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WEIGHTY CONSEQUENCES: HOW GLP-1 AGONIST LITIGATION HIGHLIGHTS THE NEED FOR GREATER FDA OFF-LABEL PRESCRIPTION OVERSIGHT

❖ Note ❖

*Carson Poupore**

I. INTRODUCTION

With 42.4 percent of United States adults suffering from clinical obesity and 9.2 percent of adults suffering from it severely,[1] the following archetypical story is far too familiar in recent years. Seeking dietary control and weight loss, a patient consults their physician. The physician, comporting with their standard of care, prescribes *Ozempic*, which is popularly understood to resolve the patient's issue. Based on information communicated by Novo Nordisk, *Ozempic*'s manufacturer,[2] the physician fully informs their patient of *Ozempic*'s side effect risks. The patient starts the prescription and feels a newfound sense of hopeful control. But this feeling is short-lived. Soon after, the patient constantly feels nauseous, vomits after eating, and suffers from abdominal pain.[3] The patient never expected this. After correlating these unforeseen symptoms with *Ozempic* prescription, the patient concludes that they would never have taken the drug had they known these newfound issues might arise.

Millions of patients have taken drugs from the GLP-1 agonist ("GLP-1") family, which mimics GLP-1 hormones that regulate digestion.[4] GLP-1s are prescribed under names like *Ozempic*, *Wegovy*, *Mounjaro*, and *Zepbound*; about one in eight American adults

* J.D. Candidate, Class of 2027, University of Illinois College of Law.

[1] *Obesity in America*, AM. SOCIETY FOR METABOLIC & BARIATRIC SURGERY, https://asmbs.org/resources/obesity-in-america/ (last visited Apr. 19, 2025).

[2] Ronald V. Miller, Jr., *Ozempic Lawsuit*, LAW INFO. CTR. (Jan. 5, 2025), https://www.lawsuit-information-center.com/ozempic-gastroparesis-lawsuit.html.

[3] *Id.*

[4] Jamie Ducharme, *Patients Are Suing Over Alleged Side Effects of Weight-Loss Drugs*, TIME (Nov. 4, 2024, 2:15 PM), https://time.com/7130456/ozempic-side-effects-wegovy-mounjaro-gastroparesis-weight-loss/.

have taken a GLP-1.[5] GLP-1s control blood sugar and appetite and boast U.S. Food and Drug Administration ("FDA") approval for treating diabetes and obesity.[6] Furthermore, recent FDA approvals suggest that GLP-1s may decrease risks of heart attack and stroke.[7]

While most patients taking these "miracle drugs" experience negligible side effects, 1,443 cases are pending against Novo Nordisk, Eli Lilly & Co., and other pharmaceutical manufacturers alleging that GLP-1 usage has led to unexpected side effects such as stomach paralysis, pulmonary aspiration, and even thyroid cancer.[8] On-label information for GLP-1s has allegedly failed to warn about these outcomes, potentially violating state consumer protection laws.[9] Since media coverage of mass tort litigation has contributed to the past declines of beneficial FDA-approved pharmaceuticals,[10] the forefront issue posed by GLP-1 litigation is the FDA's ability to monitor approved drugs post-approval to ensure their safe supply and prevent their decline in marketability.

Ultimately, Congress should enable the FDA to promulgate regulations that provide greater post-market oversight of off-label uses of approved pharmaceuticals to incrementally reduce unexpected side effect incidents, even if such oversight is *de minimis* and does not represent a regulatory overhaul. Part II of this Note discusses existing FDA regulatory capabilities in monitoring off-label prescriptions. Part III examines the case law surrounding off-label prescription and, in light of the case law, executes a cost-benefit analysis over greater post-market FDA regulatory capabilities.[11] Part IV takes the aforementioned cost-benefit analysis and recommends that Congress should enable the FDA to better collect post-market data to examine, monitor, and respond to off-label prescription in practice, even if such a move would merely reduce patient adverse side effect incidence marginally.

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[5] Alex Montero et al., *KFF Health Tracking Poll May 2024: The Public's Use and Views of GLP-1 Drugs*, KFF (May 10, 2024), https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-may-2024-the-publics-use-and-views-of-glp-1-drugs/.

[6] Ducharme, *supra* note 4.

[7] Press Release, U.S. Food & Drug Admin., FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight (Mar. 8, 2024), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-reduce-risk-serious-heart-problems-specifically-adults-obesity-or.

[8] Miller, *supra* note 2.

[9] *See, e.g.*, Complaint & Demand for Jury Trial at ¶ 124, Jones v. Eli Lilly & Co., No. 2:25-cv-00686 (E.D. Pa. Feb. 7, 2025).

[10] *See* L.E. Nigrovic & K.M. Thompson, *The Lyme Vaccine: A Cautionary Tale*, 135 EPIDEMIOLOGY & INFECTION 1, 5 (2007).

[11] Amy Todd, Note and Comment, *No Need for More Regulation: Payors and Their Role in Balancing the Cost and Safety Considerations of Off-Label Prescriptions*, 37 AM. J. L. & MED. 422, 430 (2011).

II. BACKGROUND

A. FDA Regulation of On-Label Prescription

In 1906, President Theodore Roosevelt signed the Food and Drugs Act into law, the first federal law enforcing the proper and accurate labeling of ingredients in food and drug products.[12] The agency charged with enforcement of this law was the FDA, which grew from a single U.S. Department of Agriculture chemist in 1862 into the agency it is today – one boasting a $4 billion budget, twenty district offices, and oversight over approximately twenty-five percent of consumer purchase value.[13] The decades immediately following the enactment of the Food and Drugs Act brought consumer protection pressures to strengthen the authority of the FDA, particularly in medical, pharmaceutical and cosmetic spaces uncontemplated by the initial statute.[14] Congress ultimately granted the FDA comprehensive authority over the on-label details, descriptions, and cautions of medical, pharmaceutical, and cosmetic products[15] – an authority that persists in the contemporary pharmaceutical market with drugs like GLP-1s.[16]

The congressional statute enabling FDA prescription regulation is the Federal Food, Drug, and Cosmetic Act ("FDCA"), which was enacted in 1938.[17] The FDCA authorizes the FDA to approve, monitor, recall, and regulate the marketing of pharmaceutical products to protect consumers and enforce quality standards.[18] In addition, Congress empowers the FDA through 21 U.S.C. §§ 393(b)(2)(B) and (b)(2)(D) to ensure that "human . . . drugs are safe and effective"[19] and "cosmetics are safe and properly labeled."[20]

Federal regulations additionally govern the labeling, advertising, and marketing of prescription drugs exists under 21 C.F.R. § 201.100(d) and 21 C.F.R. § 201.56.[21] Title 21 C.F.R. § 201.100(d) requires that all prescriptions contain "adequate information for such use" on labels, including "any relevant warnings, hazards, contraindications, side effects, and precautions" for "all conditions for which [the drug] is advertised or

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[12] Stephen Daily, *A Brief History of the FDA*, CATARACT & REFRACTIVE SURGERY TODAY (Oct. 2011), https://crstoday.com/articles/2011-oct/a-brief-history-of-the-fda.

[13] *Id.*

[14] *Id.*

[15] HASSAN SHEIKH, CONG. RSCH. SERV., R45792, OFF-LABEL USE OF PRESCRIPTION DRUGS 8 (2021).

[16] *See id.*

[17] 21 U.S.C. § 393.

[18] Clinton Lam & Preeti Patel, *Food, Drug, and Cosmetic Act*, NIH NAT'L LIBR. OF MED.: NAT'L CTR. FOR BIOTECHNOLOGY INFO. (July 31, 2023), https://www.ncbi.nlm.nih.gov/books/NBK585046/.

[19] 21 U.S.C. § 393(b)(2)(B).

[20] 21 U.S.C. § 393(b)(2)(D).

[21] 21 C.F.R. § 201.56 (2025); 21 C.F.R. § 201.100 (2025).

represented."[22] This information is ascertained through clinical trials, observational studies, and post-market spontaneous reports.[23] The FDA mandates post-market spontaneous reports from all companies with approved pharmaceuticals on the market,[24] and requires fifteen-day "[a]lert reports" after any firm becomes aware of a "serious and unexpected" adverse event.[25] Granted, it is unclear how efficacious these post-market spontaneous reports are in achieving the underlying purpose of 21 C.F.R. § 201.100(d) because most reports of side-effects come from pre-market trials and studies.[26]

21 C.F.R. § 201.56 expands upon the FDA's general 21 C.F.R. § 201.100(d) reporting requirements and mandates that notices and warnings are "informative," "accurate," and "neither promotional in tone nor false or misleading" in any fashion.[27] Furthermore, 21 C.F.R. § 201.56 requires that prescription drug labeling "must be based whenever possible on data derived from human experience."[28] With GLP-1s, for instance, the FDA deployed its on-label authority under 21 C.F.R. § 201.56 to add a warning to *Ozempic*'s label amid allegations that GLP-1s may cause bowel obstructions.[29]

These regulations play a critical role in the FDA process that drug manufacturers must comply with before marketing new pharmaceuticals.[30] Following three clinical trial phases and the submission and filing of a new drug application, an FDA review team examines the safety and efficacy of the proposed drug and its accompanying marketing.[31] This review scrutinizes the drug's proposed label based on the preceding clinical trials' empirical outcomes.[32] As all pharmaceuticals must gain on-label approval from the FDA, *Ozempic*, the GLP-1 "poster child," went through this process in 2017, gaining FDA approval for the specific purpose of lowering blood sugar in diabetics.[33]

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[22] 21 C.F.R. § 201.100(d) (2025).

[23] Jeanne Herndon, *Adverse Reaction Information in the Prescribing Information*, U.S. FOOD & DRUG ADMIN. (Dec. 4, 2019), https://www.fda.gov/media/133940/download.

[24] *Postmarketing Adverse Event Reporting Compliance Program*, U.S. FOOD & DRUG ADMIN. (May 5, 2020), https://www.fda.gov/drugs/surveillance/postmarketing-adverse-event-reporting-compliance-program.

[25] 21 C.F.R. § 314.80(c)(1) (2025).

[26] Charlie Plain, *Drug Companies Failing to Properly Report Side Effects*, UNIV. MINN. SCH. PUB. HEALTH (July 30, 2015), https://www.sph.umn.edu/news/drug-companies-failing-properly-report-side-effects/.

[27] 21 C.F.R. § 201.56(a)(2) (2025).

[28] 21 C.F.R. § 201.56(a)(3) (2025).

[29] Interview by Todd Unger with Andrea Garcia, Vice President of Sci., Med., & Pub. Health, AMA, in Chi., Ill. (Oct. 4, 2023).

[30] *FDA's Drug Review Process: Continued*, U.S. FOOD & DRUG ADMIN. (Aug. 24, 2015), https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-continued.

[31] *Id.*

[32] *Id.*

[33] Pierce Logan, *On the Increase in Use of GLP-1s*, IND. UNIV. SCH. OF MED. (June 27, 2024), https://medicine.iu.edu/blogs/bioethics/on-the-increase-in-use-of-glp-1s.

However, the FDA only approved *Ozempic*'s primary active ingredient, semaglutide, for weight loss after Novo Nordisk submitted a new drug application for *Wegovy* in 2021.[34]

B. FDA Regulation of Off-Label Prescription

21 C.F.R. § 201's labeling requirements generally notify a prescription drug's "intended" on-label use as "advertised or represented" by pharmaceutical companies.[35] However, a large proportion of prescriptions are off-label and outside of the prescription's intended purpose.[36] While ubiquitous, off-label prescription uses can carry adverse effects not reflected in FDA-approved labeling.[37]

To alleviate concerns surrounding off-label drug prescription, its ubiquity, and associated adverse side effect incidence, Congress has bestowed the FDA with some regulatory power over "unintended" prescription uses.[38] The FDA prohibits mislabeling and requires labeling to reflect communicated post-market findings.[39] Furthermore, the FDA prohibits the dissemination, marketing, and advertising of prescription drugs for unapproved uses by manufacturers in interstate commerce.[40] The FDA may examine marketing "expressions, the design or composition of the [marketing] article, or . . . the circumstances surrounding the distribution of the [marketing] article" to extrapolate the "objective intent" of a manufacturer in prescription product launch.[41]

Even though the FDA has significant authority over off-label prescription sales, state medical boards, not the FDA, regulate the practice of medicine.[42] Accordingly, the FDA concedes regulation over the practice of off-label prescription and explicitly does not sanction pharmaceutical manufacturers for their "knowledge that . . . [a] drug was being prescribed or used by health care providers for . . . [unintended] use."[43]

Because the FDA lacks the requisite authority to regulate off-label prescription, it has proliferated and often defines the physician's standard of care for guideline-

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[34] *Id.*

[35] 21 C.F.R. § 201.100(d) (2025).

[36] Christopher Wittich, et al., *Ten Common Questions (and Their Answers) About Off-label Drug Use*, 2012 MAYO CLINIC PROC. 982, 988 (2012).

[37] *Understanding Unapproved Use of Approved Drugs "Off Label"*, U.S. FOOD & DRUG ADMIN. (Feb. 5, 2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label.

[38] Wittich, et al., *supra* note 36.

[39] 21 C.F.R. §§ 201.56(a)(2)–(3) (2025).

[40] 21 C.F.R. § 201.128 (2025).

[41] *Id.*

[42] *Understanding Medical Regulation in the United States*, FED'N OF STATE MED. BDS., https://www.fsmb.org/education/understanding-medical-regulation-in-the-united-states/ (last visited Feb. 17, 2025).

[43] 21 C.F.R. § 201.128 (2025).

recommended practice, last-resort therapy, and first-line therapy.[44] While off-label prescription facilitates treatment innovation and expedites treatment access, it is often criticized as undercutting safety standards and increasing health care costs.[45] Recognizing the interests at stake, the FDA has adopted the middle ground of issuing guidelines allowing manufacturers to distribute peer-reviewed studies on new off-label risk information to health care providers.[46]

C. Off-Label Prescription of GLP-1 Agonists

Recent studies reveal that current GLP-1 patient utilization rates are not correlated with the local population incidence of diabetes and other GLP-1-treatable conditions in patients – empirically an odd result given that pharmaceutical market analysis would anticipate more GLP-1 usage where more of the conditions GLP-1s are designed to treat arise.[47] These findings signal greater off-label prescription, presumably to combat obesity given GLP-1 media coverage.[48] While the proportion of GLP-1s prescribed off-label is unclear, some studies suggest that it is about thirty-three percent, up from sixteen percent in 2021.[49] Medical professionals harbor concern about the rise in GLP-1 off-label prescription chiefly because the long term effects of GLP-1 usage are unknown.[50] Medical professionals also recognize the possibility of short-term adverse effects in patients prescribed GLP-1s off-label.[51] These short-term side effects include gastrointestinal issues correlated with dosage – mirroring the same concerns litigants assert against GLP-1 manufacturers.[52]

Increased off-label GLP-1 prescription also has limited access to on-label prescriptions for diabetics and other intended beneficiaries.[53] From 2022 through 2024, the FDA listed GLP-1s on its Drug Shortages Database, recognizing

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[44] Randall Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

[45] *Id.*

[46] *Guidance for Industry: Distributing Scientific and Medical Publication on Risk Information for Approved Prescription Drugs and Biological Products – Recommended Practices*, U.S. FOOD & DRUG ADMIN. (June 2014), https://www.fda.gov/media/88674/download.

[47] Sanjula Jain, *GLP-1 Utilization in New York City Is Not Correlated with Clinical Indication*, TRILLIANT HEALTH (Sept. 10, 2023), https://www.trillianthealth.com/market-research/studies/glp-1-utilization-in-new-york-city-is-not-correlated-with-clinical-indication.

[48] *Id.*

[49] Logan, *supra* note 33.

[50] Grace Niewijk, *Research Shows GLP-1 Receptor Agonist Drugs Are Effective but Come with Complex Concerns*, UNIV. CHI. MED. (May 30, 2024), https://www.uchicagomedicine.org/forefront/research-and-discoveries-articles/research-on-glp-1-drugs.

[51] *Id.*

[52] *Id.*

[53] David Lipanovic, *GLP-1 Receptor Agonist Shortage Expected to Continue for All of 2024*, THE PHARM. J. (Jan. 4, 2024), https://pharmaceutical-journal.com/article/news/glp-1-receptor-agonist-shortage-expected-to-continue-for-all-of-2024.

pharmaceutical manufacturers could not meet aggregate demand for the drugs.[54] The FDA removed GLP-1s from this listing in February 2025,[55] but Eli Lilly & Co. and Novo Nordisk have since sued the FDA on allegations that it prematurely removed their GLP-1s from the database before shortage resolution.[56] Before the FDA's alleged improper action, the pharmaceutical manufacturers' February 2025 Form-F SEC filings claimed that expected supply constraints and drug shortage notifications were to "continue into the foreseeable future."[57] Relatedly, medical professionals expect long-term GLP-1 supply chain disruptions to continue so long as cosmetic off-label demand remains high, hurting the FDA-intended consumers who rely on GLP-1s the most.[58]

The medical community is concerned with the FDA's handling of off-label GLP-1 prescription for three reasons: the short-term side effects featured in tort litigation, the long-term side effects unknown without post-market data, and the inability of intended users to receive on-label treatment.[59] Given that FDA off-label oversight is limited to pharmaceutical marketing, some commentators have raised concerns about the safety and efficacy of GLP-1 off-label prescription without FDA analysis of the drug family's off-label applications.[60] These commentators imply that the medical community must either maintain the status quo while placing the burden of safe, efficacious treatment on the market or that the FDA should be better equipped to oversee off-label prescription of pharmaceuticals like GLP-1s.[61]

III. ANALYSIS

A. Case Law on FDA Regulation of Off-Label Prescription

FDA off-label prescription regulation is already limited to pharmaceutical marketing, but courts have further limited attempted FDA regulation within that

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[54] *Drug Shortages*, U.S. FOOD & DRUG ADMIN. (Mar. 13, 2025), https://www.fda.gov/drugs/drug-safey-and-availability/drug-shortages.

[55] *FDA Clarifies Policies for Compounders as National GLP-1 Supply Begins to Stabilize*, U.S. FOOD & DRUG ADMIN. (Mar. 10, 2025), https://www.fda.gov/drugs/drug-safety-and-availability/fda-clarifies-policies-compounders-national-glp-1-supply-begins-stabilize.

[56] *See* Complaint at ¶ 3, Outsourcing Facilities Ass'n v. U.S. Food & Drug Admin., No. 4:25-cv-00174 (N.D. Tex. Feb. 24, 2025).

[57] *See id.* at ¶ 2.

[58] Heather Whitley et al., *Special Report: Potential Strategies for Addressing GLP-1 and Dual GLP-1/GIP Receptor Agonist Shortages*, NIH NAT'L LIBR. OF MED.: NAT'L CTR. FOR BIOTECHNOLOGY INFO. (Apr. 7, 2023), https://pmc.ncbi.nlm.nih.gov/articles/PMC10338283/.

[59] Logan, *supra* note 33.

[60] Magda Wojtara et al., *Glucagon-Like Peptide-1 Receptor Agonists for Chronic Weight Management*, NIH NAT'L LIBR. OF MED.: NAT'L CTR. FOR BIOTECHNOLOGY INFO. (Sept. 20, 2023), https://pmc.ncbi.nlm.nih.gov/articles/PMC10533252/.

[61] *Id.*

space.[62] What results is a laissez-faire approach–the FDA cannot criminally penalize truthful, non-misleading speech about off-label usages in pharmaceutical marketing.[63] This judicial limitation empowers physicians and consumers–not FDA experts charged with initial drug approval reviews–to evaluate the safety and efficacy of off-label prescription in light of adverse drug events.

In *United States v. Caronia*, the Second Circuit held that the FDA cannot criminalize the truthful and non-misleading promotion of off-label prescription.[64] The *Caronia* court relied on the Supreme Court's holding that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment"[65] and further classified regulations on off-label prescription promotion by pharmaceutical manufacturers as "content- and speaker-based restrictions on speech subject to heightened scrutiny."[66] The *Caronia* court held that criminalizing lawful off-label prescription promotion did not establish a "reasonable fit" to drug safety and public health as required by heightened scrutiny for content- and speaker-based speech restrictions.[67] Instead, criminal prosecution prohibited the free dissemination of information facilitating safe off-label use on the physician-to-consumer market.[68] Accordingly, the *Caronia* court standardized FDA non-regulation in off-label prescription, further narrowing the agency's limited authority in preventing off-label harms.[69]

Caronia's holding was extended by the U.S. District Court for the Southern District of New York in *Amarin Pharma, Inc. v. U.S. Food and Drug Admin.* to the dissemination of peer-reviewed publications, textual statements, and disclosures concerning off-label prescription.[70] In *Amarin Pharma*, the FDA urged the court to narrow *Caronia* to statements made directly to a health care provider or entity by a firm.[71] However, the court instead focused on the *actus reus* requirement of the FDCA's misbranding provisions, agreeing with *Caronia* that the provisions did not reach "*all* truthful and non-misleading promotional speech" related to prescriptions.[72] While the *Amarin Pharma* court affirmed *Caronia*'s holding on off-label prescription non-regulation, the court did highlight where the FDA maintains proper authority.[73] The FDA can regulate

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[62] Frederick R. Ball & Erin M. Duffy, *United States v. Caronia: A Brief Look at the Broader Implications for the Food Industry*, DUANE MORRIS (Apr. 2013), https://www.duanemorris.com/articles/static/ball_fdli_0313.pdf.

[63] *Id.*

[64] United States v. Caronia, 703 F.3d 149, 169 (2d Cir. 2012).

[65] Sorrell v. IMS Health, Inc., 564 U.S. 552, 557 (2011).

[66] Caronia, 703 F.3d at 162.

[67] *Id.* at 167-68 (quoting Bd. of Tr. of State Univ. of N.Y. v. Fox, 492 U.S. 469, 480 (1989)).

[68] Caronia, 703 F.3d at 168–69.

[69] *See* Ball & Duffy, *supra* note 62.

[70] Amarin Pharma, Inc. v. U.S. Food & Drug Admin., 119 F. Supp. 3d 196, 237 (S.D.N.Y. 2015).

[71] *Id.* at 208.

[72] *Id.* at 227.

[73] *Id.* at 228.

and criminalize "false or misleading commercial speech" and "non-communicative activities to promote off-label use" unprotected by the First Amendment and within the FDCA's misbranding provisions.[74]

As insinuated by the specified boundaries set in *Caronia* and *Amarin Pharma*, courts tend to defer to pharmaceutical companies, the medical profession, and state medical boards on off-label prescription, "recogniz[ing] the propriety and potential public value of unapproved" applications.[75] The Supreme Court articulated this general principle in *Buckman Co. v. Plaintiffs' Legal Comm.*, stating that off-label usage is "an accepted and necessary corollary of the FDA's mission to regulate . . . without directly interfering with the practice of medicine."[76] Furthermore, the Eighth Circuit in *Weaver v. Reagen* stood by the general assertion that FDA approval processes are not designed to "preclude physicians from using their best judgment in the interest of the patient."[77] In light of these general principles favoring off-label drug prescription and no circuit courts distinguishing the holdings in *Caronia* and *Amarin Pharma*, the consensus is that these Second Circuit precedents represent the status quo of FDA authority over off-label promotion.[78] In sum, the judiciary has limited the FDA's regulatory authority over off-label prescription, empowering companies and medical professionals—not FDA experts controlling FDA pharmaceutical approval—with pharmaceutical market safety and quality.

B. Benefits of More FDA Regulation on Off-Label Prescription

Off-label prescription deregulation and its associated empowerment of professionals and firms carry opportunity costs.[79] First, incremental off-label prescription can positively correlate with adverse events, even under the good faith standard set in *Caronia* and *Amarin Pharma*.[80] For example, with off-label GLP-1 prescription for weight loss, the FDA issued a consumer notice following "more than 392 reports of adverse events with compounded semaglutide" and "more than 215 reports of adverse events with compounded tirzepatide."[81] The FDA also mentioned in this notice that "federal law does not require state-licensed pharmacies that are not outsourcing facilities to submit adverse events to [the] FDA," so the agency's reported

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[74] *Id.*

[75] Caronia, 703 F.3d at 153.

[76] Buckman Co. v. Plaintiffs' Legal Comm. 531 U.S. 341, 350 (2001).

[77] Weaver v. Reagen, 886 F.2d 194, 198 (8th Cir. 1989).

[78] *See* George Horvath, *Off-Label Drug Risks: Toward a New FDA Regulatory Approach*, 29 ANNALS HEALTH L. & LIFE SCIS. 101, 118 (2020) (discussing *Caronia*, mentioning *Amarin Pharma, Inc.*, and stating that "trend over the past decade has been for courts to invalidate the FDA's ban on some off-label promotional activities.").

[79] *Id.* at 102.

[80] *FDA's Concerns with Unapproved GLP-1 Drugs Used for Weight Loss*, U.S. FOOD & DRUG ADMIN. (Dec. 18, 2024), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss.

[81] *Id.*

metrics may be "underreported."[82] Since minimal FDA oversight into off-label prescription may cause underreporting,[83] the FDA may be unable to issue adequate warnings and notices. While the FDA cannot enforce recalls and only retains authority to oversee company recall strategy and classify recalls,[84] greater oversight may facilitate informational exchanges, allowing for more efficient warnings, notices, and recalls that marginally prevent adverse drug events.[85]

Additionally, off-label prescription is prevalent because, under current FDA regulatory oversight, it is cost-prohibitive, time-consuming, and evidence-intensive to attain FDA approval for an additional on-label use.[86] The FDA approval process for a new indication on a previously approved drug is facilitated under 21 C.F.R. § 314, which requires thorough research through the "list of all published studies or publicly available reports of clinical investigations" to show that the FDA needs to conduct a "new clinical investigation . . . essential to approval.[87] While this rigorous standard ensures methodically sound accreditation, commentators have suggested that pharmaceutical companies have subverted the FDA approval process for off-label indications due to compliance costs.[88] Greater FDA off-label prescription oversight may partially erode the informational barriers behind FDA on-label conversion of off-label uses, as efficacious off-label usages can be easily communicated, monitored, and approved via off-label data collection.[89]

C. Costs of More FDA Regulation on Off-Label Prescription

Nonetheless, off-label prescription carries considerable benefits warranting at least a somewhat deregulated landscape, one furthered by *Caronia* and *Amarin Pharma*.[90] Outside the judicial rationale, insurance effectively curbs off-label prescription by denying reimbursement for off-label care without evidence of pharmaceutical quality and efficacy.[91] While data are not available on the percentage of off-label prescription claims submitted to and denied by payors, off-label prescription typically requires prior authorization given its unapproved nature.[92] With around 3.2 million prior

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[82] *Id.*

[83] *See, e.g., id.*

[84] *FDA's Role in Drug Recalls*, U.S. FOOD & DRUG ADMIN. (Aug. 22, 2024), https://www.fda.gov/drugs/drug-recalls/fdas-role-drug-recalls.

[85] *See* Horvath, *supra* note 78, at 133 (proposing policy solution allowing FDA to collect more post-market data from manufacturers when off-label use exceeds certain threshold to minimize off-label risk).

[86] Stafford, *supra* note 44.

[87] 21 C.F.R. § 314.50(j)(4) (2025).

[88] Stafford, *supra* note 44.

[89] *Id.*

[90] *See* Christian Tomaszewski, *Off-Label: Just What the Doctor Ordered*, 2 J. MED. TOXICOLOGY 87, 87 (2006).

[91] Joshua Cohen et al., *Off-Label Use Reimbursement*, 64 Food Drug L. J. 391, 394 (2009).

[92] SHEIKH, *supra* note 15.

authorization requests fully or partially denied by payors in 2023,[93] commentators suggest that insurance plays a gatekeeping role in limiting unnecessary off-label prescription. With off-label GLP-1 prescription, prescriptions to treat obesity hold "minimal to no coverage on most ACA Marketplace formularies," whereas GLP-1s prescribed on-label for diabetes are "included in 82% of Marketplace plan formularies."[94] The limited data reveal that insurance guards from off-label overprescription, arguably making further FDA off-label regulation red tape that would not significantly mitigate adverse drug events.

Furthermore, FDA off-label prescription non-regulation has created practitioner norms that may make further oversight disruptive without careful implementation. Despite a lack of FDA approval, efficacious off-label prescriptions mold a physician's standard of care;[95] increased complexity of the simplified regulatory environment, if hastily implemented to curtail off-label prescription, might hinder physicians' abilities to provide effective treatments pursuant to their standard of care.[96] An example of this includes tricyclic antidepressants, which have proven effective through clinical trial and physician practice as a first-line treatment option for neuropathic pain.[97] The FDA has not approved use of tricyclic antidepressants for this application although their prescription falls within the physician's standard of care.[98] A stringent framework enabling the FDA to monitor, limit, or barricade off-label usage might unreasonably disrupt physician and patient reliance interests, especially given the fact that almost eighty percent of certain patient subpopulations are taking at least one off-label medication.[99] Any reform must be cautiously applied.

D. A Distinct Need for "Soft Power" Off-Label Prescription Regulation

The current regulatory framework and the mantras of *Caronia* and *Amarin Pharma* are insufficient for maintaining a safe, yet effective pharmaceutical market adequately policed by the FDA. Some scholars have suggested the proper focus of FDA off-label prescription regulation should not be "off-label promotion" but rather "off-label

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[93] Jeannie Biniek et al., *Medicare Advantage Insurers Made Nearly 50 Million Prior Authorization Determinations in 2023*, KFF (Jan. 28, 2025), https://www.kff.org/medicare/issue-brief/nearly-50-million-prior-authorization-requests-were-sent-to-medicare-advantage-insurers-in-2023/.

[94] Justin Lo & Cynthia Cox, *Insurer Strategies to Control Costs Associated with Weight Loss Drugs*, PETERSON-KFF HEALTH SYSTEM TRACKER (June 12, 2024), https://www.healthsystemtracker.org/brief/insurer-strategies-to-control-costs-associated-with-weight-loss-drugs/.

[95] Wittich, et al., *supra* note 36.

[96] *Id.*

[97] Robert H. Dworkin, et al., *Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update*, 85 MAYO CLINIC PROC. S3, S3 (2010).

[98] Wittich et al., *supra* note 36.

[99] Samir S. Shah, et al., *Off-label Drug Use in Hospitalized Children*, NIH NAT'L LIBR. OF MED.: NAT'L CTR. FOR BIOTECHNOLOGY INFO. (Mar. 2007), https://pubmed.ncbi.nlm.nih.gov/17339510/.

prescribing."[100] These scholars assert the FDA should be able to exert a "soft power" to better gather available post-market data to make informed decisions.[101] In light of the variegated harms posed by increased GLP-1 off-label prescription, "soft power" policy recommendations, including the imposition of a duty on manufacturers to disclose off-label prescription data,[102] gain appeal.

That said, the cost-benefit analysis of FDA off-label prescription demands a nuanced solution sensitive to the ubiquity of off-label practice, even if such a solution is *de minimis* and only marginally mitigates harm within the pharmaceutical market. The same commentators advocating for the "soft power" approach to FDA off-label prescription regulation highlight a requisite consideration of the "sensitivity of the burdens that would be imposed on the FDA and drug manufacturers."[103] Significant burdens may arise from navigating incremental displacements of the empowerment accorded to pharmaceutical manufacturers, physicians, and consumers under the current FDA regulatory regime – after all, according even incremental FDA oversight may chill the current practice of prescribing off-label so long as supported by peer-reviewed publications.[104] Intersecting market, health, and professional interests necessitate a compromise to make off-label prescription safer without eliminating its benefits. However, given off-label prescription's risks absent FDA monitoring power, Congress must authorize FDA regulations that improve – or at least marginally improve – the off-label communicative framework between the FDA, manufacturers, physicians, and consumers in the physician-to-consumer market.[105]

IV. RECOMMENDATION

The best way to implement *de minimis* FDA off-label prescription oversight is neither overhauling its laissez-faire approach nor maintaining the status quo. Rather, the appropriate market-player compromise would be Congress' authorization of FDA regulations for greater off-label prescription data collection and monitoring of its associated adverse drug events. Such an authorization would adequately respond to communicative needs between pharmaceutical manufacturers, physicians, consumers, and the FDA in the off-label prescription space while respecting the practice's inseparable presence within the medical profession.

In seeking to incrementally enhance off-label prescription safety, part of the FDA's regulatory role *must* remain the same. It is not the FDA's role, but rather that of state medical boards, to directly regulate the prescription of off-label drugs by physicians.

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[100] Horvath, *supra* note 78, at 127.

[101] *Id.*

[102] *Id.* at 127–28.

[103] *Id.* at 127.

[104] Melanie Chansky et al., *Influence of Data Disclosures on Physician Decisions About Off-Label Uses: Findings From a Qualitative Study*, BMC PRIMARY CARE (Apr. 19, 2022), https://doi.org/10.1186/s12875-022-01666-2.

[105] Horvath, *supra* note 78, at 133.

Some studies have found that upwards of seventy-eight percent of certain patient subpopulations are taking at least one off-label medication.[106] As a result, the proper solution to mitigate litigation, like that associated with GLP-1 off-label usage, is not motivating the FDA to disrupt medical practice through an extreme regulatory overhaul. Instead, Congress should authorize the FDA to promulgate necessary regulations for greater data collection, monitoring, and oversight of off-label prescription and its associated adverse events.

While the FDA requires companies with approved pharmaceuticals on the market to "submit postmarketing safety information,"[107] including fifteen-day "Alert reports" after any "serious and unexpected" adverse event that comes to a firm's knowledge,[108] physician reporting of adverse events to the FDA is currently voluntary.[109] If Congress were to incrementally authorize the FDA to mandate physician reporting of adverse events derived from off-label prescription, the FDA may be able to better issue notices and recalls without overstepping into the medical profession's domain.

Regulations under 21 C.F.R. § 314.80 take *de jure* measures in ensuring adverse events are reported,[110] but some studies posit that pharmaceutical companies, *de facto*, fail to comply with these self-reporting regulations.[111] While it is unclear how many adverse events would be mitigated by mandatory physician reporting of merely off-label adverse events, the state of FDA regulation reveals a practical pain that requires a regulatory solution. Accordingly, Congress should incrementally resolve the issue by enabling the FDA to collect physician data to monitor off-label prescriptions significantly associated with adverse drug reactions due to off-label prescription's unapproved nature.[112] What Congress should authorize the FDA to do is supplement the off-label adverse event reporting burden placed on pharmaceutical manufacturers by 21 C.F.R. § 314.80 with new reporting requirements for physicians,[113] enabling more reliable post-market data pooling on off-label prescription.

One possible roadblock to the effective implementation of off-label adverse event reporting requirements for physicians might be the short-term administrative burdens placed on them.[114] Physicians are ethically obligated to report all adverse events to

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[106] Shah, et al., *supra* note 99.

[107] *Postmarketing Adverse Event Reporting Compliance Program*, *supra* note 23.

[108] 21 C.F.R. § 314.80(c)(1) (2025).

[109] *Reporting By Health Professionals*, U.S. FOOD & DRUG ADMIN. (Mar. 25, 2016), https://www.fda.gov/safety/reporting-serious-problems-fda/reporting-health-professionals.

[110] 21 C.F.R. § 314.80 (2025).

[111] Plain, *supra* note 26.

[112] Benjamin Horen, et al., *Adverse Drug Reactions and Off-Label Drug Use in Paedriatric Outpatients*, NIH NAT'L LIBR. MED.: NAT'L CTR. FOR BIOTECHNOLOGY INFO. (Dec. 2002), https://pmc.ncbi.nlm.nih.gov/articles/PMC1874497/.

[113] 21 C.F.R. § 314.80 (2025).

[114] *See* Eran Klein & Dennis Bourdette, *Postmarketing Adverse Drug Reactions*, NIH NAT'L LIBR. MED.: NAT'L CTR. FOR BIOTECHNOLOGY INFO. (Aug. 2013), https://pmc.ncbi.nlm.nih.gov/articles/PMC3787113/ (discussing need for physician reporting that is "more timely, standardized, and useful for the practicing clinician" than status quo, encompassing administrative concerns).

appropriate regulatory agencies,[115] but the FDA currently boasts no mandatory reporting system procedurally binding physicians to report adverse events.[116] This additional cost to practitioners must be fairly weighed against the putative benefits of Congress' authorization of mandatory off-label adverse event physician reporting, but it does not tip the scales against authorization.[117] While implementation costs may disrupt practitioners in the short-term, the data mining capabilities granted to the FDA through robust reporting would catalyze long-term benefits in accurate drug labeling and communicative speed of contraindications to the physician-to-consumer market.[118] Prudently looking ahead at the downstream effects of its policy decisions, Congress should not let short-term practitioner burdens bar it from authorizing the FDA to better enhance long-term public welfare with greater off-label prescription data collection capabilities.[119]

V. CONCLUSION

Multidistrict litigation is ongoing over unexpected adverse effects from the prevalent usage of GLP-1s.[120] While any regulatory fallout is yet to be determined, the litigation's nationwide scope and alleged consumer-level harms necessitate a re-examination of whether the FDA's post-market oversight is adequate. While the FDA significantly controls approved, on-label prescription, its authority over unapproved, off-label usage is limited by current regulations and further curtailed by the prevailing case law.[121] Some commentators have suggested a need for an increased FDA "soft power" over off-label prescription,[122] and ongoing GLP-1 litigation, at least partially characterized by off-label prescription, makes this recommendation appealing. In balancing the costs and benefits of greater FDA off-label prescription oversight, the appropriate "soft power" compromise is Congress' authorization of new FDA regulations mandating physician reporting of adverse drug events from off-label prescription. Given medical community concerns about off-label prescription of GLP-1s for unapproved – namely cosmetic – applications,[123] congressional authorization of such regulatory power might make the physician-to-consumer market safer, protect

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[115] *8.8. Required Reporting of Adverse Events*, AMA PRINCIPLES MED. ETHICS, https://code-medical-ethics.ama-assn.org/sites/default/files/2022-09/8.8%20Required%20reporting%20of%20adverse%20events%20--%20background%20reports.pdf (last visited Mar. 13, 2025).

[116] Klein & Bourdette, *supra* note 114.

[117] *Id.*

[118] Jasmine C. Gatti, *The Importance of Physicians Identifying and Reporting Adverse Drug Events*, AM. FAM. PHYSICIAN (Feb. 15, 2012), https://www.aafp.org/pubs/afp/issues/2012/0215/p318.html.

[119] Klein & Bourdette, *supra* note 114.

[120] Miller, *supra* note 2.

[121] Mikaela Wells et al., *Regulating Off-Label Prescribing*, Regul. REV. (June 22, 2024), https://www.theregreview.org/2024/06/22/regulating-off-label-prescribing/.

[122] Horvath, *supra* note 78, at 127.

[123] Logan, *supra* note 33.

pharmaceutical companies from avoidable liability, and allow GLP-1s to be beneficially prescribed without negative publicity or safety question marks.