more than a decade. After the U.S. Surgeon General issued ''A Call to Action to Prevent Skin Cancer,'' which concluded that nearly 5 million people are treated

[122] https://www.federalregister.gov/documents/2017/01/19/2017-01073/advice-about-eating-fish-from-the-environmental-protection-agency-and-food-and-drug-administration

[123] https://www.fda.gov/Food/ResourcesForYou/Consumers/ucm393070.htm

annually for all skin cancers at a cost of approximately $8.1 billion per year, Congress passed the Sunscreen Innovation Act of 2014 to improve the process by which the FDA reviews sunscreen ingredients and to require the FDA to finalize an effective sunscreen monograph within 5 years. The Committee directs the FDA to work with stakeholders to develop a testing regimen, consistent with current scientific standards, that appropriately balances the benefit of additional skin cancer prevention tools versus the risk of skin cancer within 90 days of enactment. The Committee also directs FDA to maintain funding for agency efforts to clear this backlog of sunscreen applications.

In addition, the Committee is disappointed that FDA has not yet finalized a rule limiting the maximum Sun Protection Factor [SPF] to ''50'' or ''50+'' as directed by the fiscal year 2017 Consolidated Appropriations Act, and as such the Committee directs FDA to finalize the rule immediately. The Committee is also disappointed that FDA failed to issue a proposed rule to establish testing and labeling standards for sunscreen sprays and directs FDA to do so immediately.

FDA Response:

Given the recognized public health benefits of sunscreen use, the FDA is committed to finding ways to help facilitate the marketing of safe and effective sunscreen products that include additional over-the-counter (OTC) sunscreen active ingredients. As noted in the GAO's November 2017 report *FDA Reviewed Applications for Additional Active Ingredients and Determined More Data Needed*, the FDA relies on industry to submit the data needed to make the required safety and effectiveness determinations for each pending sunscreen active ingredient currently being evaluated under the SIA framework. In every case, the FDA has determined that the evidence supplied to date is insufficient to support a determination that the active ingredient is Generally Recognized as Safe and Effective (GRASE) for use in sunscreens.[124]

There is no backlog of pending sunscreen applications. The agency has identified current data gaps for each active ingredient being evaluated under the SIA framework and communicated them in proposed sunscreen orders and, when requested, granted meetings with active ingredient sponsors. To date, the agency has not received any additional data from manufacturers for any of the pending sunscreen ingredients that were the subject of SIA-required proposed sunscreen orders issued in 2015.

The FDA will continue to work with industry and public health stakeholders as it implements the SIA to help ensure that the sunscreens consumers use every day on themselves and their families are safe and effective for daily, life-long use.

To date, FDA has met all statutorily mandated SIA deadlines and remains committed to achieving that goal in the future. As required by the SIA, the FDA is working to finalize OTC monograph regulations for sunscreens by November 26, 2019. The agency anticipates including provisions related to the effectiveness of various SPF levels and dosage forms for sunscreens. The FDA also intends to publish a proposed rulemaking on sunscreens in order to provide the opportunity for public comment.

[124] US Government Accountability Office (November 15, 2017). Retrieved November 15, 2017, from www.gao.gov/products/GAO-18-61.

25. Vibrio

The Committee is aware of the public health challenge related to the naturally occurring bacteria called Vibrio parahaemolyticus that can accumulate in shellfish and believes that more scientific research is necessary to develop 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:

In FY 2016, FDA's Center for Food Safety and Applied Nutrition (CFSAN) awarded an annual cooperative agreement to the Interstate Shellfish Sanitation Conference (ISSC) for $440,000. This cooperative agreement supported funding of state, academic, and shellfish industry studies to advance the science of Vibrio parahaemolyticus (Vp) through, among other things, improving risk assessment and identifying opportunities to develop and validate methods to detect virulent Vp strains. CFSAN funded this partnership in FY 2017 and will continue this funding in future fiscal years, subject to funding availability. The cooperative agreement helps fund research to assess the efficacy of various control strategies for reducing the risk of Vp illness associated with raw shellfish consumption, which FDA uses to inform its guidance to industry. Most recently the ISSC held a workshop to disseminate the latest practices that industry could use to minimize and mitigate risks associated with raw bivalve shellfish consumption.

FDA will continue to offer program assistance to states and industry for research and technical assistance aimed at improving the science and expanding and enhancing measures for the control of Vp in molluscan shellfish. FDA's Vibrio Assistance Review Board (VARB) reviews, prioritizes, and tracks submissions to FDA from State Shellfish Control Authorities (SSCA) and industry requesting Vibrio species-related research and technical assistance. To date, the VARB has supported joint FDA-SSCA projects, with industry participation in many cases, that generated data used to inform control practices for Vp. For example, a project established baseline levels of Vp to aid states in the determination of whether to allow the summer harvest of shellfish, such as in South Carolina, and in the understanding of Vp levels in a location associated with illnesses, such as in Massachusetts. The most recent joint FDA-SSCA project evaluates risk mitigation strategies that could be applied to typical aquaculture practices that could otherwise promote Vibrio species growth.

In addition, FDA will continue to work directly with the ISSC Vibrio Management Committee and the Centers for Disease Control and Prevention to examine the incidence of Vp illness as part of FDA and ISSC efforts to understand illness trends to aid in the adoption of improved controls into the National Shellfish Sanitation Program.

26. White Oak Expansion

The Committee is aware of the need for FDA facilities to accommodate an anticipated expanded workforce due to broader missions related to food safety and other mandates in legislation over the last few years. Due to the challenging fiscal environment, the Committee encourages the FDA and GSA to consider innovative financing options to allow for the space allocation required. In particular, the Committee directs the FDA and GSA to consider partnership opportunities with non-Federal Government entities that provide reasonable cost options that will enable the FDA to

maintain very close proximity to its campus headquarters in White Oak, including space contiguous to the White Oak campus.

FDA Response:

The Consolidated Appropriations Act, 2016, authorized $5,000,000 for FDA to complete a feasibility study to update and issue a revised Master Plan for land inside and contiguous to the White Oak campus to address its expanded workforce and the facilities needed to accommodate them.

FDA provided GSA with a $5,000,000 Reimbursable Work Authorization in 2016. Since then, GSA and FDA have collaborated and awarded contracts for development of an FDA Headquarters Housing Strategy/Migration Plan and a new Federal Research Center (FRC) Master Plan at White Oak. These documents, which are still under development, will address the feasibility of and options for accommodating FDA 's existing headquarters staff that have not yet been consolidated at White Oak, as well as FDA's growing headquarters staff on or near the FRC. Alternatives being considered as part of the effort include both additional federal construction and leasing office space in close proximity to the FRC to support Congress' intent to geographically consolidate FDA Headquarters.

FDA must depend on GSA to satisfy its office housing needs. GSA considered a partnership opportunity proposed by a non-Federal Government entity that provided a leasing option to enable the FDA to maintain very close proximity to its campus headquarters in White Oak, including space contiguous to the White Oak campus. In response to the proposal, GSA determined that FDA’s housing need first had to be documented through the process of developing the Housing Strategy/Migration Plan before the acquisition of space could occur. GSA also determined that FDA’s housing need required Congressional prospectus authority and, after Congressional approval, it would have to be satisfied through a competitive leasing process. Sufficient progress has been made on the development of the Housing Strategy/Migration Plan to provide the data needed for GSA and FDA to collaborate on a lease prospectus to be submitted for FY 2019 approval.