**FDA In Review – Highlights for Food and Other FDA-Regulated Companies** ***Authors: Allison Fulton and Abby Meyer, Sheppard, Mullin, Richter & Hampton LLP***

## 1. FDA Commissioner Gottlieb Steps Down, Acting Commissioner Sharpless Steps Up

This Spring, Norman E. (Ned) Sharpless, M.D., took the helm as Acting Commissioner of the US Food and Drug Administration (FDA). Dr. Sharpless most recently served as the director of the National Cancer Institute, part of the National Institutes of Health (NIH), which serves as the government's principal agency for cancer research. Dr. Sharpless's appointment comes on the heels of the resignation of former Commissioner Scott Gottlieb, M.D. on April 5, 2019.

Dr. Gottlieb was an agent for change at the FDA. He led initiatives in combating the opioid crisis, curbing the marketing of e-cigarettes to youth, promoting innovative pathways for Digital Health, reducing drug prices by promoting generic competition, and accelerating approvals of new drugs. Dr. Gottlieb was an active user of social media and published numerous press releases to garner attention and support for his initiatives.

Given his background in cancer research, Dr. Sharpless likely will forge ahead with many of Dr. Gottlieb's initiatives—particularly in accelerating approvals of drugs and biologics for oncology indications and promoting the development of gene and cell therapies. He also will continue to deter the marketing of tobacco products to kids by, for example, wielding the agency's enforcement powers. Sharpless also has expressed interest in big data—i.e., harnessing the power of analytics on large data sets—to inform healthcare decisions, and we may expect to see continued initiatives to collect real-world evidence globally.

## 2. Cannabis and CBD Was All the Buzz

On May 31, 2019, the FDA held its much anticipated public hearing on cannabis and cannabis-derived compounds, and drew a wide audience of participants, with strong views on how the FDA should (or should not) regulate the controversial plant. In an amazingly short period of time, hemp-derived products, including those containing cannabidiol, have moved from the fringe to the mainstream, from state-licensed dispensaries to traditional brick-and-mortar retailers. And yet, the FDA's position has been clear — it is illegal to sell human food, pet food, dietary supplements and unapproved drugs that contain cannabidiol (CBD).

The hearing focused on the use of CBD in food and dietary supplements, which accounts for a large part of the market growth. Dr. Norman (Ned) Sharpless, acting commissioner of the FDA, stated at the outset that the FDA treats substances derived from cannabis "just like any other substances," meaning they are subject to the same premarket requirements and other authorities. For example, a food additive must be approved by the FDA as safe before being put into the food supply, unless the substance is generally recognized as safe, or GRAS. New ingredients in dietary supplements must undergo a similar safety review as a new dietary ingredient (NDI). CBD has not been the subject of an approved GRAS or NDI submission.

CBD is not prohibited in cosmetics. Unlike foods and dietary supplements, cosmetic ingredients do not go through safety review prior to commercial use.

Learnings from the FDA hearing include:

### *FDA Does Not Intend to Exercise Enforcement Discretion*

Sharpless stated that the FDA does not plan to exercise a policy of enforcement discretion with respect to CBD products. Nevertheless, the FDA has garnered criticism from some for not

aggressively pursuing marketers of online retailers of CBD gummies and edibles, despite the FDA's stated safety concerns. While the FDA has issued a handful of warning letters to companies making egregious therapeutic claims, such as those claiming to cure cancer or Alzheimer's, it has not initiated an aggressive pursuit of CBD marketers.

***Much Is Unknown, and Industry Needs to Fill the Gaps***

FDA's questions and the responses from the public revealed a lack of common understanding of CBD and delta-9-tetrahydrocannabinol, or THC, and the scientific bases for their therapeutic benefits. The FDA questioned commenters, for example, on how to properly define industry terms (e.g., full-spectrum versus broad-spectrum versus CBD isolate), and commenters' presentations appeared to provide inconsistent information.

Along with the basic lexicon for cannabis, the FDA asked pointed questions on the mechanisms of actions for CBD and its therapeutic benefits. While some patient advocates provided powerful stories of specific benefits, including for preventing pediatric seizures, many consumer advocates spoke of more qualitative effects, such as feelings of "overall well-being" and anxiety relief. It is clear that the FDA wants more data on CBD use in the consumer context, including scientific and empirical data regarding how cannabis-derived compounds affect the public.

***Commenters Largely Agreed That Some Regulatory Protections Would Be Beneficial***

Public commenters seemed to agree — at some level — that some FDA regulation is beneficial for the protection of consumers. Some consumers expressed concerns over the quality of CBD in products, including inconsistent purity levels and undeclared ingredients that contaminate the product. Consumer advocates and business owners recommended, for example, that the FDA apply well-established protections in its current legal framework, such as labeling requirements and good manufacturing practice, or GMP, standards. Some manufacturers urged the FDA to adopt a GMP framework that reflects the natural variability of CBD compounds in the plant and elaborated on the disparate state of manufacturing and quality controls currently implemented in the industry.

***There Is Pressure on the FDA to Act Fast***

The very recent explosion of CBD-infused foods, edibles (e.g., gummies, candy), and beverages in the marketplace, coupled with conflicting, lenient or nonexistent state laws on the sale of hemp-CBD products, puts pressure on the FDA to act quickly in an area that is squarely within its domain. Multiple stakeholders urged the FDA to act fast — researchers urged the FDA to move quickly so that cannabis could be more readily available for scientific studies; business owners asked for clarity so that they could understand their legal risks and opportunities; and consumer advocates sought clear post-market requirements, such as labeling and manufacturing standards, to protect consumers from contaminated products.

As in the past, the FDA will apply a rigorous, evidence-based approach to regulation. The FDA will have to balance, however, the considerable time it will take to wade through the scientific data with industry and public demand for action.

***Youth Access Is a Significant Concern***

The FDA specifically requested information on how vulnerable populations, and in particular minors, would be affected by the proliferation of CBD products. The FDA asked companies selling CBD products to consumers how they were restricting sales to youth, including physical restraints in stores (for example, prohibiting minors from entering retail stores), and whether the age restrictions were determined based on scientific evidence. With the FDA's laser-like focus

on preventing the marketing of electronic cigarettes to minors, industry can expect similar scrutiny on companies selling CBD products, and in particular those that may be inhaled/vaped.

**Moving Forward — FDA Near-Term Actions on Cannabis**

In the near term, the FDA will be collecting and reviewing data from industry on the safety of cannabis and cannabis-derived compounds. FDA encouraged industry to submit scientific data to support the safe, widespread use of cannabis-derived compounds. FDA will remain focused on enabling a regulatory pathway, but it can only act after a methodical and deliberate review of scientific information. And that process takes time.

**3. Changes to the Nutrition Facts Label – Added Sugars, Serving Size Changes, and More**

Starting January 1, 2020, large food companies will have to comply with the Nutrition Facts and Supplement Facts Label and Serving Size final rule. Manufacturers with less than $10 million in annual food sales receive an extra year to comply – until January 1, 2021. The changes reflect FDA's efforts to provide consumers with information that reflects updated scientific information, new nutrition and public health research, and dietary recommendations from expert groups.

The general look of the label remains the same, but changes will be noticeable to the consumer. For example, FDA now requires a declaration for "Added sugars." FDA has stated that excess consumption of added sugars makes it difficult to meet nutrient needs within daily suggested calorie limits, and healthy dietary patterns, characterized in part by lower amounts of sugary foods and beverages, are associated with a reduced risk of cardiovascular disease. Also, reference serving sizes have increased, as have the type size of words such as "Calories" on the label.

A summary of significant changes include:

- "Added sugars," in grams and as percent Daily Value, is now required on the label.
- Vitamin D and potassium will now be required on the label. Calcium and iron will continue to be required. Vitamins A and C will no longer be required but can be included on a voluntary basis.
- The footnote is changing to better explain what percent Daily Value means. It will read: "*The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice."
- While continuing to require "Total Fat," "Saturated Fat," and "*Trans Fat*" on the label, "Calories from Fat" is being removed.
- Daily values for nutrients like sodium, dietary fiber and vitamin D are being updated based on newer scientific evidence. Daily values are reference amounts of nutrients to consume or not to exceed and are used to calculate the percent Daily Value (% DV) that manufacturers include on the label.
- Serving sizes have increased. By law, serving sizes must be based on amounts of foods and beverages that people are actually eating, not what they should be eating. The amount people eat and drink has increased since the previous serving size requirements were published in 1993. For example, the reference amount for a serving of ice cream was previously 1/2 cup but is changing to 2/3 cup; the reference amount of soda is changing from 8 ounces to 12 ounces.
- For certain products that are larger than a single serving but that could be consumed in one sitting or multiple sittings, manufacturers will have to provide "dual column" labels to

indicate the amount of calories and nutrients on both a “per serving” and “per package”/“per unit” basis. Package sizes that are between one and two servings will be required to be labeled as one serving because people typically consume it in one sitting.

### 4. Food Safety Modernization Act (FSMA) and The Intentional Adulteration Rule

The Food Safety Modernization Act (FSMA) introduced the most sweeping changes in food law in seventy years. FSMA applies to food manufacturers, distributors, and other partners in the supply chain, and creates compliance obligations focused on preventing food safety issues before they occur. Among these compliance obligations is the Intentional Adulteration (IA) rule, which requires food facilities to implement strategies to prevent the intentional contamination of food in the facility or during transit.

The IA rule requires covered facilities to prepare and implement a food defense plan. There are several main components to the plan. First, facilities must conduct a vulnerability assessment, which means finding the points in their processes that pose the greatest risk for intentional adulteration. Second, facilities must put in place mitigation, or preventive, strategies to address these vulnerabilities. Third, a system must be put in place for food defense monitoring, food defense corrective action, and food defense verification, which together ensure the system is working as intended to address the vulnerabilities. Fourth is recordkeeping. Finally, there are training requirements. Personnel, and their supervisors, working at the most vulnerable points in a facility are required to take food defense awareness training and to have the education, training, or experience to properly implement mitigation strategies. In addition, preparing the food defense plan, conducting vulnerability assessments, identifying mitigation strategies, and engaging in reanalysis activities must be done or overseen by personnel with additional training or experience.

The rule is designed to cover large companies (including international ones) whose products reach many people. The requirements do not apply to very small businesses averaging less than $10 million in sales per year.

Larger businesses—those that are not considered small or very small businesses under the rule—are required to comply with the IA rule as of July 26, 2019. Small businesses, which employ fewer than 500 people, have until July 27, 2020 to comply. Very small businesses are exempt from most of the requirements, but by July 26, 2021, they must document that they meet the requirement to be exempt.

### 5. AAFCO Issues Updated Guidelines Regarding Hemp in Animal Food

On May 1, 2019, AAFCO provided updated guidelines regarding the use of hemp in animal food, including how this market is affected by the Agricultural Improvement Act of 2018 (the “Farm Bill”). Although the AAFCO is not a government agency, its members are government agencies that represent the 50 states, the US Food and Drug Administration (FDA) Center for Veterinary Medicine, and the Canadian Food Inspection Agency.

In the guidelines, AAFCO maintains that hemp and hemp products currently may not be used in feed in the United States. Although the Farm Bill removed hemp from the list of controlled substances, it did not authorize the use of hemp as an ingredient in animal feed. In order for hemp to be used as an ingredient in animal feed, it will still need to go through same FDA review process as any other potential ingredient. AAFCO does not view CBD-infused products as eligible for this process, due to discussions with FDA which indicate that such products would be categorized as drugs, rather than food.

In 2015, AAFCO previously asked the hemp industry to present data showing that ingredients derived from the hemp plant (such as hemp seed oil, hemp seed meal, and whole hemp seeds) are safe and useful in animal food. However, AAFCO has not yet received any such data from industry. AAFCO concludes these guidelines with a renewed call for interested parties to work on submitting an application through the AAFCO or FDA review process.

### 6. FDA Issues First Warning Letter to Food Importer under the FSVP Program

In August 2019, the FDA issued the first Warning Letter using its authority under the FDA Food Safety Modernization Act (FSMA) Final Rule on Foreign Supplier Verification Programs (FSVP) for Importers of Food for Humans and Animals. Since 2017, the FDA has been conducting FSVP inspections, with a primary focus on helping importers understand the requirements and how to take corrective actions if deficiencies are observed. Moving forward, the FDA will take more steps to ensure compliance with FSVP, including re-inspecting importers that had deficiencies in previous inspections and by acting immediately when FSVP deficiencies are found that pose an imminent public health risk.

The Warning Letter was issued to a Florida-based importer of tahini product from Israel. The imported tahini was implicated in a Salmonella outbreak in May 2019 and was recalled. FDA investigators found the importer to be in significant violation of the FSVP rule, which requires that importers perform certain risk-based activities to verify that food imported has been produced in a manner that meets applicable U.S. food safety standards. Importers covered by the FSVP rule also have to verify that their suppliers' food is not adulterated or misbranded with respect to allergens.

### 7. Medical Devices – Artificial Intelligence is On The Rise

In April 2019, the FDA released a discussion paper, Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML) – Based Software as a Medical Device (SaMD), which proposed a novel regulatory framework for artificial intelligence (AI)-based medical devices. The public docket closed on June 3, 2019, and FDA received over one hundred comments from manufacturers, industry associations, and other interested parties. The comments vary in support of FDA's framework and largely urge FDA to align with external stakeholders that are already developing industry standards and clarify the agency's expectations under the proposed framework.

In its discussion paper, FDA recognized that its current approach to the regulation of medical devices—which is based on devices that are static in nature with planned, discrete changes—is ill-suited for AI algorithms. For example, under the current framework, changes in an AI algorithm due to real-world use, depending on the significance or risk posed to patients of that modification, could trigger premarket review by FDA. The consequence would be that whenever the algorithm learns or adapts (which ideally it would with every use), the manufacturer would have to ask FDA to clear (or approve) the algorithm change. That scenario is unworkable—both for the manufacturer and for FDA. FDA's approach introduced a framework that considers the adaptive nature of AI and machine-learning (ML) based technologies, and proposed a streamlined approach that should lessen regulatory burden on industry.

The framework proposed a total lifecycle approach, based on four principles: (1) good ML practices (GMLP) from software development through distribution; (2) initial pre-market review that would include a pre-determined plan for modifications; (3) risk management approach to modifications after pre-market review; and (4) post-marketing monitoring and reporting of

product performance. At the heart of FDA's proposed framework, and the most unique aspect of the approach, is the second principle—the option for manufacturers to submit a plan of predetermined modifications during the initial premarket review of an AI or ML device.

The plan, called a "predetermined change control plan," would disclose changes that are anticipated based on the software's adaptive learning, and the methodology for implementing those changes in a controlled manner. In other words, the plan would lay out a roadmap, or region, of potential changes as the machine learns, and would describe the methods in place to control the risks anticipated with those algorithm changes. Changes within the scope of the plan would not require FDA premarket review. Changes outside the scope of the plan, and that lead to a new intended use—for example, to diagnose a different/new disease—would require premarket review. Changes that are outside of the plan, but that do not create a new intended use, would trigger a "focused" FDA premarket review of the plan. This approach would eliminate the burdensome requirement for a company to seek clearance from FDA for every significant software change.

While the industry largely encourages FDA to react quickly to evolving technology so as not to stifle innovation, the FDA will have to take time to more clearly define foundational terms in this complex area and clarify its expectations for software developers and medical device companies.

### 8. Medical Devices – Laboratory Developed Tests (LDTs) on FDA's Radar

In an April 4, 2019 Press Release, the FDA announced its issuance of a Warning Letter to a Virginia healthcare system laboratory marketing genetic tests for predicting medication response and patient receptivity to drugs (among other things). FDA identified three genetic tests, including one designed to provide insight into how a patient would respond to drugs used for anesthesia, cancers, infections, attention-deficit/hyperactivity disorder, depression, anxiety, and diabetes. FDA deemed the tests to be adulterated and misbranded because Inova had not sought premarket clearance.

#### *Laboratory-Developed Tests and FDA Historical Enforcement*

In an October 3, 2014 Notice (the "2014 Notice") issued by the FDA, the FDA described "laboratory developed tests" (LDTs) as a category of in vitro diagnostic devices (IVDs) that are, "intended for clinical use and designed, manufactured and used within a single laboratory." Although FDA has authority over LDTs because they are medical devices under the Federal, Food, Drug, and Cosmetic Act, LDTs currently are regulated by the Centers for Medicare and Medicaid Services as high-complexity tests— the most stringent standards—under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

As a matter of practice, FDA has exercised enforcement discretion for LDTs, meaning FDA generally has not enforced the premarket review and other FDA legal requirements that apply to LDTs. Still, the FDA retains discretion to take action when appropriate, such as to address significant public health concerns.

Notwithstanding this history, FDA has argued in recent years that the dramatic increase in the number and complexity of LDTs, particularly in the field of genetic testing, necessitates that some LDTs be cleared or approved by the FDA to ensure their safe and effective use in patient care. *See*, 2014 Notice and the FDA's "Discussion Paper on Laboratory Developed tests (LDTs)" (Jan. 13, 2017). As described by the FDA, "LDTs have evolved and proliferated significantly since the FDA first obtained comprehensive authority to regulate all in vitro diagnostics as devices in 1976. Some LDTs are now much more complex, have a nationwide

reach and present higher risks, such as detection of risk for breast cancer and Alzheimer's disease, which are similar to those of other IVDs that have undergone premarket review."

***Warning Letter***

The FDA's Warning Letter cited the healthcare system laboratory for illegally marketing certain genetic tests without seeking and obtaining premarket clearance from the FDA. The FDA wrote that the tests, "pose significant public health concerns as inaccurate test results could impact the decision-making of healthcare providers and patients in ways that are seriously detrimental to patient health."

***What's to Come***

The Warning Letter and statements in the associated press release by the Directors of the Center for Devices and Radiological Health (CDRH) and Center for Drug Evaluation and Research (CDER) signal the FDA's renewed interest in LDTs and enforcement against healthcare providers that develop medium and high-risk LDTs without first seeking FDA clearance or approval. FDA's concern has been, and will continue to be, tests that impact the decision making of healthcare providers, such as selecting or changing drug treatment. Given the Warning Letter's focus on clinical validity, which echoes prior concerns expressed by FDA on genetic tests that have not sought premarket clearance, healthcare providers and companies that market genetic tests should ensure that they have robust evidence to support the analytical and clinical validity of their tests.

**9. Pharmaceuticals – Manufacturing Insights from FDA's Annual Report on Drug Quality**

The Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) within the US Food and Drug Administration (FDA) published its annual "Report on the Sate of Pharmaceutical Quality" in mid-May 2019. The yearly report reviews the quality of drug products during the prior year, as measured by recall and product defect information, site inspections of manufacturers, and other post market data. The report provides a few insights that companies may want to consider when working with, or acquiring, contract manufacturers.

- The US and EU Outperform Asian Countries. Sites that manufacture product for the US market must hold a FDA facility registration. The US, India, China, South Korea and Germany have the most manufacturing sites registered with FDA. The US, with 39%, has the lion's share of those. Of the inspections of the registered facilities, the inspection score for sites in the US and the EU, on average, are higher than the average scores for sites in China and India. The inspection score, on a scale of 1 to 10, reflects a site's compliance with current good manufacturing practice (cGMP). While FDA said that the average scores in Asia reflect an acceptable level of compliance, it noted that the trend highlights an opportunity for increased surveillance in certain geographies.
- The Majority of Inspections Occur Outside of the US. FDA notes that in FY 2018, 1346 inspections were performed, and the majority of those occurred outside of the US. FDA conducts inspections using a risk-based approach, so this trend makes sense, given the lower inspection scores—on average—of facilities in Asia and the Rest of the World.
- There is a Significant Increase in Outsourcing. Not surprisingly, outsourcing continues to affect the global supply chain. FDA saw an increase of 32% in registrations of Packaging & Labeling sites. Facilities that do not manufacture product, but that package/label products, must register as packaging/labeling facilities. This increase could reflect an increase in the outsourcing of packaging activities, which can increase the complexity of the supply chain.

- A Small Number of Manufacturing Sites Account for a Large Number of Drug Products. Three sites in the US account for almost 10% of all products listed with the US FDA. A similar trend is seen in Asia, where a few facilities in China and India account for more than 10% of all products listed in that region. Although the numbers reflect the number of products manufactured, not volume, the number of products is one of the risk factors FDA considers in prioritizing surveillance inspections.
- Sites Making "Non-Application" Products Consistently Underperform. When looking at data across geographies, FDA notes that sites manufacturing "non-application" products, including OTC products, homeopathic, and unapproved drug, "consistently underperform" sites that make application products (e.g., new drug applications (NDAs) and abbreviated new drug applications (ANDAs)). This trend likely has informed FDA's continued enforcement against manufacturers of homeopathic products, including a recent batch of Warning Letters to multiple companies for violations of cGMP requirements.

### 10. Tobacco: Regulating E-Cigarettes Remains Top Priority

On July 10, 2019 Ned Sharpless, M.D., the Acting Commissioner of the FDA issued a statement reaffirming FDA's commitment to overseeing the manufacturing, marketing, and sale of e-cigarettes. The statement outlined FDA's current and anticipated regulation of e-cigarettes, and discussed the balance of keeping e-cigarettes out of the hands of minors while exploring the potential for e-cigarettes to reduce adult smoking of more harmful tobacco products.

#### *FDA Shift In Focus*

In August 2016, FDA assumed authority over all electronic nicotine delivery systems ("ENDS") through its foundational "deeming rule." ENDS include finished products such as e-cigarettes, vapes, e-liquids, e-cigars, e-pipes, and e-hookahs, as well as components or parts such as atomizers, flavors, bottles containing e-liquids, and tank systems.

Regulating and overseeing ENDS has been a priority for FDA since assuming authority over these products in 2016. FDA's primary focus at the time, however, was curbing the use of combustible tobacco products, such as traditional cigarettes. FDA recognized that nicotine—a highly addictive substance—is most harmful when delivered through smoke particles in combustible cigarettes. And e-cigarettes could diminish the use of more harmful traditional cigarettes.

After market data from 2017-2018 showed an "epidemic-level rise" in youth use of e-cigarettes, however, FDA developed a laser-like focus on e-cigarettes. The market had become saturated with e-cigarette products in flavors and packaging appealing to youth. Fruit flavors such as mango, already banned in traditional cigarettes, were popular among youth. Some companies were more egregious than others in targeting adolescents. For example, in November 2018, FDA, in conjunction with the Federal Trade Commission (FTC) issued warning letters to companies selling e-liquids that closely resembled candy and cereals, such as Lucky Charms and Cinnamon Toast Crunch.

In response to the growing appeal of e-cigarettes to youth, FDA announced a shift in its compliance policy in March 2019. Under the revised policy, FDA ended its compliance policy for flavored ENDS (except mint and menthol-flavored). Previously, for all ENDS products on the market as of August 8, 2016 (the date of the deeming rule), FDA had announced its intention not to enforce premarket review requirements until August 2022, with the expectation that many such products would remain on the market. Under the revised policy, FDA put manufacturers and retailers on notice that they may be subject to FDA enforcement for selling flavored ENDS

products without authorization. FDA also tightened the deadline for companies selling all flavored ENDS products (other than tobacco-, mint-, and menthol-flavored) to submit premarket tobacco product applications (PMTAs) to August 8, 2021 (one year earlier than the agency previously proposed).

### *FDA Priorities*

Given the sharp increase in e-cigarettes among youth, and particularly teens, FDA will continue to go after retailers who sell to minors, including online outlets and brick-and-mortar stores. Companies that market their products to adolescents, whether in teen-friendly packaging or in teen-friendly flavors (e.g., fruit or food-like flavors), will continue to be targeted by FDA.

FDA also will invest in science and research to understand the short-term and long-term health effects of ENDS. Most importantly, FDA wants to understand whether e-cigarettes can be a less harmful alternative to traditional cigarettes. Acting Commissioner Sharpless recognized that there are data that show ENDS can reduce the use of combustible cigarettes and may be less harmful than traditional cigarettes. The promise in helping addicted adult smokers, however, must be balanced with the risk of exposing adolescents to e-cigarettes and potentially creating a much-larger population of nicotine addicts.