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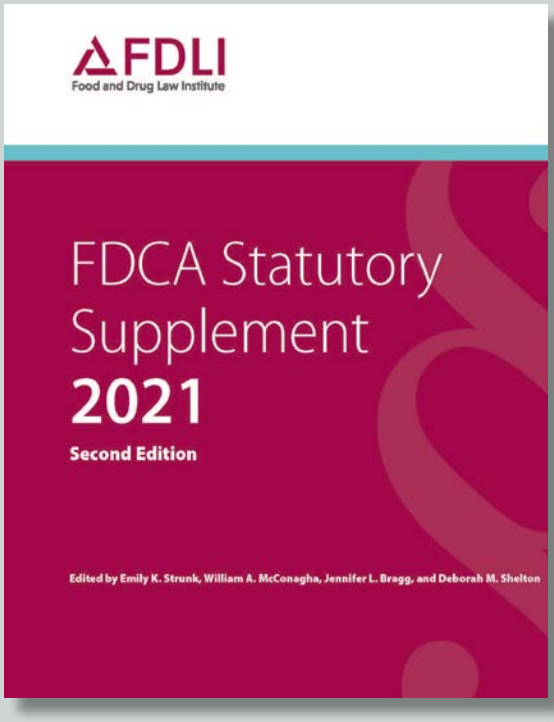
IN THIS ISSUE:

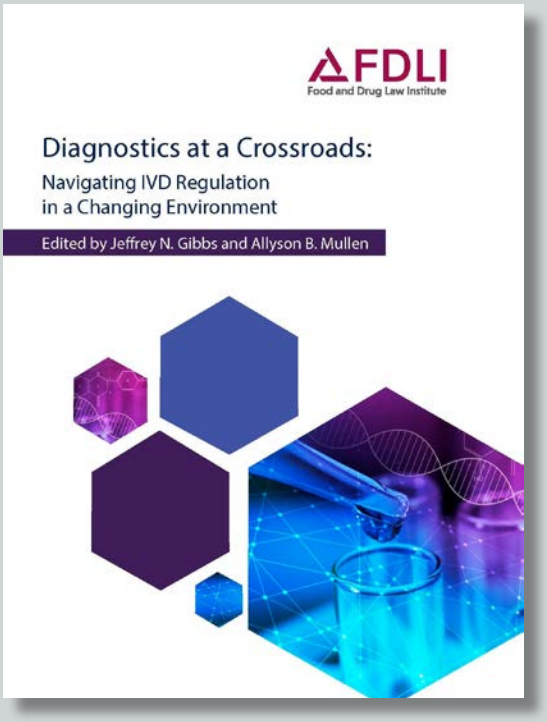
FDA Drug Manufacturing Oversight, Food and Supplement Class Action Suits, Bioengineered Food Disclosure, Juul Labs: Tobacco Harm Reduction, Pharmaceutical GMPs, Orphan Drugs in Canada

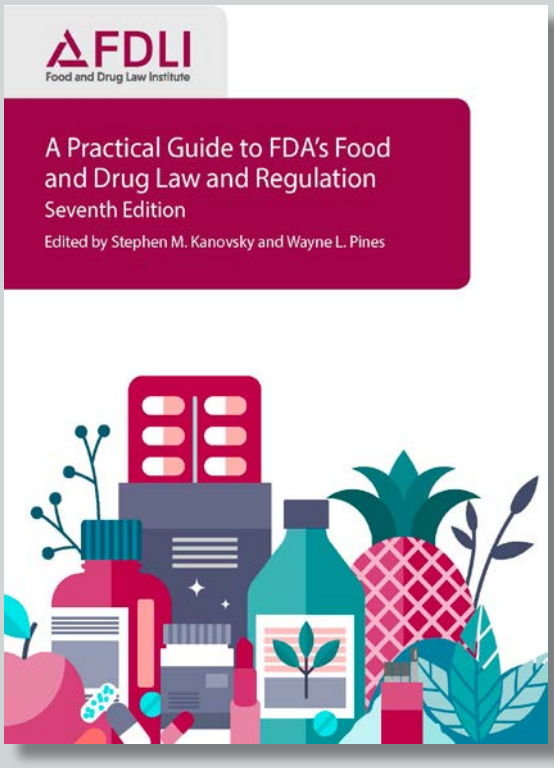
PLUS:

Recent FDA Activity in Cannabis Clinical Research, Annual 2021 Award Winners

NEW FDLI RESOURCES







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contents

Summer 2021

Features

Letter to the Editor

FDLI News

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FDA Drug Manufacturing Oversight During COVID-19: The GAO Report on the Inspections Backlog and Steps FDA is Taking to Address It

by Madeleine Giaquinto, Kalah Auchincloss, and Cynthia Schnedar

To date, restrictions put in place in light of the COVID-19 pandemic continue to impact the ability of the Food and Drug Administration (FDA or the agency) to inspect drug manufacturing facilities, which has generated a growing backlog of inspections, as well as a range of backlog-related concerns expressed by both the pharmaceutical industry (Industry) and Congress. Consequentially, on March 4, 2021, a Subcommittee of the U.S. House of Representatives' Committee on Appropriations held a hearing to better understand the inspections backlog and what could be done to address it.

The focus of this hearing was the January 28, 2021 report by the Government Accountability Office (GAO) entitled *COVID-19: Critical Vaccine Distribution, Supply Chain, Program Integrity, and Other Challenges Require Focused Federal Attention* (the GAO Report). The GAO Report provides insight into the depth of inspectional challenges faced by FDA during COVID-19, as well as possible next steps the agency could take to address these challenges. Testimony given by GAO Health Care Director Mary Denigan-Macauley at the hearing offered an update to the earlier more detailed findings conveyed in the GAO Report. In addition, GAO more recently reiterated the importance of the GAO Report recommendations regarding FDA drug manufacturing inspections through release of a new document called *Priority Open Recommendations to the Department of Health and Human Services (HHS)* (Priority Recommendations). In this latest update, GAO acknowledged that while FDA has made some improvements in its inspection planning process, FDA must continue to ensure that its inspection plans for future years "identify, analyze, and respond to the issues presented by the backlog of inspections that could jeopardize the goal of risk-driven inspections."

Since publication of the GAO Report and corresponding congressional testimony, FDA has released two other noteworthy documents related to inspections. First, on April 14, 2021, FDA released a guidance entitled *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency*, which introduced a new tool for conducting remote inspectional work during the pandemic. Second, on May 5, 2021, FDA issued its *Resiliency Roadmap for FDA Inspectional Oversight* to provide further transparency around adaption of the agency's

inspectional work during the pandemic.

In this article, we first review GAO's most recent findings on the state of the inspections backlog and its causes. We then review GAO's recommendations to FDA on addressing the backlog and FDA's response to those recommendations. Last, we review recent FDA efforts to address the backlog and potential permanent changes FDA may make going forward regarding oversight of drug manufacturing facilities.

GAO's Findings on the State of the Drug Manufacturing Inspections Backlog and its Impact on FDA Oversight

In March 2020, as the spread of COVID-19 became an established threat around the world, FDA suspended most foreign and domestic inspections of facilities that manufacture drugs intended for the U.S. market, continuing only with its "mission critical" activities. In July 2020, on-site, prioritized domestic inspections resumed, but only on a limited basis (i.e., depending on the local risk of COVID-19 infection), meaning that the agency's on-site inspections capability remained very limited.

Even before the current pandemic, GAO had existing "long-standing concerns about FDA's ability to oversee the increasingly global pharmaceutical supply chain." GAO reported that prior to COVID-19, FDA conducted pre-approval, surveillance, and for-cause inspections at all facilities that manufacture drugs intended for the U.S. market, amounting to about 1,600 inspections of approximately 4,200 facilities each year. Close to 60% of these facilities were located overseas, a third of which were in China and India. Given the backlog created by COVID-19, the GAO Report made clear that FDA now faces an even bigger challenge in overseeing the global pharmaceutical supply chain.

GAO Found a Sizeable Backlog of FDA Inspections

Notably, FDA's inspection metrics for 2020 pale in comparison to the same metrics reported in previous years. GAO reported that FDA was unable to complete more than 1,000 of its planned inspections in Fiscal Year (FY) 2020, leaving the total number of inspections of foreign and domestic facilities 56% lower than each of the previous two fiscal years. For domestic facilities, FDA conducted 52 inspections between March and October 1, 2020, but conducted about 400 inspections during the same time period in each of the two previous years. Foreign facilities experienced an even more drastic decrease, with FDA conducting only three inspections between March and October 1, 2020, compared to more than 600 inspections during the same time period in each of the previous two years.

GAO Found That the Inspections Backlog May Lead to Future Delays in Drug Approvals

In addition to quantifying the backlog, GAO expressed concerns that the agency will face challenges in carrying out its preapproval and surveillance oversight responsibilities in the future if the inspections backlog remains unaddressed. Specifically, the GAO Report noted that while FDA has not yet experienced serious delays in meeting user fee goal dates, the impact on approvals from delayed inspections may become more evident in the future.

While FDA reported that it was operating above its 90% on-time action performance goal for approval decisions as of November 2020, the GAO Report noted that the inspections pause had not yet had a significant impact on the agency's drug approval performance, because preapproval inspections typically occur months in advance of approval. Additionally, GAO noted that two of the Industry associations it spoke with

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expressed concern about this issue. Consequentially, GAO concluded that "[a] continued pause in preapproval inspections may lead to future delays in FDA drug approvals."

GAO Found That the Inspections Backlog May Require FDA to Alter Its Risk-Based Inspection Model for Surveillance Inspections

FDA conducts surveillance inspections according to a risk-based model that prioritizes the highest risk facilities for inspection in any given fiscal year, based on mandatory factors (sites that have never before been inspected or have not been inspected within the last five years) and other risk-based factors such as type of drug manufactured, length of time since last inspection, and previous compliance history. As noted above, FDA was unable to complete more than 1,000 of the approximately 1,500 planned surveillance inspections for FY20. These inspections will roll over into the site selection model for future fiscal years; thus, GAO found that the backlog could potentially threaten FDA's "strategic goal of shifting toward exclusively risk-driven surveillance inspections" if the agency does not make changes to the model.

GAO Found That FDA's Current Use of Alternative Tools is Not a Comprehensive Solution to Addressing the Inspections Backlog

GAO also noted that to keep up with some of its inspectional work during COVID-19, FDA adopted a range of alternative tools, such as use of inspections conducted by foreign regulators, use of statutory authority to request and review facility records remotely, and use of sampling and testing drug products imported from foreign manufacturers. GAO reported that despite FDA's vastly expanded use of such tools, this was not enough to avoid a backlog of mandatory on-site inspections. The GAO Report discussed each of these alternative tools and the concerns related to their longer-term utility.

FDA Use of Information From Inspections Conducted by Foreign Regulators

The first tool reviewed by GAO was use of information from inspections conducted by foreign regulators. GAO reported that FDA found information from inspections conducted by foreign regulators statutorily satisfies FDA inspectional requirements in some instances, but not in all. For example, inspections conducted in Europe by the 28 European regulators privy to the Mutual Recognition Agreement (MRA) have been deemed an acceptable substitute for an FDA inspection. Additionally, in light of COVID-19, FDA expanded recognition to inspections conducted outside of Europe by European regulators under the MRA, but only for 19 out of the 28 European regulators. No framework similar to the MRA exists to extend formal recognition of inspections conducted by regulators among the Pharmaceutical Inspection Cooperation Scheme (PIC/S), including Australia, Canada, Japan, and South Africa. Thus, information from inspections conducted outside of Europe by the other nine European regulators and by PIC/S members can only be used for purposes of "surveillance-level oversight" to inform the risk-based site selection model and are not acceptable substitutes for an FDA inspection. Moreover, like FDA, all relevant foreign regulators have also slowed their foreign inspection programs during COVID-19, limiting the ability of any regulatory authority to engage in on-site inspections.

Furthermore, FDA is most in need of information about facilities located in China and India; FDA conducted more inspections than any other foreign regulator in those countries prior to COVID-19. These countries, however, are not party to the MRA or other reliance agreements. Thus, although information from European and certain other foreign regulator inspections can substitute for FDA inspections, this information is either not available or does not qualify as a sufficient substitute for all needed inspections.

FDA Use of Records Requests "in Advance of or In Lieu of" an Inspection

The second tool reviewed by GAO, and the tool on which FDA relied most heavily during the pandemic, was use of FDA's authority to request records from facilities "in advance of or in lieu of" an inspection under Section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). A records request is not an inspection, but FDA was able to satisfactorily assess the compliance status of many facilities named in drug product applications by reviewing their records, and thus, was able to meet many user fee goal dates. However, FDA told GAO that "only FDA in-person inspections and European regulator reports can satisfy the Agency's statutory requirements for surveillance reports." GAO concluded that this tool has limited capability in mitigating the backlog of surveillance inspections, unless FDA's statutory authority is expanded or interpreted to include use of records requests as a true substitute for surveillance inspections (as opposed to merely providing supplemental information in advance of such an inspection to inform FDA's risk-based site selection model).

FDA Use of Information from Sampling and Testing of Product Obtained at the U.S. Border

The last tool reviewed by GAO was FDA's sampling and testing of drug products obtained at the U.S. border. GAO noted that FDA adjusted use of this tool during the pandemic to specifically target high risk drugs manufactured at foreign facilities where inspections had been postponed. Significantly, FDA pointed out that sampling and testing alone will not confirm if a manufacturing facility is meeting quality standards. Thus, this tool can only supplement an FDA inspection, but can never act as a substitute for one.

GAO's Recommendations to FDA for Improving Its Drug Manufacturing Oversight

The GAO Report made two recommendations intended to help FDA adapt its inspections program to most effectively carry out its drug manufacturing oversight responsibilities.

GAO Recommendation to Assess Use of Alternative Inspection Tools

GAO recommended that FDA "fully assess the agency's alternative inspection tools and consider whether these tools or others could provide the information needed to supplement the agency's regular inspection activities or help meet its drug oversight objectives when inspections are not possible in the future." Although listed second in the GAO Report, this recommendation captured the interest of Industry and Congress.

GAO observed that while FDA has substantially increased its use of Section 704(a)(4) records request authority, "the agency has not yet finalized a policy for how it can use this information to supplement its inspection activities." Note, however, that on January 29, 2021, one day after the GAO published its report, FDA issued revised guidance outlining its new interim process for communicating issues identified following a Section 704(a)(4) records request issued "in advance of or in lieu of" a pre-approval inspection. The revised guidance also provides information about FDA's expanded recognition practice under the MRA, as discussed earlier, which includes use of European regulators' inspection reports for facilities located outside of Europe.

GAO also noted that "FDA has not assessed whether inspections conducted by PIC/S members are equivalent to FDA inspections." GAO did not explicitly address any of the difficulties FDA would face in trying to implement a mutual recognition framework with those authorities. However, the report acknowledged that such an assessment would not be a quick solution, noting that it took FDA five years to complete a capability assessment of each European regulator in order to establish the MRA in the first place. We also note that in addition to the five-year timeline that accrued when conducting capability assessments in initial development of the MRA, the MRA also required a years-long negotiation between FDA and European regulators before assessments could even begin. Thus, while there may be agreement as to the concept, establishing additional mutual recognition agreements with other regulators could take many years to implement.

Most significantly, GAO recommended that FDA assess whether there are "additional tools" the agency should be using, specifically pointing to virtual inspections. GAO reported that four of five Industry associations it spoke with mentioned successful implementation of virtual inspections by foreign regulators, explaining that these regulators have used a range of virtual technologies to remotely conduct facility inspections. FDA reported to GAO that "the agency is in the process of assessing the potential use, including its authority to use, other tools to serve as supplements to FDA inspections, including using remote video and other remote and live interactions with establishment staff and records to evaluate drug manufacturing operations."

GAO Recommendation to Develop a Plan for Addressing the Inspections Backlog

Second, GAO recommended that FDA ensure "inspection plans for future fiscal years identify, analyze, and respond to the issues presented by the backlog of inspections that could jeopardize its goal of risk-driven inspections." In particular, GAO explained that FDA should adapt the risk-based model it uses to select inspection sites in order to loosen its definition or prioritization of "mandatory surveillance inspection." FDA's model, as of the date of the GAO Report, defined never-inspected facilities or facilities not inspected within the past five years as "mandatory surveillance inspections" because they present significant risks to pharmaceutical quality. Historically, FDA has prioritized mandatory surveillance inspections and used its remaining resources for inspections of other high risk facilities identified through the risk-based model. In its report, GAO expressed concern that unless more resources are allocated to the drug inspection program, the backlog of mandatory surveillance inspections would "dominate" FDA's surveillance inspection program, creating a situation where other high risk facilities would not be inspected.

Recent FDA Efforts Aimed at Addressing the Drug Manufacturing Inspections Backlog and Possible Longer-Term Oversight Changes

FDA made clear in its response to GAO that it would consider both recommendations as it assesses how to address the inspections backlog, although its ongoing pandemic response, and preexisting statutory and resource limitations, continue to burden implementation of significant change. Significantly, since release of the GAO Report in January and GAO congressional testimony in March, FDA has issued two documents that provide further transparency around how it will address inspectional concerns highlighted in the GAO Report. We review those documents below.

FDA Announces a New Tool Called Remote Interactive Evaluations

On April 14, 2021, FDA released a guidance entitled *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency*, introducing a new tool for conducting remote inspectional work during the pandemic. In the guidance, FDA describes a Remote Interactive Evaluation (RIE) as "any combination of [various remote] interactive tools" used to evaluate a drug or biologic manufacturing facility. RIEs apply to all drug inspection programs, including pre-approval or pre-licensing inspections; post-approval, routine surveillance inspections; follow-up and compliance inspections; bioresearch monitoring (BIMO) inspections; and inspections of 503B outsourcing facilities.

Importantly, however, RIEs are not outright inspections, and thus, the start and close of an RIE will not trigger issuance of FDA Form 482s and Form 483s. RIEs are instead intended to provide information to meet user fee commitments, update FDA's relevant internal databases, and inform the risk-based surveillance inspection site selection model. FDA will follow several similar inspection procedures in carrying out an RIE, such as holding closeout meetings and providing a written list of observations in which the facility will have 15 business days to respond. FDA will also issue final "remote interactive evaluation reports" in closing out an RIE.

RIEs are meant to complement other remote tools used by FDA during the pandemic. For example, an RIE may precede a request for information, possibly under Section 704(a)(4), in order to most efficiently conduct the RIE. Additionally, FDA will apply "risk management tools" to determine the need to conduct an RIE, similar to its approach taken with respect to other types of evaluations throughout the pandemic.

FDA's adoption of virtual technologies as a component of RIEs and other remote evaluations is encouraging news for Industry, which sees this approach as a more meaningful way to address the inspections backlog. However, since FDA caveated in discussions with GAO, as well as in the RIE guidance, that any remote evaluation is not a substitute for an on-site inspection under its current statutory authority, questions still remain as to how the agency will manage the inspections backlog in the longer-term. These questions will likely persist across Industry until more information is provided.

FDA Publishes Its Resiliency Roadmap for FDA Inspectional Oversight Moving Forward

On May 5, 2021, FDA issued a report entitled *Resiliency Roadmap for FDA Inspectional Oversight* (the Resiliency Roadmap). This report, which covers inspectional activities for all FDA-regulated commodities, provides updated information regarding FDA's inspectional activities during the pandemic and a roadmap for how it intends to prioritize its inspectional work as the pandemic continues.

Of particular interest, FDA provided updated statistics regarding delayed applications. According to the Resiliency Roadmap, FDA received more than 13,500 applications for all medical product approval/authorization between March 2020 and March 2021, and determined that of those applications, approximately 600 needed inspectional oversight of some type before action could be taken on the application. FDA reported that only 48 drug products were delayed solely because a GMP inspection could not be conducted. FDA noted that only six of the 48 delayed products were considered mission critical and that it had scheduled the inspections for those six mission critical products to occur by September 30, 2021.

FDA also reported on its queue of for-cause domestic inspections that are follow-up compliance actions after a previous domestic inspection resulted in "official action indicated" (OAI) classification. FDA reported that it was able to complete 90% of these OAI follow-up inspections in FY20 and noted that it had 79 OAI follow-up inspections still to be conducted for human and animal drug domestic facilities in FY21. However, FDA did not provide any statistics related to the number of OAI follow-up for-cause inspections in its queue for foreign inspections.

For surveillance inspections, FDA indicated that it was able to use remote tools to provide oversight on the relative

risk of some establishments. As a result, when reassessing facility risk to create the surveillance site selection list for FY21, some facilities that were included in the FY20 model are no longer included in the FY21 model. FDA did report that it had 857 remaining surveillance inspections for drug facilities planned for FY21, with the majority being domestic facilities.

In addition to providing inspectional statistics during the pandemic, the Resiliency Roadmap also includes an outline of FDA's plans for conducting inspections going forward, while noting that these plans will depend heavily on the course of the COVID-19 pandemic. In general, FDA will first conduct mission critical inspections (Tier 1) and then prioritize PAI/PLI inspections and for-cause inspections (Tier 2). Lower priority inspections that do not meet these criteria (Tier 3) may be postponed, which could include some routine surveillance inspections. FDA said that it will continue to use risk-based measures going forward, with longer intervals occurring between non-priority surveillance inspections. FDA is clear that the volume of surveillance work presents a significant challenge even in the best case scenario, and that as a result, FDA will continue to use remote alternative tools whenever possible.

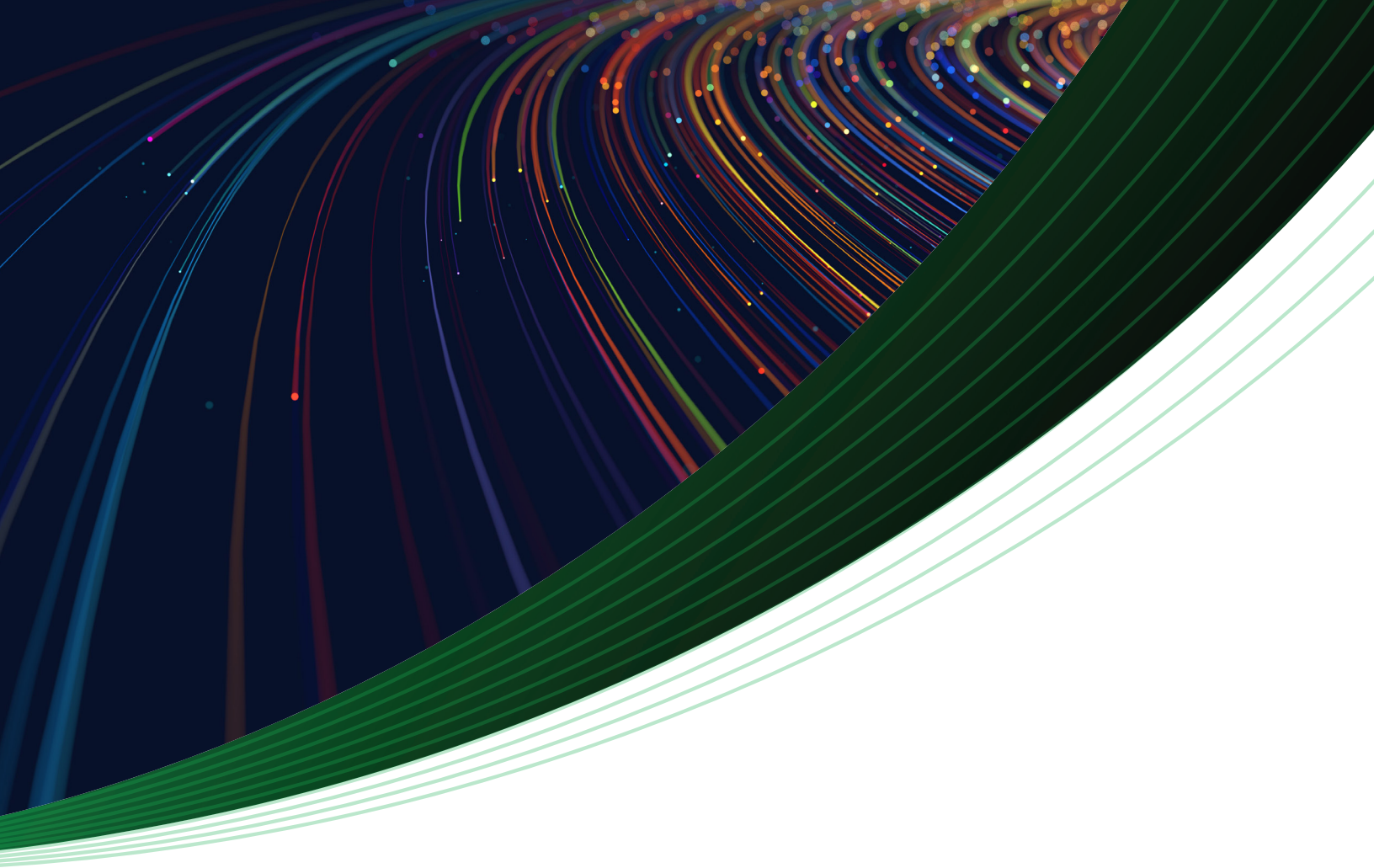
Notably, the workload estimates focus on domestic inspections and the small number of foreign inspections that can be accomplished by in-country FDA investigators, assuming that FDA will continue to prioritize mission critical foreign inspections, but that travel restrictions and other limitations will prevent FDA travel for foreign routine surveillance inspections. FDA also assumes that foreign authorities will conduct 25% of remaining medical product inspections.

Conclusion

In sum, the GAO Report captured concerns about the impact of the pandemic on FDA's inspections backlog and the risk it poses to the agency's oversight capabilities in the foreseeable future. Congressional testimony, as well as mounting calls from Industry, set the stage for FDA's recent adoption of certain additional oversight tools, as well as its longer range plans for use of other tools with more complex implementation requirements. FDA has made significant progress in implementing the GAO recommendations with its use of more innovative inspection alternatives, such as RIEs and the increased transparency provided in the Resiliency Roadmap. GAO subsequently acknowledged that FDA made some improvements, but reiterated its concern that FDA should continue to prioritize addressing inspection delays caused by the pandemic. Thus, while FDA's adoption of some additional tools to address the inspection backlog has been positively received, all eyes still will remain on FDA as it moves forward with implementing its use of these new tools and potentially adopts newer approaches to its drug manufacturing oversight in the future.

1. GAO Report, "COVID-19: Critical Vaccine Distribution, Supply Chain, Program Integrity, and Other Challenges Require Focused Federal Attention" (January 2021), available at https://www.gao.gov/assets/gao-21-265.pdf. This report was the GAO's fifth installment in its series of reports to fulfill the mandate imposed by the CARES Act to monitor and report on the federal response to the coronavirus pandemic (COVID-19).
2. Statement of Mary Denigan-Macauley, Testimony before the Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, Committee on Appropriations, House of Representatives, "Drug Safety: FDA's Future Inspection Plans Need to Address Issues Presented by COVID-19 Backlog" (March 2021), available at https://www.gao.gov/assets/720/712761.pdf.
3. GAO, "Priority Open Recommendations to the Department of Health and Human Services" (May 2021), available at https://www.gao.gov/assets/gao-21-527pr.pdf.
4. *Id.*
5. FDA Guidance, "Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency" (April 2021), available at https://www.fda.gov/media/147582/download.
6. FDA Report, "Resiliency Roadmap for FDA Inspectional Oversight" (May 2021), available at https://www.fda.gov/media/148197/download?utm_medium=email&utm_source=govdelivery.
7. *See supra* note 1 at 150, *citing* "Coronavirus Disease 2019 Update: Foreign Inspections" (March 2020), available at https://www.fda.gov/news-events/press-announcements/coronavirus-disease-2019-covid-19-update-foreign-inspections.
8. *See supra* note 1 at p. 151, *citing* "Coronavirus Update: FDA Focuses on Safety of regulated Products While Scaling Back Domestic Inspections" (March 2020), available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-focuses-safety-regulated-products-while-scaling-back-domestic#:~:text=Today%2C%20we're%20announcing%20that,domestic%20routine%20surveillance%20facility%20inspections.
9. *Id.*, *citing* "Coronavirus Update: FDA prepares for resumption of domestic inspections with new risk assessment system" (July 2020), available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-prepares-resumption-domestic-inspections-new-risk-assessment-system.
10. *Id.* at p. 148.
11. *Id.* at p. 149.
12. *Id.* at 155.
13. *Id.* at p. 149.
14. *Id.* at p. 151.
15. *Id.* at p. 154–55.

16. *Id.* at p. 155.
17. *Id.*
18. *Id.*
19. *Id.* at p. 154.
20. *Id.* at Executive Summary.
21. *Id.* at p. 157.
22. FDA Updated Guidance, "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers" (January 2021), available at https://www.fda.gov/media/141312/download.
23. *See supra* note 1 at p. 157.
24. *Id.*
25. *Id.* at Executive Summary.
26. *Id.* at p. 155.
27. *Id.*
28. *Id.* at p. 156.
29. *See supra* note 5.
30. *Id.*
31. *Id.*
32. *Id.*
33. *Id.*
34. *See supra* note 6.
35. The 13,500 applications included human drugs, animal drugs, devices, biologics, BIMO, and tobacco. FDA did not breakdown the number of applications by commodity.
36. *See supra* note 6 at p. 8.
37. *Id.* at p. 9.
38. *Id.* at p. 11.
39. *Id.* at p. 12.
40. *Id.* at p. 13–15.
41. *Id.*
42. *Id.*



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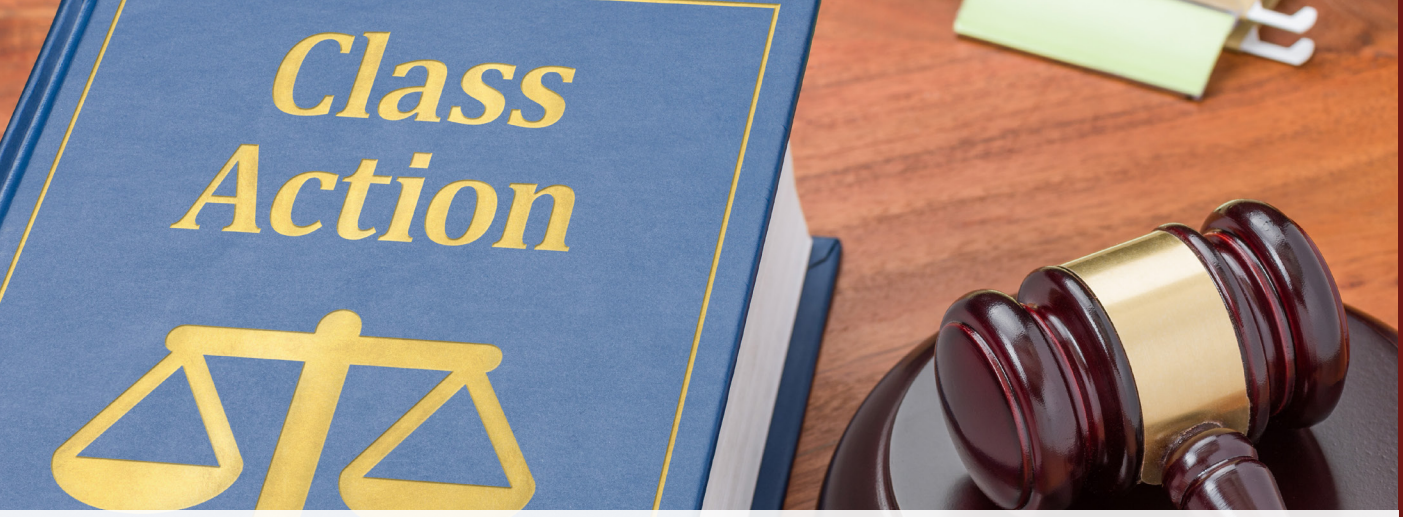

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Food and Supplement Class Action Suits

That Rely on Alleged Regulatory Violations

by Theodora McCormick

Historically, the majority of consumer class actions against food and dietary supplement companies were brought under state consumer protection statutes and premised on claims that consumers were misled by a product's advertising or labeling. In other words, class actions against food and supplement companies have traditionally been based on allegations of deceptive advertising, not regulatory compliance.

That, however, is starting to change.[1] As the food and supplement industries have evolved, and companies have streamlined their advertising and stopped using obviously problematic claims like "natural," "all natural," or "no artificial ingredients," challenges have emerged that are premised instead on alleged violations of complex regulatory schemes, as opposed to deceptive advertising or marketing, per se.

While it is well settled that consumers cannot privately enforce the Federal Food, Drug, and Cosmetic Act (FDCA),[2] litigants have employed a variety of approaches premised on state consumer protection statutes to indirectly bring the FDCA into play.

Most of these cases have been filed in California, with the U.S. District Court for the Northern District of California being the most frequent forum. California's Unfair Competition Law gives consumers a cause of action for almost any regulatory violation, even if the regulation does not expressly permit consumer enforcement.

This article highlights risk mitigation approaches companies may employ to address these types of claims.

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Product Classification Cases

Often prompted by warning letters from the Food and Drug Administration ("FDA Warning Letters"), these cases have primarily been brought against supplement companies selling products containing ingredients (CBD, for example) that are still under review by FDA. They are premised on the notion that such products are adulterated under the Dietary Supplement Health and Education Act of 1994 (DSHEA) and the

FDCA and are not dietary supplements at all, but rather unapproved drugs.

In an early case espousing this theory, the plaintiffs alleged that a supplement company was improperly marketing certain sports nutrition products as dietary supplements because they contained new dietary ingredients and the company had not complied with FDA's 75-day pre-market notice requirement. Because the plaintiffs' claims were premised on an alleged violation of the FDCA, the defendant moved to dismiss on the grounds that the plaintiff was improperly attempting to privately enforce the FDCA.

The district court agreed and granted the plaintiffs' motion, ruling that the plaintiffs' attempt to hold the defendant liable for an alleged violation of the FDCA via California and Illinois consumer protection statutes and unfair competition law was improper and dismissed all of the plaintiffs' claims premised on violation of the 75-day premarket notice requirement.[3]

Recently, two different sets of plaintiffs sought to employ class actions against a supplement company alleging that the company's weight loss products contained an ingredient that had not been approved by FDA and the products were therefore adulterated and not properly classified as dietary supplements. The plaintiffs alleged violations of various California and New York consumer protection laws.[4]

While the plaintiffs based their claims on deceptive labeling, their argument was predicated on the fact that the products were labeled as "dietary supplements." The plaintiffs relied on FDA Warning Letters and asserted that the challenged ingredient was either a "new dietary ingredient" for which FDA had not received the required new dietary ingredient (NDI) notification or it was an unsafe food additive.

The defendant responded that the matter wasn't an advertising case at all, but a product classification case. Namely, the plaintiffs were asking the court to assume regulatory powers and determine whether a product met the statutory definition of a dietary supplement under DSHEA, which was outside of the court's remit. Ultimately, both courts, one in the Central District of California and the other in the Northern District of California, agreed. The Central District dismissed the case on primary jurisdiction grounds and the Northern District entered a stay until June 2021, which will be converted to a dismissal without prejudice if FDA does not take final agency action before then in connection with the ingredient in question.[5]

Similar theories have been employed against companies selling CBD products. Such class actions allege that CBD products are illegally labeled and marketed as either dietary supplements or food.

FDA's position on CBD has been widely publicized in agency statements and in numerous FDA Warning Letters.[6] Because FDA Warning Letters do not constitute final agency action, and FDA in guidance statements has made it clear that it is working on developing regulatory pathways for the lawful marketing of cannabis and cannabis-derived products, motions to stay based on the primary jurisdiction doctrine[7] continue to be effective in addressing these suits.

Most recently, the Central District of California issued a pair of orders staying two class action suits against different companies selling CBD products on primary jurisdiction grounds. The court granted both companies indefinite stays until "the FDA completes its rulemaking and/or Congress passes legislation regarding the definitions, marketing, and labeling of CBD products."[8] The court observed that greater clarity was needed on whether CBD products are drugs, dietary supplements, or food products, and what standards should apply to these products.

Vanilla Flavoring Cases

In the last two years, the food and beverage industry has encountered lawsuits predicated on the absence in the product labeling of certain qualifying language required by FDA regulations. When a product does not contain enough of a commonly expected ingredient to independently characterize the flavor, and instead uses natural and/or artificial flavors, certain qualifying language is required such as "flavored," "naturally flavored," or "artificially flavored," among others, to signal there are additional flavor ingredients in the product.[9]

Plaintiffs assert that when a product (*e.g.*, vanilla flavored dairy or alternative dairy products, ice cream, almond milk, or soy milk) is characterized as "vanilla" without the required qualifying terms, consumers presume that the entire flavor profile is derived from vanilla beans and therefore, any product labeling that does not exactly match FDA regulations is misleading.

Most of these cases are in their infancy, and it is unclear whether courts will leave the technical compliance issue to FDA or let the cases proceed. Since the focus of these actions is on consumer deception, as opposed to technical compliance with FDA regulations, it seems likely that courts will allow the cases to proceed. However, there are a large number of motions to dismiss pending, and the landscape for "Vanilla flavored" litigation may change.

Nutrient Content Claims

Nutrient content claims refer to the amount of a nutrient in a product or compare the levels of a nutrient in that food to a similar food. When referring to the amount of a nutrient in a product, words such as "low," "free," and "high" are often used. Examples include "low-calorie," "high-fiber," "sugar free," and "fat free." Nutrient content claims that compare levels of a nutrient employ words like "reduced," "more," and "light." Examples include "reduced sodium" or "more fiber." The Nutrition Labeling and Education Act of 1990 permits the use of label claims that characterize the level of a nutrient in a food (*i.e.*, nutrient content claims) if they have been authorized by FDA and are made in accordance with FDA's authorizing regulations.

Food and supplement makers have recently seen class action lawsuits predicated on an alleged failure to comply with FDA's authorizing regulations related to nutrient content claims. For example, FDA regulations require that products that are labeled "sugar fee" that are not "low" or "reduced calorie" foods must include immediately accompanying warnings disclosing that the product is "not a reduced calorie food," or "not a low calorie food" or "not for weight control."[10]

Some might argue that failure to include the required warning is merely a technical violation that could not possibly mislead a reasonable consumer because the number of calories is listed on the label. In other words, the information that is intended to be conveyed by the missing qualification is actually available on the label itself.

However, plaintiffs' lawyers have maintained that in the 9th Circuit, the "reasonable consumer test"[11] is a requirement under the "unlawful" prong of California's Unfair Competition Law (UCL) only when it is an element of the predicate violation, relying on the 9th Circuit's decision in *Bruton v. Gerber Products Company*.[12] Plaintiffs have asserted that because these types of claims are predicated on violations of California's Sherman Law, which incorporates standards set by FDA regulations, and because FDA regulations such as the one requiring certain warnings for foods that are "sugar free" but not low calorie include no requirement that a reasonable consumer be deceived, even a bare technical violation of FDA regulations gives rise to a claim under California's UCL.

Despite these arguments, the 9th Circuit does not appear ready to abandon the "reasonable consumer" test. Recently, the Northern District of California held that no reasonable consumer could be deceived regarding a product's sugar content and whether it may or may not be healthy as a result, "when the product's label plainly discloses the amount of sugar in the product."[13] Similarly, the Northern District of California also held that "[n]o consumer, on notice of the actual ingredients described on the packing including honey and sugar, could reasonably overestimate the health benefits of the bar merely because the packaging elsewhere refers to it as a health bar . . . ."[14]

While these lawsuits seem to be on the rise, it is difficult to track to what extent. Most start with private, pre-suit demand letters, and while there are many filed lawsuits asserting these kinds of claims, most are disposed of outside of court to avoid the time and expense associated with protracted litigation.

Conclusion

While these types of cases may be on the rise, food and supplement companies can take steps to mitigate the risks:

First, a manufacturer should ensure that labels comply with governing FDA regulations. If a company has never done a label review, or hasn't done one in several years, it's always beneficial to conduct an audit of all current labeling and marketing materials to ensure that they are compliant with current FDA regulations.

Second, manufacturers should review labeling and advertising not just from a technical compliance perspective, but also from the vantage point of a consumer to ensure that the company isn't making express or implied claims that cannot be substantiated.

Third, a manufacturer should review and ensure adequate and solid substantiation for any and all claims (express or implied) about products.

Finally, a manufacturer encountering such a suit may wish to consider whether preemption or primary jurisdiction defenses can be asserted at the outset to avoid protracted litigation.

1. The Center for Science in the Public Interest (CSPI) was an early adopter of using regulatory violations to undergird claims that certain advertising violated state consumer protection laws. In October 2016, CSPI filed a complaint in the U.S. District Court for the Eastern District of New York alleging that PepsiCo marketed its Naked line of beverages in a false and misleading manner, in violation of state consumer protection and unfair competition laws. *Lipkind v. Pepsico, Inc.* No. 1:16cv-05506. In furtherance of these allegations, CSPI asserted that PepsiCo's "no sugar added" claim was misleading and violated 21 C.F.R. §§ 101.2 and 101.60(c)(2)(v) because it was not sufficiently prominent and omitted the instruction to seek "further information on sugar and calorie content." The

Complaint was voluntarily dismissed in September 2017.

2. 21 U.S.C. § 337(a) ("[A]ll such proceedings for the enforcement, or to restrain violations, of [the FD&C Act] shall be by and in the name of the United States.").
3. *Dabish v. Muscelpharm Corp.*, Civil Action No. 3:15cv02848 – CAB-RBB.
4. *Rosas v. Hi-Tech Pharmaceuticals*, Case No. CV 20-00433-DOC-DFM, 2020 WL 5361878 (July 29, 2020); *Ottesen v. Hi-Tech Pharmaceuticals, Inc.*, Case No. 19-cv-07271-JST.
5. *Rosas v. Hi-Tech Pharmaceuticals*, Case No. CV 20-00433-DOC-DFM, 2020 WL 5361878 (July 29, 2020); *Ottesen v. Hi-Tech Pharmaceuticals, Inc.*, Case NO. 19-cv-07271-JST, Document No. 56.
6. *See* Press Release, U.S. Food & Drug Admin. FDA Warns Companies Illegally Selling Over-the-Counter CBD Products for Pain Relief (Mar. 22, 2021), https://www.fda.gov/news-events/press-announcements/fda-warns-companies-illegally-selling-over-counter-cbd-products-pain-relief.
7. Primary jurisdiction is a prudential court doctrine that allows courts to stay, or less commonly, dismiss, matters pending initial decision-making within the competence of an administrative agency. *Clark v. Time Warner Cable*, 523 F.3d 1110 (9th Cir. 2008).
8. *Dasilva v. Infinite Prod. Co.*, No. 2:19-cv-10148 (C.D. Cal. Mar. 3, 2021); *David v. cbdMD, Inc.*, No. 2:19-cv-10241 (C.D. Cal. Mar. 3, 2021).
9. 21 C.F.R. § 101.22 (i).
10. 21 C.F.R. § 101.60(c)(1)(iii).
11. Because a claim's meaning can be subjective, nearly all states use the "reasonable consumer" standard. It is an objective standard that is not based on whether the consumer filing the suit was misled, but rather on whether a reasonable consumer would likely have been misled under the circumstances.
12. 703 Fed. Appx. 468, 2017 WL 3016740 *2 (9th Cir. July 17, 2017).
13. *Truxel v. General Mills Sales, Inc.*, 2019 WL 3940956 (N.D. Cal. Aug. 13, 2019).
14. *Clark v. Perfect Bar, LLC*, 2018 7048788 (N.D. Cal. Dec. 21, 2018).

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New Bioengineered (aka GM) Food Disclosure Law: Useful Information or Consumer Confusion?

by Gregory Jaffe and Jennifer Kuzma

Farmers began growing genetically modified (GM) crops in 1996, and today, U.S. farmers grow GM varieties of ten crops, including the vast majority of U.S. acreage of corn, soybean, upland cotton, sugar beets, and canola. However, their introduction has not been without public controversy, including calls to label food products made from those crops. In 2016, Congress passed, and President Obama signed, the National Bioengineered Food Disclosure Law (NBFDL), establishing an obligation for food manufacturers to disclose to consumers whether their food products are bioengineered or contain bioengineered ingredients. The U.S. Department of Agriculture (USDA) finalized regulations for implementing that law in late 2018, requiring food manufacturers to comply by January 1, 2022.

In this article, we explore whether the law and associated regulations provide consumers who want to know whether foods are bioengineered with adequate information to make informed decisions about bioengineering as part of their food choices. We first describe the events that led up the passage of the NBFDL and then briefly explain how the law will operate.

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Then, we analyze how the law will be implemented and whether it will inform or confuse consumers. Finally, we provide recommendations for regulatory revisions and consumer education that are necessary to make the law useful to consumers.

Background

Until 2016, there was no mandatory requirement to label or disclose whether foods came from GM crops. The U.S. Food and Drug Administration (FDA), the agency tasked with regulating food safety and nutrition labeling for most of the U.S. food supply, has stated that "bioengineered foods do not differ in any meaningful or uniform way or present any different or greater safety concern than food developed from traditional breeding." They also concluded that "the method of development of a new plant variety is generally not material information . . . and would not usually be required to be disclosed in the labeling for the food."[1] However, they did develop a guidance for industry, which they finalized in 2015 and revised in 2019, that allowed manufacturers on a voluntary basis to label foods with information about whether the food was or was not derived from genetically engineered plants.[2]

To date, many manufacturers have voluntarily labeled foods as "non-GMO" using various standards established by NGOs and industry. However, very few, if any, food manufacturers voluntarily labeled foods as affirmatively containing GM ingredients. Separately, the National Organic Program at the USDA excludes foods made with GM ingredients from being labeled as "organic" (7 U.S.C. 6524). Consumers seeking to avoid GM products have been able to do so by buying organic, although often those foods are more expensive than non-organic foods. They can also purchase foods with a "non-GMO" designation, or foods made solely from crops and animals that are not GM. However, for many consumers wishing to avoid GM products, the marketplace is confusing.

Congress Passes the National Bioengineered Food Disclosure Law

In 2016, Congress passed, and President Obama signed, the NBFDL, establishing an obligation for food manufacturers to disclose to consumers whether their food products are bioengineered or contain bioengineered ingredients.[3] Passage of the NBFDL was largely prompted by (1) polls and other data supporting mandatory labeling of GM foods; and (2) legislative action at the state level that could have created a patchwork of different requirements. Studies show that, overall, consumers desire GM food labels and prioritize them over other types of labels.[4] Consumers are willing to pay a premium for foods labeled as non-GM over those labeled as GM under different labeling conditions proposed by the NBFDL,[5] although there is heterogeneity among types of consumers in their GM food choices and labeling preferences.[6]

Prior to the NBFDL, consumer and organic foods advocacy groups pushed for GM labeling laws, and many states had introduced bills and ballot initiatives to require mandatory GM labeling. In 2016 alone, 70 bills were introduced in 25 states to address the labeling of GE foods.[7] Three states—Vermont, Maine, and Connecticut—enacted mandatory labeling laws.[8] However, it was the Vermont law that pushed Congress to act as it went into effect on July 1, 2016, forcing food companies to begin labeling their food packages. The need to label all their food products because of the Vermont law (because food companies do not produce products for just one state) and the possibility of a confusing patchwork of GM labeling requirements if other states enacted laws with different obligations were likely to be burdensome to food manufacturers, producers, and suppliers.[9]

The NBFDL preempted all state laws, rendering the Vermont law moot. The federal government would become the place for mandatory bioengineered disclosure instead of state governments. USDA's Agricultural Marketing Services, not FDA, was designated as the agency to oversee implementing bioengineered disclosure.[10]

The Mechanics of Disclosure under the NBFDL and USDA's Regulations

Who Discloses and How

The NBFDL[11] and USDA's regulations[12] put the burden of disclosing GM products and ingredients on food manufacturers, who can make the disclosure in four different ways: (1) a textual description on the package that the food is "bioengineered" or "contains bioengineered ingredients"; (2) a USDA-designed symbol on their package indicating "bioengineered" (Figure 1); (3) an electronic or digital link on the package, which when scanned by the consumer, goes to a website disclosure; or (4) a telephone number on the package that consumers can text to receive the disclosure.

When the law was being developed, many food manufacturers pushed for the electronic or digital-link option. That option requires consumers to take an active step to access the information at the point of sale. An electronic QR code

would be on the package, which consumers scan to get the disclosure information. Since the bioengineered content information is provided to the consumer electronically, the law is characterized as requiring "disclosure" rather than "labeling."

What Terms Can Be Used.

The NBFDL uses "bioengineered" but provides USDA with the discretion to allow other "similar" terms.[13] In the regulations, USDA determined that "bioengineering and bioengineered food accurately reflected the disclosure and the products and potential technology at issue," and that using additional terms might cause marketplace confusion.[14] Thus, manufacturers may use only the term "bioengineered" and are prohibited from using "genetically engineered," "genetically modified," or "GMO"—terms more commonly understood by consumers.

The manufacturer either states the food product is "bioengineered" (if all ingredients are bioengineered) or "contains bioengineered ingredients." The regulations prohibit the manufacturer from identifying specific ingredients from bioengineered organisms. The same terms and language must be used for the electronic and text disclosure options.[15]

Which Foods Do and Do Not Require a Disclosure

The NBFDL defines "bioengineered" as any food "(a) that contains genetic material that has been modified through in vitro recombinant DNA techniques; and (b) for which the modification could not otherwise be obtained through conventional breeding or not found in nature."[16] USDA's regulations interpreted this definition to only cover foods with detectable levels of altered genetic material (e.g., a piece of GM sweet corn) or food products with ingredients containing detectable levels of altered genetic material (e.g., frozen mixed vegetables with GM sweet corn).[17] USDA decided that refined products originating from bioengineered crops but without engineered DNA are not "bioengineered." Foods containing highly refined ingredients such as soybean oil from GM soybeans or sugar from GM sugar beets will not require disclosure. That decision is consistent with the GM labeling requirements in some countries (e.g., Japan and Australia) but not others (e.g., the European Union). USDA published a list of bioengineered crops and animals that need disclosure and will update that list periodically.[18]

The NBFDL and regulations do not require disclosure for certain bioengineered foods including: (1) restaurant food; (2) foods produced by "very small manufacturers," defined as having receipts less than $2,500,000; (3) food made from animals fed bioengineered organisms; and (4) foods where one or more ingredients have BE content that is inadvertent or technically unavoidable if it is not more than 5% of any ingredient.[19]

The disclosure requirement applies to all food regulated by FDA but does not apply to certain foods containing pork, beef, sheep, goat, catfish, chicken, turkey, domesticated birds, and egg products, which are regulated by USDA.[20] Bioengineered animals, except for fish, seafood, and game animals, and foods that contain ingredients from those animals are exempt. The law and regulations require disclosure for foods containing non-bioengineered meat, poultry, or eggs which contain a bioengineered ingredient if either: (1) the first ingredient is something other than meat, poultry, or egg; or (2) the first ingredient is water, stock, or broth and the second ingredient is something other than meat, poultry, or eggs.[21]

What Can Be Voluntarily Disclosed

While food manufacturers wanted to voluntarily disclose additional details about bioengineered foods, USDA's final rule limits voluntary disclosures. The regulations only allow manufacturers to voluntarily disclose in two situations.[22]

First, a manufacturer may disclose that a refined food or ingredient in that food originated from a bioengineered food, such as disclosing that corn syrup in a carbonated beverage originated from bioengineered corn. The refined product disclosure can state "derived from bioengineering" or "ingredient(s) derived from a bioengineered source," and the word "ingredient" can be replaced with the specific crop or food ingredient (contrary to the mandatory "bioengineered" disclosure, which does not permit identifying specific bioengineered ingredients).[23] The voluntary disclosure also can use a USDA-designed "derived from bioengineering" symbol (Figure 1).

The second voluntary disclosure allowed is for very small food manufacturers, who are exempt from mandatory disclosure but can voluntarily disclose that their foods are bioengineered or contain bioengineered-derived ingredients.[24]

Analysis

When the bioengineered foods disclosure requirement is implemented in 2022, will it provide information useful to consumers or will it lead to more confusion? While the NBFDL establishes mandatory disclosure for bioengineered food content, the information disclosed may not be useful for several reasons.

The Disclosure Itself is Confusing. The NBFDL switches from the common term "GM," which is more familiar to consumers, to "bioengineered" (BE). The intent of this change may have been

to avoid the contentious history of "GM foods" by renaming them, but it could instead undermine consumer trust if consumers see it as a tactic to mask terms they commonly understand.[25]

Also, the regulations do not allow for manufacturers to identify the specific bioengineered ingredients in their product, which could result in consumers making incorrect assumptions about what is bioengineered in the food supply. For example, a frozen vegetable pizza with some GM green squash would be disclosed as "contains a bioengineered ingredient." However, the consumer is likely to incorrectly assume that one of the major ingredients in pizza—the wheat, the tomato sauce, or the cheese—is bioengineered, not a minor ingredient such as squash. Disclosure by ingredient, which is required in the European Union, would provide useful information to consumers instead of consumers potentially misinterpreting the scope of the product's bioengineering.

The Electronic Option May Not Be Accessible. By allowing manufacturers to choose their disclosure option, the regulations may make it difficult for some consumers to access the information, especially at the point of sale. Some consumers may not know how to scan electronic codes or realize that they can get the disclosure from a telephone text. A Deloitte study commissioned by USDA found: "Of 40 in-depth conversations with consumers, all 40 either did not recognize the on-package digital link or did not associate it with food information. Retailers were also unfamiliar with digital links and thus were unable to assist consumers."[26] Furthermore, in rural areas, access to broadband internet is an issue. Recently, a lawsuit was initiated challenging USDA's regulations, claiming that some disclosure options are discriminatory since not everyone has a smartphone or internet access.[27] It is currently not clear whether manufacturers will choose the digital disclosure option. Recently, one major food company, Ahold Delhaize USA, announced that its private label products will have "clear on-package Bioengineered Food labeling."[28]

While an electronic disclosure may be difficult for some consumers to access, it does have some advantages. Stating that a food has bioengineered content does not really provide sufficient information for many consumers, who might want to know not only which ingredients came from genetic engineering, but why genetic engineering was used. By providing the information on a website, the food manufacturer can provide additional information other than the required few word disclosure and link to additional resources, resulting in consumer education on the topic.

The Exemptions are Confusing. Excluding highly refined ingredients without "modified DNA" will significantly limit the number of food products requiring disclosure. It is unclear whether manufacturers will voluntarily disclose highly refined ingredients derived from bioengineered crops. During the rule-making process, some manufacturers advocated for disclosing highly refined ingredients because that's what their consumers want, they wanted to be more transparent, or they wanted uniform disclosures.[29] Manufacturers provided evidence to USDA that consumers expected these products to have a disclosure and that they wanted to meet consumer expectations.[30] If there are two identical products (e.g., corn oil), but only one makes a voluntary disclosure, consumers might make their choice based on a distinction that does not exist.

Additionally, the exemption for certain products that have ingredients regulated by USDA will make it difficult for consumers to be confident that a food without a disclosure is not bioengineered. For products like soups or pizzas with meat ingredients, the relative quantity of meat in the product will determine if it requires disclosure. As an illustration, Figure 2 has the label of two Progresso chicken noodle soups. Disclosure is not required if chicken is the first or second ingredient (after broth or water), but it is required when it is the third ingredient. Determining whether a product falls within an exemption will require consumers to understand the exemptions and then closely read the ingredient list.

USDA Did Not Address Absence Claims. The law and regulations do not address the issue of absence claims, which are claims that a product does not contain bioengineered ingredients. The law states that any certified "organic" food can make an absence claim as the National Organic Standards exclude GM ingredients from being certified as organic (7 U.S.C. 6524). Also, the law states that if a food does not require disclosure as "bioengineered," it does not mean it can claim to be "not bioengineered" or "non-GMO."[31] USDA did not include in the regulations any provisions specifying when a food can be labeled "not bioengineered" or "non-GMO."

For many years, private labeling bodies and individual companies have set their own standards for when a food is "non-GMO." Non-GM foods sales increased from $12.9 billion in 2021 to $21.2 billion in 2016, and 46% of U.S. consumers report actively avoiding GM foods.[32] Those claims receive no oversight by USDA.

They may be covered by FDA's guidance on voluntary labeling for foods from GM plants.[33] However, that guidance only applies to FDA-regulated food products, not products with meat or poultry ingredients, and FDA has not enforced compliance for absence claims. Currently, non-GM claims can be misleading to consumers, as some non-GMO claims are made on products where there are no GM varieties (e.g., 100% orange juice when no GM oranges exist).[34] USDA could have cleared up this confusion in its regulations but chose not to do so.

Conclusion: A Better Path Forward

The impacts of the NBFDL remain to be seen, but it is apparent that when the disclosures arrive, it is likely to be confusing to consumers for all the reasons stated above. The disclosure will enter a marketplace with an already-confusing landscape of GM-related information (including organic and non-GMO claims) (Figure 1).

To remedy the confusion, we propose four interventions. First, we believe there should be education and information dissemination campaigns by the federal government (primarily FDA and USDA), food manufacturers, and retailers. Implementation will require resources to FDA and USDA and coordination between federal agencies and industry. Those campaigns should explain the NFBDL so consumers can access and understand the information being provided. The campaign should introduce consumers to the term "bioengineered," explaining that this is the same as "GMO," or "genetically engineered." The campaign also should provide information about accessing the disclosure, as well as alert consumers to the exemptions and types of voluntary disclosures. Finally, an education campaign should provide information about the lack of food safety or nutritional differences between bioengineered and conventional foods and information explaining that risks or benefits vary by product. FDA was tasked by Congress several years ago to develop an educational initiative to better understand GM foods. The result of this initiative has been the publication of fact-based information on their website, which is a useful resource.[35] However, FDA's information does not explain the disclosure requirements in detail, nor does FDA have the resources to reach the average consumer with that information.

Secondly, given the consumer confusion that the regulations are likely to cause, USDA should reconsider whether to allow the substitution use of similar terms to bioengineering, such as "genetic engineering" or GM. As described above, the USDA rules currently do not allow for these substitutions.

Third, USDA should reconsider disclosure of highly refined ingredients in recognition that consumers would be best served by consistent disclosure of products "derived from bioengineering." USDA should also allow manufacturers to specify the bioengineered ingredients. This would enable consumers to associate bioengineering with specific crops and ingredients, educating them about where the technology is used in agriculture and food and providing detailed information about which bioengineered ingredients are in a food.

Finally, USDA should consider regulating absence claims. A national standard would provide uniformity ensuring consumers who want to purchase non-GMO foods are getting what they paid for.

In conclusion, now is the time for the government and the food industry to address the potential consumer confusion before the disclosures in 2022 result in consumer frustration and mistrust. If the goal of greater information to consumers is to be realized, USDA should rethink its regulations and consumers should be educated about the disclosures being provided.

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Figure 1: **Different Information That Will be Available to Consumers Starting in 2022.**

The text in red and italics in each column represents the categories to which labels in the corresponding column would apply. Black text in each column represents the text that would constitute the food label.

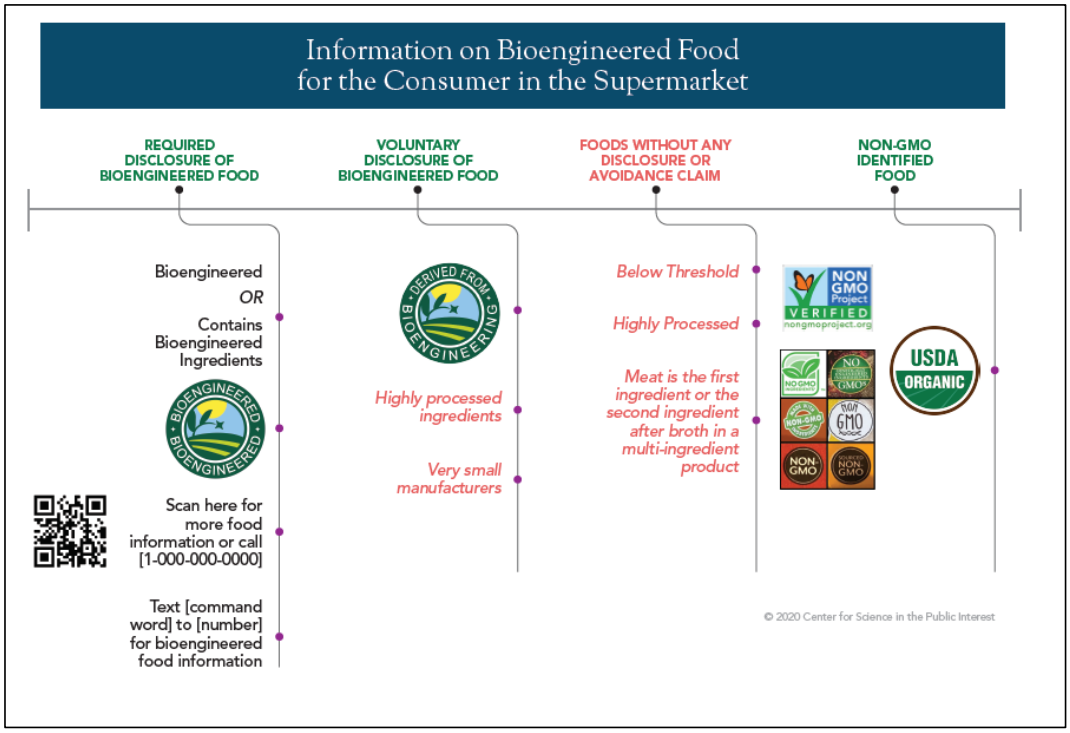

Figure 2: **Example of Consumer Confusion Through Two Cans of Soup**

The figure shows how the NBFDL applies to products that contain meat as a major ingredient. The first soup can for Progresso Chicken Noodle Soup (A and B) has broth as a first ingredient and chicken as the second ingredient; it is not covered by the NBFDL and will not disclose if any ingredients are bioengineered. The second soup can for Progresso Roasted Chicken Noodle Soup (C and D) has broth as the first ingredient, carrots as the second ingredient, and chicken as the THIRD ingredient; this soup is covered by NBFDL and will require disclosure if it has bioengineered ingredients.

Juul Labs: Advancing the Scientific Dialogue About Tobacco Harm Reduction

by Joe Murillo

2021 will be a transformational year for the U.S. nicotine and tobacco landscape. The Food and Drug Administration (FDA or agency) is expected to make decisions on marketing orders on premarket tobacco product applications (PMTAs) for new tobacco products, including electronic nicotine delivery systems (ENDS). The FDA's PMTA pathway to market, established by the Family Smoking Prevention and Tobacco Control Act, is a rigorous science- and evidence-based process of evaluating new tobacco products to determine whether they are appropriate for the protection of public health. The PMTA process is unique throughout the world and, without a doubt, will provide the most comprehensive scientific assessment by regulators of the public health impact of new, noncombustible tobacco products.

Determining the public health impact of alternative noncombustible tobacco products, and providing a process for their marketing authorization, is a key tenet of the agency's 2017 Comprehensive Plan for Tobacco and Nicotine Regulation. Under the Comprehensive Plan, FDA seeks to implement science-based regulations that will help smokers who would not otherwise quit move down the continuum of risk to less harmful noncombustible nicotine alternatives. The Comprehensive Plan is firmly rooted in the concept of tobacco harm reduction—and nicotine is its centerpiece. The PMTA process is crucial to realizing FDA's vision because it provides a regulatory process for promoting innovation and ensuring a well-populated marketplace of scientifically validated, less harmful noncombustible nicotine alternatives.

In addition to its focus on helping adult smokers, the agency is also prioritizing the prevention of underage use of all tobacco and nicotine products through both enforcement, including flavor restrictions, and education initiatives. Chief among these is the December 2019 enactment of Tobacco 21 (raising the minimum age of purchase for tobacco products to 21) and FDA's efforts to ensure its immediate and uniform enforcement. We are beginning to see trends moving in the right direction as the 2020 National Youth Tobacco Survey data found

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an approximately 30% decline in all past-30 day underage vaping, and a 70% decrease in the number of youth who self-reported JUUL as a primary brand. We are encouraged that underage use has declined significantly, which shows the importance of evidence-based interventions, but realize more must be done. We remain committed to working with regulators and stakeholders to combat underage use.

Juul Labs supports and respects FDA's oversight role of our category. Our July 2020 PMTA submission was based upon rigorous scientific research. The submission detailed the science and evidence responsive to FDA's requirements, including information about our products' impact on the individual user, their ability to help adult smokers transition away from combustible cigarettes, and their net-population impact on public health. As part of the PMTA process, we provided FDA all the scientific data we have collected on our submitted products, in addition to the statistical code underlying our analyses.

Our submission includes scientific evidence for the JUUL Device and JUULpods in Virginia Tobacco and Menthol flavors at nicotine concentrations of 5.0% and 3.0%, as well as information on data-driven measures we are implementing to combat underage use of our products. In all, it contains over 110 original scientific studies and 125,000+ pages of data and analysis across a whole range of disciplines. From chemistry, to toxicology, to clinical studies, to behavioral research, to a population model that ties it all together.

While FDA is ultimately responsible for analyzing the scientific evidence about our products and making a determination regarding their public health impact, we also appreciate that scientists and the public health community have an important interest in better understanding our research. In addition to our own studies, many independent researchers are actively involved with ENDS research, including research on JUUL products. As of this writing, over 150 scientific papers have been published with "JUUL" in the title and/or abstract. The company has benefited and learned from much of this research, particularly in our efforts to develop and implement evidence-based underage use prevention measures.

As a company, we are committed to working collaboratively with regulators, policymakers, public health leaders, and other stakeholders as we strive to earn a license to operate in society. We understand that in order to foster this much-needed scientific dialogue about the harm reduction potential of ENDS products, including JUUL, we must engage with the public health community on the science and facts underlying our products. In furtherance of this goal, we have published five articles and presented over 45 posters at various scientific and policy conferences around the world.

Following submission of our PMTA last summer and the tremendous effort it entailed, our science team refocused their efforts to publish the key research underlying our application through peer-reviewed manuscripts. This month we celebrate a significant milestone in those efforts with the publication of 11 articles in a monograph edition of the American Journal of Health Behavior (AJHB).

The monograph focuses on the centerpiece of our behavioral research program: the Adult Juul User Switching and Smoking Trajectories (ADJUSST) study. The ADJUSST study sought to understand patterns of tobacco product use among adult JUUL product purchasers, and collected data on over 55,000 current, former, and never smokers over the course of a year.

The ADJUSST study found high switching rates—defined as no past-30 day smoking, not even a puff—of over 50% across established smokers. The study also tracked the behavior of former and never smokers, with a particular interest in any subsequent cigarette smoking after initiating on JUUL products. Former smokers who have quit in the past year are particularly vulnerable to smoking relapse, with over 90% returning to cigarettes.[1] As discussed in the AJBH publication, prevalence rates of smoking were low and stable among former smokers across the 12-month period, suggesting former smokers were not resuming smoking in large numbers. A similar pattern was observed for never smokers.

The research also examined patterns of tobacco use across populations of special interest, including smokers of different ethnic groups, income levels, and mental health comorbidities. Encouragingly, results from the ADJUSST study demonstrate very similar high switching patterns among these cohorts compared to the general population.

Dual use—the use of cigarettes simultaneously with another tobacco product like ENDS—is also of critical interest in the public health analysis. As explained in another of the AJBH articles, the majority of adult smokers who began by dual-using JUUL and cigarettes ultimately switched completely away from cigarettes after the 12-month period. Of the remaining dual users at 6 months and 12 months, more than 60% reduced their average daily cigarette consumption by over half. This research supports the conclusion that dual use is often a transitional stage characterized by reductions in cigarette consumption followed by complete switching away from cigarettes.

In addition to adult behavioral data, the monograph also includes an article

assessing the potential effectiveness of enhanced access controls implemented at retail stores selling JUUL products. Juul Labs firmly believes the harm reduction potential of ENDS for adult smokers is at risk with high levels of underage use. As part of the PMTA, Juul Labs submitted to the agency a data-driven underage use prevention plan focused on limiting appeal, restricting access, and supporting enforcement efforts. Through the Tobacco Control Act and review of PMTAs, FDA has authority to impose sales and distribution restrictions as part of a product's specific marketing authorization. One such potential restriction includes a requirement that authorized new tobacco products be sold under enhanced access controls at retail to automate age verification via ID scanning and impose product quantity limits. The article included in AJBH describes results from the company's test of one such automated point-of-sale system, finding that compliance failure rates significantly declined following implementation of the upgraded point-of-sale system.

Finally, the monograph closes with an article detailing the population health model submitted to FDA, taking into account both intended and unintended use of our products. Relying on data from ADJUSST and other sources (PATH, NYTS, Royal College of Physicians, etc.), the model projects that continued availability of ENDS like JUUL could prevent up to 2.5 million premature deaths by the year 2100.

The articles published in the AJHB represent a significant aspect of our research portfolio and address many of the key topics of public health concern and interest. We look forward to continuing to share results from our science and research program with the public health community as we work to support the scientific basis for the category and advance the agency's Comprehensive Plan. Our scientists are currently drafting or have already submitted for peer review an additional 15+ manuscripts—and more are planned. Our hope is that the AJBH monograph published this month helps to further the necessary scientific dialogue about the harm reduction potential of our products, and the role they may play in reducing the smoking-related death and disease which kills almost half a million Americans each year.

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Pharmaceutical GMPs, Quality Control, and Data: A Deeper Look at FDA's FY 2020 FDA Observations

by Amy Scanlin

Good Manufacturing Practices—those minimum requirements for methods, facilities, and controls used in manufacturing, processing, and packing of drug products.[1] Though clearly articulated by FDA, a review of FY 2020 pharmaceutical inspection observational findings shows their execution is frequently lacking.

Though 2020 posed many challenges for the pharmaceutical industry, supply chain and product shortages,[2] to name two, FDA's focus on GMPs remained central to the agency's regulatory enforcement and compliance strategy for protecting the American consumer.[3] The COVID-19 pandemic created difficulties in materials sourcing and shuttered many on-site contract manufacturing, testing audits, and qualification activities, resulting in increased testing costs and a myriad of staffing challenges. Quality systems and oversight had to be adjusted on the fly to meet the evolving paradigm of transitioning from wholly on-site work models to hybrid virtual working team environments. From the executive level to the manufacturing floor, procedures for assuring a continuum of quality had to be flexible while remaining robust. Even those companies well equipped with GMP systems and solid experience found their routine operations strained by the ever-changing impact of the aforementioned factors.

Given that FDA is once again actively returning to the field to conduct prioritized inspections and follow-up on previous non-compliance issues, an increased focus on GMPs at the site level is urged. Drug firms must assure that their quality operations and control systems are delivering as they should, taking into account the potential for new risks that have emerged as a result of the pandemic world in which we now live.

A key issue for manufacturers this year: Supplier disruptions. Many had to ask the difficult question of whether to seek new, yet unqualified, supplier alternatives in order to fill gaps and maintain production schedules. Vetting and qualifying a new supplier is a time-consuming and costly venture. It is a relationship built on trust and defined in documentation. Quality agreements

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must spell out expectations for audits, assessments, specification testing, and materials/product performance evaluations, all of which must meet FDA and manufacturer expectations. Additionally, requirements for supplier testing must include parameters for documentation for data audits, facility audits, and appropriate confirmation testing.

How many tests are appropriate? The number of tests is set by product specification and/or product submission dossiers (NDA/ANDA/IND), so there is no universal FDA reference or required number of tests. Many in the industry recommend testing a minimum of three unique material lots so that a supplier's compliance to a specification and the reliability of the vendor-provided Certificate of Analysis (COA) can be assessed independently. Whether vetting a new material or material supplier or requalifying an existing supplier or material, the key issue remains the sponsor's ability to demonstrate the reliability and integrity of the materials and substantiation of data to meet the GMP requirements.

In the agency's 2018 Guidance for Industry Q&A4 related to data integrity and GMP compliance, FDA noted that pharmaceutical facility inspection findings showed increased challenges with meeting data integrity requirements. As it turns out, not much has changed between 2018 and now. In FY 2020, FDA found documentation and verification of quality control as required under 21 C.F.R. Part 211 is a key issue. From input/output verification (21 C.F.R. 211.68(b)), component identify verification to include reliability of the Certificate of Analysis (21 C.F.R. 211.84(d)(1)), and verification of component additions (21 C.F.R. 211.101(d)) to computer control over master of records (21 C.F.R. 211.68(b)), a significant number of observations encompass the ability to verify quality through integrity of data.

Data integrity plays a key role in all areas of GMP compliance. FDA expects data to be meaningful and reliable, taking into consideration the design, operation, and monitoring of systems and controls based on a risk to patient, process, and product. It should be able to provide valid demonstrations of integrity and verification for an ingredient and/or a final product's safety, identity, strength, quality, purity, reproducibility, and so on.[5]

All data generated becomes part of the GMP record and must be recorded and saved at the time of performance to be compliant with FDA requirements. This includes specific conformance requirements per 21 C.F.R. Part 11 for electronic records and signatures, of which validation of the electronic system itself is one component.[6] FDA says each GMP workflow, "such as creation of an electronic master production and control record (MPCR), is an intended use of a computer system to be checked through validation." The concern is when using the same system to perform both GMP and non-GMP functions, workflows must be checked to ensure they run appropriately. GMPs and integrity of the data support in them are a lifeline of a drug company. Any lack of compliance in any GMP area will have direct consequences on a firm's ability to bring products to and stay on the market.

The purpose of all this data, of course, is to support informed quality decisions as to the acceptability of materials and finished goods. Much of the data will be generated through laboratory testing in support of validation of analytical methods and processes. Sections 211.160 and 211.165 stipulate that components, containers and closures, in-process materials, and finished products must conform to specifications, including stability. The 1993 "Barr Decision" handed down in the civil case *United States vs. Barr Laboratories, Inc.* solidified federal expectations for appropriate GMPs with regards to U.S. Pharmacopeia's (USP) established standards. A firm cannot retest an Out of Specification result into specification (i.e., testing into compliance). In addition, per the 2006 Guidance for Industry on Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production,[7] a decision to invalidate a test result to exclude it from quality unit decisions about conformance to a specification requires a valid, documented, scientifically sound justification; and in those cases where a scientifically sound investigation justifies the legitimacy for invalidation, a full GMP batch record must be kept, including the original (invalidated) data, along with the investigation report that justifies invalidating the result.[8]

Data storage is another area critical to successful demonstration of sound GMPs and data integrity. Not surprisingly, numerous violations were seen in 2020 observations, with examples including 21 C.F.R. Section 211.68(b) where backup data was not assured as exact or complete and back up files were not maintained. Per 21 C.F.R. Sections 211.68 and 212.110(b), not only should exact, unaltered, and complete copies of back up data be kept, but any risk of inadvertent deletion (including by an individual), loss, or deterioration of data (i.e., computer hard drive or server crash) must be evaluated, assessed, and subject to a risk mitigation plan.

While on the surface it may seem confusing, FDA's intentional decision to not prescribe specifics to its GMP requirements enables each firm to

develop protocols suitable to their specific operations. This allows flexibility as new systems, equipment, and products are brought on-line. However, it also means that GMPs must be updated and reviewed accordingly, including change control, SOPs, validations, specifications, and more. Third-party reviewers, such as consultants, can bring fresh eyes to standard development and GMP reviews for accuracy and completeness.

Quality control coupled with data integrity can make or break a company's GMPs and increase the risk of FDA regulatory action. It is important to ensure controls are in place to capture a complete data picture, including when and by whom activities were performed. Data must be reviewed for accuracy, completeness, and compliance with appropriate standards, and it must be securely maintained and retained until such time that disposition is appropriate.

Don't close the books, paper or electronic, on your company's compliance. FDA is watching.

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Orphan Drugs in Canada: A "One Size Fits All" Regulatory Regime

by Eileen M. McMahon and Denise Ramsden[1]

Introduction

Medicines targeting rare diseases, also known as orphan drugs,[2] once faced an uphill battle for research funding and market approval. The need for robust commercial incentives to create rare disease treatments spurred the establishment of international orphan drug regulations—first in the United States with the passage of the 1983 *Orphan Drug Act*, and later in the European Union (EU), Japan, Singapore, and elsewhere.[3] Today, there are over 400 designated orphan drugs in the global marketplace and dozens of orphan-specific regulatory initiatives to drive investment and ensure public access to orphan medicines.[4]

These specialized orphan drug frameworks stand in contrast to Canada's regulatory regime. While Canada has considered implementing an orphan drug framework, such a step has never been taken. Instead, Canada relies on generally applicable mechanisms in its domestic drug approval regime to drive market entry of orphan drug therapeutics. For example, "innovative drugs" are eligible for data protection in Canada. Additional patent term protection in the form of Certificates of Supplementary Protection (CSPs) and measures such as patent listing under the Patented Medicines (Notice of Compliance) framework (analogous to patent listing in the Orange Book) also offer certain rights to innovators.

Based on recent policy announcements, a specialized orphan drug regulatory regime is not likely coming to Canada in the near future. Instead of crafting a specialized regulatory regime, in the first quarter of 2021, the Canadian federal government formally announced its proposal to develop a National Strategy for High-Cost Drugs for Rare Diseases.[5] While consultations are ongoing, the government's strategy is targeted at creating a framework that provides consistent and cohesive drug cost

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funding for patients with rare diseases, rather than driving market availability of such orphan drugs through regulatory incentives.

Orphan Drug Regulation in the United States and Europe

On most life sciences regulatory matters, Canada aims to align itself with the United States and the EU. Although Canada does offer certain incentives to orphan drug manufacturers (e.g., accelerated review of drug submissions, fee waivers, tax credits),[6] which are similar to the pre-market economic incentives available in the U.S. and EU, when it comes to the protection for the orphan drug products themselves, Canada has fallen substantially out of alignment with the international community.

In the United States, drugs targeting rare diseases are eligible for several specifically targeted economic incentives, including market exclusivity, fee waivers, direct funding for research and development, and tax credits. There is no government oversight for pricing of orphan drugs or other medicines.[7] Similarly, in the EU, orphan drugs are eligible for a range of economic incentives, comparable to those available in the United States, including market exclusivity, administrative assistance, and fee waivers. The price of orphan drugs, and all other medicines, is subject to national laws and policy instruments in each member state.[8]

Canada's Efforts to Regulate Orphan Drugs

The absence of a Canadian orphan drug framework has been a conscious decision on the part of the Canadian government, as such a framework has been considered over the years.

Over the past several decades, as other jurisdictions implemented orphan drug frameworks, Health Canada (Canada's version of the FDA and EMA) considered whether such a framework might be beneficial but ultimately concluded that an orphan drug framework was not needed because Canadians already had access to the majority of orphan drugs approved in the United States,[9] either because the drugs had been approved for sale[10] or were available through the Canadian Emergency Drug Release Program (now known as the Special Access Programme or "SAP").[11] Others dispute Health Canada's position on accessibility of orphan drugs.[12]

In 2012, Health Canada revisited the decision to forego an orphan drug policy and proposed a draft regulatory framework.[13] The draft framework may have been motivated by a desire to harmonize Canada's regulatory regime with its international trading partners.[14] Canadians were also lagging behind their United States counterparts in temporal access to orphan drugs.[15] However, Health Canada's plan was abandoned in 2017, when Health Canada indicated it would continue to pursue the interests of rare disease patients through other means.[16]

The Current Status of Orphan Drugs in Canada

Given that Canada lacks a regime that protects orphan drugs specifically, the current regulatory scheme presents several key considerations for orphan drug manufacturers.

1. Data Protection

Data protection in Canada is available only if the manufacturer's new drug is considered an "innovative drug."[17] The statutory definition of "innovative drug" is restricted to new medicinal ingredients not previously approved by Health Canada and that are not variations of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate, or polymorph. This means that a previously approved drug with a new, promising rare disease application will not be eligible for data protection in Canada. In contrast, in the U.S. and EU, orphan drug designation (and the corresponding exclusivity) can be received for a new drug or an already marketed drug with a new use.[18] Unlike the U.S., in Canada, a manufacturer will not be eligible for data protection where it has conducted trials[19] to support the safety and efficacy of a new use, new formulation, new dosage form, or new dosing regimen of an orphan drug (or indeed any drug) previously approved by Health Canada.

Should an orphan drug qualify as an "innovative drug" in Canada, it will be eligible for an eight-year period of data protection. Generic and biosimilar manufacturers are barred from filing for a marketing authorization (a Notice of Compliance or "NOC") on the basis of a direct or indirect comparison to the qualifying innovative drug for the first six years, and Health Canada cannot issue an NOC for eight years. If the innovative drug manufacturer files clinical trial data "conducted for the purpose of increasing knowledge about the use of the pediatric populations" within the first five years of the data protection period, the innovative drug may also be eligible for a six-month data protection extension.[20]

2. Price Regulation Issues

Canada's unique pricing regime for patented medicines, overseen by the Patented Medicines Price Review Board (PMPRB), is also an area which frequently

impacts orphan drug manufacturers. The PMPRB can exercise price control over drugs sold in Canada, including orphan drugs, where there is at least one Canadian patent which "pertains to" the medicine.[21] If the PMPRB determines that the price of a patented medicine is excessive, the PMPRB can order a price reduction based on factors specified in the Patented Medicines Regulations. To date, the PMPRB's price regulation framework has not approached orphan drugs any differently than other therapeutic products.

However, amendments to the Patented Medicines Regulations are expected to come into force on July 1, 2021, after several delays due to COVID and a series of court challenges.[22] The amendments add new factors to the PMPRB's excessive pricing analysis which may impact orphan drugs, including the medicine's pharmacoeconomic value in Canada and the size of the market for the medicine in Canada.[23]

Updated PMPRB Guidelines,[24] which provide details of the complex tests the PMPRB uses when assessing whether a drug is excessively priced, will also come into effect to support the amended Regulations.[25] Early drafts of the updated Guidelines did not specifically address orphan drugs. Following significant stakeholder feedback, the updated Guidelines were further revised and the PMPRB has included a specific carveout for high-cost medicines that are expected to realize below a certain minimum amount in annual revenue. Medicines which realize less than $12 million in annual revenue will not be subject to the most stringent price test, even if they exceed the cost threshold which would normally trigger such review.[26] Specifically, such high cost medicines will not be subject to a "maximum rebated price" ceiling even where the annual treatment cost would otherwise require such a price ceiling.[27] As a result, a high cost medicine with annual revenues under $12 million may be subject to a higher price ceiling than another similarly priced medicine, with greater annual sales.

The Canadian government has acknowledged that this concession was specifically included in the further revised, updated Guidelines to ensure that manufacturers of orphan drugs are "not discouraged from coming to Canada out of concern that their net price will be substantially reduced by regulation."[28] Prior to the release of the further revised, updated Guidelines, the PMPRB had maintained that the current regulatory regime, and the absence of an orphan-drug-specific framework, had not impacted Canadians' access to orphan medicines.[29] The dispensation for drugs with a smaller market cap, reflected in the final updated Guidelines, is one of the first acknowledgements from the PMPRB that Canadian price regulation may be having a dampening effect on the availability of orphan drugs in Canada. Until these updated pricing Guidelines are applied in practice, it is unclear whether these concessions will provide sufficient comfort to orphan drug manufacturers to launch their orphan drugs in Canada.

3. Standard Patent-Derived Protections

Like all other therapeutic products in Canada, orphan drug manufacturers may seek protections derived from patents. In Canada, the standard term of a patent is twenty years from the Canadian filing date of the application. Drugs with patents pertaining to a medicinal ingredient, or a combination of medicinal ingredients, may be eligible for a two-year extension to the patent term through a Certificate for Supplementary Protection (CSP), provided the medicinal ingredient or combination of medicinal ingredients has not been previously authorized for sale in Canada.

Patent protected drugs may also benefit from additional rights under the Patented Medicines (Notice of Compliance) (PM(NOC)) Regulations. If there is a patent that claims what is approved in a New Drug Submission (NDS) or in a supplemental NDS—such as a claim to the medicinal ingredient, its use, formulation, or dosage form—and subject to certain timing requirements, the patent may be listed on Health Canada's Patent Register (Canada's version of the Orange Book). The rights of a manufacturer who has listed a patent on Canada's Patent Register kick in if another manufacturer directly or indirectly compares its drug with, or makes reference to, the drug in respect of which the patent list was submitted. Subsequent entry is permissible if the patent expires, with the permission of the original manufacturer or sponsor, or once proceedings under the PM(NOC) Regulations have run their course.

Conclusion

Canada's approach to orphan drugs is likely to face further scrutiny in the coming years. The newly announced National Strategy for High-Cost Drugs for Rare Diseases will not likely be implemented for several years, so changes to the funding patients receive for orphan drugs will be slow to materialize. Further, the true impact of the new PMPRB pricing rules on orphan drugs will not be known until those rules have been applied in practice.

In the interim, orphan drug patient advocacy groups and the PMPRB remain at odds. Orphan drug patient advocacy groups have been critical of the

PMPRB's reluctance to specifically relax price regulation on orphan drugs. From their perspective, the specific price regulation exceptions that have been created for COVID-19 vaccines are an acknowledgement that "the [pricing] rules block speedy access to medicines" in Canada.[30] At the same time, the PMPRB remains adamant that their price regulation is not impacting Canadians' access to new drugs as new drugs have continued to enter Canada at a steady rate over the last five years.[31]

Add to this dynamic the widespread criticism of the Canadian government and Health Canada in relation to the COVID-19 vaccine rollout,[32] characterized by media as "utterly botched," "bungled," and "lagging." As Tracey Lindeman of *The Atlantic* recently reported, "Canadians—usually so smug about our universal health care—are looking on [the United States] with jealousy."[33] Per capita vaccination numbers lag behind more than forty-five other countries (vaccinations per 100 people).[34] The pandemic has shone a light on Canada's lack of domestic manufacturing capabilities. As a result, the federal government is focusing its attention on a national biomanufacturing strategy.[35]

Against this backdrop, it is unlikely that Canada's approach to regulating orphan drugs and offering market exclusivities to encourage orphan drug manufacturers to launch orphan drugs in Canada will change in the short term. Instead, the federal government's focus is more likely to continue to be domestic manufacturing and procurement.

If efforts to manage orphan drug access through patient funding and pricing regulation are not successful in the coming years and orphan drug manufacturers become increasingly reluctant to launch orphan drugs in Canada, the Canadian government may re-consider the need for a bespoke orphan drug regulatory regime. However, at this point, the Canadian government has not signaled any intention to re-open that debate.

1. We are grateful for the assistance of Amanda Wolczanski, Summer Student. The law and guidance referenced in this article is current to May 21, 2021.
2. The definitions of "rare disease" and "orphan drug" vary across jurisdictions, and given the absence of a bespoke orphan drug regulatory regime, Canada does not have a statutory definition. Health Canada refers to the European definition of a condition that afflicts no more than five in 10,000 people, and the U.S. definition of a condition that affects no more than 200,000 people in the U.S. *See* Health Canada, About orphan drugs and rare diseases (updated August 14, 2018), https://www.canada.ca/en/health-canada/services/licences-authorizations-registrations-drug-health-products/regulatory-approach-drugs-rare-diseases/about-drugs-rare-diseases.html.
3. Todd Gammie, Christine Y. Lu & Zaheer Ud-Din Babar, *Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries*, 10 PLOS One 10 (2015).
4. *FAQs About Rare Diseases*, National Institutes of Health, Genetic and Rare Disease Information Center (updated January 26, 2021), https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.
5. *National Strategy for High-Cost Drugs for Rare Diseases Online Engagement*, Health Canada (updated January 28, 2021), https://www.canada.ca/en/health-canada/programs/consultation-national-strategy-high-cost-drugs-rare-diseases-online-engagement.html.
6. *Canada's regulatory approach to drugs for rare diseases: orphan drugs*, Health Canada (updated July 3, 2020), https://www.canada.ca/en/health-canada/services/licences-authorizations-registrations-drug-health-products/regulatory-approach-drugs-rare-diseases.html.
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9. Matthew Herder & Timothy Mark Krahn, *Some Numbers Behind Canada's Decision to Adopt an Orphan Drug Policy: US Orphan Drug Approvals in Canada, 1997-2012*, 11 Healthcare Policy 72 (2016).
10. *Id.*
11. *Id.*
12. Hugh J. McMillan & Craig Campbell, *We Need a "Made in Canada" Orphan Drug Framework*, 189 CMAJ E1274 (October 16, 2017), https://www.cmaj.ca/content/189/41/E1274. Emma Jones, *Canada May Fall Behind Without an 'Orphan' Drug Strategy*, Healthing (December 8, 2020), https://www.healthing.ca/policy/canada-needs-a-separate-orphan-drug-strategy-says-rare-disease-group.
13. Office of Legislative and Regulatory Modernization, *Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework* (December 13, 2012), www.orpha.net/national/data/CA-EN/www/uploads/Initial-Draft-Discussion-Document-for-A-Canadian-Orphan-Drug--Regulatory-Framework.doc.
14. Matthew Herder & Timothy Mark Krahn, *Some Numbers Behind Canada's Decision to Adopt an Orphan Drug Policy: US Orphan Drug Approvals in Canada, 1997-2012*, 11 Healthcare Policy 70 (2016).
15. *Id.* at 78.
16. Maura Forrest, *Health Canada Gives 'Kiss of Death' to Planned Policy for Rare-Disease Drugs*, National Post (October 16, 2017), https://nationalpost.com/news/politics/health-canada-gives-kiss-of-death-to-planned-policy-for-rare-disease-drugs.
17. "Innovative drug" means a drug that contains a medicinal ingredient not previously approved in a drug by the Minister and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate, or polymorph. C.08.004.1 (1), *Food and Drug Regulations*, C.R.C., c. 870.
18. 21 C.F.R. § 316.20(a); Regulation (EC) No 141/200.
19. A manufacturer is required to have generated data to support the approval of the medicinal ingredient under consideration and the generation of that data must have required considerable effort. *See* Health Canada, *Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations* (updated April 8, 2021), https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/

guidance-documents/guidance-document-data-protection-under-08-004-1-food-drug-regulations.html.

20. *Id.* at § 2.1, https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/guidance-document-data-protection-under-08-004-1-food-drug-regulations.html#a21.
21. Section 79(1) of the *Patent Act*, in relation to patented medicines, defines "patentee" as follows: "in respect of an invention pertaining to a medicine, means the person for the time being entitled to the benefit of that invention and includes, where any other person is entitled to exercise any rights in relation to that patent other than under a licence continued by subsection 11(1) of the Patent Act Amendment Act, 1992, that other person in respect of those rights." Patent Act, R.S.C. 1985, c P-4.
22. The amendments to the Regulations have been subject to several court challenges, but the majority of the amendments have withstood these challenges. *Innovative Medicines Canada v. Canada (Attorney General)*, 2020 FC 725; *Merck et al. v. Canada (Attorney General)*, Court File No. 500-17-109270-192. See Torys' Bulletin for further discussion: Yael Bienenstock, Teresa A. Reguly, Marie-Ève Gingras & Sylvie Rodrigue, *A Decision and a Delay: PMPRB News for the New Year*, Torys LLP (January 5, 2021) https://www.torys.com/insights/publications/2021/01/a-decision-and-a-delay.
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25. The new Guidelines are currently being challenged in Federal Court. *Innovative Medicines Canada et al. v. Canada (Attorney General)*, Court File No. T-1419-20.
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Letter to the Editor

Recent FDA Activity on Cannabis Clinical Research

April 30, 2021

Dear Editor:

We appreciate the discussion of cannabis clinical research in the recent article, "Sourcing Cannabis Lawfully for CBD Consumer Products: Challenges and Opportunities" by Suzie Trigg, Steve Armstrong, and Joanna Pearce. The article presents an important discussion of the role of DEA in various aspects of cannabis cultivation, distribution, sampling and testing issues, among other topics. As the authors note, "Medical research involving marijuana comes with its own set of requirements." Some of those requirements are within FDA's purview, and we wanted to ensure that FDLI *Update*'s readers were aware of recent agency activity on this issue.

In July 2020, FDA issued a draft guidance for industry, "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research, Guidance for Industry," to help support clinical research into development of cannabis and cannabis-derived human drug products. This draft guidance outlines FDA's current thinking on several topics relevant to the development of cannabis and cannabis-derived human drug products: the source of cannabis and cannabis-derived compounds for clinical research and how this fits with existing FDA requirements; general quality considerations for developing drugs that contain cannabis and cannabis-derived compounds; and review practice regarding the calculation of percent delta-9 tetrahydrocannabinol (THC) in botanical raw materials, extracts, and finished products. FDA is currently reviewing the comments submitted to this draft guidance.

FDA supports sound, scientifically based research into the medicinal uses of drug products containing cannabis or cannabis-derived compounds and will continue to work with companies interested in bringing safe, effective, and quality products to market. Those interested in cannabis-derived and cannabis-related drug development are encouraged to review our web page, FDA and Cannabis: Research and Drug Approval Process, and to contact the relevant CDER review division and CDER's Botanical Review Team (BRT) to answer questions related to their specific drug development program. The BRT serves as an expert resource on botanical issues and has developed the Botanical Drug Development Guidance for Industry to assist those pursuing drug development in this area. FDA also encourages drug developers to meet with FDA early in their development programs—ideally, before submitting an investigational new drug (IND) application. The pre-IND meeting is an opportunity to obtain FDA input on research plans and required content for an IND submission. The pre-IND meeting can be valuable in planning a drug development program, especially if developers' questions are not fully answered by guidances and other information provided by FDA. Early interactions with FDA staff through a pre-IND meeting can answer sponsors' questions related to a specific drug development program and provide information that will assist them in preparing complete IND applications.

Additional FDA web resources that may be useful to those interested in developing medical products that contain cannabis or cannabis-derived compounds include:

- Investigational New Drug (IND) Application, which contains resources for preparing and submitting an IND;
- Pre-IND Consultation Program, which describes how to obtain a meeting to obtain guidance on the data necessary to warrant IND submission;
- New Drug Application (NDA), which describes how drug sponsors formally propose that FDA approve a new pharmaceutical;
- Better Data for a Better Understanding of the Use and Safety Profile of Cannabidiol (CBD) Products, which provides a brief overview of our work on CBD and a framework for building a more robust evidentiary foundation to inform public health decisions; and
- FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD), which includes a robust FAQ section as well as links to other regulatory resources.

We recognize that there is considerable interest in marketing and accessing CBD in a variety of products. As part of our work, the FDA continues to explore potential pathways for various types of CBD products to be lawfully marketed. While that is not the subject of today's letter, we emphasize that an important component of this work is obtaining and evaluating information to address outstanding questions related to the safety of CBD products that will inform our consideration of potential regulatory frameworks for CBD while maintaining the FDA's rigorous public health standards. Our goal is to provide additional guidance, and we have made substantial progress. However, many questions remain regarding the science, safety, effectiveness, and quality of products containing CBD. Our first priority is to protect the health and safety of Americans.

Sincerely,

Cassandra Taylor, Ph.D and Amy Muhlberg, Ph.D
Center for Drug Evaluation and Research
U.S. Food and Drug Administration, Silver Spring, MD

Cassandra Taylor is a chemist in the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration.

Amy Muhlberg is a staff fellow in the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration.

Honoring Community Leaders

During FDLI's Annual Conference on May 18–20, 2021, FDLI was pleased to have the opportunity to recognize exceptional contributors to the field of food and drug law. These awards honor members of the community whose contributions advance both the mission of FDLI and the field as a whole. Please join FDLI in thanking and congratulating the winner of the Service to FDLI Award and the winners of the Distinguished Service and Leadership Awards.

August T. Horvath

Service to FDLI Award

The Service to FDLI Award originated in 2017 to celebrate members who have consistently provided exceptional volunteer services, furthering FDLI's mission as a neutral convener to educate and spark innovative change. This award is chosen by FDLI's Board of Directions and team of staff members. This year, we had the honor of presenting this distinction to **August T. Horvath.** Mr. Horvath has greatly assisted FDLI throughout the years with his invaluable expertise and willingness to help wherever he can.

Mr. Horvath is a partner and co-chair of Foley Hoag's Advertising & Marketing practice where he is a noted advertising and antitrust attorney. He is a fellow of the American Bar Foundation where he serves as the co-chair of the American Bar Association Antitrust Law Section's Agriculture and Food Committee.

Some of his many notable contributions to FDLI and the food and drug law community include his participation as a speaker in our webinars and other programs, his authorship in *Update* magazine, and his advice as a member and chair of planning committees. For the past few years, he has edited the publication, *Top Cases in Food and Drug Law*, a written companion to the popular panel at our Annual Conference. In addition to his role as editor of the publication, he participates as a presenter for the panel, where he consistently provides an engaging and informative overview of the most significant cases each year. Whether he serves as a planner, presenter, or author, Mr. Horvath ensures that FDLI's content is always relevant and timely to our membership. His work is greatly appreciated not only by FDLI's team, but also by the entire community, and we are honored to present him with this well-deserved recognition.

The presentation of this award, as well as more information about Mr. Horvath, can be viewed **here.**

Distinguished Service and Leadership Awards

Established in 1993, the FDLI Distinguished Service Award is given annually to recognize individuals for their contributions that have helped advance and innovate the field of food and drug law. The recipients are selected by a committee of peers and colleagues consisting of recent FDLI award winners. This year's awardees were: **Peter Marks, Mark Raza,** and **Kathleen M. Sanzo**. Colleagues joined FDLI in a virtual presentation to honor the recipients and say a few words.

Peter Marks

Mr. Marks currently serves as the Director of the Center for Biologics Evaluation and Research (CBER) at FDA where he has been a critical figure in the COVID-19 vaccine review, approval, and authorization processes. Throughout this entire pandemic, Mr. Marks has exhibited a strong commitment to transparency and accessibility. He traveled to organizations to discuss FDA's plans for the COVID-19 crisis and took the time to explain the decision-making process to the public. His colleagues and peers describe him as a pleasure to work with and as someone whose kindness always shows through. Outside of his work with FDA, Mr. Marks also assists in the development of FDLI's programs and supports the growth of his team by encouraging them to do the same. After a very difficult year, FDLI is pleased to honor a member of our community who has done so much for food and drug law and for public health.

Mark Raza

Mr. Raza, Acting Chief Counsel with FDA's Office of the Chief Counsel (OCC), was joined during the presentation by a number of his colleagues to celebrate his years of strong service to the agency. He has played an integral role in FDA's pandemic response as the lead for the OCC COVID-19 emergency team where he drew on decades of experience serving in leadership roles for emergency preparedness and response. He assisted his team through times of uncertainty and transition to identify and implement solutions while providing steadfast support for his attorneys and staff. Throughout his career, Mr. Raza has exhibited great dedication to the professional development of his attorneys, the careers of law students and interns, and the protection of public health. His colleagues praise him for his genuine kindness and care for his team and for keeping morale high as an exemplary model of leadership. FDLI is happy to join with his staff in congratulating him for this award.

Kathleen M. Sanzo

Ms. Sanzo currently works as a partner at Morgan, Lewis & Bockius LLP, though she was joined by several colleagues from a variety of organizations for the presentation of this award. Ms. Sanzo is a strong leader in the FDLI community, where she has engaged with FDLI as an author, speaker, and committee member. She is a nationally recognized FDA law expert who excels at analyzing issues, developing solutions, and communicating with clients. She has committed herself to the advancement of food and drug law with her belief that a strong FDA community would ultimately increase everyone's quality of work, expand how people interact with FDA, and improve public health. Her peers laud her as not just a leader, but a leader that people would like to emulate, and someone who greatly deserves this award.

You may read more about each of the winners and watch their acceptances of their awards **here.**

SHARE YOUR IDEAS WITH FDLI!

Submit Paper and Commentary Abstracts

The Path Forward: Seeking Racial Equity in Food and Drug Law: *Food and Drug Law Journal* 2021 Symposium encourages thoughtful scholarship on topics addressing racial inequities in food and drug law and regulation. Calls for submissions are open now through June 28, 2021.

Suggest Webinar Ideas

Have a subject you'd like to learn more about?

The FDLI Webinar Programs Committee invites food and drug law community stakeholders to submit a proposal recommending a topic using our webinar portal!

Submit a Law Over Lunch Topic

Member-Only Opportunity

What timely, interesting topics would you like to discuss with other FDLI members? Submit a proposal to facilitate a discussion about a timely topic at an upcoming virtual Law Over Lunch program!

Author Articles

What legal and regulatory issues interest you?

Share your expertise by submitting articles to FDLI publications, including *Update* magazine and *Food and Drug Law Journal*. For questions, please contact publications@fdli.org.

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September 21-23 | Virtual Course

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Introduction to Advertising and Promotion for Medical Products

October 12 | Virtual Course

Advertising and Promotion for Medical Products Conference

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October 26 | Virtual Course

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