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UPDATE

Food and Drug Law Institute

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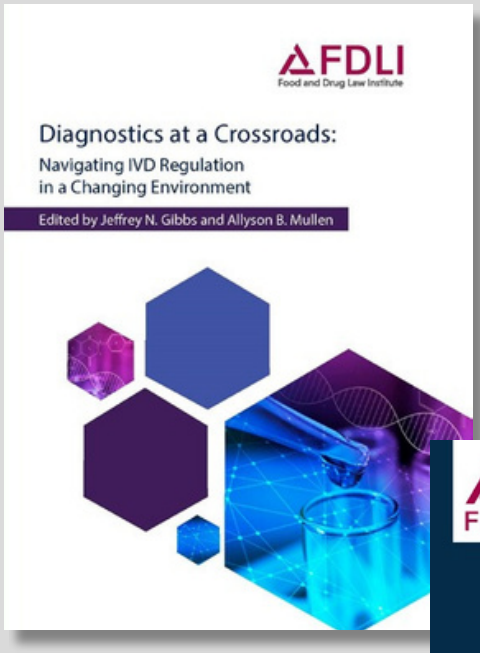

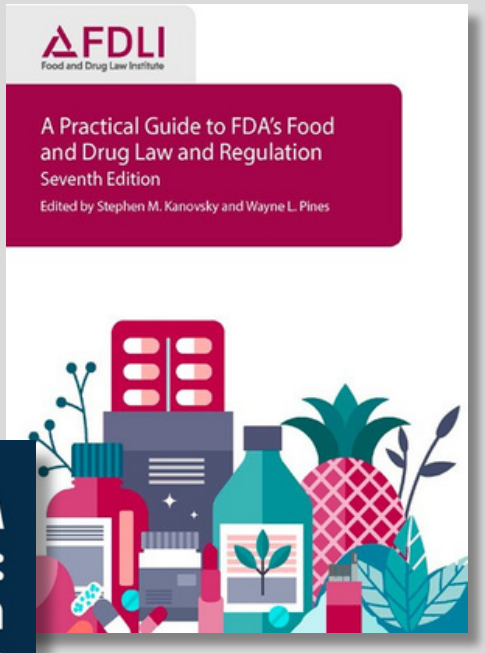

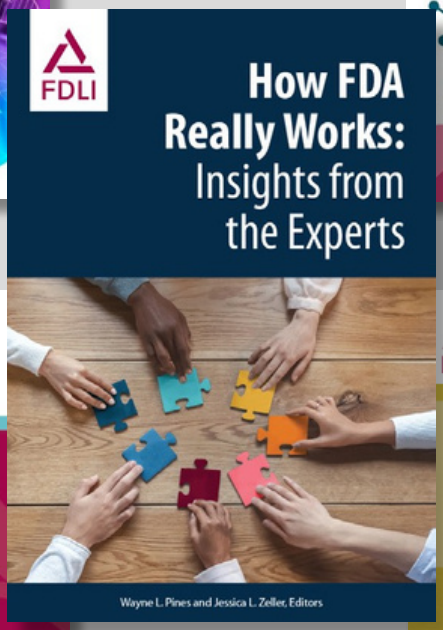

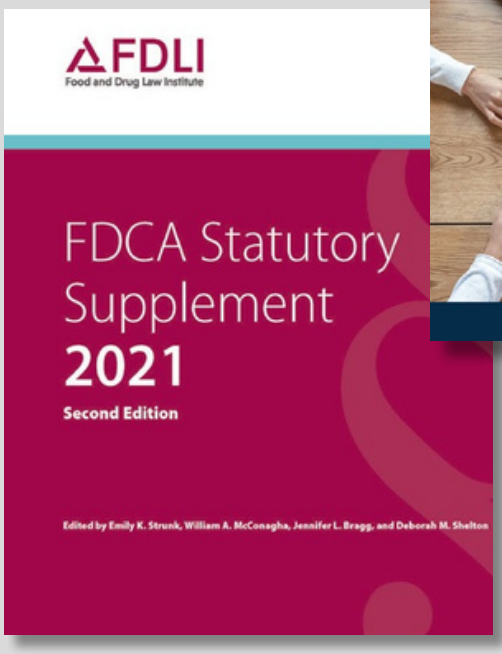

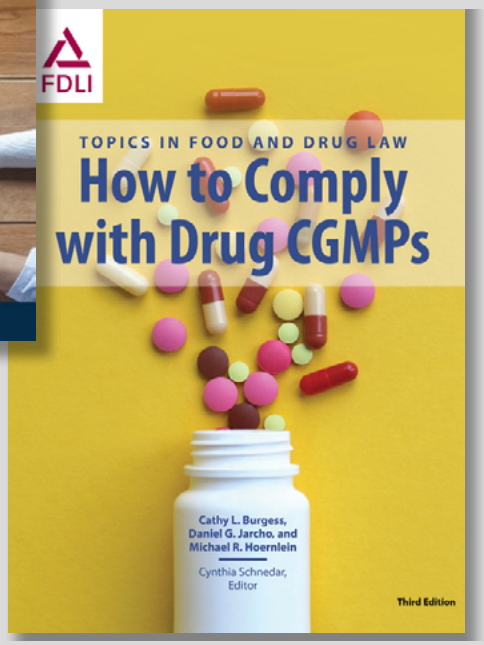

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Ferrari v. Vitamin Shoppe: A Favorable Ruling for a Manufacturer Facing a Challenge to Its Dietary Supplement Structure/Function Claims

by Jennifer Hill

In *Ferrari v. Vitamin Shoppe Industries LLC*, 70 F.4th 64 (1st Cir. 2023), the First Circuit became the latest U.S. Court of Appeals to analyze the appropriateness of labeling claims that emphasize the health benefits of nutrients contained in dietary supplements. With the dietary supplement industry experiencing significant growth over the past two decades,[1] it is no surprise that labeling claims have drawn close attention.

The First Circuit's decision in favor of a manufacturer reinforces that challenging dietary supplement labeling under state law can be difficult given that satisfying U.S. Food and Drug Administration (FDA) requirements preempts such a challenge.

FDA's Regulation of Dietary Supplement Labeling

FDA regulates dietary supplements under the Dietary Supplement Health and Education Act of 1994 (DSHEA). The DSHEA amended the Federal Food, Drug, and Cosmetic Act (FDCA) to "establish standards with respect to dietary supplements."[2] This framework permits dietary supplement manufacturers to make labeling statements commonly known as "structure/function claims." A structure/function claim is permissible when:

> (A) the statement . . . describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption of a nutrient or dietary ingredient,
>
> (B) the manufacturer of the dietary supplement has substantiation that such statement is truthful and not misleading, and
>
> (C) the statement contains, prominently displayed and in boldface type, the following: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."[3]

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Structure/function claims are distinguishable from "disease claims," which are claims that a product will "diagnose, mitigate, treat, cure, or prevent disease."[4] Disease claims include explicit or implicit claims that "the product . . . has an effect on a specific disease or class of diseases."[5]

Background in *Ferrari*

The plaintiffs in *Ferrari* purchased three formulations of a glutamine supplement manufactured and sold by Vitamin Shoppe under the brand name "BodyTech." Glutamine is an amino acid produced naturally by the body. Because it has been reported to have a role in supporting immune system functions and preserving muscle tissue, glutamine supplements have become a popular component of sports nutrition.[6] BodyTech glutamine supplements are one of many similar products marketed towards athletes to support muscle growth and recovery.

Dissatisfied with their own use of the BodyTech supplements, the plaintiffs brought a putative class action against Vitamin Shoppe, alleging that BodyTech's labeling was false and misleading. They sought to recover under Massachusetts and Illinois statutes governing false advertising and deceptive business practices, as well as various common law tort theories.

The district court granted summary judgment in favor of Vitamin Shoppe, finding that the challenged labeling statements were permitted under the FDCA as structure/function claims. The district court, therefore, concluded that federal law preempted all of the plaintiffs' state law claims. The plaintiffs appealed the decision to the First Circuit.

First Circuit's Decision

The arguments on appeal required the court to consider the parameters of appropriate structure/function claims under the FDCA and the type of substantiation it requires. First, the plaintiffs challenged the district court's finding that Vitamin Shoppe's statements regarding BodyTech supplements qualified as structure/function claims. According to the plaintiffs, BodyTech's labeling impermissibly made representations about the product itself (supplemental glutamine), rather than the nutrient's general effect on the body's structure or function, and described the "specific situation and usage" for the product.[7]

To support this theory, the plaintiffs pointed to specific labeling statements they said extended beyond the qualities of glutamine as an ingredient. For example, the plaintiffs took issue with the statement that "[i]ntense exercise can deplete glutamine stores, however, supplemental glutamine is thought to replenish these stores allowing for enhanced recovery."[8] The plaintiffs argued that by describing the effects of "supplemental" glutamine and the situation for which it would be useful (following "intense exercise"), the statements no longer qualified as structure/function claims.

The First Circuit disagreed, noting this statement "fits comfortably within the definition of a structure/function claim" because it explains how supplemental glutamine helps maintain glutamine stores, i.e., the mechanism by which the nutrient acts to maintain the structure or function.[9]

The plaintiffs also challenged the statement that the supplement "combines" three nutrients, each with certain health benefits, asserting that this characterization made it a disease claim. The court rejected this argument, because "merely noting that the nutrient is in the product" was not a reason to negate "an otherwise acceptable structure/function claim."[10]

Next, the plaintiffs argued that the challenged statements were still impermissible because they lacked substantiation required for structure/function claims. The plaintiffs argued that Vitamin Shoppe must have evidence substantiating its claims based on glutamine in the supplemental form, as it is delivered in the product, rather than as naturally occurring glutamine.

The court accepted this premise, given that Vitamin Shoppe made claims about "supplemental glutamine" or glutamine that was "added" to the product.[11] But, the court found this to be a distinction without a difference because the parties agreed that supplemental glutamine and naturally occurring glutamine had the same function in the human body.

The plaintiffs urged the court to adopt a broader view of substantiation, arguing that it requires a showing of the product's efficacy in supporting the structure or function of the body as claimed. According to the plaintiffs, Vitamin Shoppe did not meet this threshold because most people produce enough natural glutamine such that additional glutamine in the form of a supplement would provide no actual benefit.[12]

The court drew a careful distinction in the type of substantiation needed for structure/function claims. Relying on the plain text of the DSHEA, the court concluded that a manufacturer is only required to have substantiation of the nutrient's claimed effect on the body's structure or function.[13] According to the court, the statute did not require evidence that the product itself has the claimed benefits. In reaching its conclusion, the court contrasted Congress' treatment of dietary supplements and

drugs. New drugs require "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested."[14] While dietary supplements that make disease claims are subject to the same efficacy requirement, it is not the case for dietary supplements making structure/function claims.[15]

The plaintiffs' reliance on FDA's Guidance for Industry did not change this conclusion.[16] The court acknowledged that FDA's guidance recommends having evidence that the supplement will affect the body as claimed, under conditions similar to those described for the supplement. However, the court found no statutory ambiguity to justify deferring to FDA's nonbinding guidance.

Finally, the plaintiffs challenged the truthful and non-misleading nature of Vitamin Shoppe's structure/function claim. The plaintiffs argued, in part, that the labeling statements were misleading in that they claimed that "the actual pills in the bottle provide certain benefits,"[17] when, according to the plaintiffs, they did not. The court disagreed. A manufacturer must have substantiation for the nutrient's claimed physiological role, but it is not required to disclose whether using the product as directed will provide a health benefit to the consumer.

Having found no genuine dispute that the BodyTech labeling claims met the standards for structure/function claims under the DSHEA, the court concluded that federal law expressly preempted all of the plaintiffs' state law claims. Indeed, the FDCA prohibits any state from establishing "any requirement respecting any claim described in section 343(r)(1) . . . made in the label or labeling of food that is not identical to the requirement of section 343(r)(6)."[18]

Because structure/function claims fall within this scope, the court affirmed summary judgment in favor of Vitamin Shoppe.

Conclusion

Ferrari demonstrates that manufacturers can face aggressive legal attacks from consumers against dietary supplement labeling claims, yet still obtain a favorable ruling. As new products emerge, so too will new theories for challenges under state law. Courts will continue to be called on to define the parameters of acceptable structure/function claims and the corresponding substantiation required by federal law.

Ferrari adds to that body of law and illustrates the need for manufacturers to be vigilant of the legal requirements for making a structure/function claim. *Ferrari* also reinforces that manufacturers (and consumers considering court challenges) should focus on whether supplement labels satisfy FDA requirements, while also providing some guidance on how the FDA requirements are interpreted.

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2. Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417 (1994).
3. 21 U.S.C. § 343(r)(6).
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8. *Id.*
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10. *Id.* at 71.
11. *Id.* at 72.
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13. *Ferrari*, 70 F.4th at 73.
14. 21 U.S.C. § 355(d).
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FDA's Adoption of NSF/ANSI 455-3 National GMP Cosmetic Standard Under MoCRA Could Model World Class Example of Public–Private Partnership in a Once-a-Century Opportunity

by Brandi Reinbold

At the close of 2022, Congress made waves in the cosmetics industry with the passage of the Modernization of Cosmetics Regulation Act (MoCRA), which represents the largest change to cosmetic regulations since the Federal Food, Drug, and Cosmetic Act of 1938, and the most expansive new legislation for any U.S. industry since the Food Safety Modernization Act (FSMA).[1] Among other new requirements, the U.S. Food and Drug Administration (FDA) is now tasked to create Good Manufacturing Practice (GMP) regulations for the cosmetics industry with proposed regulations by December 2024 and final regulations by December 2025.[2]

With MoCRA, Congress directed FDA to seek existing consensus standards where practicable, to avoid overly burdensome requirements, and to allow for flexibility within the regulations such that manufacturers of all sizes and types can comply without undue economic hardship.[3] The importance of these details and their implications for industry are hard to overstate. Those interested in the outcome of FDA's approach to GMP regulations for cosmetics should thus heed this as a call to action and participate in shaping the cosmetics industry of the future.

There is a rare opportunity at this moment to enact a modern regulation that maximizes all the possible benefits for stakeholders in the regulatory design. With smart and targeted regulation that leverages existing consensus standards and the public standards process, FDA can use existing best practices for maximum risk reduction and brand protection to protect the health and safety of U.S. consumers in an optimally efficient manner.

Public–Private Partnership on MoCRA Follows Federal Precedent

The directives to FDA within MoCRA exemplify the shift within the United States over the past decades towards public–private partnership (PPP) within government. This shift was accelerated by the National Technology Transfer and Advancement Act (NTTAA) of 1995, Section 12, Standards of Conformity, in which, for the first time, Congress directed regulators to "coordinate the use by Federal agencies of private sector standards, emphasizing where

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possible the use of standards developed by private, consensus organizations," and to "coordinate technical standards activities and conformity assessment activities of Federal, State, and local governments with private sector technical standards activities and conformity assessment activities, with the goal of eliminating unnecessary duplication and complexity . . . ." NTTAA gives agencies discretion to write new standards when existing consensus standards are "inconsistent with applicable law or otherwise impractical." If existing consensus standards are not inconsistent with applicable law or impractical, such standards should be adopted.[4]

NTTAA is supported by executive branch policy of the Office of Management and Budget's (OMB) Circular A-119-1, which sets policies to guide federal agencies on implementation of NTTAA. Circular A-119-1 states that "[a]ll federal agencies must use voluntary consensus standards in . . . their procurement and regulatory activities, except where inconsistent with law or otherwise impractical." Agencies can choose to incorporate the standard by duplicating the text within the written regulation or by referring to the standard in whole or in part within the regulation. Agencies can best eliminate duplication by using references to a standard.[5]

MoCRA echoes the language of NTTAA and OMB regarding "practicability," understanding that the task before FDA now must be considered in the context of this legislation and policy.

Before delving into the options up for consideration, it is important to understand what agencies are trying to accomplish by execution of these directives.

Private Sector Expertise, Cost-Effectiveness, and Time Savings Are Proven Benefits of Adopting Existing Consensus Standards

The benefits to adopting existing consensus standards rather than writing agency-unique standards include enabling a more cost-effective and timely rulemaking process, allowing the regulating agency to take advantage of the technical expertise of the private sector, and naturally aligning regulation with the best practices of industry rather than imposing a new status quo. In turn, this lessens the burden of compliance on industry by reducing confusion, costs, and time. An additional benefit is an ongoing opportunity for industry to participate in the standard-setting process, which provides a means to address new public health threats as they emerge, implement new best practices over time, and eliminate requirements as they become obsolete.

Similar benefits are gained when agencies use existing conformity assessment activities in lieu of more direct agency activity. Accredited third-party conformance assessments can reduce the operating costs of the agency if the agency is able to access the data for use in its oversight procedures. The private third-party conformance assessment infrastructure is larger than the regulatory apparatus and capable of reaching a greater portion of industry facilities in any given year. Unlike other forms of PPP, the third-party conformance assessment infrastructure is not funded by taxpayers but by industry itself.

Third-party independent certification allows for early intervention on potential noncompliance issues. Since these independent assessors are not affiliated with FDA, manufacturers are often more open with data and processes during certification inspections. This leads to the most important benefit of adopting existing consensus standards: FDA could enhance industry's level of compliance without ever setting foot in the door or requiring an additional budget. Voluntary compliance benefits the consumer with safe, more uniform products and allows FDA to impact change in the industry without deploying costly resources.

FDA must set the standard before determining whether using third-party conformance assessments would be feasible. MoCRA continues the trend towards greater PPP by directing FDA to consider national and international standards. FDA must first consider whether the existing standards are "practicable." If FDA identifies such standards, it should then choose the one that would maximize the benefits to the agency, consumers, and industry.

NSF/ANSI 455-3 Is the Solution

Public consensus standards can be national or international. International standards may facilitate global trade more seamlessly when such standards are recognized and accepted on a global scale. The current international standard for Cosmetics GMP is International Organization for Standardization (ISO) 22716:2007, which enjoys widespread recognition and acceptance.[6] Another benefit of ISO 22716 is that a majority of the industry already complies with it to some extent, especially those doing business outside of the United States. Adoption of this standard would thus reduce the overall cost of industry compliance. However, because committee membership for voting on international standards is limited to one representative per country, such standards have a very limited platform for national control, and thus are inflexible to the specific

regulatory needs of the United States. Furthermore, the requirements of ISO 22716 are vague, with no guidance on what compliance looks like, and may be inadequate to protect U.S. consumers from adulterated products. This deficiency led FDA to publish draft guidance, hereinafter FDA GMP Compliance, articulating its view of quality management activities and systems that should be in place in U.S. manufacturing facilities, such as requirements for adverse event reporting and microbiological testing.[7]

National standards designated as American National Standards (ANS), in contrast, achieve balance in a different way. These standards do not limit participation to one representative per stakeholder, but instead follow the American National Standards Institute's (ANSI) essential requirements for due process, including openness, balance, and consensus.[8]

Participation in ANSI's proceedings is thus open to parties of all nations who participate in ANSI standards development with an interest in the standard, and timely public notice of all development activity surrounding such standards is required. The voting member committee consists of a diverse representation of interests in the areas of public health, manufacturing, consumer groups, and users of the standard, and the committee must consider all written views and objections. As new public health threats are identified or existing practices advance or become obsolete, the committee can enact changes via the ANSI process more quickly than is possible under regulation.[9]

NSF/ANSI 455-3 was developed in 2018 in partnership with the Global Retailer and Manufacturer Alliance (GRMA), a consortium of retailers and manufacturers, to address the need to comply with the ISO 22716 international standard globally, and with FDA GMP Guidance domestically.

NSF/ANSI 455-3 is now an ANSI-accredited standard that incorporates and harmonizes the ISO 22716 and FDA GMP Guidance. Unlike ISO 22716, it provides a platform for national participation and control. In other words, it retains the international trade benefits of a regulatory reference to ISO 22716, which often requires compliance with ISO 22716, while including the additional protective requirements for U.S. consumers of cosmetic products.

Complementing NSF/ANSI 455-3 is a guidance document entitled "Audit Requirements Guideline for NSF/ANSI 455-3 Good Manufacturing Practices for Cosmetics" that provides interpretation on expectations in a flexible way to accommodate a variety of manufacturer processes and situations. Information in the guidance is used to help manufacturers comply without imposing requirements on industry. This allows manufacturers to demonstrate compliance with the standard requirement in other ways where appropriate to their operations. This addresses an important directive of MoCRA: the directive that FDA make its regulations flexible to avoid imposing an undue burden on small entities. The FDA GMP Guidance provides this room for flexibility while maintaining the integrity of the quality requirement in the standard itself, thereby protecting consumers from harm.

NSF/ANSI 455-3 is the GMP consensus standard that meets all the mandates of MoCRA, NTTAA, and OMB A-119-1. It optimizes the desired benefits of a PPP and minimizes the potential limitations of such a regulatory reference. Given the legislative directives in MoCRA, it is the most "practicable" solution. NSF/ANSI 455-3 is aligned with current best industry practices, including those previously conveyed in the FDA GMP Guidance, meets international standards, and is within national control for management over time. To minimize the administrative burden, FDA might incorporate NSF/ANSI 455-3 by reference into its GMP regulations so that it does not have to revise its regulations each time NSF/ANSI 455-3 is updated. FDA should also maintain an open channel of conversation between FDA and stakeholders through Joint Committee participation. Importantly, industry can voluntarily comply with interim standard versions between reference updates, which can provide years of advance notice on what FDA is thinking and where the industry is coalescing. This gives regulated parties the advantage of a longer runway for changes that impact their operations and time to gradually update procedures to stay compliant. This is a best-case scenario of quality and compliance that can be achieved voluntarily by FDA's participation in the ANSI standard-setting process.

Potential Drawbacks and Limitations of Consensus Standards in Regulations

There are a few drawbacks to incorporating a consensus standard by reference into FDA's GMP regulations. One potential drawback is that FDA would have incomplete control over the development of standards over time. However, the balance of stakeholders is intended to prevent undue influence of any one interest over the content of a standard, significantly limiting the ability of any one interest group's ability to make an undesirable change. Further, it is in the best interests of all to develop practical but strong standards. Over a hundred years of consensus standards writing in

pharmaceutical, plumbing, water, and other industries provides thousands of examples of the strength of this framework for quality standards development.

Another general limitation on a government agency's use of reference to a consensus standard is the regulatory requirement under 1 C.F.R § 51.9(b)(2) to include a version.[10] It is burdensome for FDA to revise this reference each time the standard is updated, as it requires a public notice period for any update under 1 C.F.R. § 51.11. However, agencies have to go through this process for any regulations they promulgate, so this limitation does not impose an additional burden and can be overcome.

A Deep Dive into NSF/ANSI 455-3

NSF/ANSI 455-3 Section 5 describes audit-scheme requirements followed by Certification Bodies (CBs) that certify cosmetic GMP requirements. This section standardizes the audit scheme so that when combined with ISO 17065 accreditation of the Certification Body, it ensures a high level of competency and impartiality in conformance assessments. ISO 17065 is the international standard for conformity assessment of products, services, and processes. It is the gold standard for such activities as evidenced by its global recognition and acceptance. This private ISO 17065-accredited conformance assessment infrastructure can be utilized by FDA to leverage third-party certification to make risk-based enforcement decisions on a voluntary basis with very limited agency resources. Such a scheme not only reduces duplication between private and public efforts but could greatly expand FDA's reach and visibility into the compliance status of industry.

To illustrate, as part of FSMA, FDA enacted the Accredited Third-Party Certification Program aspect of the Voluntary Qualified Importer Program (VQIP).[11] Here, FDA only partially incorporated existing third-party conformance assessments. FDA customized the accreditation requirements that the Accreditation Bodies use to approve Certification Bodies. In this program, Certification Bodies have, in a sense, been deputized by FDA and they still have reporting requirements to FDA. The food safety risk to public health was presumably weighed against existing conformance assessment activity, and in this case FDA determined partial customization was appropriate.

Regarding cosmetic manufacturing and the prospect of a regulatory oversight scheme incorporating these activities, a slightly different solution is reasonable.

Because most cosmetic products do not cause serious adverse events, they pose an inherently lower risk than adulterated foods to public health. Accordingly, greater utilization of the existing conformity assessment infrastructure of accreditation to ISO 17065 is appropriate. A custom FDA accreditation program in this instance would be an unnecessary duplication of efforts. By using the existing accreditation system for certification to the public national consensus standard, FDA has access to an extremely efficient oversight tool at no cost to the agency.

Participation in a third-party certification program would need to be voluntary to avoid imposing additional mandatory costs upon industry. Audit reports should remain the property of the manufacturer and may be submitted as part of facility registration on a voluntary and annual basis. FDA could review the report as part of a risk assessment when prioritizing scheduling of routine inspections. Certification Bodies would not have reporting requirements to FDA for voluntary audits because this requirement would introduce a much greater level of complexity into the scheme. A custom accreditation scheme becomes necessary if this is required due to confidentiality requirements of ISO 17065 accreditation. In this way—by ceding any reporting requirement upon CBs—FDA can gain access to a great deal of compliance data from industry as part of facility registration, enabling it to use its resources with precision and to greater effect. Since the agency uses risk-based decision-making to allocate limited resources, facilities that share data could be designated as low-risk and deprioritized on the audit schedule. This scenario maximizes the benefits to all stakeholders.

Conclusion

Because of the continuous management practices of NSF as a standard-writing body, NSF/ANSI 455-3 is the only public standard that can still easily be modified to meet any rulemaking criteria prior to the compliance deadline. As FDA navigates this rulemaking process and reviews the standard, it can engage the NSF/ANSI 455-3 Joint Committee with industry to incorporate new requirements or modify the language of existing requirements. This will ensure that the initial reference serves its purpose for years to come before requiring any update.

NSF/ANSI 455-3 is the existing GMP standard with the greatest utility to maximize benefits and minimize limitations of a regulatory reference. It has the versatility and national control needed to meet current and future needs of U.S. consumers, manufacturers of all sizes, and both domestic and global regulators.

By incorporating the national standard into regulation, FDA could also create an

opportunity to harmonize and reduce redundancy in compliance-assessment efforts between government and industry. As part of the process to roll out new regulations, FDA must plan how it will enforce compliance with the goal to protect public health and safety while maximizing the return on investment of expending limited financial resources. Enacting a policy to incorporate third-party conformity assessment activities into federal conformity assessment activities is compliant with Section 12(b) of NTTAA, which requires regulators to look to the availability of existing public consensus standards that are practicable before moving to writing new regulation. It also achieves the benefits sought by eliminating "unnecessary duplication and complexity in the development and promulgation of conformity assessment requirements and measures," per OMB policy.

For the next year and a half or so, NSF, cosmetics manufacturers, consumers, regulators, retailers, and all of those who are a part of this industry will be able to take advantage of a once-in-a-hundred-year opportunity. By working together in the public space to design a solution that is forward-thinking and practical, we can all reap the benefit of global access to high-quality, affordable cosmetic products made in a regulatory environment that is a world-class example of how PPPs could and should be executed.

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The Grocer Will Fill Your Order Now: Modernizing Online Food Shopping Becomes a Priority for Federal Agencies

by Jean Mancheno & Joanne Hawana

Introduction

Over the past three years, online grocery shopping has increased exponentially in the United States. Between 2019 and 2020, sales rose more than 50%, from $62.2 billion to $95.82 billion dollars.[1] The COVID-19 pandemic was a catalyst for this increase and enabled consumers to obtain groceries from the safety of their homes. However, the trend has continued well past the height of the pandemic, with online grocery sales projected to comprise 20% of all grocery sales by 2025. There are several features of online grocery shopping, such as efficiency, flexibility, and the ability to easily compare products, that have resulted in it becoming a preferred method amongst shoppers. Indeed, there are a breadth of digital applications and platforms, such as Amazon Fresh, InstaCart, FreshDirect, Walmart, and Peapod, that allow consumers to purchase groceries for pick up or delivery. Furthermore, in addition to its practical benefits, online grocery shopping can remove physical constraints from the shopping experience, increase one's ability to monitor spending, and enable food access in rural areas.

Though online grocery shopping presents clear benefits for consumers, it does not come without its drawbacks. First, though online grocery shopping has increased, not all consumers in the United States are able to take advantage of its

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benefits. In addition, consumers report a much different experience in reviewing food labels available online compared to food labels available in a brick-and-mortar grocery store. When a consumer is shopping in a brick-and-mortar grocery store, it is common to peruse the labels of potential purchases, for both comparative purposes and to gain an understanding of their ingredients and nutritional value. The same experience is sought by consumers who are shopping for their groceries online. However, consumers have reported a much different experience when reviewing food label information online, indicating that the information may be presented inconsistently, inaccessibly, or inaccurately.

As online grocery shopping increases in the United States, there is a parallel need to improve both access and labeling, and the federal government is keen on doing so. This article will provide an overview of the federal government's efforts to improve the online grocery shopping experience for all consumers. We will discuss the White House's National Strategy on Nutrition and Health (National Strategy), which outlines the Biden–Harris Administration's (Administration) plan to improve both online grocery shopping access and online food labeling.[2] We then examine efforts of various federal agencies to further the Administration's goals. Regarding efforts of federal agencies, first, we discuss initiatives undertaken by the United States Food and Nutrition Services (FNS) to upgrade the Supplemental Nutritional Assistance Program (SNAP) and Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) programs to allow for online food purchases. Second, we will review initiatives by the U.S. Food and Drug Administration (FDA) to understand and address the challenges imposed by online food label information. Finally, the article will conclude with a discussion of how these initiatives go hand-in-hand with the Administration's overall goal of improving population health.[3]

White House Initiatives for Improving Access to Grocery Shopping and Improving Online Food Labeling

In September 2022, President Biden convened the White House Conference on Hunger, Nutrition, and Health (Conference). During the Conference, President Biden introduced the National Strategy, which is intended to address the nation's hunger problems and promote healthier eating across the United States. Embedded in the National Strategy are plans to improve online grocery shopping and online food label information, with the White House articulating a goal of bringing "federal nutrition assistance programs into the 21st century" through expanding online shopping. Noting that online shopping has only been piloted thus far in WIC agencies, the White House commits that the United States Department of Agriculture (USDA), through funds from the American Rescue Plan Act, will expand this program to other agencies, bringing these programs beyond pilots and into permanence for shoppers (further discussed below).[4] The White House emphasizes the positive impact that this could have on marginalized communities and the elderly, who may face discrimination, stigma, increased health risks, lack of transportation or mobility, and how online shopping can improve and even enable a better shopping experience.

The National Strategy also addresses the need to improve the information found on online food labels.[5] It informs the public that FDA will publish a request for information to gather the public's input on the industry practices, technology, and current challenges so that it can inform guidance that FDA will promulgate on the topic. This request for information, entitled *Food Labeling in Online Grocery Shopping; Request for Information*, was published in April 2023 and is discussed in more detail below. The White House also suggests that online grocery companies redesign their websites' search algorithms to ensure that healthier food options will appear to their consumers, and that their offerings include ingredient and nutritional label information in an accessible manner.

On March 24, 2023, the White House renewed its commitment to these improvements and announced the *Challenge to End Hunger and Build Healthy Communities*.[6] In the press release for the challenge, the White House announced several initiatives geared at improving online grocery shopping and food label information. For example, in addition to announcing its intent to remove barriers from using WIC online, it announced a major partnership to offer SNAP EBT grocery delivery throughout the United States. DoorDash, an online shopping platform, will partner with local, regional, and national grocers to increase the number of healthy options and work with USDA to offer access to SNAP EBT grocery delivery in all 50 states, Washington, D.C., and Puerto Rico by 2025.

Food and Nutrition Service Enables Online Grocery Shopping for WIC and SNAP Program Beneficiaries

As mentioned above, not all consumers in the United States are able to make their grocery purchases online. In particular, individuals who use WIC and SNAP benefits are typically unable to do so because of regulatory requirements that purchases under those programs be made in person. USDA, primarily through its agency the FNS, has taken steps toward changing this paradigm. USDA has entered into a partnership with the Gretchen Swanson Center for Nutrition (GCSN) to establish the WIC Online Shopping Grant (Shopping Grant). The Shopping Grant involves two phases. First, the GCSN conducted a study to identify recommendations for implementing WIC online shopping with online and in-person transactions. The second component of the project enabled four "sub-grant" projects with funding to implement WIC online shopping programs. The sub-grant projects began in December 2021 across seven states. In Minnesota, Iowa, and Nebraska, the sub-grant was geared toward implementing an online shopping program for WIC participants at Hy-Vee grocery stores. In Washington and Massachusetts, the sub-grant was geared toward bringing online shopping to WIC participants at Walmart grocery stores. In South Dakota and for the Rosebud Sioux Tribe, an online grocery shopping program was implemented for the Buche Foods grocery store. In Nevada, the WIC agency used its sub-grant to reset the integration of the WIC online shopping using the WICShopper app.

As a result of this pilot program, FNS announced proposed regulatory changes to allow for online ordering through the WIC program on February 17, 2023. The proposed rules would remove barriers in the WIC shopping experience. Currently, WIC regulations require program participants to pick up "food instruments," such as cash-value vouchers, Electronic Benefits Transfer (EBT) cards, and paper food instruments in person and also require WIC transactions to occur within the physical space of a store. The proposed rule would allow WIC participants to use their EBT cards with approved online grocery retailers and would also expand the program to allow for online grocery delivery, online-only retailers, and mobile grocery platform retailers. In addition to removing barriers in access to grocery shopping, it is thought that online grocery shopping will help reduce the stigma associated with receiving WIC benefits.

FNS is also focused on bringing online grocery shopping to SNAP participants as well. On July 7, 2022, FNS announced that it would award a $5 million dollar competitive grant to help expand the number of retailers offering SNAP for online shopping. Specifically, the purpose of the grant is to fund the technology and systems needed to enable SNAP recipients to shop online, to diversify the pool of stores at which SNAP beneficiaries can make purchases, and to enable smaller, independent grocery stores to provide online shopping. After an application and selection process, FNS awarded this grant to the National Grocers Association Foundation (NGAF) on January 5, 2023. The NGAF intends to use the funds to create the SNAP EBT Modernization Technical Assistance Center, enable independent community grocers to expand their online purchasing platforms, and increase online grocery shopping in rural communities across the United States.[7]

FDA Initiatives to Understand Food Labeling in Online Grocery Shopping

FDA has addressed the issue of food label information found on the Internet through different mechanisms over the past two decades. FDA first commented generally on the subject in response to a petition filed by the Washington Legal Foundation (WLF) in 2001. The petition, filed on April 16, 2001, requested that FDA not deem information on company websites to be "labeling," contending that FDA regulation of website content could have negative implications on freedom of speech.[8] In FDA's response to WLF,[9] it suggested that if a company is promoting and selling a product over the Internet, it could come within the scope of "labeling" under the Federal Food, Drug, and Cosmetic Act (FDCA) and be subject to applicable regulatory requirements.[10] FDA reiterated this point in a January 1, 2007 *Dear Manufacturer Letter Regarding Food Labeling*,[11] which was sent to members of the industry. Recognizing that the Internet is a valuable resource in disseminating truthful information about food to consumers, the letter encouraged manufacturers and distributors to ensure that claims about their food products posted online are consistent with FDA regulations and law.

More recently, FDA hosted the *New Era of Smarter Food Safety Summit on E-Commerce: Ensuring the Safety of Foods Ordered Online and Delivered Directly to Consumers* (Summit) from October 19–21, 2021. The Summit was a virtual public meeting that convened government officials from FDA, state-level health agencies, and even international health agencies to discuss topics surrounding food safety during panel sessions. Following these discussions, there was opportunity for public comment

during the session and through a public docket.[12] On the Summit's second day, there was a session on food labeling, which provided the opportunity for discussion on food labeling issues surrounding foods sold through e-commerce. During the session, panelists discussed the need for food labeling regulations to keep pace with the trends of consumers, noting the growth of online grocery ordering and current barriers to accessing nutritional facts in online shopping. The panelists noted how the location of food label information on websites is often unintuitive and that it can often be inaccurate or misleading. Commenters also pointed out that they often notice websites including disclaimers regarding the accuracy of the information provided online. They therefore encouraged FDA to issue guidance on how nutrition information should be displayed online.[13] In response, panelists from FDA reiterated their desire to gather more information from consumers and retailers to understand how food labeling in online grocery shopping could be improved.

Making good on that promise, on April 24, 2023, FDA published the notice *Food Labeling in Online Grocery Shopping; Request for Information* (Docket No. FDA-2023-N-0624-0002). FDA's notice and request for information (RFI) identifies several topics related to online grocery retailers, food manufacturers, and third-party online grocery providers. The three topics, as well as the questions that FDA is seeking responses, supporting data, and evidence for, are as follows:

RFI #1: Food Labeling Information Provided Through Online Grocery Shopping

- "The mandatory label requirements on most packaged foods include, in part, nutrition information (*e.g.*, Nutrition Facts label), ingredient information, and major food allergens information (when applicable). What mandatory label information is currently available through online grocery shopping platforms? How consistently is mandatory label information presented across online grocery shopping platforms?"
- "How is nutrition, ingredient, and major food allergens information presented through online grocery shopping platforms? For example, where is the information available on the webpage in relation to the product?"
- "When provided, is the nutrition, ingredient, and major food allergens information in the same format as on the packaged product (*e.g.*, Nutrition Facts label format)? If pictures of the product are used, how does the manufacturer, retailer, or third-party online grocery provider ensure the information in the picture is consistent with the package label, readable, and accessible on all devices (*e.g.*, laptops, smartphones etc.)?"

RFI #2: Industry Considerations and Logistics of Food Labeling in Online Grocery Shopping

- "Grocery foods may be sold in various ways through e-commerce, (*e.g.*, directly from the manufacturer, a retailer, or through a third-party online grocery provider). How do manufacturers, grocery retailers, and third-party online grocery providers decide what label information to display for grocery foods sold through online platforms (websites, mobile applications, etc.)?"
- "What challenges and limitations do online grocery retailers, manufacturers and third-party online grocery providers encounter when seeking to display food labeling information on their respective platforms? Please provide any data and evidence to support your response. Also, what, if any, are the labeling challenges for international websites selling groceries online?"
- "How do manufacturers, retailers, and third-party online grocery providers ensure that information online is consistent with the actual product package and that the information is accurate and up to date? Please provide any data and evidence to support your response."
- "How do online retailers and third-party online grocery providers address manufacturer reformulations that may alter a product's nutrition, ingredient, or major food allergens information? If there is a change or error detected, how do online grocery shopping platforms collect the information and update the website (*e.g.*, is there a customer feedback loop or internal quality assurance process to detect and correct online labeling errors)?"
- "What measures are online grocery shopping platforms taking to ensure that consumers can access accurate nutrition, ingredient, and major food allergens information when purchasing groceries online? Have online grocery shopping platforms identified or capitalized on opportunities to leverage online platforms (*e.g.*, interactive labeling) to improve consumer engagement with and accessibility to food labeling information? Please provide any data and evidence to support your response."
- "How are online grocery shopping platforms seeking to ensure online access to labeling information is

equitable for consumers? Do current online labeling presentations present barriers to accessing labeling information for certain consumers?"

RFI #3: Consumer Use of Food Label Information in Online Grocery Shopping

- "What food label information do consumers expect to see when shopping for groceries online? For example, do consumers expect all the information presented online to be the same as the retail food package label? When there is a picture of a product label online, do consumers expect the picture of the label to be the same as the label on the retail food package?"
- "To what extent, and how, do consumers use nutrition, ingredient, and major food allergens information when grocery shopping online? For example, what percentage of consumers use the label to get information to support eating healthier? What percentage of consumers use the label information because of specific dietary concerns? We would be especially interested in demographic data on consumers who view label information when grocery shopping online."
- "What do consumers find most challenging about navigating online shopping platforms for specific label information needs?"
- "What data are available on the most effective ways for presenting nutrition, ingredient, and major food allergens information specifically through online grocery shopping platforms (websites, mobile applications, etc.), so that consumers can easily access the information? For example, is there a specific format (*e.g.*, Nutrition Facts label format) that consumers find useful in an online grocery shopping platform? What are effective means of displaying this information on the platform (*e.g.*, link to additional product information, viewable on the top 50 percent of the web page) to ensure consumers have ready access?"

The comment period for this RFI closed on July 24, 2023, so responses from various stakeholder groups can be reviewed in the docket on Regulations.gov.[14] In total, 31 comments were electronically submitted by various stakeholders, including grocer organizations, food scientists, and individual consumers to FDA for review and consideration.

Conclusion

Several components of the federal government, including the White House, USDA, and FDA, have prioritized finding ways to empower people in the United States to make healthier, informed choices about their nutrition and food consumption. Two initiatives that can aid in this mission are increasing access to healthier foods and to nutritional information—both of which can occur through online grocery shopping.

The hope is that better access will enable consumers to identify healthier alternatives, improve diets, and, with time, lead to improved public health. A long-term goal of the White House's National Strategy is to decrease the incidence of diet-related diseases, such as hypertension, obesity, and diabetes, which could be prevented with improved nutrition. These diseases also tend to disproportionately impact communities of color, regions with lower socioeconomic status, and rural communities.

The United States appears to be on the horizon of enacting serious regulatory reform for the WIC program, funding major projects to bring access to SNAP recipients, and better understanding the challenges in online food labeling. With the notice and comment period on FDA's *Food Labeling in Online Grocery Shopping; Request for Information* closing over the summer, we can also anticipate FDA's response and publication of guidance on the topic in the foreseeable future.[15] As a collective, in undertaking these initiatives to improve online grocery shopping and online food label information, the U.S. government is taking key steps to drive meaningful change in nutritional outcomes.

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2. *Biden–Harris Administration National Strategy on Hunger, Nutrition, and Health*, The White House (Sept. 2022), https://www.whitehouse.gov/wp-content/uploads/2022/09/White-House-National-Strategy-on-Hunger-Nutrition-and-Health-FINAL.pdf.
3. *Id.*
4. *Id.*
5. *Id.* at 22.
6. *Fact Sheet: Biden–Harris Administration Launches the White House Challenge to End Hunger and Build Healthy Communities, Announces New Public & Private Sector Actions to Continue Momentum from Historic Hunger, Nutrition, and Health Conference*, The White House (Mar. 24, 2023), https://www.whitehouse.gov/briefing-room/statements-releases/2023/03/24/fact-sheet-biden-harris-administration-launches-the-white-house-challenge-to-end-hunger-and-build-healthy-communities-announces-new-public-private-sector-actions-to-continue-momentum-from-hist/.
7. *NGA Foundation Awarded $5M USDA Grant to Advance SNAP Online Programs*, Winsight Grocery Bus. (Jan. 5, 2023), https://www.

winsightgrocerybusiness.com/industry-partners/nga-foundation-awarded-5m-usda-grant-advance-snap-online-programs.

8. *Washington Legal Foundation – Citizen Petition*, U.S. Food & Drug Admin. (Apr. 16, 2001), https://www.regulations.gov/document/FDA-2001-P-0321-0001.
9. *FDA/Associate Commissioner for Policy Response to the Washington Legal Foundation – Petition Denial*, U.S. Food & Drug Admin. (Nov. 1, 2001), https://www.regulations.gov/document/FDA-2001-P-0321-0003.
10. The FDCA defines "labeling" as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). Federal courts, including the Supreme Court, have upheld a broad application of the phrase "accompanying such article" to mean more than physical association with the product, such that it extends to materials like posters, brochures, and other advertisements so long as they have been created by or on behalf of the product's manufacturer with the intent of "accompanying" the product in commerce. Since the 2001 WLF petition response, the concept of manufacturers' websites as promotional labeling for their products has become embedded in various agency policies.
11. *Guidance for Industry and FDA: Dear Manufacturer Letter Regarding Food Labeling*, U.S. Food & Drug Admin. (Jan. 2007), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-and-fda-dear-manufacturer-letter-regarding-food-labeling.
12. *FDA New Era of Smarter Food Safety Summit on E-Commerce; Public Meeting; Request for Comments*, U.S. Food & Drug Admin. (Oct. 19, 2021), https://www.regulations.gov/docket/FDA-2021-N-0929.
13. *Transcript: New Era of Smarter Food Safety Summit on E-Commerce – Day 2 (October 20, 2021)*, U.S. Food & Drug Admin. 147–55 (Oct. 20, 2021), https://www.fda.gov/media/154860/download.
14. The electronic comments that FDA received on the docket can be viewed at https://www.regulations.gov/document/FDA-2023-N-0624-0002/comment.
15. On July 6, 2023, FDA updated the list of guidance documents that it is intending to promulgate or revise by the end of December 2023. Guidance addressing food labeling in online grocery shopping is not included on this list. However, FDA is not precluded from issuing a guidance document on topics not included prior to December 2023. *See Food Program Guidance Under Development*, U.S. Food & Drug Admin. (July 6, 2023), https://www.fda.gov/food/guidance-documents-regulatory-information-topic-food-and-dietary-supplements/foods-program-guidance-under-development.

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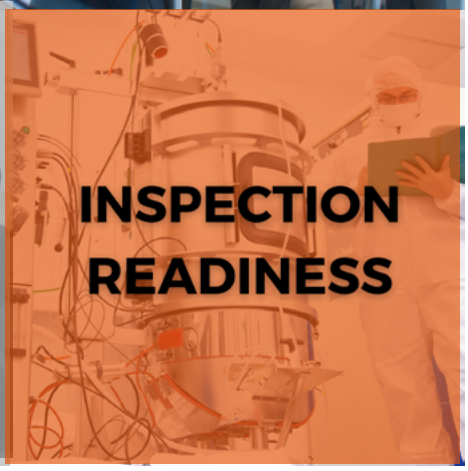

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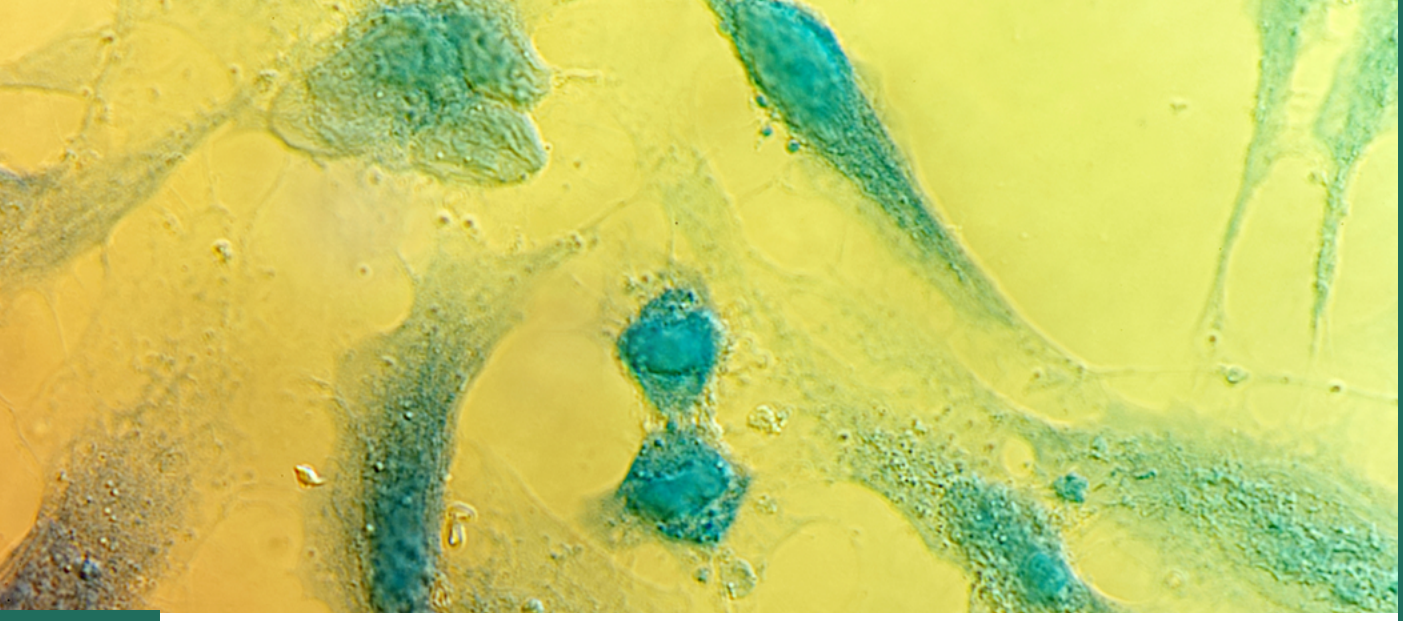

Lacks v. Thermo Fisher Scientific Inc.— An Extraordinary Event from More than 70 Years Ago That Led to a Lawsuit, Resulting in a Settlement

by Véronique Li

The recent settlement agreement between Ron L. Lacks, grandson of Henrietta Lacks and executor of Ms. Lacks' estate, and Thermo Fisher Scientific Inc., one of the largest life science companies in the world, came about after tissue from Ms. Lacks was surgically removed more than 70 years ago without her knowledge or consent.

Would this unprecedented settlement have happened if not for the publicity generated by Rebecca Skloot and her 2010 best-selling book *The Immoral Life of Henrietta Lacks*,[1] which became the subject behind the 2017 HBO adaptation starring Oprah Winfrey? And what does the complaint, filed by the estate of Ms. Lacks, mean for other entities that have similarly benefited from the HeLa cell line, so named using the first letters of Ms. Lacks' first and last names? What are the broader implications of this case? We explore these questions below.

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Henrietta Lacks

Henrietta Lacks was born Loretta Pleasant on August 1, 1920.[2] As a young child, Ms. Lacks worked as a tobacco farmer and cared for animals and the garden. When she was in the sixth grade, she dropped out of school to help support her family.

After her mother's passing, she moved to live with her paternal grandfather. She eventually married David "Day" Lacks in 1941 and moved to Turner Station, Maryland, where the couple had five children.[3]

Months after giving birth to her fifth child, she felt a "painful knot in her cervix" and experienced vaginal bleeding. She went to Johns Hopkins Hospital, which was one of the few hospitals that would treat Black patients—although only in racially segregated wards.

At the time when Ms. Lacks was referred to Johns Hopkins, the chair of gynecology at the hospital, Dr. Richard Wesley TeLinde, faced criticism for frequently removing the cervix, uterus, and portions of the vagina of patients with carcinoma in situ. If he could demonstrate that carcinoma in situ behaved the way other forms of cervical cancer did, he believed he could justify his aggressive surgical techniques.

He recruited Dr. George Gey, head of tissue research at Johns Hopkins, to use samples that Dr. TeLinde would provide. Dr. Gey would then attempt to grow cells that could survive in a laboratory. The proposal aligned with Dr. Gey's research

interests to understand how human cell samples could survive in laboratory conditions.

Dr. TeLinde would go on to direct other doctors to take samples from Black patients with cervical cancer in Johns Hopkins' segregated wards.

Treatment

On February 5, 1951, Dr. Jones took a biopsy of Ms. Lacks' cervix and discovered a large, malignant tumor, which, upon examination, was different from any tumor he had ever seen before.

Following the biopsy and diagnosis of cancer, Ms. Lacks began undergoing treatment with radium tube inserts. Such treatment required a patient to be placed under anesthesia. It also left Ms. Lacks infertile. When she found out about her infertility, she stated she would never have agreed to be treated.[4] The treatment did not slow her cervical cancer, which she would succumb to on October 4, 1951. (As an aside, the complaint was dated October 4, 2021, marking the 70th anniversary of her passing. October 4 was also designated Henrietta Lacks Day in 2017 by then-Baltimore, Maryland Mayor Catherine Pugh.)

During one of the treatment sessions and while under anesthesia, two parts of Ms. Lacks' cervix were removed without her knowledge or permission. Removing the tissue samples was neither medically necessary nor germane to radium treatment.

Discovery

The tissue samples were then sent to Dr. Gey's tissue lab. He discovered that Ms. Lacks' cells were "immortal" (i.e., cells did not die after a few cell divisions). This cell line, which would eventually become known as HeLa cells, was the first to reproduce indefinitely. In contrast, samples obtained from other patients would typically only survive for a few days.

The novelty of HeLa cells were used for many experiments and led to medical breakthroughs such as the polio vaccine, gene mapping, and *in vitro* fertilization. HeLa cells were also employed to understand the effects of radiation on human cells and cited in over 110,000 scientific publications.[5]

It also resulted in the first known human biological materials ever bought and sold. "One scientist estimates that if you could pile all HeLa cells ever grown on a scale, they'd weigh more than 50 million metric tons."[6] That is a staggering amount, reflecting the outsized impact on scientific and medical research and development and subsequent profits from Ms. Lacks' cells.

Ms. Lacks' family did not learn about her "immortal cells" until more than 25 years after her death. Her family received no profits from the selling of HeLa cells.

Informed Consent

The standard procedure during Ms. Lacks' time did not require a doctor to obtain consent or inform the patient when cells or tissue were taken. In fact, it was common practice to collect tissue samples from cervical cancer patients without them knowing (especially at Johns Hopkins) because of a lack of established practice in the 1950s.

As summarized in the table below, the current practice of informed consent very much differs from the practice in the 1950s.

Table 1: High-Level Comparison of Clinical Research Processes[7]

	1950s	Current Practices
Informed Consent	No established practice for informing or obtaining consent from cell or tissue donors	Medical research centers maintain strict patient consent processes for those who donate tissue and cellular materials for research
Collecting Patient Samples	Common practice to collect tissue samples from cervical cancer patients	Any request for samples for research purposes would fall under regulatory and legal standards, and the oversight of an Institutional Review Board (IRB) *Note*: IRBs uphold strict standards of informed consent for all potential participants in human research involving cell or tissue donation
Using Patient Cells	No local or national regulations on the use of cells in research	Standard practice to have an IRB examine every research study involving human participants before it is approved
Medical Records Privacy	Patients had no right to see or retain a copy of their medical records. No state or federal laws prohibited sharing of medical record information for research	Patients have a right to see and have a copy of these medical records. Both state and federal laws regulate patient consent and the use and sharing of medical record information

In sum, the taking and subsequent use of Ms. Lacks' tissue would not pass muster under today's standards.

The manner in which human subjects consent (either electronically, verbally, or manually) can vary as does the contents of the informed consent itself. It is now expected that the informed consent form will explain what might happen to human tissue and how long it will be stored. This also includes specifying whether tissue, collected during the course of a clinical trial or other procedure, might be used in the future for research and what this future research might entail.

The general requirements for informed consent in U.S. Food and Drug Administration-regulated clinical research are outlined in 21 C.F.R. § 50.20. Of note: "Except as provided in §§ 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative." The U.S. Department of Health and Human Services also has broader regulations for the protection of human subjects in research that require informed consent of the research subject or the subject's legal representative (see 45 C.F.R. Part 46).

The removal of Ms. Lacks' cells predates the development of informed consent regulations. At the time of the removal of Ms. Lacks' cells, Thermo Fisher Scientific did not exist. The conflict that existed at the time of the procedure was with Johns Hopkins and the doctors. They were the ones who stood to benefit.

Complaint

The complaint filed by the estate of Henrietta Lacks alleged that Thermo Fisher Scientific had acknowledged publicly that Ms. Lacks' cells were taken from her body without her consent. The complaint further stated that the estate of Ms. Lacks neither provided permission for use of her cells nor was contacted about it.

According to the lawsuit, Thermo Fisher Scientific then mass-produced HeLa cells for commercial research use and received millions of dollars in profit as a result. They also capitalized on "contract development and manufacturing services to other biotechnology companies."[8] The plaintiff alleged the company commercialized and profited off HeLa cells without consent of or compensation to the estate of Ms. Lacks.

The sole count and single cause of action in this case is that of unjust enrichment. The estate of Ms. Lacks complained that Thermo Fisher Scientific profited from the unlawful conduct of Ms. Lacks' doctors at Johns Hopkins. As stated in the Third Restatement of Restitution, "a defendant who is enriched by misconduct and who acts [] with knowledge of the underlying wrong to the claimant" is a conscious wrongdoer liable for its profits.[9]

The complaint goes on to claim that the company was "unjustly enriched because it received a benefit from Henrietta Lacks, understood it received a benefit from Ms. Lacks, and did so in circumstances in which acceptance or retention of the benefit was inequitable without payment or permission."[10] Acceptance or retention of the HeLa cell line is further considered inequitable without payment or permission "through breach of a relation of trust and confidence," "unlawful conduct," and "because of the totality of circumstances surrounding the creation and acquisition of the HeLa cell line."[11]

Because Thermo Fisher Scientific allegedly knew of the underlying wrong to Ms. Lacks, the estate of Ms. Lacks contends that Thermo Fisher Scientific is "liable for their net profits incurred as a result of their unjust enrichment."[12]

Impact of Settlement

The complaint was brought forth as a result of an action that occurred more than 70 years prior. There was no dispute that Ms. Lacks' cells were taken from her without her knowledge or consent by individuals who should have had her best interest at heart. In the ensuing 70 years, Ms. Lacks' immortal cells were researched, patented, and commercialized over and over again.

As a result, individuals and companies have repeatedly and significantly benefited from the conduct that stemmed from the actions of doctors at Johns Hopkins. The complaint asserted that Thermo Fisher Scientific was aware of the conduct that led to the acquisition of Ms. Lacks' cells. Their website recognized the "unsanctioned use of HeLa cells from Henrietta Lacks."[13]

This kind of recognition, along with those of other companies, was the focus of the complaint against Thermo Fisher Scientific and a subsequent one against Ultragenyx Pharmaceutical, Inc.

Lacks v. Ultragenyx Pharmaceutical, Inc.

Thermo Fisher Scientific was the first company to be sued by the estate of Ms. Lacks. It was not the last.

On August 10, 2023, the estate of Ms. Lacks filed a suit against Ultragenyx Pharmaceutical Inc., a biopharmaceutical corporation for the same single cause of action—unjust enrichment.[14] According to its corporate presentation from August 2023, Ultragenyx's portfolio includes four approved therapies for the treatment of rare diseases. The

company's stock symbol goes by RARE.

"The first human cells that could survive indefinitely in laboratory conditions," the HeLa cells have allegedly been developed and mass-produced by Ultragenyx for commercial research and therapeutic use.[15] According to the complaint, profits from these activities would not have been possible without the HeLa cells.

Their proprietary HeLa Producer Cell Line (PCL) platform allegedly allows Ultragenyx to also profit from licenses and partnerships. The estate alleges that the company knowingly participates in efforts that allow the company to be compensated for the sale of products and services that are affiliated with tissue from Ms. Lacks.

Given the ubiquity of the HeLa cell lines in the biopharmaceutical industry, it may be that other companies would also potentially be targets for future claims by the estate. Thus, the implications for other research and use from biological materials across the industry may be great. While the HeLa cell line is perhaps the most famous, there were undoubtedly other tissues and biological materials that were removed from individuals decades ago without meeting current standards of informed consent. That raises the issue of possible vulnerability of other companies to these kinds of claims. It remains to be seen whether these types of risks will need to be disclosed in SEC filings or become the subject of due diligence investigations.

Publicity

It is hard to understate the role that publicity has played in this matter. What happened to Ms. Lacks received widespread attention after it became the subject of a book and movie and was referenced numerous times in scientific articles. This spotlight undoubtedly prompted the litigation, but it does not form the basis for the legal claims. Similar claims presumably could be grounded in the treatment of other individuals.

One should avoid the temptation to paint the narrative in stark terms as simply good and bad, judged solely by modern standards. The widespread use of the HeLa cell line undoubtedly led to major innovations in basic scientific knowledge and important medical breakthroughs. Still, individuals and companies have publicly acknowledged that they never sought or received permission from Ms. Lacks or her estate, yet published, manufactured, and licensed the HeLa cells. Her doctors should have focused on treating her cancer and providing the best patient outcomes. However, they improperly extracted from her cells that would ultimately prove to be reproducible.

Lessons

The case is important. It highlights what can happen without informed consent (namely that genetic material can be removed from a person without their knowledge or permission), what then happens to the genetic material (in this case, it was harvested and used numerous times in scientific and medical research and development for personal and corporate gains), who benefits from use of personal material (researchers, doctors, international companies, and patients but the individual providing the tissue), and potential legal risks to other entities who have and continue to use the HeLa cell line. That Ms. Lacks herself stated she would not have consented poses an ethical quandary for those who knowingly continue to use her cells for commercial and research purposes.

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Admittedly, it is disconcerting to learn that one person's cellular materials can be repurposed for financial gains for all those but her and her family. However, in this digital age, we also have to consider privacy infringement. How much of our digital DNA is lurking in the ether for those to exploit and monetize? While it remains to be seen what will happen in the case against Ultragenyx and possibly other companies, we do have to consider whether our informed consent is necessary for other activities. Just how much do we permit our own information or material to be used when we sign, whether electronically or manually, waivers and authorizations, informed consent forms, and other documents that are long, complex, and often never read? Do we as participants have the right to benefit from any commercial products, partnerships, and licenses? It's something to think about the next time you are presented with text-heavy documents in which you agree to give away rights to your own personal information and tissue.

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Reality-Based Healthcare Reform

by Peter J. Pitts

Introduction: Reality Isn't Negotiable

When it comes to innovation in the development of new medicines, a key focus is on "Real World Evidence,"[1] or data based on what's really happening in the real world (aka: reality). Unfortunately, as I've previously argued,[2] when it comes to healthcare policy, "real" seems to be conveniently ignored when it doesn't suit the shibboleths of political agendas that prefer easy answers to complicated questions. As H. L. Mencken said, "For every complex problem there is an answer that is clear, simple, and wrong."[3] Case in point—the Inflation Reduction Act (IRA) and its call for government price controls for certain prescription medicines.[4]

Under the IRA, which was signed into law last August, Medicare will be able to negotiate certain prescription drug prices with pharmaceutical companies. This provision will initially apply to 10 drugs starting in 2026, and will expand to 20 drugs in 2029.[5] In practice, these "negotiations" are federally mandated price controls. Under the IRA, the government now has enormous power to name its own price for an increasing range of advanced medicines, and drugmakers will have little choice but to submit to such power.

The predictable outcome of price controls is the significant dis-incentivization of the research-and-development system that makes America the world leader in medical innovation. In the words of Philip Dick, "Reality is that which, when you stop believing in it, doesn't go away."

Will Direct Federal Negotiations Lower Costs?

According to the Congressional Budget Office (CBO), Medicare Part D plans have "secured rebates somewhat larger than the average rebates observed in commercial health plans." Additionally, the Medicare Trustees report that many brand-name prescription drugs carry substantial rebates, often as much as 20 to 30%, and on average, rebate levels have increased in each year of the program across all program spending.[6]

According to the CBO, revoking the Kennedy/Daschle Non-Interference Clause, would

"have a negligible effect on federal spending" because CBO estimates that substantial savings will be obtained by the private plans and that the Secretary would not be able to negotiate prices that further reduce federal spending to a significant degree. Because they will be at substantial financial risk, private plans will have strong incentives to negotiate price discounts, both to control their own costs in providing the drug benefit

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and to attract enrollees with low premiums and cost-sharing requirements.[7]

The noninterference clause says: "[T]he Secretary: (1) may not interfere with the negotiations between drug manufacturers and pharmacies and [prescription drug plan] sponsors; and (2) may not require a particular formulary or institute a price structure for the reimbursement of covered Part D drugs." According to the Senate Republican Policy Committee, "It leaves negotiations to insurers and other private businesses. Medicare Part D plans negotiate drug prices, determine which drugs are covered, and what patients will pay."[8]

In 2007, after two years of experience with bids in the Part D program, CBO found that striking noninterference "would have a negligible effect on federal spending because . . . the Secretary would be unable to negotiate prices across the broad range of covered Part D drugs that are more favorable than those obtained by PDPs under current law."[9]

In 2009, after even further program experience, CBO reiterated its previous views, stating that it "still believe[s] that granting the Secretary of HHS additional authority to negotiate for lower drug prices would have little, if any, effect on prices for the same reason that my predecessors have explained, which is that the private drug plans are already negotiating drug prices . . . ."[10] Importantly, CBO states that no further savings are possible unless the government restricts beneficiary access to medicines or establishes market-distorting price interventions.[11]

Is the Juice Worth the Squeeze?

There are many issues and opinions regarding the benefits and risks of direct government negotiations of drug prices. But one key question remains . . . is the juice worth the squeeze? Is the imposition of price controls worth the benefit to society?

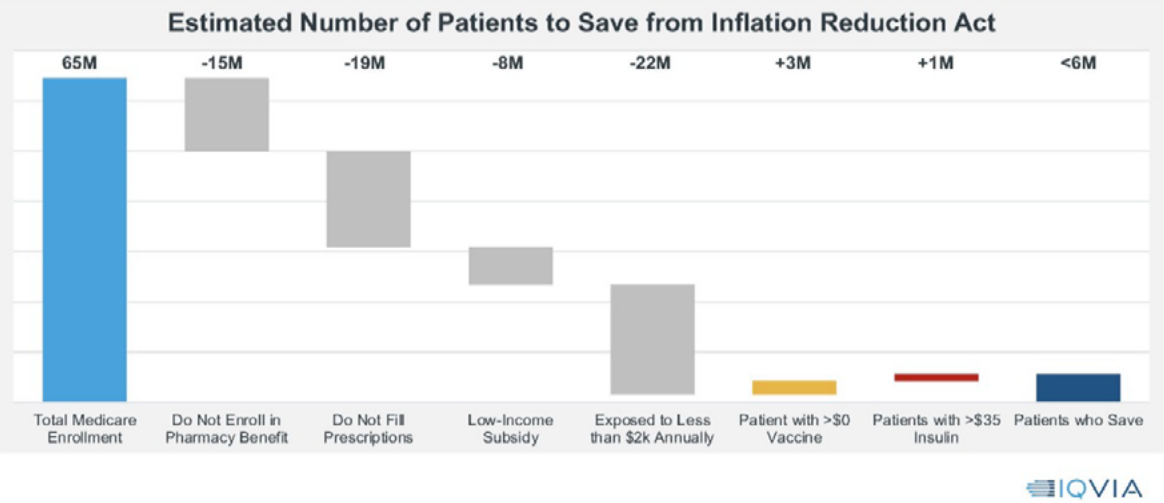
As Douglas Holtz-Eakin argues, while the IRA is advertised as substantially reducing drug costs for a wide swath of Medicare beneficiaries, under 6 million beneficiaries—less than 10%—will benefit at all (see Figure 1). For those who do benefit, savings are typically modest—69% of those with any saving will save less than $300.

The bottom line is striking. Of the 65 million Medicare beneficiaries, only 5.6 million are benefited by the IRA.[12] Is the juice worth the squeeze?

Price Controls Equal Choice Controls: Veterans Administration's Experience

The U.S. Department of Veterans Affairs' (VA) health insurance plan offers 1,300 drugs, compared with 4,300 available under Part D, prompting more than one-third of retired veterans to enroll in Medicare drug plans.[13] Patients vote with their feet. VA employs a narrow, exclusionary formulary to generate savings, and comparisons of coverage between VA and Medicare demonstrate that VA offers fewer choices, particularly of the most cutting-edge and innovative medicines. Of the top 200 Part D brand medicines, approximately 74% were covered by Medicare, compared to just 52% that could be covered by the VA formulary.[14] Similarly, the VA National Formulary[15] covers just 40% of first-in-class Part D medicines, compared to more than 62% in Medicare Part D.

Figure 1



According to the Government Accountability Office, "VA can steer utilization toward a limited number of drugs within a given therapeutic class. Medicare Part D plans, on the other hand, generally have broad networks of pharmacies and as such may have broader formularies than VA's."[16] Similar access restrictions are likely to appear in Medicare if Part D prices reference VA prices. A study from Columbia University found that just 19% of all new drugs approved since 2000 were covered by VA. And just 38% of drugs approved since 1990 were covered.[17] VA negotiating tactics are driving out some drug providers from the program, leaving patients with fewer treatment options.[18]

Developing medicines is already a risky business. It costs, on average, nearly $3 billion over 10 to 15 years for each approved new medicine.[19] That's partly due to the direct expense of the research-and-development activity itself and partly because only 12% of potential medicines entering Phase I clinical trials ultimately win approval.[20] Private investors are willing to take such risks because a successful drug has the potential to earn back those costs—and then some.

During his 2022 State of the Union, President Biden claimed that under a price control regime, "Drug companies will still do very well."[21] In fact, such a policy could reduce the revenue of the innovative biopharmaceutical industry by $1.5 trillion over the next decade.[22] These biopharmaceutical companies, on average, dedicate nearly one-fifth of revenue to research and development (R&D). Simple math suggests that price control legislation would cut funding for R&D spending by hundreds of billions of dollars.[23] Economic modeling estimates that price control legislation would snuff out 56 new drugs—including 16 cancer treatments—that would have otherwise reached patients.[24]

Where Do Drugs Come From?

There is a fundamental misunderstanding about the government's role in drug development. Senator Elizabeth Warren (D-MA), for example, believes that pharmaceutical innovation is primarily driven by the National Institutes of Health (NIH), the federal medical research organization.[25] But that has never been true.

A study by two Columbia University scholars in the journal *Health Affairs* uses historical data to reveal the real role NIH serves in drug development.[26] This study shows that fewer than 10% of drugs are covered by a public sector patent. And this slice of drugs only accounts for 2.5% of total annual drugs sales. Drugs that relied on federal funds for development, meanwhile, comprise only about a quarter of sales. The primary engine of drug innovation is private industry, which spends more than $50 billion annually on R&D.[27]

NIH focuses on basic research—that is, the study of fundamental aspects of organic phenomena without regard to specific medical applications. The biopharmaceutical industry, on the other hands, directs most of its R&D toward clinical research. Private science is centered on the actual development of new medicines. Both NIH and private firms provide research financing to academic institutions. But it is industry that employs most of the scientists that conduct the hands-on development work.[28] Drug development is a team effort and mustn't be positioned by politicians, pundits, and agenda-driven advocates as an industry vs. government proposition.

Wither Innovation?

Government price controls will reduce the chances of an innovator's opportunity to recoup a medicine's development costs, which will plummet as a result, with the logical result being that new research will dry up. Everything from cancer breakthroughs to new treatments for Alzheimer's disease, amyotrophic lateral sclerosis (ALS), COVID vaccines, and heart medications would become rarer. Those that did make it through the pipeline could be even more expensive, since, with fewer molecules in the pipeline, commercial competition will not act to reduce prices.

A recent review, led by University of Chicago economist Tomas Philipson, notes that studies consistently show that a 1% reduction in industry revenue leads to a 1.5% reduction in R&D activity. It finds that this legislation would reduce industry revenue by 12% through 2039 and R&D activity by 18.5%, or $663 billion. It also estimates that 135 fewer medications would be developed in that period as a result—a crippling shortfall that will also be measured in lives lost.[29]

Are Drugs too Expensive? Follow the Money

The list price of a medicine is meaningless to patients. When Americans with health insurance say that their drugs are "too expensive," what they mean is that their copays and co-insurance rates are too high. Those rates aren't set by pharmaceutical companies—but are the domain of the pharmacy benefit managers (PBMs) and insurance companies. During the last few years, pharmaceutical spending has increased by 38%, while the average individual health insurance premium has increased by 107%.[30] During the same period, rebates, discounts, and fees paid by the biopharmaceutical industry to insurers and pharmacy benefit managers have risen from $74 billion to $166 billion.[31]

That's 37% of our nation's entire expense on drugs.

Government policies should encourage rebate dollars to flow back to patients who need to take prescription drugs. Will greater transparency of contracting practices on the state level drive better pharmacy benefit manager behavior? That's one theory. Such transparency efforts in New York and Connecticut, for example,[32] will be the bellwether. But greed often trumps shame and, without penalties, will PBMs choose to do the right thing by patients and reduce their hefty profits?

Pharmaceutical company rebates to pharmacy benefit managers that are tied to formulary restrictions create an incentive for entrenched market leaders to "bid" incremental rebates to prevent or limit access to competitive medicines. This model, coupled with escalating cost-sharing requirements, harms patients by driving up prices, resulting in reduced access to innovative drugs.

Allowing pharmacy benefit managers to continue with business-as-usual means a continued disincentive to promote a more aggressive uptake of both biosimilars and less-expensive generic drugs. Worse, reinforcing the status quo moves us even further away from a health care ecosystem based on competitive, predictable, free-market principles.

As I have argued elsewhere,[33] not following through on the proposed rule to ban rebates[34] is harmful to patient health and the public purse. One of the biggest threats to the body politic is nonadherence to the medicines physicians have prescribed: It causes 125,000 deaths each year[35] and is responsible for 10% of hospitalizations. Why don't people take their medicines? Often because their copays and co-insurance rates are too high.

One of the troubling issues with the IRA is its continued lack of transparency. CMS has expressed an intent to bind drugmakers to confidentiality in price negotiations.[36] The American public will not see "the sausage" of how negotiated prices are determined, and confidentiality requirements will limit the extent to which the government can be held accountable for consistent and fair price determination decisions.

At the heart of the debate is whether we are going to improve our health care system using smart and evolving free-market principles, such as more focused regulation that addresses the exclusionary contracting that locks out savings from biosimilars, or go down the sound-bite-laden path of "free health care."

Perverse Incentives Deny Patient Options

Per my argument in "The White House's About-Face on Drug Rebates is a Loss for Public Health," "Pharmaceutical company rebates to pharmacy benefit managers that are tied to formulary restrictions create an incentive for entrenched market leaders to 'bid' incremental rebates to prevent or limit access to competitive medicines. This model, coupled with escalating cost-sharing requirements, harms patients by driving up prices, which results in reducing access to innovative drugs."[37]

FTC Weighs In

In June 2022, the Federal Trade Commission (FTC) voted 5-0 to conduct a study of pharmacy benefits managers' business practices.[38] FTC has since announced that the agency's inquiry "will scrutinize the impact of vertically integrated pharmacy benefit managers on the access and affordability of prescription drugs."[39] As part of this inquiry, FTC will send compulsory orders to CVS Caremark; Express Scripts, Inc.; OptumRx, Inc.; Humana Inc.; Prime Therapeutics LLC; and MedImpact Healthcare Systems, Inc.

The inquiry is aimed at shedding light on several practices that have drawn scrutiny in recent years, including[40]:

- fees and clawbacks charged to unaffiliated pharmacies,
- methods to steer patients towards pharmacy benefit manager-owned pharmacies,
- potentially unfair audits of independent pharmacies,
- complicated and opaque methods to determine pharmacy reimbursement,
- the prevalence of prior authorizations and other administrative restrictions,
- the use of specialty drug lists and surrounding specialty drug policies, and
- the impact of rebates and fees from drug manufacturers on formulary design and the costs of prescription drugs to payers and patients.

"Although many people have never heard of pharmacy benefit managers, these powerful middlemen have enormous influence over the U.S. prescription drug system," says Federal Trade Commission Chair Lina M. Khan. "This study will shine a light on these companies' practices and their impact on pharmacies, payers, doctors, and patients."[41]

Sliding Down the Slippery Slope

The concept of federal "negotiations" on biopharmaceuticals is a slippery slope.[42] Yet, even as we're debating the highly controversial implementation of the IRA, there's already a cry that the IRA doesn't go far enough. But those critics jumping on that manic toboggan are heading for a rude awakening, named "reality."

According to the Orwellian-named "Strengthening Medicare and Reducing Taxpayer (SMART) Prices Act,"[43]

(sponsored by Senators Amy Klobuchar (D-MN), Peter Welch (D-VT), and 23 of their colleagues), "This legislation builds on Klobuchar and Welch's provision included in the IRA that empowered Medicare to negotiate prescription drug prices for the first time, unleashing the power of Medicare's 50 million seniors to help lower drug prices for all Americans." That's quite an extraordinary statement considering, as Holtz-Eakin argues above,[44] that of the 65 million Medicare beneficiaries, only 5.6 million Medicare enrollees will benefit from the existing pricing codicils of the IRA. But with that kind of hyperbole, why stop there? The Klobuchar–Welch bill is a headlong dive down the slippery slope of even broader federal control of healthcare.

Consider this, the SMART Act calls for:

- creating a national formulary;
- increasing direct price controls for 20 drugs in 2026 (vs. the IRA's current 10) and 40 drugs in 2027 (vs. 15-20 under the IRA);
- accelerating price controls for Part B drugs to 2027;
- ending the exclusion of drugs with generics/biosimilars since they won't be on the market after three years. This is a considerably shorter time than small molecule data exclusivity under the IRA (5.5 years if awarded pediatric exclusivity); and
- changing the ceilings for the non-FAMP (Federal Average Manufacturer Price) formula prong of the MFP (Maximum Fair Price) from 75% to 76% for so-called "short monopoly drugs" and vaccines, from 65% to 55% for "extended monopoly drugs," and from 40% to 30% for "long monopoly drugs."

Note the nomenclature change. Rather than calling these healthcare technologies what they are—innovative and lifesaving—the authors of the bill view them as "monopolies." Considering that the U.S. Department of Health and Human Services and the U.S. Department of Commerce have announced efforts to pursue a whole-of-government approach to review its march-in authority, as laid out in the Bayh–Dole Act,[45] via an Interagency Working Group empowered to "develop a framework for implementation of the march-in provision that clearly articulates guiding criteria and processes for making determinations where different factors, including price, may be a consideration in agencies' assessments,"[46] it's fair to ask—is aggressive patent expropriation the next step in the process?

In 2019, the House of Representatives, under Speaker Nancy Pelosi, made the "Lower Costs Now Act" (the infamous H.R. 3)[47] their top legislative priority. It called for price controls via an international pricing index. Common sense prevailed and H.R. 3 was relegated to the ash heap of history. Today, before we can even fully understand the consequences (both intended and unintended) of the IRA, some members of Congress—this time in the U.S. Senate—are ready to take what they consider to be a Great Leap Forward in American healthcare reform. It is ill-considered and dangerous.

Sunshine is the Best Medicine: Reality-Based Legislation

In 2019, Senators Mike Braun (R-IN) and Mitt Romney (R-UT) introduced the "Prescription Drug Rebate Reform Act."[48]

According to Senator Romney:

> Patients in Utah and across the country are strapped with skyrocketing prescription drug costs, while insurance companies and drug manufacturers benefit from a complex system of rebates that results in higher drug costs. By changing the rules of cost-sharing, our bill aims to bring transparency to the prescription drug pricing system and lower out-of-pocket costs for medication.[49]

And, per Senator Braun:

> The current system of government-sanctioned rebates for prescription drugs has distorted the drug pricing market. Drug prices—and out of pocket expenses paid by consumers—seem to continually be on the rise. What is not talked about enough, however, is the inherent conflict of interest arising from negotiated rebates that affect the actual cost of drugs, which are paid by drug makers to pharmacy benefit managers (PBMs) in exchange for preferred status on insurers' health plan formularies. This creates a perverse incentive for drug makers to continually increase drug list prices—at the expense of consumers. And even when drugs are covered by insurance—consumers with cost-sharing obligations are often required to pay 30 to 40 percent of high drug list prices out of their own pocket. These rebates are often hidden from consumers, contribute to high list prices for prescription drugs, and leave consumers with all, or a big part of the tab.[50]

Rethinking the Inflation Reduction Act

On June 6, 2023, Merck & Co. sued to halt the Medicare drug price negotiation program contained in the IRA. Merck's

position is that the IRA violates the Fifth and First Amendments to the U.S. Constitution, arguing that under the law, drugmakers would be forced to negotiate prices for drugs at below-market rates.[51]

Merck called the government's tactics "coercive" and said it forces drugmakers to participate in "political Kabuki theater" by pretending negotiations are voluntary. "This is not 'negotiation.' It is tantamount to extortion," Merck said in the suit. Merck also argues that the law will force companies to sign agreements conceding that the prices are fair, which it claims is a violation of the First Amendment's protections of free speech.[52] Considering that the U.S. government is Merck's biggest customer, this lawsuit takes guts.

Whether or not the Merck lawsuit is successful, the heart of the debate remains whether we are going to improve our health care system using smart and evolving free-market principles or go down the sound-bite-laden path of "government negotiation" (today) and "free health care" (tomorrow). IRA "implementation" is in the details—as is somebody else. As the late Admiral Hyman G. Rickover reminds us, "The Devil is in the details, but so is salvation."[53]

Read CMPI's Comments in regard to the initial implementation guidance for the Inflation Reduction Act's "Medicare Drug Price Negotiation Program" for initial price applicability year 2026.

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Suggestions for Improvement of FDA Review of New Tobacco Products

by Dave Dobbins

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Pub. L. No. 111-31 (2009)) provides two primary pathways for marketing authorization of non-therapeutic nicotine products. Products on the market as of February 15, 2007 are "pre-existing tobacco products" and authorized to be sold in the United States.[1] Products that are "substantially equivalent" to pre-existing tobacco products are authorized so long as they do not have characteristics that "raise different questions of public health."[2] For products that do not fit within these paths, they must be authorized as new tobacco products through Section 910 of the Act. For new tobacco products, a manufacturer must establish that the introduction of the product into the market is "appropriate for the protection of the public health."[3] This is referred to as "the APPH standard."[4]

The APPH standard is entirely new in U.S. law. Thus, there is no regulatory or case history to help define the term. Likewise, this standard is not used in other jurisdictions that might provide guidance as to its content.[5] This lack of guidance has led to a predictable vacuum in the understanding of the standard, and to date, there have been over 26 million applications for new tobacco products since the U.S. Food and Drug Administration (FDA) deemed e-cigarettes to be subject to the APPH standard, and only 23 marketing authorizations for e-cigarette products and a handful for one heat-not-burn system, one brand of Swedish snus, and very low nicotine content cigarettes. Given these numbers, it is fair to say that the process is either very burdensome, poorly understood by the regulator and regulated manufacturers, or perhaps all of the above. The recent Operational Evaluation of the Center for Tobacco Products (CTP) by the Reagan-Udall Foundation echoes these concerns.[6]

The statute does give some context for the APPH standard, stating that determinations should consider:

> the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account—(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.[7]

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This language makes it clear that the APPH standard is not to be considered in a vacuum but rather against the current state of nicotine and tobacco use (i.e., cigarette smoking). If a new, less harmful product can encourage users of more toxic products to switch, it should be considered for authorization provided that this benefit is not offset by harms to those who otherwise would not have used nicotine products. However, the language of the statute (and the legislative history) gives no guidance on how to weigh those concerns, and that language appears to be the prime source of the current, apparently nearly unachievable, regulatory hurdle for the premarket authorization of new commercial nicotine products. Nevertheless, the language must have *some* meaning, and it clearly contemplates *a* pathway for new products. It cannot be nullified by the agency adopting an interpretation that is a de facto ban, and that seems close to what is happening in the current environment.

In December 2022, the Reagan-Udall Foundation, at FDA's request, conducted an operation evaluation of certain components of FDA's tobacco regulatory program and had this to say on new product authorization standards:

> The Panel heard from multiple stakeholders that the application review process, in general, requires a new approach. Although some processes are perceived as working . . . , PMTAs [premarket tobacco product authorizations] are generally perceived as ineffective and problematic. Concerns included lack of adequate guidance and transparency regarding CTP expectations, lack of clarity regarding review standards, [and] an unsustainable process of requiring a complete PMTA filing for each product . . . .[8]

The review encourages CTP to "develop a more clear and predictable framework for high-quality PMTA . . . application submission and reviews by" including "development and completion of policy and scientific standards" for new tobacco product submissions.[9] It is difficult to disagree given the current state of the administration of this pathway, and the call for a more transparent and predictable framework is not new.[10]

How are manufacturers to adequately meet the APPH standard when it is becoming increasingly apparent that the regulating agency doesn't have a consistent view of what it means? At one point, FDA felt comfortable authorizing a menthol version of the IQOS heat-not-burn system. Under the new leadership of Dr. Brian King, Director of CTP, it now appears highly unlikely that any further flavored products (including menthol) will be authorized given that he personally overruled a recommendation from CTP's Office of Science that the Logic menthol e-cigarette be authorized.[11] At least the staff at the Office of Science appeared to be confused about what standard should be used to evaluate such products when it initially suggested authorization of the device. Another example is FDA's decision in July 2021 that flavored e-cigarettes would not be authorized unless applications included randomized control studies (RCTs) showing smoker switching behavior to the flavored product (the "fatal flaw" memo).[12] This is despite previous advice that such studies would not be necessary.[13]

Industry has responded to the flood of marketing denial orders (MDO) and the unicorn likelihood of receiving a marketing granted order (MGO) by turning to the courts. The record has been mixed, although at this point over 100 MDOs have been stayed in various jurisdictions. The D.C. Circuit and the Third, Fourth, and Seventh Circuits have upheld MDOs despite the "fatal flaw" analysis.[14] The Second Circuit recently joined this group.[15] The Eleventh Circuit has overruled an MDO on the basis that FDA failed to fully review applications that did not include RCTs without directly addressing the issue of whether the change in guidance itself was arbitrary and capricious.[16] However, the strongest ruling yet has come from the Fifth Circuit in *R.J. Reynolds v. FDA*, 65 F.4th 182 (5th Cir. 2023), finding that the agency's actions have constituted a de facto flavor ban and that this is a substantive rule that the agency adopted without required notice and comment, noting the decision was "not close."[17] This conflicts with a previous Fifth Circuit opinion in *Wages and White Lions Invs. LLC v. FDA*, 16 F.4th 1130 (5th Cir. 2021) ("*Wages I*" or "*Triton*") that has now been vacated and is being considered by the court *en banc*. It is fair to suspect that the final decision there will not be kind to FDA's process, given the history of the case and that Judge Jones had dissented in *Reynolds* and had written for the majority in *Wages I*.

We will see what the playing field may look like after the Fifth Circuit issues an opinion in *Wages I*, but if the ruling goes as suspected, unless (or until) the Supreme Court weighs in on the issue, the Fifth and Eleventh Circuits will effectively be the courts reviewing the vast majority of MDO decisions in the FDA application review process, as sensible manufacturers with appropriate jurisdiction and venue requirements will simply bring cases there. While the vaping and tobacco industries are not favored

litigants, the current Supreme Court has not been receptive to vague agency standards and unlimited discretion due to unclear principles from administrative agencies.

There is also a deeper problem that has yet to be squarely addressed by current litigation: that there are no precise quantitative guidance to help applicants through the PMTA process, as the Reagan-Udall report found. FDA has issued guidance making its primary concerns relatively clear—toxicity of products, likelihood of current users switching to less toxic products, and prevention of youth use—but it has given no guidance on *what exactly* a manufacturer needs to show to address these concerns. For example:

- How much switching does a manufacturer have to demonstrate?
- Which products will FDA consider when looking at a switching analysis?
- How much higher is this burden with flavored products?
- How much youth uptake is tolerable?[18]
- What levels of potentially harmful chemicals are permissible?
- What nicotine strengths will the agency consider?
- What sort of manufacturing practices is FDA looking for regarding e-cigarette devices?[19]

It cannot be that a list of concerns is all a manufacturer is given, without any guidance on how these concerns can be addressed. This would be like an EPA regulation that simply said "Don't Pollute," without any quantitative guidance on what levels the agency viewed as unsafe, or it would be like a rule prohibiting "vulgar" speech on television without any explanation of what is considered vulgar, like *FCC v. Fox Television Stations*, 567 U.S. 239 (2012).

FDA, as Reagan-Udall recommended, could substantially reduce litigation risk and number of inadequate applications and add clarity to the review process by simply telling manufacturers what the agency is looking for with specificity instead of vague concerns. There seems to be little reason not to proceed in this manner, as the agency must be using some set of precise quantitative standards for review already. While FDA has authorized only 23 vaping devices, it presumably viewed those applications with such standards in mind. If not, the problem is deeper than feared, because it indicates that reviewers may be making it up as they go along. If so, that issue also raises deep concerns of arbitrary and capricious decision making. For example, it is hard to imagine that FDA could deny a marketing order based on toxicity concerns if the product in question emits lower levels of harmful constituents than a currently authorized product and expect such a denial to survive judicial review.

There is, of course, a higher imperative here than simply making the process fair under the law by making it easier, more well understood, and transparent. This is an issue where *real lives are at stake*. The Centers for Disease Control and Prevention estimates that nearly 500,000 adults a year die prematurely due to smoking and that there are over 30 million smokers in the country. These adults would be well served by a suite of substantially less harmful products that allow them to exercise reasoned and informed choice to switch. In countries where products have been introduced alongside factual information regarding harms, smoking has not only decreased, but so has smoking-related disease. The most famous real-life case of this is that of snus in Sweden. While the product is inexplicably banned in much of the EU, the actual experience in Sweden was such that, when the product became popular there in the 1970s, over time, Sweden had the lowest smoking rate in Europe and correspondingly lower incidence of tobacco-related disease.[20] Similarly, England *encourages* smokers to switch to vaping and is now giving away devices for free to those smokers looking to switch.[21] New Zealand has adopted an ambitious plan to eliminate smoking in that country largely by encouraging users to switch to less harmful products.[22] In Australia, where the government has taken draconian measures against vaping, both smoking *and* vaping rose in response.[23]

The current state of the new product authorization process is arguably arbitrary and capricious, and criminal enforcement for violating the law may run into problems of vagueness without further agency clarification. Setting clear standards will not only help manufacturers, but will also help the agency receive fewer inadequate applications, speed up work, and rely on clear standards when denials are inevitably challenged in court. While a healthy suspicion of nicotine products is justified by FDA's history, this suspicion is not an excuse for inaction. With transparency, consistency, and appropriate public messaging, there is an opportunity to transform the nicotine market from the leading cause of death and disease in America to a country wherein the greatest risk from nicotine use is dependence.

1. 21 U.S.C. § 387j (2023).
2. 21 U.S.C. § 387j(a)(3) (2023).
3. 21 U.S.C. § 387j(c)(2) (2023).
4. Therapeutic nicotine products with an indication as treatment for smoking dependence are governed by the "safe

and effective" standard, used by the Center for Drug Evaluation and Research (CDER). For more detail on CDER's approach to such products, see https://www.regulations.gov/document/FDA-2019-D-0297-0015. Suffice it to say, this describes a quite burdensome process.

5. For a longer discussion of the vagaries of the standard, see Eric N. Lindblom, *What Is "Appropriate for the Protection of the Public Health" Under the U.S. Tobacco Control Act?*, 74 Food & Drug L.J. 523 (2020).
6. Reagan-Udall Foundation, Operational Evaluation of Certain Components of FDA's Tobacco Program 8–19 (Dec. 2022), https://reaganudall.org/operational-evaluation-fdas-tobacco-program [hereinafter Reagan-Udall Report].
7. 21 U.S.C. § 387f(d)(1) (2023).
8. Reagan-Udall Report, *supra* note 6, at 18.
9. *Id.* at 19.
10. *See, e.g.*, Lindblom, *supra* note 5.
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12. So called because it instructed reviewers to check if an application had an RCT and instructed that if it did not, then it should be denied without further review. This led to the denial of hundreds of thousands of applications due to the "fatal flaw" of not having an RCT.
13. Avail Vapor's petition for cert petition challenging the Fourth Circuit's decision upholding a marketing denial order for their flavored nicotine liquids lays out this story in detail, available at https://static1.squarespace.com/static/5f6002fa681995196b0b45cc/t/645e43e4182b1706c29d1fdb/1683899365371/Avail+Vapor+LLC+v+US+-Food+and+Drug+Administration+-+Petition.pdf.
14. Liquid Labs LLC v. FDA, 52 F.4th 533 (3d Cir. 2022); Gripum, LLC v. FDA, 47 F.4th 533 (7th Cir. 2022); Prohibition Juice Co. v. FDA, 45 F.4th 8 (D.C. Cir. 2022); Avail Vapor, LLC v. FDA, 44 F.4th 409 (4th Cir. 2022).
15. Jim McDonald, *Second Circuit Rejects Magellan MDO Appeal*, Vaping360 (June 16, 2023), https://vaping360.com/vape-news/124709/second-circuit-court-rejects-magellan-mdo-appeal/.
16. Bidi Vapor LLC v. FDA, 47 F.4th 1191 (11th Cir. 2022).
17. The court reached this conclusion based on the handling of applications for flavored products (e.g., the King memo re: menthol products) and the fact that none, in fact, have been authorized.
18. On this point, the current CTP Director has indicated that the answer to this question may be zero (i.e., remarks at the E-Cigarette Summit 2023 and the FDLI Annual Conference 2023). Since that is obviously unachievable, that itself is a de facto ban of all new tobacco and nicotine products that, under the Fifth Circuit's reasoning, should be subject to rule making. Moreover, that position is likely outside of the clear language of the statute that makes plain that at least *some* sorts of products should be authorized under Section 910 and completely disregards the tremendous health benefits current smokers can achieve by quitting, which have been acknowledged by the Director in those very same forums.
19. There may be some progress here, as FDA recently held a hearing in preparation for a proposed rule in tobacco product manufacturing practices. However, even this proposal has no quantitative guidance for manufacture of e-cigarette devices. Requirements for Tobacco Product Manufacturing Practice, 88 Fed. Reg. 15174 (proposed Mar. 10, 2023) (to be codified at 21 C.F.R. pt. 1120), https://www.federalregister.gov/documents/2023/03/10/2023-04591/requirements-for-tobacco-product-manufacturing-practice.
20. Elizabeth Clarke, Keith Thompson, Sarah Weaver, Joseph Thompson & Grant O'Connell, *Snus: A Compelling Harm Reduction Alternative to Cigarettes*, Harm Reduction J. 16, 62 (2019), https://doi.org/10.1186/s12954-019-0335-1.
21. Sean Seddon & Rachel Russel, *Vaping: Free E-Cigarettes to be Handed out in Anti-Smoking Drive*, BBC News (Apr. 11), https://www.bbc.com/news/uk-65235343.
22. *See Harm Reduction and Vaping*, Action for Smokefree 2025, https://www.ash.org.nz/vaping-and-harm-reduction.
23. *See* Cait Kelly, *Australia's Teenage Smoking Rates Rise for First Time in 25 Years, Research Reveals*, The Guardian (June 2, 2023), https://www.theguardian.com/australia-news/2023/jun/02/australia-teenage-smoking-rates-rise-for-first-time-in-25-years-research-reveals.

FDA Review of New Tobacco Products: A Public Health Narrative

by Dennis A. Henigan

In "Suggestions for Improvement of FDA Review of New Tobacco Products," (Update, Fall 2023) Altria consultant Dave Dobbins faithfully presents the tobacco industry's narrative about the shortcomings of the U.S. Food and Drug Administration (FDA)'s "premarket review" of new tobacco products. That narrative is grossly incomplete and fundamentally misleading.

It is fair to say that no informed observer can be satisfied with the way the premarket review system has functioned to date, particularly in addressing the explosion of the e-cigarette market in recent years and the resulting epidemic of e-cigarette use and addiction among young people. The introduction of new tobacco products that cause great damage to public health is precisely the harm that premarket review is intended to prevent, yet that is exactly what has occurred with the advent of e-cigarettes. That Dobbins never mentions the widespread youth usage of e-cigarettes, its adverse consequences for public health, and FDA's failure to prevent it, is an indication that the industry's narrative badly misstates the real problem.

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The Flawed Industry Narrative

For Dobbins, the central weakness of FDA's premarket review is that it is too tough on applicants for marketing orders. For him, that the system is fundamentally flawed is evident from the fact that premarket tobacco product applications (PMTAs) have been filed for some 26 million e-cigarette products, but marketing orders have been granted for only 23, along with a handful of orders for other tobacco products. Since, according to Dobbins, the Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31 (2009) (Tobacco Control Act or TCA), was intended to provide a "pathway" for new tobacco products to reach the market, the fact that so few have been authorized by FDA is itself evidence that the premarket process is flawed; in his words, "either very burdensome, poorly understood by the regulator and regulated manufacturers, or perhaps all of the above."

As a threshold matter, this view reflects a misunderstanding of the role of premarket review under the TCA. The statute was not designed to provide an easy pathway to market for new products. That existed before the statute. Prior to the TCA, tobacco companies had unlimited freedom to determine what products reached the market and their characteristics, without any review to determine their impact on public health. The absence of regulation resulted in new products being introduced that were more hazardous, addictive, and appealing than those preceding them. Under the TCA, with certain exceptions, manufacturers seeking to introduce new tobacco products (i.e.,

those first marketed after February 15, 2007) now have the burden of demonstrating that doing so would be "appropriate for the protection of the public health" (APPH). Congress did not intend this standard to be easily met; indeed, the U.S. Court of Appeals for the Fifth Circuit has described the premarket review process set out in the TCA as "onerous, requiring manufacturers to gather significant amounts of information."[1]

As Dobbins points out, under the TCA, whether the APPH standard is met involves an assessment of "the risks and benefits to the population as a whole, including users and nonusers of the tobacco product" and weighs the likelihood that "existing users of tobacco products will stop using such products" against the likelihood that "those who do not use tobacco products will start using such products."[2] In *Nicopure Labs, LLC v. FDA*,[3] the DC Circuit rejected the argument that, because e-cigarettes are claimed to be "less risky" to the individual than other tobacco products, they should be subject to "less stringent authorization" through the premarket review process. "In requesting an easier path," the court wrote, "the Industry impermissibly assumes the very public health conclusion that premarket authorization requires be substantiated before a product may be sold: that e-cigarettes are no more risky to the population as a whole than preexisting tobacco products, balancing the prospect that they may lead existing users to less harmful products or usage patterns against the risks that existing tobacco users will postpone reductions or intensify their usage and that non-users will start."[4] Thus, the fact that few e-cigarettes have been authorized does not suggest that the premarket review process as conducted by FDA has been flawed with respect to e-cigarettes or other claimed "reduced risk" products; it may mean simply that companies are failing to meet the high standard set by Congress.

Contrary to Dobbins' suggestion, FDA's denial of marketing orders to virtually all e-cigarette products thus far does not constitute a "de facto ban," but rather reflects the real-world, observable public health consequences of the flavored products that have fueled the explosion of youth usage of these products. In the Technical Project Lead reviews that have accompanied the marketing denial orders (MDOs),[5] FDA has determined that because there is overwhelming evidence that flavors appeal to youth far more than tobacco-flavored e-cigarette products and are driving youth usage, companies seeking to market flavored products must produce "the strongest types of evidence" demonstrating that, compared to tobacco-flavored products, flavored products benefit smokers by helping them to stop smoking cigarettes. FDA has indicated that evidence from a randomized controlled trial, longitudinal cohort study, or similarly "reliable and robust" evidence would be required.

MDOs for millions of flavored products have been issued based on the failure of companies to produce such evidence in support of their applications for flavored products. On the other hand, marketing authorizations have been granted for certain tobacco-flavored e-cigarette products. Recently, in *Lotus Vaping Technologies LLC v. FDA*,[6] the Ninth Circuit joined the Second, Third, Fourth, Seventh, and DC Circuits in finding FDA's approach to flavored products to be entirely within FDA's statutory authority under the TCA and not arbitrary and capricious under the Administrative Procedure Act.[7] These courts also rejected the industry's argument, relied on by Dobbins, that FDA committed a "surprise switcheroo" by failing to give adequate notice of the special evidentiary burden that must be borne by flavored products.[8]

Only in the Fifth Circuit do the court's rulings indicate uncertainty as to the legality of requiring particularly compelling evidence of a smoking cessation benefit for flavored products.[9] As Dobbins points out, a Fifth Circuit panel's ruling upholding an MDO in *Wages and White Lion Investments, d/b/a Triton Distribution v. FDA* (*Triton*)[10] has been vacated and the case is being reheard *en banc*. Dobbins cites the Fifth Circuit panel ruling in *R.J. Reynolds v. FDA*,[11] issuing a stay of an MDO for a menthol e-cigarette, but that was not a decision on the merits and the court relied on facts unique to FDA's consideration of menthol-flavored products. In any event, the *Reynolds* case likely will be controlled by the *en banc* court's ruling in *Triton*.

Although the courts have yet to write the final chapter on the FDA's review of flavored products, and eventual Supreme Court consideration is possible, Dobbins' characterization of the court decisions as "mixed" does not accurately reflect the near-unanimous judicial endorsement of the FDA's application of the TCA's APPH standard to e-cigarettes. The industry narrative repeatedly has been the basis for legal challenges to MDOs for e-cigarettes. Six federal circuits have rejected it, while only one court—the Eleventh Circuit—has vacated an MDO, and that was on procedural grounds.[12]

The Real Story

Far from creating an insurmountable barrier to the market for e-cigarettes, FDA has allowed millions of e-cigarette products, including flavored products, to remain on the market for lengthy periods of time without any marketing authorization whatsoever. This is in utter defiance of the TCA, which prohibits the

marketing of new tobacco products *for a single day* without a marketing order. Even today, virtually the entire e-cigarette market consists of illegal products. This remarkable situation is the result of a "perfect storm" of ill-advised FDA policy decisions and delays, with the industry able to exploit those agency failures to its benefit and to the detriment of public health and, particularly, our young people.

First, FDA's inexcusable delay in issuing the Deeming Rule subjecting e-cigarettes to its regulatory authority, including premarket review, allowed the e-cigarette market to become a "wild, wild West" of unregulated, highly addictive flavored products marketed to young people. The agency announced its intention to deem e-cigarettes within its regulatory jurisdiction in April 2011.[13] It did not issue a final rule until May 2016. In the meantime, the e-cigarette market exploded and, driven by flavored products, youth usage of e-cigarettes began to increase, from 1.5% of high school students in 2011 to 16% in 2015.[14] What should have been premarket review of e-cigarettes inevitably became postmarket review.

Second, barely one year after the Deeming Rule became final, FDA substantially deregulated e-cigarettes by issuing a Guidance purporting to suspend premarket review of e-cigarettes that were on the market as of the effective date of the Deeming Rule by extending the deadline for filing PMTAs for four years (until August 2022). In a lawsuit brought by public health groups, a federal court in Maryland rejected FDA's claim that the Guidance was a legitimate exercise of enforcement discretion, ruling that it was beyond FDA's statutory authority.[15] The court characterized the Guidance as giving manufacturers a "holiday from meeting the obligations of the law,"[16] noting that "manufacturers can continue to advertise and sell products that are addictive and that target a youth market . . . at a time when minors' use of tobacco products like e-cigarettes is at an epidemic level and rising."[17] The court also noted the industry's intentional failure to engage the regulatory process until absolutely required to do so.[18] The court set new deadlines by which companies had to file PMTAs (September 9, 2020) and FDA had to issue marketing orders (September 9, 2021).

Third, when FDA finally began to issue MDOs for flavored e-cigarette products, companies introduced synthetic nicotine products in a wide variety of flavors in a transparent effort to evade FDA regulatory authority altogether, which under the TCA applied only to products with tobacco-derived nicotine. In March 2022, Congress acted to close this loophole, setting new deadlines for the submission of PMTAs for synthetic products (May 14, 2022) and for FDA action on those applications (July 13, 2022).[19]

Fourth, FDA has been deluged with a flood of PMTAs far in excess of what it had anticipated. The agency received applications for more than 6.5 million products by the deadline of September 9, 2020 set by the court and applications for nearly 1 million synthetic nicotine products by the May 14, 2022 deadline set by Congress.[20] It is obvious, however, that the volume of applications reflects an intentional strategy by some companies to cripple the premarket review process. For example, of the 6.5 million products for which applications were filed prior to September 9, 2020, a single company's application accounted for more than 4.5 million products.[21] Even more revealing, of the 26 million products for which PMTAs have been filed, more than 18 million were received *after* the September 9, 2020 deadline.[22] Applications for synthetic products also were an abuse of the system, as FDA issued refuse-to-accept letters for more than 925,000 of the 1 million products that filed by the May 14, 2022 deadline.[23]

Fifth, there have been lengthy delays in FDA decision-making on e-cigarettes, allowing many of the products with the largest market shares to remain on the market far after the September 9, 2021 deadline set by the Maryland court. According to periodic status reports FDA is required to file with the court, FDA will not complete its review of these products until December 2023,[24] more than two years after the deadline set by the court for decisions on all e-cigarette products with applications filed by the September 9, 2020 deadline.

Sixth, FDA delayed decisions on menthol-flavored e-cigarettes, citing "unique considerations" applicable to those products,[25] even though the data showed significant youth usage of menthol e-cigarettes, particularly in the wake of increased FDA enforcement activity against other flavors.[26] More recently, FDA has begun issuing MDOs for menthol products,[27] a development that Dobbins views as evidence that the agency "doesn't have a consistent view of what [the APPH standard] means." Actually, these MDOs bring the agency's decision-making on menthol in line with FDA's consistent approach to other flavors. There never were "unique considerations" justifying special treatment for menthol products, yet major menthol e-cigarettes, like JUUL, remain on the market today, helping to feed continued high youth usage.

Seventh, FDA has yet to take any enforcement actions against products with pending PMTAs, even though

they have no more legal right to be on the market than products that have never filed a PMTA. There appears to be an unstated FDA policy of exercising across-the-board enforcement discretion protecting these products, even though the Maryland court established a date (September 9, 2021) by which marketing orders must be issued for products to stay on the market without being subject to FDA enforcement.

Finally, even though the market is glutted with illegal e-cigarette products, FDA and its enforcement partner, the U.S. Department of Justice, rarely employ enforcement tools stronger than warning letters against renegade actors in the industry. The tobacco industry has shown little respect for the regulatory process, and the enforcement response has been weak[28] when measured against the dimensions of the problem.

Where to Go from Here

The central problem of premarket review is not, as Dobbins contends, that FDA has made it too difficult to get e-cigarettes to market, but that the agency has allowed so many manufacturers, particularly of flavored products, to market their products while avoiding the obligation to demonstrate, prior to reaching the market, that their e-cigarettes are "appropriate for the protection of the public health." This regulatory "holiday" has caused, and continues to cause, great harm to public health. It must end.

Understanding the nature of the problem dictates the appropriate strategies in response:

- FDA, the Department of Justice and other federal law enforcement authorities must use their power to the fullest to take illegal e-cigarettes off the market, prioritizing flavored products—including menthol-flavored products—regardless of whether they are the subject of pending PMTAs.
- FDA must complete its review of e-cigarette products that have timely pending applications—including synthetic products—as soon as possible and, in any event, by December 31, 2023.
- Going forward, FDA must ensure that no new tobacco product reaches the market without marketing authorization and must meaningfully sanction companies that violate this fundamental statutory requirement.

In short, *premarket* review must finally become a reality. It must finally function to protect the public, and particularly young people, from new public health threats from tobacco products. It must be acknowledged that, through a series of serious policy blunders, FDA has failed to implement the premarket review process as the TCA intended. But the agency's recent application of the APPH standard to flavored e-cigarettes, strongly endorsed by the federal courts against the industry's repeated attacks, is a hopeful sign that it is righting the ship.

1. *Big Time Vapes, Inc. v. FDA*, 963 F.3d 436, 439 (5th Cir. 2020).
2. 21 U.S.C. § 387j(c)(4).
3. 944 F.3d 267, 281 (D.C. Cir. 2019).
4. *Id.*
5. *See, e.g.*, Technical Project Lead Review of PMTAs (Sept. 17, 2021), https://www.fda.gov/media/152504/download?attachment.
6. 2023 WL 4384447 (9th Cir. 2023).
7. *See id.* at *2 and cases cited therein.
8. *See id.* at *12–13 and cases cited therein.
9. As Dobbins notes, a divided panel of the Eleventh Circuit vacated the MDOs at issue in *Bidi Vapor LLC v. FDA*, 47 F.4th 1191 (11th Cir. 2022). However, that decision was based on FDA's asserted failure to take into account the applicant's plans for marketing and sales access restrictions for its flavored products to reduce youth usage, a failing the court described as "procedural." The court remanded the application back to FDA for the agency to consider the proposed marketing and sales access restrictions which, as the dissent argued, is likely to result in exactly the same result, based on FDA's prior findings that such restrictions are destined to be ineffective in preventing youth usage of flavored products. 47 F.4th at 1208–09, 1217–18 (Rosenbaum, J., dissenting). The Second, Third, Fourth, Ninth, and D.C. Circuits have found that any FDA error in failing to adequately consider proposed marketing and access restrictions was harmless and therefore not a basis to vacate the MDO. *Lotus Vaping*, 2023 WL 4384447, at *13–15 and cases cited therein.
10. 41 F.4th 427 (5th Cir. 2022).
11. 65 F.4th 182 (5th Cir. 2023).
12. *See id.*
13. Associated Press, *Regulator Will Treat E-Cigarettes Like Tobacco*, N.Y. Times (Apr. 25, 2011), https://www.nytimes.com/2011/04/26/business/26tobacco.html.
14. Tushar Singh, René A. Arrazola, Catherine G. Corey, Corinne G. Husten, Linda J. Neff, David M. Homa & Brian A. King, *Tobacco Use Among Middle and High School Students—United States, 2011–2015*, 65 Morbidity & Mortality Wkly. Rep. 361, 363 (2016), https://www.cdc.gov/mmwr/volumes/65/wr/mm6514a1.htm.
15. *Am. Acad. of Pediatrics v. FDA (AAP)*, 379 F.Supp.3d 461, 492 (D. Md. 2019), *appeal dismissed sub nom.*, *In re Cigar Ass'n of Am.*, 812 F.App'x 128 (4th Cir. 2020).
16. *Id.* at 493.
17. *Id.* at 492.
18. *AAP*, 399 F.Supp.3d 479, 485 (D. Md. 2019).
19. Consolidated Appropriations Act, 2022, Pub. L. No. 117-103, div. P, tit. 1, subtit. B, § 111, 136 Stat. 49, 789–90 (2022).
20. *FDA Makes Determinations on More Than 99% of the 26 Million Tobacco Products For Which Applications Were Submitted*, U.S. Food & Drug Admin. (Mar. 15, 2023), https://www.fda.gov/tobacco-products/ctp-newsroom/fda-makes-determinations-more-99-26-million-to-

bacco-products-which-applications-were-submitted.

21. *FDA Makes Significant Progress in Science-Based Public Health Application Review, Taking Action on Over 90% of More Than 6.5 Million 'Deemed' New Tobacco Products Submitted*, U.S. Food & Drug Admin. (Sept. 9, 2021). https://www.fda.gov/news-events/press-announcements/fda-makes-significant-progress-science-based-public-health-application-review-taking-action-over-90.
22. *FDA Makes Determinations*, *supra* note 20.
23. Brian King, *Looking Back, Looking Ahead: FDA's Progress on Tobacco Product Regulation in 2022* (Jan. 31, 2023), https://www.fda.gov/tobacco-products/ctp-newsroom/looking-back-looking-ahead-fdas-progress-tobacco-product-regulation-2022.
24. Status Report at 2, *AAP*, 399 F.Supp.3d 479 (D. Md. 2019) (No. 8:18-cv-883), ECF 215 (July 24, 2023).
25. *See e.g.*, Press Release, U.S. Food & Drug Admin., FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health (Aug. 26, 2021), https://www.fda.gov/news-events/press-announcements/fda-denies-marketing-applications-about-55000-flavored-e-cigarette-products-failing-provide-evidence.
26. Maria Cooper, Eunice Park-Lee, Chunfeng Ren, Monica Cornelius, Ahmed Jamal & Karen A. Cullen, *Notes from the Field: E-Cigarette Use Among Middle and High School Students—United States, 2022*, 71 Morbidity & Mortality Wkly. Rep. 1283, 1283 (2022), https://www.cdc.gov/mmwr/volumes/71/wr/mm7140a3.htm.
27. Press Release, U.S. Food & Drug Admin., FDA Denies Marketing of Logic's Menthol E-Cigarette Products Following Determination They Do Not Meet Public Health Standard (Oct. 26, 2022), https://www.fda.gov/news-events/press-announcements/fda-denies-marketing-logics-menthol-e-cigarette-products-following-determination-they-do-not-meet.
28. There are recent signs that FDA tobacco enforcement may be using stronger tools against manufacturers selling unauthorized e-cigarettes. *See, e.g.*, Press Release, U.S. Food & Drug Admin., FDA, DOJ Seek Permanent Injunctions Against Six E-cigarette Manufacturers (Oct. 18, 2022), https://www.fda.gov/news-events/press-announcements/fda-doj-seek-permanent-injunctions-against-six-e-cigarette-manufacturers; Press Release, U.S. Food & Drug Admin., FDA Files Civil Money Penalty Complaints Against Four E-Cigarette Product Manufacturers (Feb. 22, 2023), https://www.fda.gov/news-events/press-announcements/fda-files-civil-money-penalty-complaints-against-four-e-cigarette-product-manufacturers.

How to Comply With Drug CGMPs, Third Edition

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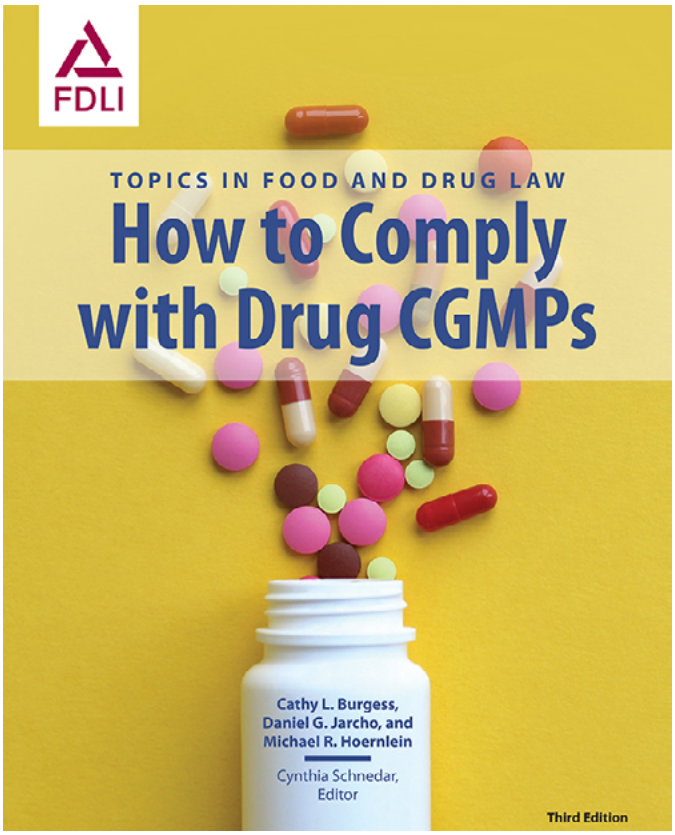
INTRODUCTION

It has been 30 years since the U.S. District Court for the District of New Jersey issued its opinion in United States v. Barr Laboratories, Inc., 812 F. Supp. 458 (D.N.J. 1993), widely recognized as the landmark case in the area of current Good Manufacturing Practice (CGMP) regulation, the main regulatory standard FDA enforces in order to ensure pharmaceutical quality. The Barr case was significant because it changed the way that the Food and Drug Administration (FDA) and industry began to think about "current" standards for good manufacturing practices.

At that time, there was a lack of well-articulated standards, which prompted the presiding judge to describe the pharmaceutical industry as "mired in uncertainty and conflict, guided by vague regulations which produce tugs-of-war of varying intensity."[1] Certain FDA officials took that message to heart, requiring FDA investigators to carry copies of the opinion with them during FDA inspections. Barr continues to influence FDA's thinking on certain issues, particularly with respect to out-of-specification result (OOS)[2] investigations, and many details in FDA's OOS guidance came directly from the opinion. Some of the opinion's flaws (e.g., the number of retests required as part of an investigation, "7 out of 8 testing")[3] forced FDA to develop new guidance that reflected an evolving, science-based approach to CGMPs for pharmaceutical products. Moreover, given the court's holding that firms should look to scientific literature if FDA's regulations or guidance were ambiguous, FDA began to work diligently to remove ambiguity and provide uniform standards for compliance.

For almost 10 years, CGMP compliance was heavily influenced by the Barr decision. In August 2002, FDA launched its "Pharmaceutical CGMPs for the 21st Century" initiative, with the stated goal of "moderniz[ing] the regulation of pharmaceutical manufacturing and product quality" for human and veterinary drugs, as well as certain biological products, such as vaccines.[4] The initiative was designed to encourage adoption of new technologies, a focus on quality systems, and decision-making based on science and an assessment of product and patient safety risks.



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As FDA moved to a new paradigm for regulatory compliance, changes in the pharmaceutical industry continued to outpace FDA's efforts. A variety of factors, such as flat growth in the prescription drug market, the need to reduce healthcare costs, and increasing government involvement in management of prescription drug costs, has forced manufacturers to search for lower-cost suppliers.[5] As the drug manufacturing supply chain continued to expand beyond U.S. borders, unanticipated compliance issues emerged: too few FDA investigators in the

international inspection cadre to inspect the growing number of regulated firms outside the U.S., language barriers, cultural issues, and economically motivated adulteration. In light of these developments, FDA sought, and obtained, CGMP authority from Congress to address the complex issues associated with globalization of the pharmaceutical industry. Those new authorities, particularly the authority to conduct record reviews, enabled FDA to conduct facility surveillance activities following the postponement of foreign and domestic inspections during the COVID-19 public health emergency. The use of voluntary and mandatory record reviews is likely to expand and evolve as FDA works to reduce the inspection backlog that developed during the public health emergency, and it could expand FDA's ability to obtain information quickly as it becomes aware of emerging risks to product quality and patient safety.

The purpose of this book is to provide members of the legal community and regulated industry a resource that describes the historical and legal bases for, and the governing principles of, CGMPs. It also provides information about current standards for compliance. It is likely that these standards will change over time, but the underlying concepts that we discuss should help the reader understand these changes and why implementing "current" Good Manufacturing Practices is essential for regulatory compliance.

1. *United States v. Barr Labs., Inc.*, 812 F. Supp. 458, 464 (D.N.J. 1993)
2. FDA defines the term "out of specification results" to include "all test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMFs), official compendia, or by the manufacturer. The term also applies to all in-process laboratory tests that are outside of established specifications." *See* U.S. Food & Drug Admin., Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production: Guidance for Industry 1 (May 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigating-out-specification-oos-test-results-pharmaceutical-production-level-2-revision.
3. *Barr Labs*, 812 F. Supp. at 470 n.9.
4. U.S. Food & Drug Admin., Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach Final Report at 1 (2004), https://www.fda.gov/media/77391/download.
5. For example, the cost of active pharmaceutical ingredients is 15-40 percent lower in India than in the United States. U.S. Food & Drug Admin., Pathway to Global Product Safety and Quality 13 (2011). *See also* Press Release, U.S. Pharmacopeia Medicine Supply Map Releases Global API Manufacturing Findings (Mar. 16, 2022), https://www.usp.org/news/medicine-supply-map-releases-global-api-manufacturing-findings. The U.S. Pharmacopeia's findings published in March 2022 highlights the high reliance on Indian manufacturers for APIs.

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