Finalizing the Final Rule: Why the FDCA Requires Safe Harbors

*Kelly Reynolds**

I. INTRODUCTION

After the Food and Drug Administration's ("FDA") six-year journey to enact a final rule regarding the relevant types of evidence to be considered when determining a medical product's intended use(s) under the Federal Food, Drug, and Cosmetic Act of 1938 ("FDCA"), the FDA has introduced its final language.[1] The rule became effective on September 1, 2021.[2] The evolution of the "intended use" rule began in 2015 with the purpose of clarifying the evidence that the FDA requires to establish a product's "intended use," and of mitigating First and Fifth Amendment concerns.[3]

*Kelly Reynolds, J.D., Class of 2023, Seton Hall University School of Law. I am grateful to Professor Jacob Elberg for providing me with his insightful guidance during the drafting of this comment. I'd like to recognize the members of the Seton Hall Legislative Journal for their helpful suggestions and edits during the publication process. My deepest appreciation to my parents, Peter and Franci Reynolds, for their endless love, support, and encouragement.

[1] *See* Regulations Regarding Intended Uses, 86 Fed. Reg. 41383 (proposed Aug. 2, 2021) (modifying 21 C.F.R.§ 201.128 and 21 C.F.R. § 801.4).

[2] *See id*.

[3] Jennifer L. Bragg et al., *FDA's Final Rule on Intended Use: 'Getting Right Back to Where We Started From'*, SKADDEN: INSIGHTS (Aug. 18, 2021), https://www.skadden.com/en/insights/publications/2021/08/fdas-final-rule-on-intended-use; *see also* James M. Beck, *Off-Label Use in the Twenty-First Century: Most Myths and Misconceptions Mitigated*, 54 UIC J. MARSHALL L. REV. 1, 49–60 (2021).

The final rule is the regulatory mechanism that the FDA uses to determine a product's intended use under the FDCA.[4] The rule decides what regulatory requirements apply throughout the life of a medical product in order for manufacturers to market their products without facing penalties under the FDCA.[5] The intended use rule ensures that a manufacturing firm markets its product solely for FDA-approved or "on-label" uses.[6] The new rule's purpose is to reflect current practices and avoid the litigious issues that plagued the prior iterations of the rule.[7]

Industry professionals advocated for an updated rule throughout the six years to the present "final rule." There was, and continues to be, a lack of clarity in situations involving off-label marketing and communications of medical products. Unfortunately, these off-label practices are a large part of standard practice for product manufacturers and those they need to communicate with, such as health care professionals.

This Comment argues that the only option for the new rule's success is an addition of a safe harbor provision enacted within the final rule. Accordingly, the federal government must act to expand the final rule to include a safe harbor provision to preempt any individual state from adopting state-specific safe harbors. Part one will discuss the history of the intended use rule, focusing on the different iterations of the rule and the critical problems which were addressed in subsequent iterations.

Part two of this Comment navigates several additions and alternatives that will enhance the new rule to achieve the "final" product the FDA is striving towards. Additionally, this Comment discusses individual states' role in regulating off-label marketing and how this affects the overall success of the FDCA. Finally, this Comment argues that the addition of a safe harbor provision and specific guidelines for individual states will create uniformity across the industry.

II. HISTORY OF THE "INTENDED USE" RULE

Before reaching a solution, it is essential to understand the broad impact of the intended use regulation, and this section begins with

4 *See* Regulations Regarding Intended Uses, 86 Fed. Reg. at 41383 (discussing the scope and purpose of the proposed regulation).

5 *Id.*

6 *See id*.

7 *A Question of Intent: FDA Amends Intended Use Regulations with Goal to Provide More Clarity, but Significant Questions Remain*, ROPES & GRAY (Aug. 12, 2021) [hereinafter *A Question of Intent*], https://www.ropesgray.com/en/newsroom/alerts/2021/August/A-Question-of-Intent-FDA-Amends-Intended-Use-Regulations-with-Goal-to-Provide-More-Clarity.

considering its origins and evolution. The FDCA empowered the FDA to review and regulate medical products on the market.[8] The FDCA's purpose is to ensure the safety and well-being of consumers who are prescribed and choose to use different medical products.[9] The manufacturer who creates a medical product need only receive approval for a single intended use to be able to market the product.[10] Thus, the FDA will grant its authorization through this process as long as the manufacturers produce the required evidence for at least one intended use.[11] Frequently, many possible uses will become apparent after a product has received authorization for the original intended use.[12] Such uses outside of the original intended use are known as "off-label" uses.[13]

The rule aims to ensure that manufacturers properly market their products to the general public and individual healthcare professionals.[14] "Off-label" uses are legal and part of routine medical practice.[15] For example, a healthcare professional can legally and ethically prescribe drugs with one intended use to a patient to treat an issue not covered in the product's approved intended uses.[16]

In the context of this Comment, "off-label" uses of medical products are a "matter of discretionary medical practice" and are not regulated by the FDA.[17] "Off Label" prescribing is legal and common in the medical community, but product manufacturers face much stricter regulations.[18]

The FDA enforces the FDCA through a series of "administrative mechanisms."[19] To understand the process of determining intended use, it is crucial to understand the language of the law from which it was derived. A medical product will be regulated as a drug or device under

8 Jeffrey K. Shapiro, *The 6-Year Saga Finally Ends: FDA Issues Final Rule Modifying the Intended Use Regulation*, HYMAN, PHELPS & MCNAMARA: FDA L. BLOG (Aug. 16, 2021), https://www.thefdalawblog.com/2021/08/the-6-year-saga-finally-ends-fda-issues-final-rule-modifying-the-intended-use-regulation/; *see* 21 U.S.C. § 353(g)(1)(A).

9 Shapiro, *supra* note 8.

10 Beck, *supra* note 3, at 7.

11 Beck, *supra* note 3, at 7.

12 Beck, *supra* note 3, at 7.

13 Beck, *supra* note 3, at 7.

14 Beck, *supra* note 3, at 7.

15 *See* Christopher M. Wittich et al., *Ten Common Questions (and Their Answers) About Off-Label Drug Use*, 87 MAYO CLINIC PROC. 982 (2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/pdf/main.pdf.

16 *Id*.

17 Beck, *supra* note 3, at 7.

18 *See* Wittich, *supra* note 15, at 983, 988.

19 Shariful A. Syed et al., *The Law and Practice of Off-Label Prescribing and Physician Promotion*, 49 J. AM. ACAD. PSYCHIATRY L. 1, 2 (2020).

the FDCA "if it is 'intended for use' in the diagnosis, cure, mitigation, treatment, or prevention of disease, or (unless it is a food) 'intended' to affect the structure or any function of the body."[20]

The FDA only approves drugs that are shown to be safe and effective for their specifically indicated uses, and manufacturers are required to provide on-labeling that is consistent with such a showing.[21] This includes premarket authority, post-market authority, examinations, investigations, publicizing information, and the ability to issue warnings.[22] Once a manufacturer submits a use or uses for a new product, it must be prepared to meet the criteria for each of the previously mentioned steps to achieve an approved or medical use.[23] After completing this process, the product is considered an "approved or cleared medical product."[24] In the 2020 proposed final rule, an "approved or cleared medical product" is officially a "medical product that may be legally introduced into interstate commerce for at least one use . . . ."[25]

The FDA's definition of "intended use" within the language of the FDCA is as follows: "objective intent of the persons legally responsible for the labeling of [the drug or medical device]."[26] This definition has few limitations.[27] The language of the rule states, "objective intent covers a wide array of activities and speech that includes, for example, 'labeling claims, advertising matter, or oral or written statements by such persons or their representatives,' according to the final rule."[28] Narrowing the definition in some respects, the FDA "explicitly objected to comments that such an assessment should rely primarily or only on promotional claims."[29] This broad definition allows for the FDA to continue to practice "wide latitude of discretion."[30]

Since the 1950s, the FDCA has included a definition for the intended use regulation.[31] The original rule placed significant weight on

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20 Daniel Dwyer, *FDA's Regulations on "Intended Use": One More Try*, KKB (Sept. 28, 2020), https://www.kkblaw.com/fdas-regulations-on-intended-use-one-more-try/.

21 *See* Wittich, *supra* note 15.

22 Syed, *supra* note 19, at 2.

23 *See generally* 85 Fed. Reg. 59718, 59720 (Sept. 23, 2020) (2020 Proposed Rule).

24 *Id*.

25 *Id*.

26 Jaclyn Jaeger, *Compliance Takeaways from FDA's Final 'Intended Use' Rule*, COMPLIANCE WK. (Sept. 7, 2021), https://www.complianceweek.com/regulatory-policy/compliance-takeaways-from-fdas-final-intended-use-rule/30770.article.

27 *See id*.

28 *Id*.

29 *Id*.

30 *Id*.

31 Beck, *supra* note 3, at 8–9.

determining the manufacturer's knowledge as it pertained to their marketing efforts and intended uses derived from such expressions.[32] The 1950s definition reads, "[b]ut if a manufacturer knows, or has knowledge of facts that would give him notice that [an article] introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it . . . ."[33] The rule also outlined that such knowledge a manufacturer possesses would require the firm to include adequate labeling for those uses.[34]

In 1976, Congress enacted the Medical Device Amendment, introducing the 510(k) process.[35] The 510(k) process allowed, among other things, for medical products that were similar to products already on the market to go through an abbreviated approval process.[36] This rule stood for several decades and made a lengthy process easier for medical products that would aid in the health and well-being of the consumer market.[37]

In 2015, after several decades of debate, the six-year journey to the updated 2021 rule began[38] when the FDA sought to clarify whether to classify tobacco products as drugs or medical devices.[39] The FDA proposed a rule meant to provide clarity which was then revised and made "final" in 2017.[40] The 2017 rule amended the last sentence of § 201.128.[41] It introduced the "totality of the evidence test," which created a regulatory device to apply to both drugs and medical devices.[42] This version of the rule stated, "manufacturer's knowledge, alone, that its product is prescribed or used by physicians for an unclear/unapproved use is not proof in and of itself that the manufacturer intends such use, nor is it sufficient to trigger the

32 Beck, *supra* note 3, at 8–9.

33 Beck, *supra* note 3, at 8.

34 Beck, *supra* note 3, at 8.

35 Gregory Gentry, *Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions*, 64 FOOD DRUG L. J. 441, 448 (2009).

36 *Id.*

37 *Id.*

38 Shapiro, *supra* note 8.

39 *See* 80 Fed. Reg. 57756 (Sept. 25, 2015) (2015 Proposed Rule).

40 Michael Mezher, *FDA Finalizes Long-Awaited Intended Use Rule*, REGUL. AFF. PRO. SOC'Y (Aug. 2, 2021), https://www.raps.org/news-and-articles/news-articles/2021/8/fda-finalizes-long-awaited-intended-use-rule.

41 *See* 82 Fed. Reg. 2194 (Jan. 9, 2017) (section B existing "intended use" regulations (§§ 201.128 and 801.4)).

42 *Id.*

obligation to provide adequate labeling for that unapproved use."[43] A manufacturer was only required to provide adequate labeling for a new intended use if the "totality of the evidence" suggests that the manufacturer "objectively intends" a medical product to be used for unapproved uses.[44] Once again, the focus of the change was on how to measure the evidence that would determine a product's intended use.

After considerable concern from impacted groups in the industry, industry professionals petitioned the FDA to address their concerns.[45] The petition encouraged the FDA to consider delaying the implementation of the 2017 finalized rule to ensure it would accomplish what it set out to achieve.[46] The FDA was also asked to reassess the amendment's language for something more equitable.[47] In response, the FDA delayed the date the final rule would become effective.[48] Ultimately, the FDA announced that the delay would be indefinite, and the proposed 2017 rule would not be published.[49] Finally, in September 2020, after more than two years of uncertainty, the FDA proposed language to amend the intended use rule once and for all.[50]

The clarifications were meant to address the role of the manufacturer's subjective and objective intent in determining its product's intended use.[51] The FDA sought to reinforce that intended use could be based on any relevant source of evidence rather than merely the manufacturer's "subjective" intent.[52] The FDA explicitly ensured that "objective" intent would also be considered.[53] The FDA went as far as to highlight examples and several scenarios.[54]

The first category of examples concerns the acknowledged but not enacted "safe harbors."[55] This category includes situations where a medical product firm tracks sales and notes that a product, which is

43 *FDA Clarifies "Intended Use" Regulations: Knowledge Alone ≠ Intent, But Knowledge Certainly Can Be One Element in Establishing the Totality of the Evidence*, HOGAN LOVELLS (Jan. 19, 2017), https://www.hoganlovells.com/en/pdfdownload?page={A70E79B7-12D7-4279-AC49-68CD912DFEBF}&p=1 [hereinafter *FDA Clarifies "Intended Use" Regulations*].

44 *FDA Clarifies "Intended Use" Regulations*, *supra* note 43.

45 *A Question of Intent*, *supra* note 7.

46 *See A Question of Intent*, *supra* note 7.

47 *A Question of Intent*, *supra* note 7.

48 *A Question of Intent*, *supra* note 7.

49 *A Question of Intent*, *supra* note 7.

50 *See* 85 Fed. Reg. 59718, 59720 (Sept. 23, 2020) (2020 Proposed Rule).

51 *See id.*

52 *See id* at 59721.

53 *Id*. at 59721.

54 *Id*. at 59722.

55 *Id*. at 59725.

approved only for adults, is used for pediatric care.[56] The firm had not given any direction to its sales teams to sell to this population of medical practices.[57] This is one example demonstrating that the FDA will not interpret a firm as intending an unapproved use based solely on the knowledge that a product is being sold and used for a specific use.[58] Additionally, the proposed rule addresses an example of how knowledge in combination with conduct would fall in the range of an acknowledged "safe harbor" and would not be determinative of a firm's intended use.[59] Similar to the previous example, a firm disseminated copies of an outside source's recommendation of using its product while following all recommendations of the draft guidelines for "Distributing Scientific and Medical Publication on Unapproved New Uses–Recommended Practices."[60] The draft guidelines provide an extensive checklist of sorts for companies to use to ensure they are not stepping outside the bounds of acceptable promotion of scientific and medical publication.[61] Further examples that would not be determinative of intended use include mitigating potential safety risks.[62]

In August 2021, the FDA approved the amendments to the intended use regulation, which were essentially unchanged from the September 2020 proposal.[63] The impact of the new final rule was to "better reflect the Agency's current practices in evaluating whether a product is intended for use as a drug or device . . . ."[64] The new rule confirmed how the FDA will consider a manufacturer's intent.[65] The determination must no longer rely solely on the manufacturer's "expressions" or promotional claims.[66] The rule's language changed from "is determined by" to "may be shown."[67] Now, those promotional claims or

56 Regulations Regarding "Intended Uses," 85 Fed. Reg. 59718, 59725 (proposed Sept. 23, 2020) (to be codified at 21 C.F.R. pts. 201, 801).

57 *Id*.

58 *Id*.

59 *Id*.

60 *Id*.

61 *Id.*

62 Regulations Regarding "Intended Uses," 85 Fed. Reg. 59718, 59725 (proposed Sept. 23, 2020) (to be codified at 21 C.F.R. pts. 201, 801).

63 *See* Regulations Regarding "Intended Uses," 86 Fed. Reg. 41383, 41383 (proposed Aug. 2, 2021) (to be codified at 21 C.F.R. pts. 201, 801).

64 *Id*. at 41384.

65 Regulations Regarding "Intended Uses," 85 Fed. Reg. 59718, 59723 (proposed Sept. 23, 2020) (to be codified at 21 C.F.R. pts. 201, 801).

66 *Four Ways FDA's New Intended Use Regul.'s Affect Drug and Med. Device Co.'s*, SIDLEY (Nov. 3, 2021), https://www.sidley.com/en/insights/newsupdates/2021/11/four-ways-fdas-new-intended-use-regulations-affect-drug-and-medical-device-companies [hereinafter *FDA's Use Regul.'s Affect Drug and Med. Device Co.'s*].

67 *Id*.

"expressions" will be just one of several factors to consider.[68] Once again, objective intent remains the overarching standard.

III. PRIOR "INTENDED USE" RULE IMPACT

Before the adoption of the "final" rule, earlier versions of the rule created holes in the regulatory scheme for evaluating instances of off-label promotion of medical products. In addition, the FDA faced challenges in enforcing the FDCA over different manufacturers.[69] It was evident that the FDCA, as it stood, would not be an effective regulatory scheme long term. The following cases involving regulatory issues regulating off-label conduct under the FDCA illustrate the lack of concrete answer to a decades-old problem.

The *United States v. Caronia*[70] case went before the Second Circuit after the trial court held that Caronia had violated the FDCA when he introduced a misbranded drug into interstate commerce.[71] On appeal, the court addressed "whether the government's prosecution of Caronia under the FDCA only for promoting an FDA-approved drug for off-label use was constitutionally permissible."[72] Caronia argued that the FDCA's misbranding provisions prohibited off-label promotion, which unconstitutionally restricted speech.[73] The court found that the FDCA does not "expressly prohibit or criminalize off-label promotion."[74] The Second Circuit clarified that the statute only references "promotion" as evidence of a product's intended use.[75]

The Second Circuit's decision in Caronia was a massive win for medical product manufacturers, showing that they would not face criminal penalties for simply promoting a product's off-label uses. The court noted that even had the government used only Caronia's speech as evidence of intent, that evidence would have been subjected to heightened scrutiny.[76] The Second Circuit established that "such testimony is to be scrutinized with care to be certain the statements are not expressions of mere lawful and permissible difference of opinion with our own government."[77] Additionally, the court looked to the

68 *Id*.
69 See *id.*
70 United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).
71 *Id*. at 152.
72 *Id*. at 160.
73 *Id*. at 159.
74 *Id*. at 160.
75 *Id*.
76 *Caronia*, 703 F.3d at 161.
77 *Id*.

Supreme Court's decision in *Sorrell v. IMS Health, Inc.*,[78] which previously established that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the *Free Speech Clause of the First Amendment*."[79]

The Second Circuit concluded that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."[80] Accordingly, the court vacated the prior judgment and remanded the case to the district court.[81]

Following the Second Circuit's decision in *Caronia*, the Southern District of New York ("S.D.N.Y.") relied on the Second Circuit's decision to find for Amarin Pharma, Inc. in *Amarin Pharma, Inc. v. United States Food & Drug Administration*.[82] Amarin argued that the FDA's threat to bring charges against its solely truthful and non-misleading speech would prevent doctors from receiving and engaging in "constitutionally protected speech."[83] Further, Amarin contended that their specific statements at issue were protected under *Caronia*.[84] The court agreed with Amarin's interpretation of the *Caronia* decision and held that Amarin's proposed communications were "presently truthful and non-misleading."[85]

The Second Circuit and the S.D.N.Y. released decisions in favor of this Comment's argument. After *Caronia*, the government was forced to focus on the truth or falsity of an off-label statement in potential violation of the FDCA.[86] *Caronia* established the importance of distinguishing between truthful and misleading statements. The Second Circuit's holding determining that the government could not prosecute for off-label speech alone created space for medical product manufacturers to work within the limits of the FDCA. Still, the issue remains that the lack of enacted guidance did not remedy the obstacles that industry members had to combat prior to *Caronia* and *Amarin*.

78 Sorrell v. IMS Health, Inc., 564 U.S. 552 (2011).

79 *Caronia*, 703 F.3d at 162.

80 *Id*. at 169.

81 *Id*.

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

83 *Id*. at 219.

84 *Id*. at 222.

85 *Id*. at 236.

86 *See* John C. Richter & Daniel C. Sale, *The Future of Off-Label Promotion Enforcement in the Wake of Caronia – Toward a First Amendment Safe Harbor*, 14 SEDONA CONF. J. 19, 20 (2013).

These decisions recognize the importance of protecting truthful and non-misleading off-label communications under the FDCA and in the medical community. Now, nearly a decade after these decisions, it is time to enact safe harbors to explicitly protect truthful communication between medical product manufacturers and health care professionals. These additions will create uniformity rather than remaining precedent in the Second Circuit alone.

IV. DOUBTS ABOUT THE FINALITY OF THE "FINAL" RULE

After a six-year effort to achieve the "final" rule, there is still skepticism over whether it would achieve the desired outcome.[87] The final rule that went into effect on September 1, 2021, replaced earlier vague language.[88] The newest version of the rule's desired outcome was to ensure that the new language of the rule reflects the FDA's current practices of intended use rule application.[89] Still, a significant amount of discretion is placed in the hands of the FDA when evaluating medical products to be approved for market promotion, as well as possible violations of promotional information for off-label uses of medical products.[90] This broad approach means that manufacturers of medical products will continue to struggle navigating the intended use regulations.[91]

One of the main contentions with earlier versions of the intended use rule was that it allowed the FDA to determine new intended uses based "solely" on a manufacturer's knowledge of possible off-label use.[92] The new rule's reliance on manufacturer knowledge when determining regulation under the FDCA continues to worry industry professionals.[93] Although the new rule states that evidence determining the existence of new intended uses will not be based solely on manufacturer knowledge, the FDA would still be "free to consider a firm's knowledge of an off-label use in conjunction with other evidence of intended use . . . ."[94] For industry professionals, it appears that the FDA attempted to meet the demands of the industry while protecting their desire for broad discretion.[95]

87 *FDA Clarifies "Intended Use" Regulations*, *supra* note 43.
88 *FDA Clarifies "Intended Use" Regulations*, *supra* note 43.
89 *See* 86 Fed. Reg. 41383 (Aug. 2, 2021) (2021 Final Rule).
90 *FDA Clarifies "Intended Use" Regulations*, *supra* note 43.
91 Bragg, *supra* note 3.
92 *A Question of Intent*, *supra* note 7.
93 *A Question of Intent*, *supra* note 7.
94 *A Question of Intent*, *supra* note 7.
95 *A Question of Intent*, *supra* note 7.

Before announcing the final language, the industry requested that the FDA include language clarifying how the "safe harbor" guidance protects manufacturers.[96] A safe harbor is an additional provision in a statute or regulation that grants "protection from liability or penalty if certain conditions are met."[97] Unfortunately, the FDA decided against enacting such language in their "final" rule.[98] The FDA maintained that such requests were outside the scope of their rule-making parameters.[99] Although, when the FDA addressed the desire to codify the safe harbors, the agency noted that the rule's preamble included policies and practices from existing guidance documents.[100] The rule's approach to the safe harbor policy has been relatively conservative. A more significant commitment to adopting a safe harbor could create opportunities for the medical product industry, healthcare professionals, and consumers to communicate, provide, and receive adequate care.

While the FDA did not explicitly include a safe harbor provision, the new rule's preamble states that the FDA will be permitted to "point to safe-harbored communications as evidence of a new intended use."[101] The preamble clarifies that the examples of such communication on its own would not be considered evidence of its intended use but would be "relevant" to such establishing intent.[102] The preamble further identifies five "safe harbor" guidance documents that one should consult in determining circumstances in which manufacturers would be allowed to disseminate information such as "off-label" uses.[103] The appropriate guidance documents are as follows: communications consistent with FDA-approved labeling;[104] payer communications;[105]

96 *Non-binding Guidance: FDA's Intended Use Final Rule*, ROPES & GRAY, (Sept. 21, 2021), https://www.ropesgray.com/en/newsroom/podcasts/2021/September/Podcast-Non-binding-Guidance-FDAs-Intended-Use-Final-Rule#page=1.

97 LEGAL INFO. INST., https://www.law.cornell.edu/wex/safe_harbor (last visited May 10, 2023).

98 *Non-binding Guidance: FDA's Intended Use Final Rule*, *supra* note 96.

99 *Non-binding Guidance: FDA's Intended Use Final Rule*, *supra* note 96.

100 Bragg, *supra* note 3.

101 *FDA's Use Regul.'s Affect Drug and Med. Device Co.'s*, *supra* note 66.

102 *FDA's Use Regul.'s Affect Drug and Med. Device Co.'s*, *supra* note 66.

103 *FDA's Use Regul.'s Affect Drug and Med. Device Co.'s*, *supra* note 66.

104 Lisa M. Dwyer et al., *"Consistent Commc'n:" FDA's Incremental Expansion of Promotional Bounds*, FOOD AND DRUG L. INST. (Aug. 2017), https://www.fdli.org/2017/08/consistent-communications-fdas-incremental-expansion-promotional-bounds/.

105 Peter J. Neumann & Harry Weissman, *The FDA's New Guidance on Payer Commc'n: Implication for Real-World Data and Value-Based* Contracts, HEALTH AFFAIRS (Jul. 17, 2018), https://www.healthaffairs.org/do/10.1377/forefront.20180712.816686/abs/.

industry-supported scientific and educational activities;[106] responses to unsolicited requests (draft);[107] distribution of scientific and medical publications (scientific or medical journal articles, scientific or medical reference texts, and clinical practice guidelines) (draft).[108]

V. GUIDANCE DOCUMENTS

The previously mentioned guidance documents support the importance of codifying a safe-harbor provision into the FDCA. The FDA's five FDCA guidance documents do not establish legally enforceable responsibilities.[109] Each of the guidance documents are only considered recommendations for manufacturers.[110]

The first guidance document the FDA has pointed to covers communications consistent with FDA-approved labeling. In the industry, the guidance document was a meaningful step forward.[111] The first guidance provides assurances that the FDA will maintain enforcement discretion over the marketing of information that "(1) is not contained in the FDA-required labeling, but (2) is consistent with the FDA-required labeling."[112] It existed to clarify what is indeed considered "off-label."[113] The FDA further clarified the meaning of "consistent communication," introducing three factors to consider.[114] Additionally, the document made it clear that while this guidance aimed to help manufacturers determine whether the FDA permitted their communications, they would still have to adhere to previous standards requiring truthful and non-misleading information.[115]

The second guidance document guides payer communications. This document aimed to provide clear guidance on the rules for sharing "real-world data or economic models about a product's value."[116] The payer communication guidance is more data-driven than the previously

106 Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64093 (Dec. 3, 1997).

107 Draft Guidance for Industry on Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices; Availability, 76 Fed. Reg. 82303 (Dec. 30, 2011).

108 Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses, 79 Fed. Reg. 11793 (Mar. 3, 2014).

109 Drug and Device Manufacturer Communication with Payors, Formulary Committees, and Similar Entities, 83 Fed. Reg. 27605, 27607 (Jul. 13, 2018).

110 *Id.*

111 Dwyer et al., *supra* note 104.

112 Dwyer et al., *supra* note 104.

113 Dwyer et al., *supra* note 104.

114 Dwyer et al., *supra* note 104.

115 Dwyer et al., *supra* note 104.

116 Neumann & Weissman, *supra* note 105.

mentioned guidance document but again stresses the importance of truthful and non-misleading communications in off-label promotion.[117]

The third guidance document covers how industry members can "support scientific and educational activities without being subject to regulation under the [FDCA]."[118] The fourth guidance document is more relevant to this Comment. In 2009, the FDA released guidance covering the implications of manufacturers' promotion of off-label uses of medical products via unsolicited information requests.[119] The unsolicited information request guidance seemingly created a safe harbor for the "dissemination of information on off-label uses of FDA-approved drugs."[120] It stated that "if a manufacturer follows [its] recommendations … the FDA does not intend to consider the distribution of such medical and scientific information in accordance with the recommendations in this guidance as establishing intent that the product be used for an unapproved new use."[121] Like the other guidance documents, this document does not affect the law's effect or force, and the FDA's legal authority remains under the FDCA.[122]

For the purpose of the unsolicited information request guidance, the FDA defines unsolicited requests as those "initiated by persons or entities that are completely independent of the relevant firm."[123] The distinction is that if someone within the manufacturing firm or a representative to be solicited initiates the request, such solicited requests "may be considered evidence of a firm's intent that a drug or medical device be used for a use other than specifically approved or cleared by the FDA."[124] By distinguishing solicited and unsolicited requests, the FDA is ensuring that healthcare professionals can ask

117 *See* Neumann & Weissman, *supra* note 105.

118 Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64093 (Dec. 3, 1997).

119 *FDA Guidance Regarding the Promotion of Off-Label Uses of Drugs: Legal Issues*, CONG. RSCH. SERV. (Mar. 19, 2009), https://www.everycrsreport.com/reports/R40458.html; Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 74 Fed. Reg. 1694 (Jan. 13, 2009).

120 *FDA Guidance Regarding the Promotion of Off-Label Uses of Drugs: Legal Issues*, CONG. RSCH. SERV. (Mar. 19, 2009), https://www.everycrsreport.com/reports/R40458.html.

121 *Id*.

122 *Id*.

123 Draft Guidance for Industry on Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices; Availability, 76 Fed. Reg. 82303 (Dec. 30, 2011).

124 *Id*.

manufacturers critical questions about their products with "truthful and non-misleading" information.

Aspects of the unsolicited information request guidance document will establish the safe harbor provision that this Comment argues should be included in the final rule. First, this document provides broad protection for responses to unsolicited requests for information.[125] The FDA provided examples for manufacturing firms to determine whether their situation involves a solicited or unsolicited request for information.[126] Further, the document distinguishes the two types of unsolicited requests, public and non-public requests, and the information deemed appropriate to include in a response without triggering FDCA regulations.[127] It is essential to include this guidance document in the final rule because it provides a way for companies to share information that ensures the medical products they distribute are being used safely. Even though this guidance document is focused on those requests that come to the medical product manufacturers organically, it proves that there is space in the FDCA to make room for truthful and non-misleading information.

Finally, the last relevant guidance document covers "distributing scientific and medical publications on unapproved [new] uses."[128] Like the previous, unsolicited information request, guidance document, this FDA guidance will establish the language of the safe-harbor provision that the FDA should include in the final rule. The FDA accepts that it is customarily appropriate for "medical information concerning the safety or effectiveness of a medical product" to be "published in scientific or medical journal articles, scientific or medical reference texts, and/or in CPGs."[129] Further, the guidance document states the specific guidelines for information to be included in each previously mentioned source.[130]

The FDA released and endorsed each document, warning that they would not be considered statutory law and that the FDCA would govern such circumstances above all else. Each of these guidance documents fill in different gaps that are all but left to the imagination of manufacturers interpreting and attempting to adhere to the FDCA. Including aspects of each safe-harbor guidance document into the codified final rule would create an opportunity for manufacturers to

125 *See id*.

126 *Id*.

127 *Id*.

128 Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses, 79 Fed. Reg. 11793 (Mar. 3, 2014).

129 *Id.*

130 *Id.*

distribute as much helpful information as possible regarding different medical products with the knowledge that they are complying with the FDCA, and not exposing themselves to criminal penalties.

VI. STATES REGULATE THE INTENDED USE RULE

While the federal government has been hesitant to formally include a much-desired safe harbor provision, individual states have taken steps to include such a provision in their capacities. Typically, when the federal government is silent on an issue, it is acceptable for states to regulate that topic by enacting their own laws.[131] Here, the lines are blurred because the FDCA does exist, but the FDA has failed to codify a safe harbor provision within the language of the law.

Unlike the regulatory power the FDCA grants to the FDA, the FDCA does not grant regulatory power for off-label medical practice.[132] While manufacturers are at the will of the FDA, health care professionals have more discretion in deciding how to use and prescribe medical products.[133] For the most part, "interventions restricting the off-label uses of prescription medical products have been infrequent."[134] Congress has recognized the "havoc" it would have created had it implemented legislation that required healthcare professionals to follow "the expensive and time-consuming procedure of obtaining FDA approval before putting drugs to new uses."[135] Similarly, the FDA expressly disclaims that the FDCA intends to regulate medical practices.[136]

In the years leading up to the final rule regulating how the FDA will evaluate manufacturers' intended uses, individual states have taken their own steps to ensure clarity for manufacturers.[137] In contrast to the FDCA, two states have implemented legislation protecting pharmaceutical companies when engaging in truthful off-label uses.[138] In 2017, Arizona passed HB 2382, "Free Speech in Medicine Act," into

131 U.S. CONST. art. VI, para. 2.

132 Beck, *supra* note 3, at 10.

133 *See generally* Off-Label Use of Prescription Drugs, CONG. RSCH. SERV. (Feb. 19, 2021), https://sgp.fas.org/crs/misc/R45792.pdf.

134 Beck, *supra* note 3, at 11.

135 Beck, *supra* note 3, at 12.

136 Beck, *supra* note 3, at 12.

137 *See* Thomas Sullivan, *Off-Label Promotion: Tennessee Becomes Second State to Allow Pharmaceutical Companies to Engage in Truthful Promotion of Off*, POLICY & MEDICINE (May 15, 2018), https://www.policymed.com/2018/05/off-label-promotion-tennessee-becomes-second-state-to-allow-pharmaceutical-companies-to-engage-in-truthful-promotion-of-off.html [hereinafter Sullivan Tennessee Article].

138 *Id.*

law.[139] The law "safeguards the free speech rights of pharmaceutical industry members to share truthful research and information about FDA-approved medicines."[140]

Arizona's Free Speech in Medicine Act states, "[n]otwithstanding any other law, a pharmaceutical manufacturer or its representative may engage in the truthful promotion of an off-label use of a drug, biological product or device."[141] Further, it includes the language, "[n]otwithstanding any other law, an official, employee or agent of this state may not enforce or apply section § 32-1967 against or otherwise prosecute a pharmaceutical manufacturer or its representative for engaging in the truthful promotion of an off-label use of a drug, biological product or device," to address the potential of prosecutions.[142] The use of the language "[n]otwithstanding any other law" implies that Arizona intends to overrule the FDCA in the event of a conflict.

Arizona lawmakers made sure to highlight that this law's purpose is to allow the source of the medical product to communicate relevant information.[143] Arizona's law was enacted in an effort to allow the manufacturers of medical products to legally communicate with those physicians regarding uses that would be considered "off-label."[144]

The Arizona law is modest in its parameters.[145] The law limits its protections to sharing information that is "not misleading, not contrary to facts, and consistent with generally accepted scientific principles."[146] The law also limits the protected communication to those between manufacturers and healthcare professionals.[147] Regardless of the language in Arizona law, it is limited in power because it is still preempted.[148] Manufacturers cannot rely solely on the new law to

139 Thomas Sullivan, *Arizona Enacts Law: Pharmaceutical Companies to Legally Communicate Off-Label Treatment to Medical Professionals*, POLICY & MEDICINE (May 5, 2018), https://www.policymed.com/2017/03/arizona-now-allows-pharmaceutical-companies-to-legally-communicate-off-label-treatment-to-medical-pr.html.

140 *Id.*

141 ARIZ. REV. STAT. ANN. § 32-1997(A) (2017).

142 ARIZ. REV. STAT. ANN. § 32-1997(C) (2017).

143 *See* Sullivan Arizona Article, *supra* note 139.

144 H.B. 2382, 53rd Leg., 1st Sess. (Az. 2017).

145 Sullivan Arizona Article, *supra* note 139.

146 ARIZ. REV. STAT. ANN. § 32-1997(E)(4) (2017).

147 Sullivan Arizona Article, *supra* note 139.

148 Alan G. Minsk, *Arizona Enacts Law Permitting Off-Label Promotion*, ARNALL GOLDEN GREGORY LLP (Apr. 10, 2017), https://www.agg.com/news-insights/publications/arizona-enacts-law-permitting-off-label-promotion-04-10-2017/.

evade prosecution because the federal law still stands.[149] This Arizona law addresses an issue the FDA continuously pushes back on, yet, it will have little effect on prohibiting prosecution by the federal government as it only speaks to prohibition on Arizona state officials pursuing prosecution.

In July 2018, Tennessee followed suit.[150] The southern state adopted an amendment to legislation that permitted pharmaceutical companies to "engage in [the] truthful promotion of off-label uses."[151] Tennessee's HB 2220 and companion SB 2306 authorize "a pharmaceutical manufacturer or its representatives [to] engage in [the] truthful promotion of off-label uses."[152] Like Arizona's law, Tennessee's amended legislation prohibits any state's official, employee, or agent from prosecuting a "pharmaceutical manufacturer or its representatives for engaging in truthful promotion of off-label uses."[153] Additionally, the amended law prohibits a "state regulatory board [from] revok[ing], fail[ing], or renew[ing] or tak[ing] any other action against a pharmaceutical manufacturer's or representative's, healthcare institution's, or physician's license solely for engaging in truthful promotion of off-label uses."[154]

Arizona and Tennessee's laws are not identical.[155] The most significant distinction between Arizona and Tennessee's laws is that Tennessee does not define "truthful promotion" within its legislation.[156] Following Tennessee, an increasing number of states have introduced legislation that would decriminalize the truthful promotion of off-label uses of medical products.[157]

While this Comment champions fewer restrictions regarding the distribution of "off-label" information, the FDA would be doing a disservice to the health care system if it left too much control to the states. So many of the applicable medical products meant to be regulated by the FDCA are used across the country. Instead, the FDA should look to the laws passed in Arizona and Tennessee as a framework for exceptions to the final rule that would act as safe harbors.

149 *Id*.

150 Sullivan Tennessee Article, *supra* note 137.

151 H.B. 2220, 2018 Leg., 63rd Sess. (Tn. 2018); S.B. 2361, 2018 Leg., 74th Sess. (Tn. 2018); *see also* TENN. CODE ANN. § 53-10-113.

152 S.B. 2361, 2018 Leg., 74th Sess. (Tn. 2018).

153 *Id*.

154 *Id*.

155 Sullivan Tennessee Article, *supra* note 137.

156 Sullivan Tennessee Article, *supra* note 137.

157 Sullivan Tennessee Article, *supra* note 137.

It is crucial to consider the impact that individual states' adoption of safe harbors will have on the rest of the nation. For example, Arizona's law clarifies that protected communication is between manufacturers and healthcare professionals. This is not a concern of marketing material leaving the state and entering the stream of commerce in neighboring states through public expressions. Instead, the law is concerned with private, truthful, non-misleading communication between manufacturers and healthcare professionals. This Comment highlights the impact this state-specific regulation would create when the transmission of information is between parties in two or more different states, and the impact it would have on states not involved in the exchange, with these laws being at a disadvantage in their access to information.

The lines will blur on what the appropriate action and law will be when an issue arises. However, there must be uniformity within the regulatory process when it comes to medical products that will impact the safety and well-being of Americans. The overall intentions of the previously discussed state laws are valid and would most likely increase the survival of the FDA's final intended use rule. To ensure success, it must be done at the federal level, meaning that every state would be preempted from adopting any law that would contradict the intentions of the FDA's law. Ultimately, the result would be to create a uniform system to allow states to regulate the spread of information regarding off-label uses of medical products.

VII. ARGUMENTS FOR A SAFE HARBOR PROVISION

Safe harbors provide parties with greater latitude to ensure that their practices fit within whatever regulation they must comply with. There are examples of this across federal healthcare fraud and abuse statutes. For example, the Anti-Kickback Statute ("AKS"), 42 C.F.R. § 1001.952, has several exceptions called "safe harbors."[158] The AKS safe harbors list conditions that parties must follow to protect themselves from criminal and civil enforcement under the statute.[159] The safe harbors protect against liability in specific instances related to personal services, rental agreements, investments in ambulatory surgery centers, discounted items of services, and payments to bona fide employees.[160]

Historically, the FDA has taken a "paternalistic" approach to regulating new intended uses and the promotional information shared

158 42 C.F.R. § 1001.952.

159 *See generally* 42 C.F.R. § 1001.952.

160 42 C.F.R. § 1001.952.

about such uses.[161] Given the decades of debate and confusion over the truthful and non-misleading communication of information on off-label uses of medical products, a clear set of guidelines for industry professionals is needed. This Comment demonstrates the importance of being able to share truthful information about off-label uses. In addition, doctors and consumers rely on the promotional information that medical product manufacturers release about their products to advocate for patients and their own healthcare needs.[162] Therefore, the FDA should loosen regulations and include additional safe harbor provisions within the "intended use" rule to allow individuals and healthcare professionals to play a more active role in making healthcare decisions.[163]

One can look to the FDA's Draft Policy Statement on Industry Supported Scientific and Educational Activities to reduce the restrictions and create a safe harbor provision.[164] This statement recognizes alternative methods of permitted communication for disseminating information about off-label uses, including for scientific and educational programs.[165] Such forms of authorized communication allow for further medical advancement and ensure that medical professionals have access to valuable information.[166] The examples stated in the draft of sharing off-label information for approved medical devices are permitted because the FDA does not recognize them as "labeling" or "advertising."[167] This concept should be celebrated with the introduction of a safe harbor so these efforts can become the standard in the practice of medicine.

In 2021, following the release of the final intended use rule, the safe harbor provisions remained uncodified in the actual language of the FDA's intended use rule.[168] Even though many in the industry called for clarity regarding the safe harbor provisions, the FDA remains elusive on the topic.[169] The final rule, as it stands, may disappoint industry

161 David M. Fritch, *Speak No Evil, Hear No Evil, Harm the Patient? Why the FDA Needs to Seek More, Rather Than Less, Speech From Drug Manufacturers on Off-Label Drug Treatments*, 9 MICH. ST. J. MED. & L. 315, 320 (2005).

162 *Id*. at 319–20.

163 *Id*. at 320–21.

164 *See* 57 Fed. Reg. 56412 (Nov. 27, 1992).

165 *Id*.

166 Fritch, *supra* note 161, at 338.

167 Fritch, *supra* note 161, at 338.

168 *See A Question of Intent*, *supra* note 7.

169 *See generally* Paul Howard & James Copland, *Off-Label, Not Off-Limits: The FDA Needs to Create a Safe Harbor for Off-Label Drug Use*, 110 MISSOURI MEDICINE 106 (2013).

professionals who advocated to see changes in the final rule.[170] With the FDA's refusal to include a safe harbor and its failure reinforce its broad control, the FDA continues to restrict market growth of medical products.[171] It is vital to healthcare progress that the FDA adopts a safe harbor provision within the FDCA to create a uniform approach allowing medical product manufacturers to share truthful information with healthcare professionals.

VIII. SOLUTION

Previously, this Comment addressed the new rule's preamble and its efforts at addressing the theoretical safe-harbor provision. The preamble faced many issues that previous versions of this rule failed to address; however, the FDA did not take final steps to ensure enforcement, which would solve those issues. Therefore, the FDA must make two changes to the already established rule.

First, the FDA should look to states, such as Arizona and Tennessee, and draft guidelines that each state will be able to enforce. Following the states' lead helps provide a framework that will work for independent states, as opposed to something that would be geared to the federal level. Implementing guidelines similar to those utilized in Arizona and Tennessee will be beneficial to both manufacturers and healthcare professionals. Still, this change will not be effective if it is not uniform and broadly followed across every state. When dealing with the delicate nature of health care, it serves the FDA's best interest to ensure that access to product information is available across the country rather than in a few isolated states that enacted their own laws.

Second, the FDA needs to codify safe harbor language into the new rule. As it stands, there are no guarantees that the safe harbor provision will grant a manufacturer any protection from prosecution. FDA policy has repeatedly addressed circumstances that are appropriately protected.[172] These circumstances have also been affirmed numerous times throughout litigation.[173] Ultimately this language has proven insufficient, and professionals in the industry have sought the official addition of a safe harbor for years.

The inclusion of a safe harbor provision should be seamless. The FDA already has the guidance language and has pointed to the guidance

170 Tricia Kaufman, *FDA Finally Finalizes the Intended Use* Rule, LEXOLOGY (Aug. 9, 2021), https://www.lexology.com/library/detail.aspx?g=484f845b-0610-498c-944b-ce4831bdc26f.

171 *Id*.

172 *FDA's Use Regul.'s Affect Drug and Med. Device Co.'s*, *supra* note 66.

173 *FDA's Use Regul.'s Affect Drug and Med. Device Co.'s*, *supra* note 66.

in several official statements, including the preamble for the new rule.[174] The safe harbor provision will be a cumulation of each guidance document, leaving room for broad discretion of the industry and adequate protection from prosecution. The FDA should maintain that the safe harbor provision will not apply to manufacturing companies that market off-label information to the general public. The protection should continue to be reserved for the advantage of communications between manufacturers and healthcare professionals to ease the ability of those who have the proper education to make informed decisions; who can then relay their knowledge to their patients. While such an addition may provide medical product manufacturers with more freedom to sell their products, requiring that the safe harbor provision be used only for communications between those two groups will act as an additional protection measure.

This addition is important from a public policy standpoint alone. For example, suppose a manufacturer knows that their product might have other uses that are not already FDA-approved. In that case, the FDA should not limit the manufacturer from informing healthcare professionals of their findings. These manufacturers are not gatekeepers of unapproved information; the FDA is. Furthermore, such restrictions could put too much control in the manufacturers' hands when deciding on the initial intended uses for a new product.

While the general public should have access to information that will improve their health and well-being, protecting the integrity of the informed medical decision need not be forgotten. As discussed earlier, healthcare professionals have every right to prescribe products for off-label uses; however, these professionals are held to a standard the general public is not. Licensing boards regulate healthcare professionals to ensure that medical professionals maintain their oath.

Further, the final rule, as it stands, is not the clarifying framework that so many hoped for.[175] This exacerbates the need for additional changes to clarify the different aspects of the rule further.

IX. CONCLUSION

This Comment argues that the FDA's "final rule" for regulating intended use and "off-label" promotion through the FDCA will not fix the problems that it was introduced to combat. The FDA's 2021 rule is a band-aid for issues that have been the subject of much litigation and dispute. As the argument for free speech and technology advances, the

174 *FDA's Use Regul.'s Affect Drug and Med. Device Co.'s*, *supra* note 66.

175 *FDA's Use Regul.'s Affect Drug and Med. Device Co.'s*, *supra* note 66.

final rule will continue to do more harm than good when regulating promotional language for different uses of medical products. This Comment proposes additions to the final rule regarding intended uses and the regulation of "off-label" promotion.

This Comment aims to create a compromise between the efforts individual states have made to "decriminalize" manufacturers' ability to promote their FDA-approved products for uses other than the intended uses on a product's label and the need for a safe harbor addition to the FDCA. To accomplish this, it is necessary for the FDA to include a safe harbor provision within the intended use rule for specific circumstances of "off-label" production. Additionally, the FDA should look to states like Arizona and Tennessee when drafting and implementing guidelines for individual states to ensure uniformity across interstate commerce regulations.