

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

PAR PHARMACEUTICAL, INC.
300 Tice Boulevard
Woodcliff Lake, New Jersey 07677,

Plaintiff,

v.

UNITED STATES OF AMERICA
Serve to: U.S. Attorney General
950 Pennsylvania Avenue NW
Washington, DC 20530;

UNITED STATES FOOD & DRUG
ADMINISTRATION
10903 New Hampshire Avenue
Silver Spring, MD 20993;

MARGARET HAMBURG, M.D., in her
official capacity as Commissioner of Food
and Drugs
10903 New Hampshire Avenue
Silver Spring, MD 20993; and

KATHLEEN SEBELIUS, in her official
capacity as Secretary of the Department of
Health & Human Services
200 Independence Avenue SW
Washington, DC 20201,

Defendants.

Civil Action No. _____

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff Par Pharmaceutical, Inc. ("Par") alleges as follows:

NATURE OF ACTION

1. In this action, Par seeks a declaratory judgment that the First Amendment and the Federal Food, Drug, and Cosmetic Act (the "Act") bar application of certain regulations of the

U.S. Food & Drug Administration (“FDA”) that purport to criminalize Par’s truthful and non-misleading speech to healthcare professionals concerning the FDA-approved use of its FDA-approved prescription drug.

2. In general, FDA regulations provide that a pharmaceutical manufacturer commits a crime if it speaks to healthcare professionals about an FDA-approved prescription drug for a medical use that the FDA has not approved. The government commonly refers to manufacturers’ speech about *unapproved uses* of approved drugs as “off-label promotion.” *E.g.*, U.S. Gov’t Accountability Office, GAO-08-835, Prescription Drugs: FDA’s Oversight of the Promotion of Drugs for Off-Label Uses 2-3, 26-28 (2008). As relevant in this case, the FDA’s regulations also purport to criminalize a manufacturer’s truthful and non-misleading speech about the *FDA-approved uses* of a prescription drug to physicians who may use the drug for approved uses but are more likely to use the drug for unapproved uses.

3. As applied in this context, the regulations are contrary to both the First Amendment and the Act.

4. The ongoing threat of prosecution for alleged “off-label promotion” based on Par’s truthful and non-misleading speech to healthcare professionals concerning the *FDA-approved use* of Par’s FDA-approved prescription drug currently chills Par’s speech. Par seeks declaratory and injunctive relief to ensure its ability to engage in this protected speech free from the risk of criminal liability.

PARTIES

5. Par is a Delaware corporation with its principal place of business at 300 Tice Boulevard, Woodcliff Lake, New Jersey 07677. Par manufactures generic and branded

pharmaceutical products, including megestrol acetate oral suspension, which Par markets for prescription use under the brand name Megace® *ES*.

6. Defendant FDA is a federal agency within the U.S. Department of Health & Human Services (“HHS”). The FDA is responsible for approving, disapproving, and otherwise regulating food and drugs, among other products, under the Act. The FDA’s headquarters are located in Silver Spring, Maryland.

7. Defendant HHS is an executive department of the United States. HHS oversees the activities of the FDA, including its execution and administration of the Act. HHS’s headquarters are located in Washington, D.C.

8. Defendant Margaret Hamburg, M.D., is being sued in her official capacity as the Commissioner of Food and Drugs, the most senior official at the FDA. As Commissioner, Dr. Hamburg is directly responsible for the execution and administration of the Act.

9. Defendant Kathleen Sebelius is being sued in her official capacity as the Secretary of HHS. Secretary Sebelius is Commissioner Hamburg’s immediate superior, and as such, Secretary Sebelius is responsible for the execution and administration of the Act.

JURISDICTION AND VENUE

10. This action seeks declaratory relief under the Federal Declaratory Judgment Act of 1934, 28 U.S.C. §§ 2201-02.

11. This Court has subject matter jurisdiction under 28 U.S.C. § 1331 because Par’s causes of action arise under the United States Constitution and laws of the United States. Par also seeks review under the Administrative Procedure Act, 5 U.S.C. § 702, because the FDA’s regulations are “contrary to constitutional right” and “arbitrary, capricious, an abuse of

discretion, or otherwise not in accordance with law,” as applied to Par’s truthful and non-misleading speech to healthcare professionals. 5 U.S.C. § 706(2)(A), (B).

12. Venue is proper in this district under 28 U.S.C. § 1391(e).

FACTUAL ALLEGATIONS

A. The Federal Food, Drug, and Cosmetic Act

13. The Act prohibits the introduction or delivery for introduction into interstate commerce of any “new drug” that the FDA has not approved. 21 U.S.C. §§ 331(d), 355(a). The Act also prohibits the introduction or delivery for introduction into interstate commerce of any drug that is “misbranded,” even if the FDA has approved the drug. 21 U.S.C. §§ 331(a), 352.

14. Violations of the Act’s “new drug” and “misbranding” requirements constitute criminal offenses subject to imprisonment for up to three years as well as substantial fines and penalties. 21 U.S.C. § 333(a). Introduction of an unapproved “new drug” or a “misbranded” drug is generally a misdemeanor, but the offense may become a felony under certain circumstances. *See id.*

15. Conviction under the Act also may have severe collateral consequences. The Secretary of HHS may exclude from participation in any federal healthcare program an individual or entity that has been convicted of a criminal offense “relating to fraud, theft, embezzlement, breach of fiduciary responsibility, or other financial misconduct . . . in connection with the delivery of a health care item or service or with respect to any act or omission” in a government-operated healthcare program. 42 U.S.C. § 1320a-7(b)(1)(A)(i). If the conviction is for a felony offense, exclusion from federal healthcare programs is mandatory. 42 U.S.C. § 1320a-7(a)(3). To the extent a “new drug” or “misbranding” violation falls within the scope of Section 1320a-7, conviction carries the risk of exclusion from participation in, and

reimbursement under, federal healthcare programs, including Medicare and Medicaid. Such exclusion can be financially devastating for manufacturers and individuals.

16. Conviction under the Act also exposes individual manufacturer executives and employees to the risks of prison, fines, penalties, and exclusion from participation in the Medicare and Medicaid programs. *See* 42 U.S.C. § 1320a-7(b)(15).

17. A pharmaceutical manufacturer seeking approval for a new drug must submit a detailed application to the FDA, including, among other information, reports of pre-clinical and clinical trials demonstrating the drug's safety and efficacy as well as proposed labeling for the drug. 21 U.S.C. §§ 355(b)(1), (b)(2). The FDA evaluates whether the drug is safe and effective under the conditions "prescribed, recommended, or suggested" in the labeling, and ensures that the labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d).

18. If the FDA approves a new drug application, the approval extends only to the uses "prescribed, recommended, or suggested" on the drug's FDA-approved "labeling." 21 U.S.C. § 321(p). Even after the FDA has approved a drug for a particular use, if the manufacturer alters the drug's "labeling" to prescribe, recommend, or suggest a new use, the drug constitutes a "new drug" under 21 U.S.C. § 321(p), and the manufacturer violates the Act's prohibition against selling the drug without obtaining FDA approval for the new use. 21 U.S.C. § 355(a).

19. The Act defines a drug's "labeling" to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). The Act defines a drug's "label" to mean "a display of written, printed, or graphic matter upon the immediate container of any article." 21 U.S.C. § 321(k). Materials are considered to be "accompanying" a drug if they are sent from the same

location, to the same destination, as part of an “integrated” transaction, and the two have a “textual relationship.” *Kordel v. United States*, 335 U.S. 345, 348-50 (1948).

20. With regard to the Act’s “misbranding” provision, 21 U.S.C. § 352 sets forth the circumstances in which a drug “shall be deemed to be misbranded.” As relevant here, a drug generally is misbranded under the Act “[u]nless its labeling bears . . . adequate directions for use.” 21 U.S.C. § 352(f)(1). Section 352 authorizes the Secretary of HHS to promulgate regulations exempting certain drugs from the requirement of “adequate directions for use” where that requirement is “not necessary for the protection of the public health.” *Id.*

21. In addition, the Act provides that “a drug dispensed by filling or refilling a written or oral prescription of a [licensed practitioner] shall be exempt” from the “adequate directions” requirement and certain other “misbranding” provisions of Section 352. 21 U.S.C. § 353(b)(2). The Section 353(b)(2) exemption applies as long as the prescription drug’s “label” contains, among other information, “the directions for use and cautionary statements, if any, *contained in such prescription.*” 21 U.S.C. § 353(b)(2) (emphasis added). The Act further provides that a prescription drug “shall be deemed to be misbranded if at any time prior to dispensing the label . . . fails to bear, at a minimum, the symbol ‘Rx only.’” 21 U.S.C. § 353(b)(4). Accordingly, as long as a prescription drug is dispensed with a label on the drug’s container bearing the symbol “Rx only” and the prescribing physician’s directions to the patient, the Act does not require the drug’s labeling to provide additional directions for use by consumers.

22. The Act does not limit or interfere with the authority of healthcare professionals to prescribe or administer any FDA-approved drug to any patient to treat any condition or disease. To the contrary, the FDA itself has explained that “[o]nce a drug or medical device has been approved or cleared by FDA, generally, healthcare professionals may lawfully use or

prescribe that product for uses or treatment regimens that are not included in the product's approved labeling." FDA, 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 (Jan. 2009), <http://www.fda.gov/oc/op/goodreprint.html> ("FDA Good Reprint Practices"); *see also More Information for Better Patient Care: Hearing on S. 1477 Before the Senate Comm. on Labor and Human Resources*, 104th Cong. (1996) (statement of William B. Schultz, then-FDA Deputy Commissioner for Policy) ("Schultz Statement") ("Congress did not intend FDA to interfere with the practice of medicine. Thus, once a drug is approved for marketing, FDA does not generally regulate how, and for what uses, physicians prescribe that drug. A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed in the FDA-approved labeling."); *accord* 59 Fed. Reg. 59,820, 59,821-22 (Nov. 18, 1994). Accordingly, healthcare professionals may lawfully prescribe or administer an FDA-approved drug for any use suggested on the drug's FDA-approved labeling (*i.e.*, "on-label" uses), and also for uses that the FDA has not approved and thus are not included in the drug's labeling (*i.e.*, "off-label" uses).

23. Today, many off-label uses of FDA-approved prescription drugs are widespread, medically accepted, and subsidized by the federal government under the Medicare and Medicaid programs. In some medical specialties, such as oncology, the majority of prescriptions are written for off-label uses of approved drugs. U.S. Gov't Accountability Office, GAO/T-HEHS-96-212, *Prescription Drugs: Implications of Drug Labeling and Off-Label Use* 3 & n.6 (1996); P. G. Casali, *The Off-Label Use of Drugs in Oncology*, 18 *Annals Oncology* 1923, 1923 (2007) ("The off-label use of drugs in oncology has been estimated to reach 50%, or even more."). The FDA itself has recognized that "in certain circumstances, off label uses of approved products are

appropriate, rational, and accepted medical practice. FDA knows that there are important off-label uses of approved drugs.” Schultz Statement, *supra*, at 4; *see also* FDA Good Reprint Practices, *supra* (“[O]ff-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care.”).

24. Because of the widespread, medically accepted, and government-subsidized off-label uses of numerous FDA-approved prescription drugs, it is critical that healthcare professionals have access to accurate, comprehensive, and current information concerning off-label uses. “[T]he principle for the FDA is that the very latest information that can be of value to physicians, pharmacists, and patients must be made available as soon as possible. Frequently, unlabeled use information is extremely important.” Stuart J. Nightingale, then-FDA Associate Commissioner for Health Affairs, *Unlabeled Uses of Approved Drugs*, 26 *Drug Info. J.* 141, 145 (1992); *see also* FDA Good Reprint Practices, *supra* (“FDA does recognize . . . the important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities.”).

B. The Regulatory Regime

25. The FDA has issued regulations that purport to criminalize a manufacturer’s speech regarding a lawful, off-label use of an FDA-approved prescription drug. As relevant here, the government interprets the regulations to prohibit a manufacturer from speaking to healthcare professionals about the FDA-approved, *on-label* uses of a prescription drug in a setting where physicians may prescribe the drug for both approved and unapproved uses.

1. The Government's "New Drug" Theory

26. Based on the government's interpretation of the Act's "new drug" provision, a manufacturer's speech concerning an off-label use of an approved prescription drug constitutes a crime. The "new drug" provision prohibits a manufacturer from selling a drug with "labeling" that prescribes, recommends, or suggests an unapproved use. 21 U.S.C. §§ 321(p), 355(a).

27. By regulation, the FDA has dramatically expanded the scope of materials that constitute "labeling." As stated above, the Act defines "labeling" to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). The FDA's regulation, however, states that:

[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the "Physicians Desk Reference") for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor *are hereby determined to be labeling as defined in section 201(m) of the act* [21 U.S.C. § 321(m)].

21 C.F.R. § 202.1(l)(2) (emphasis added). The FDA's definition of labeling thus encompasses any tangible materials distributed by the manufacturer that contain manufacturer-supplied drug information, irrespective of whether those materials are "accompanying" a drug under 21 U.S.C. § 321(m).

28. Under the FDA's definition of "labeling," it is unlawful for a manufacturer to provide any tangible materials to healthcare professionals containing manufacturer-supplied drug information if those materials prescribe, recommend, or suggest an unapproved use of an approved prescription drug. A drug with labeling that prescribes, recommends, or suggests such

an unapproved use would constitute a “new drug” under the Act, and the manufacturer thus could not lawfully sell the drug absent FDA approval for that use. 21 U.S.C. §§ 321(p), 355(a).

2. The Government’s “Misbranding” Theory

29. A manufacturer’s speech regarding an off-label use of an approved prescription drug also constitutes a crime under the government’s interpretation of the Act’s “misbranding” provision. In addition, the government interprets the “misbranding” provision to criminalize a manufacturer’s truthful and non-misleading speech to healthcare professionals regarding the approved, *on-label* uses of a prescription drug in settings where the manufacturer knows that physicians may prescribe the drug for both approved and unapproved uses.

30. Relying on a patchwork of FDA regulations, the government contends that a manufacturer’s speech expressing an off-label use renders a prescription drug criminally “misbranded,” since the drug’s “labeling” does not bear “adequate directions” for the off-label use. 21 U.S.C. § 352(f)(1).

31. In numerous criminal indictments and other court filings, the government has articulated its “misbranding” theory essentially as follows:

The [Act], at 21 U.S.C. § 352(f)(1), provided that a drug was misbranded if, among other things, the labeling did not contain “adequate directions for use.” As the phrase was used in the [Act], “adequate directions for use” could not be written for medical indications or uses for which the drug had not been proven to be safe and effective, through well-controlled clinical studies. Any uses for a drug that were not approved by FDA as safe and effective, and thus that were not included in the drug’s approved labeling, were known as “off-label” indications or uses. A drug that was promoted for an off-label indication or use did not contain “adequate directions for use,” because such an off-label indication or use was not included in the FDA-approved labeling for the drug, and that drug was therefore misbranded under Section 352(f).

Information, *United States v. Cephalon, Inc.*, No. 08-598, 2008 WL 4498615, at *1 (E.D. Pa., filed Sept. 29, 2008).

32. As described above, the Act provides that prescription drugs are exempt from the requirement under 21 U.S.C. § 352(f)(1) that a drug's "labeling" must bear "adequate directions for use," as long as the drug's "label" repeats the doctor's directions to a patient set forth in the prescription itself. *See* 21 U.S.C. § 353(b)(2). An FDA regulation, however, nullifies this exemption by providing that a prescription drug's labeling must bear "adequate directions for use" unless the labeling bears "adequate *information* for its use." 21 C.F.R. § 201.100(c)(1) (emphasis added).

33. The FDA's regulation defines "adequate information" for a prescription drug's use to mean directions under which medical professionals "can use the drug safely and for the purposes *for which it is intended.*" *Id.* (emphasis added). Under the regulation, a drug's "intended" uses are not limited to the uses set forth in its FDA-approved labeling, but rather encompass "all purposes for which [the drug] is advertised or represented." *Id.* Accordingly, if a manufacturer advertises or represents an approved prescription drug for an off-label use, the FDA's regulation purports to require the manufacturer to provide "adequate directions" or "adequate information" for that off-label use in the drug's labeling.

34. Under the Act, however, a manufacturer cannot include directions or information for any off-label use in a drug's "labeling," or else the drug would constitute a "new drug" that cannot lawfully be sold. 21 U.S.C. §§ 321(p), 355(a). Thus, a prescription drug that is "advertised or represented" for an off-label use necessarily lacks "adequate directions" and "adequate information" for that off-label use. Under the FDA's regulation, the drug is then automatically "misbranded" in criminal violation of 21 U.S.C. § 352(f)(1). 21 U.S.C. §§ 331(a), 333(a). The FDA's regulation thus criminalizes the manufacturer's truthful speech regarding a lawful, off-label use of an approved prescription drug.

35. Another FDA regulation defines a drug's "intended uses" based on a manufacturer's "objective intent," which can be established based on the manufacturer's "expressions" in any forum, including in "labeling claims, advertising matter, or oral or written statements." 21 C.F.R. § 201.128. The manufacturer's "objective intent" also can be established based on "circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised." *Id.* In addition, with regard to downstream sellers, if a manufacturer "knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such drug which accords with [those other uses]." *Id.*

36. Under the "intended use" regulations of 21 C.F.R. §§ 201.100 and 201.128, a manufacturer's speech concerning exclusively the FDA-approved, *on-label* uses of a prescription drug may demonstrate the manufacturer's "objective intent" that the drug should be used for *off-label* purposes. For instance, if a manufacturer speaks about the on-label uses of a drug in a setting where physicians exercising independent medical judgment prescribe the drug off-label, the government interprets the FDA's "intended use" regulations to require the manufacturer to provide "adequate directions" or "adequate information" for the off-label use in the drug's labeling. As discussed, however, the manufacturer cannot lawfully alter the drug's "labeling" to provide "adequate directions" or "adequate information" for the off-label use. If the manufacturer made such a modification to a drug's FDA-approved "labeling," the drug would constitute a "new drug" that could not lawfully be sold under the Act. 21 U.S.C. §§ 321(p), 355(a). No regulation or other government pronouncement narrows the circumstances in which

the government may deem a manufacturer's speech about the FDA-approved, on-label use of an approved prescription drug to constitute a crime.

37. Accordingly, when a manufacturer speaks about an on-label use of its drug in a medical facility where physicians prescribe the drug off-label, the manufacturer is caught in a Catch-22: changing the drug's labeling to add directions for the off-label use violates the Act's criminal "new drug" rule, but based on the government's view of the FDA's "intended use" regulations, *not* changing the labeling to add those directions violates the Act's criminal "misbranding" rule. The manufacturer's truthful speech about on-label use of its drug thus violates at least one of these criminal provisions.

38. Under the government's interpretation of the Act and the FDA's "intended use" regulations, the manufacturer's speech concerning lawful on-label uses of its FDA-approved prescription drug is effectively placed under a prior restraint, which is lifted, if ever, only when the FDA approves the off-label use. Pursuing FDA approval for a new use of a previously approved drug, however, can take years and cost millions of dollars, and the FDA ultimately may deny approval for the new use. Even worse, an off-label use of a drug may be so widely medically accepted that a manufacturer is unable ethically to conduct placebo-controlled clinical studies that are the standard prerequisites to obtain FDA approval for a new use of an approved drug.

C. Par Produces and Markets Megace® ES

1. Uses of Megace® ES

39. Par produces and markets megestrol acetate oral suspension for prescription use under the brand name Megace® ES. Megace® ES is a hormone that can be taken orally to stimulate a patient's appetite. In July 2005, the FDA approved Megace® ES for the treatment of anorexia (loss of appetite), cachexia (severe malnutrition), or unexplained, significant weight

loss in patients diagnosed with acquired immunodeficiency syndrome (AIDS), collectively referred to as “AIDS-related wasting.” Megace® *ES* Package Insert, *available at* http://www.megacees.com/PDF/Megace_ES_Portrait_PI.pdf. AIDS-related wasting is a serious condition and has been associated with worsening illness, physical impairment, decreased tolerance of some therapeutic agents, increased susceptibility to infection, and diminished sense of well-being.

40. The FDA first approved megestrol acetate in tablet form in 1971 exclusively for the treatment of breast cancer. In 1993, the FDA approved megestrol acetate oral suspension to treat AIDS-related wasting. The drug’s original formula was (and still is) marketed under the brand name Megace® OS.

41. Megace® *ES* provides important health benefits for patients suffering from AIDS-related wasting. In clinical studies, AIDS patients taking megestrol acetate oral suspension to treat wasting experienced increased appetite, caloric intake, body weight, and sense of well-being. For instance, one study showed that over twelve weeks, 89% of AIDS patients taking megestrol acetate oral suspension increased their appetite; patients increased their daily caloric intake by an average of 30%; and patients showed an average weight gain from baseline of more than 10 pounds at week twelve.

42. Megace® *ES* also provides other advantages for patients. For instance, Megace® *ES* is bioavailable in the unfed condition, meaning that it can be absorbed into the body when the patient has not eaten, and the patient does not need to have eaten for the drug to be effective, which is an important benefit for patients suffering from wasting, who may have trouble eating. Patients also take Megace® *ES* in substantially lower doses than Megace® OS. The dosage for Megace® *ES* is one teaspoon per day, versus four teaspoons per day of Megace® OS. And

Megace® ES has low viscosity, making the drug easier to take for some patients, including those who have trouble swallowing.

43. Physicians routinely prescribe Megace® ES for its on-label use to treat AIDS-related wasting. In addition, physicians, in the exercise of their independent medical judgment, even more frequently prescribe Megace® ES off-label, including to treat wasting in non-AIDS geriatric and cancer patients. The majority of Megace® ES prescriptions are for off-label uses. Even before the FDA approved Megace® ES, physicians frequently prescribed Megace® OS and generic versions of megestrol acetate oral suspension off-label to treat wasting in various non-AIDS patient populations, including geriatric and cancer patients.

44. Megestrol acetate is widely viewed as one of the most effective treatments for wasting in geriatric and cancer patients. In 2000, a placebo-controlled trial among elderly patients concluded that the drug was well tolerated and effective in driving weight gain. Shing-Shing Yeh et al., *Improvement in quality-of-life measures and stimulation of weight gain after treatment with megestrol acetate oral suspension in geriatric cachexia: results of a double-blind, placebo-controlled study*, 28 J. Am. Geriatric Soc'y 485 (2000); see also, e.g., Shing-Shing Yeh et al., *Report of a pilot, double-blind, placebo-controlled study of megestrol acetate in elderly dialysis patients with cachexia*, 20 J. Ren. Nutr. 52 (2009); Shing-Shing Yeh et al., *Usage of megestrol acetate in the treatment of anorexia-cachexia syndrome in the elderly*, 13 J. Nutr. Health & Aging 448 (2009).

45. The 2005 Cochrane Report and the 2010 National Comprehensive Cancer Network's regularly updated treatment guidelines recommend megestrol acetate as a treatment for cancer-related wasting. Graciela Berenstein & Zulma Ortiz, *Megestrol Acetate for Treatment of Anorexia-Cachexia Syndrome*, Cochrane Library, Issue 1 (2009); NCCN Clinical Practice

Guidelines in Oncology: Palliative Care, v. 1.2010, p. PAL-11; *see also, e.g.*, Wiktorina Lesniak et al., *Effects of megestrol acetate in patients with cancer anorexia-cachexia syndrome--a systematic review and meta-analysis*, 118 Pol. Arch. Med. Wewn. 636 (2008); Aminah Jatoi, M.D. et al., *An Eicosapentaenoic Acid Supplement Versus Megestrol Acetate Versus Both for Patients With Cancer-Associated Wasting*, 22 J. Clinical Oncology 2469 (2004).

46. In approving megestrol acetate oral suspension to treat AIDS-related wasting in 1993, the FDA itself publicly acknowledged that the drug would be prescribed off-label to treat wasting in non-AIDS geriatric and cancer patients. Nevertheless, the FDA chose to approve the drug for the treatment of AIDS-related wasting, and not to “hold the [AIDS] patients for whom benefit has been demonstrated hostage to the physicians who will use [the drug] for off-label uses.” Transcript of FDA Antiviral Drugs Advisory Committee Meeting, Comments of FDA Director of the Division of Antiviral Drug Products David Feigal, M.D., at 211 (Feb. 18, 1993) (considering approval of Megace® OS to treat AIDS-related wasting).

47. The off-label use of megestrol acetate to treat wasting in cancer and geriatric patients is medically accepted. Off-label use of the drug to treat cancer-related wasting is cited in DrugDex® Information System, one of the major drug compendia. DrugDex® Information System, DRUGDEX-EV 2345, at 21-22 (updated Mar. 2010). This off-label use is so widely accepted that Par could not conduct placebo-controlled clinical studies that are the standard prerequisites to obtain FDA approval for a new use of an approved drug. When Par attempted to set up studies to test the use of Megace® ES for the treatment of cancer-related wasting, Par encountered physicians who would not agree to administer a placebo to cancer patients suffering from wasting, because that course of treatment would be contrary to the best interests of the patients, in light of the accepted off-label use of megestrol acetate.

48. The federal government endorses and subsidizes off-label use of Megace® *ES* to treat wasting in non-AIDS cancer and geriatric patients. Megace® *ES* is reimbursable under federal healthcare programs, including Medicare and Medicaid, for “medically accepted” off-label uses. 42 U.S.C. § 1396r-8(k)(6). Furthermore, the Centers for Medicare & Medicaid Services (CMS), the federal agency within HHS that administers Medicare and Medicaid reimbursement, has recognized that in long-term care facilities, megestrol acetate may be prescribed off-label where “assessment and management of underlying correctable causes of anorexia and weight loss is not feasible or successful, and after evaluating potential benefits/risks.” CMS, State Operations Manual, App. PP, http://www.cms.gov/manuals/downloads/som107_Appendicestoc.pdf.

49. The government encourages off-label use of appetite stimulants generally, and megestrol acetate specifically, in long-term care facilities. Facilities that fall below a certain level of compliance with federal regulations, as rated by CMS’s surveyors, risk losing Medicare and Medicaid reimbursement. CMS surveyors rate facilities using the agency’s system of F-tags, which are compliance directives derived from federal regulations. The CMS F-tags require, among other things, that facilities ensure proper nutritional levels for their patients. For instance, F325 requires facilities to maintain patients’ nutrition and weight. Also, F314, which relates to pressure ulcers, requires facilities to ensure that patients without pressure ulcers do not develop them (except in circumstances where it is unavoidable). Since malnutrition is often a major contributing factor for development of pressure ulcers, facilities can comply with F314 by taking measures to increase a patient’s nutritional levels, including increasing their food intake. As described above, CMS’s State Operations Manual – the agency’s instruction manual for its surveyors – recognizes the beneficial use of appetite stimulants, including megestrol acetate, if

other means have failed. In fact, CMS's recommendation that long-term facilities use any appetite stimulant necessarily suggests an off-label use, because the FDA has not approved *any* appetite stimulant to treat wasting in geriatric patients. In light of the CMS F-tags, if an elderly non-AIDS patient has not responded to other appetite-stimulating treatment, long-term care facilities face possible termination of reimbursement if they fail to employ megestrol acetate or another appetite stimulant for an off-label use.

2. There Is A Sound Rationale For Marketing Megace® ES For Its Approved Use In Oncology And Long-Term Care Settings Where Physicians Reasonably May Encounter AIDS Patients

50. In connection with developing a marketing strategy for Megace® ES, Par evaluated the incidence of AIDS in the long-term care and oncology settings. Par's evaluation included internal deliberations among multiple departments of the company, and also the use of outside consultants. Based on this evaluation, Par concluded that physicians and other staff responsible for treating patients in long-term care facilities and oncology practices reasonably may encounter patients suffering from AIDS-related wasting, and thus may have occasion to prescribe Megace® ES for its on-label use. In those settings, physicians exercising independent medical judgment also may prescribe Megace® ES off-label to treat wasting in non-AIDS cancer and geriatric patients.

a. AIDS Is Increasingly Prevalent In Long-Term Care

51. In its internal research, Par identified data showing a rising incidence of AIDS in long-term care facilities, with several key factors contributing to this trend. Patients infected with HIV and AIDS are living longer and with more complications, including complex health problems usually associated with old age, and the HIV infection rate has increased among individuals over 50 years of age. *See, e.g.,* Kelly A. Gebo et al., *Treatment of HIV Infection in the Older Patient*, 2 Expert Rev. of Anti-Infect. Ther. 733 (2004) ("The number of HIV patients

over the age of 50 years is increasing due to increased longevity in patients treated with highly active antiretroviral therapy (HAART), in addition to new primary infections in older patients.”).

52. Dozens of reports, journal and news articles, and other materials discuss the relationship between HIV/AIDS and the elderly, and HIV/AIDS in long-term care facilities. *See, e.g., AIDS Among Persons > 50 Years -- United States, 1991-1996*, 12 *Oncology* (1998), David Hoos et al., *HIV/AIDS and Long-Term Care: A State Perspective*, 77 *J. Urban Health* 232 (2000); David R. Thomas et al., *Nutritional Management in Long-Term Care: Development of a Clinical Guideline*, 55A *J. Gerontology* M725 (2000); Eric A. Engels, *Human Immunodeficiency Virus Infection, Aging, and Cancer*, 54 *J. Clin. Epidemiol.* S29 (2001); R.J. Buchanan et al., *Profiles of Nursing Home Residents with HIV*, 13 *J. Health Care Poor Underserved* 379 (2002); William S. Pearson et al., *Treatment of HIV/AIDS in the Nursing Home: Variations in Rural and Urban Long-Term Care Settings*, 97 *S. Med. J.* 338 (2004); Kelly A. Gebo, *HIV and Aging: Implications for Patient Management*, 23 *Drugs & Aging* 897 (2006); Kelly A. Gebo, *HIV in Patients Over 50: An Increasing Problem*, 16 *The Hopkins HIV Report* 7 (2004); Sindy M. Paul et al., *Changing Trends in Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome in the Population Aged 50 and Older*, 55 *J. Am. Geriatrics Soc’y* 1393 (2007). The national media, including Time Magazine and the New York Times, have reported on the aging of the AIDS population in the United States. Christine Gorman, *The Graying of AIDS*, *Time*, Aug. 6, 2006; Jane Gross, *AIDS Patients Face Downside of Living Longer*, *N.Y. Times*, Jan. 6, 2008.

53. Par’s outside consultants independently researched and documented the incidence of AIDS among the elderly and in long-term care facilities. The findings of Par’s outside consultants reinforced what Par had found in its internal research.

54. The government's data and guidance provide evidence of the increasing incidence of AIDS in the long-term care setting. For instance, the Centers for Disease Control and Prevention has stated: "The number of persons aged 50 years and older living with HIV/AIDS has been increasing in recent years. This increase is partly due to the highly active antiretroviral therapy (HAART), which has made it possible for many HIV-infected persons to live longer, and partly due to the newly diagnosed infections in persons over the age of 50." Centers for Disease Control and Prevention, *CDC HIV/AIDS Facts: HIV/AIDS Among Persons Aged 50 and Older* (Feb. 2008).

55. State and local government programs provide further evidence of the increasing incidence of AIDS in the long-term care setting. For instance, the State of Florida assisted Broward County in establishing a Senior HIV Intervention Project to provide HIV education and support to adult living facilities. Lisa L. Agate et al., *Strategies for Reaching Retirement Communities and Aging Social Networks: HIV/AIDS Prevention Activities Among Seniors in South Florida*, 33 *J. Acquired Immune Deficiency Syndrome* 238 (2003). The then-Medical Director of Maryland's Office of Health Care Quality stated that the number of AIDS patients in long-term care facilities has risen. Joseph I. Berman, *AIDS and Long Term Care*, <http://www.dhmh.state.md.us/ohcq/download/04282004.pdf>. And the State of New York has developed a set of Quality of Care Indicators for long-term care facilities that treat patients with HIV. New York State Dep't of Health, *Quality of Care Indicators: HIV Nursing Home Indicators*, <http://www.hivguidelines.org/quality-of-care/quality-of-care-archives/new-york-state/hiv-nursing-home-indicators>.

b. The Connection Between AIDS and Cancer Is Well Established

56. Par also evaluated the incidence of AIDS among cancer patients, including through consultations with in-house and outside physicians. Based on its evaluation, Par concluded that oncologists reasonably may encounter patients suffering from AIDS-related cancers, which encompass dozens of types of cancer. For instance, the National Cancer Institute of the National Institutes of Health (NIH) has identified numerous AIDS-related cancers, including lymphoma, cervical cancer, testicular cancer, lip cancer, and lung cancer. National Cancer Institute, *AIDS-Related Cancers*, <http://nci.nih.gov/cancertopics/types/AIDS>; National Cancer Institute, *What You Need to Know About Cancer Index*, <http://www.cancer.gov/cancertopics/wyntk>; NIH Guide, AIDS-Oncology Clinical Scientist Development Program, Mar. 1997, <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-97-009.html> (“Malignancies have been associated with HIV/AIDS since the beginning of the epidemic in the early 1980s.”); Ellen G. Feigal et al., *Cancer and AIDS: National Cancer Institute’s Investment in Research*, Research Initiative Treatment Action 26 (Summer 2003). Many journal articles and other materials also discuss the connection between AIDS and many types of cancer. See, e.g., Eric A. Engels et al., *Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome and Cancer: Past, Present, and Future*, 97 J. Nat’l Cancer Inst. 407 (2005).

57. Based on both the actual and potential on-label use of Megace® ES in long-term care facilities and oncology practices, Par believes it should be permitted, without threat of criminal prosecution, to speak to healthcare professionals in those settings about the FDA-approved, on-label use of Megace® ES.

3. The FDA's Regulations Chill Par's Truthful Speech To Healthcare Professionals About On-Label Use Of Megace® ES

58. Par has designed a comprehensive marketing message, as outlined below, for its sales representatives to educate physicians and other healthcare professionals about the FDA-approved, *on-label* use of Megace® ES to treat AIDS-related wasting. Based on the fear of criminal prosecution, however, Par is significantly chilled from disseminating beneficial information about its drug to many healthcare professionals who reasonably may encounter AIDS patients, including many physicians in the long-term care and oncology settings. Thus, to avoid prosecution and civil penalty for exercising its First Amendment rights, Par has significantly limited its truthful, non-misleading speech regarding the FDA-approved, on-label use of Megace® ES in settings where physicians prescribe the drug for off-label uses.

59. Par currently limits its marketing of Megace® ES to physicians who previously have prescribed megestrol acetate oral suspension, including Megace® OS and generic versions of the drug, based on prescriber data that Par purchases from a third-party vendor. Par also markets Megace® ES only to physicians who confirm that information regarding the drug's FDA-approved indication to treat AIDS-related wasting is relevant to their medical practice. Nevertheless, in light of the government's criminal "misbranding" and "new drug" theories, Par is under a current fear of prosecution based on speaking about the on-label use of Megace® ES to past prescribers of megestrol acetate oral suspension in the long-term care and oncology settings.

60. Based on the fear of prosecution, Par does not speak about Megace® ES to physicians based on their past prescription of other anti-wasting drugs that the FDA has approved to treat AIDS-related wasting, such as Serostim® and Marinol®. Par also does not market Megace® ES to physicians based on their past prescription of other drugs that have

different FDA-approved indications, but that are frequently prescribed to patients as appetite stimulants, such as Periactin®, Oxandrin®, and Remeron®. But for the fear of prosecution, Par would speak about on-label use of Megace® *ES* to those physicians in the long-term care and oncology settings where they reasonably may encounter AIDS patients. In addition, but for the fear of prosecution, Par would speak about Megace® *ES* to other physicians in long-term care and oncology settings without regard to their past prescribing practices.

61. In the long-term care facilities and oncology practices where Par currently does not market Megace® *ES*, Par would inform healthcare professionals of the drug's FDA-approved indication to treat AIDS-related wasting. Par also would explain the health benefits of Megace® *ES* for patients suffering from AIDS-related wasting, including the potential to increase patients' appetite, body weight, caloric intake, and sense of well-being. And Par would describe other characteristics of Megace® *ES*, including its low viscosity and bioavailability in the unfed condition. All of these statements are within the FDA-approved labeling for Megace® *ES*. *See* Megace® *ES* Package Insert.

62. In addition, Par would provide healthcare professionals in long-term care facilities and oncology practices with other on-label product information about the drug. For instance, Par would explain the dosage requirements for Megace® *ES* and how they differ significantly from the dosage requirements for Megace® *OS*. The FDA-approved labeling for Megace® *ES* contains a table illustrating the "differences in dosing between Megace® *ES* and Megace® Oral Suspension." *Id.*

63. Par also would provide on-label information relating to on-label use of Megace® *ES* to treat AIDS-related wasting in particular patient populations, including the elderly. Under the heading "Geriatric Use," the FDA-approved labeling for Megace® *ES* states that "dose

selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.” *Id.* The drug’s FDA-approved labeling explains that clinical studies of megestrol acetate oral suspension to treat wasting in AIDS patients did not include sufficient numbers of elderly patients, but “[o]ther reported clinical experience has not identified differences in responses between elderly and younger patients.” *Id.*

64. Par also would provide healthcare professionals with certain on-label safety-related information regarding Megace® *ES*, including contraindications, warnings and precautions, adverse reactions, and drug interactions. *See id.*

65. Par does not engage, and does not seek to engage, in any direct-to-consumer communications concerning Megace® *ES*.

66. Par’s truthful speech to healthcare professionals about on-label use of Megace® *ES* could render the drug criminally misbranded based on the government’s view of FDA regulations, on the theory that the speech expresses an “objective intent” that physicians in long-term care facilities and oncology practices should prescribe Megace® *ES* off-label to treat wasting in non-AIDS geriatric and cancer patients. *See* 21 C.F.R. §§ 201.100(c)(1), 201.128.

67. Further, to the extent the government views Par’s written speech as promoting an off-label use based on the physician audience, Par could be exposed to a new-drug charge based on prescribing, recommending, or suggesting an unapproved use in the labeling for Megace® *ES*. Par would not alter any “written, printed, or graphic matter” found on the drug itself, its “container or wrappers,” or “accompanying such article” in commerce. 21 U.S.C. §§ 321(m), (k). Par’s speech thus would not constitute labeling as defined in the Act. *See Kordel*, 335 U.S. at 348-50. Nonetheless, Par’s speech could fall within the FDA’s extra-statutory definition of

“labeling” under 21 C.F.R. § 202.1(1)(2). The FDA thus would deem Megace® *ES* to be a new drug based on supposed written off-label speech in the drug’s labeling.

68. Par’s fear of prosecution under these theories is reasonable. The government has aggressively prosecuted pharmaceutical manufacturers for alleged “off-label promotion” based on its “misbranding” and “new drug” theories. *See* U.S. Accountability Office, GAO-08-835, Prescription Drugs: FDA’s Oversight of the Promotion of Drugs for Off-Label Uses 26-27 (2008). The government has stated unequivocally its intention to continue aggressively prosecuting pharmaceutical manufacturers for alleged “off-label promotion.” *See, e.g.*, Press Release, U.S. Dep’t of Justice, Pharmaceutical Companies to Pay \$214.5 Million to Resolve Allegations of Off-Label Promotion of Epilepsy Drug (Dec. 15, 2010) (“The FDA will continue to pursue criminal resolutions when pharmaceutical companies undermine the drug approval process by promoting drugs for uses not approved by the FDA as safe and effective.”). The government also has stated its intention to prosecute individual manufacturer executives and employees: “It’s clear we’re not getting the job done with large, monetary settlements. . . . Unless the government shows more resolve to criminally charge individuals at all levels in the company, we cannot expect to make progress in deterring off-label promotion.” Anna Edney, *Drugmaker CEOs May Be Targets for U.S. FDA in Off-Label Cases, Lawyer Says*, Bloomberg, Oct. 14, 2010 (quoting FDA Deputy Chief Counsel for Litigation).

69. In particular, in recent years, the government has prosecuted manufacturers that spoke to physicians in settings where, in the government’s view, there was insufficient likelihood of on-label use. *See* Information, *United States v. Eli Lilly & Co.*, No. 09-CR-020 (E.D. Pa., filed Jan. 15, 2009) (alleging, *inter alia*, unlawful promotion of schizophrenia drug Zyprexa in long-term care and other settings where on-label use allegedly would be rare); Information,

United States v. Pharmacia, No. 09-CR-10258 (D. Mass., filed Sept. 9, 2009) (similar allegations regarding promotion of arthritis drug Bextra to physicians who allegedly would rarely prescribe the drug on-label). And in an analogous setting, the FDA has stated that it “may consider a manufacturer’s knowledge of the purposes for which its customers offer and use [certain medical devices] to be evidence that the [device] is intended to be used for such purposes.” FDA, Draft Guidance – Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only, June 1, 2011.

70. In March 2009, the U.S. Attorney’s Office for the District of New Jersey subpoenaed Par, requesting production of documents relating to its past sales and marketing practices in connection with Megace® *ES*.

71. In its ongoing investigation into Par’s past marketing practices, the government has indicated to Par that a manufacturer wishing to speak to healthcare professionals concerning on-label use of a prescription drug in a setting where physicians prescribe the drug off-label must first confirm that there are presently a sufficient number of patients being treated for whom the drug could be prescribed on-label. The government has not provided any guidance to Par regarding what, in the government’s view, would constitute a sufficient number of on-label patients to justify promoting a drug for its on-label uses in a setting where physicians prescribe the drug off-label.

CLAIMS FOR RELIEF

COUNT I

(The FDA’s “Intended Use” Regulations Are Unconstitutional As Applied To Par’s Truthful, Non-Misleading Speech Regarding On-Label Use)

72. Par re-alleges and incorporates herein by reference paragraphs 1 through 71.

73. The First Amendment safeguards Par's truthful and non-misleading speech to healthcare professionals concerning the FDA-approved, on-label use of Megace® *ES* to treat AIDS-related wasting.

74. Based on the government's interpretation of the Act and the FDA's "intended use" regulations, Par's truthful and non-misleading speech to healthcare professionals concerning on-label use would render Megace® *ES* criminally "misbranded," since the drug's "labeling" does not bear "adequate directions" – or any directions – for off-label use to treat wasting in non-AIDS geriatric and cancer patients. 21 U.S.C. § 352(f)(1); *see also* 21 U.S.C. § 333(a).

75. Such a criminal prohibition of speech would violate the First Amendment, as applied to Par's truthful and non-misleading speech to healthcare professionals concerning on-label use in settings where those professionals prescribe Megace® *ES* for off-label uses.

76. The FDA's "intended use" regulations are "contrary to constitutional right" and "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," as applied to Par's truthful and non-misleading speech to healthcare professionals concerning on-label use of Megace® *ES*. 5 U.S.C. § 706(2)(A), (B).

77. Par has no adequate remedy at law.

78. Par therefore seeks entry of a judgment declaring that the government's interpretation of the "intended use" regulations – 21 C.F.R. §§ 201.100 and 201.128 – violate the First Amendment as applied to Par's truthful and non-misleading speech to healthcare professionals concerning on-label use of its approved drug in settings where the drug is prescribed for off-label use, and enjoining defendants from enforcing the regulations to prohibit Par's speech. In the alternative, Par seeks entry of a judgment declaring that truthful and non-

misleading speech about the FDA-approved use of a drug to healthcare professionals, who may prescribe the drug for an approved use but who are more likely to prescribe the drug for an off-label use, does not express an objective intent that the drug should be prescribed for an off-label use under the FDA's regulations.

COUNT II

(The FDA's "Intended Use" Regulations Are Unconstitutional As Applied To Truthful, Non-Misleading Speech Regarding Off-Label Use)

79. Par re-alleges and incorporates herein by reference paragraphs 1 through 78.

80. To the Par's truthful and non-misleading speech is deemed to relate to an off-label use of its drug, the First Amendment nevertheless safeguards that speech.

81. Based on the government's interpretation of the Act and the FDA's "intended use" regulations, Par's truthful and non-misleading speech to healthcare professionals would render Megace® *ES* criminally "misbranded," since the drug's "labeling" does not bear "adequate directions" – or any directions – for off-label use to treat wasting in non-AIDS geriatric and cancer patients. 21 U.S.C. § 352(f)(1).

82. Such a criminal prohibition of speech would violate the First Amendment, as applied to Par's truthful and non-misleading speech to healthcare professionals regarding Megace® *ES*.

83. The FDA's "intended use" regulations are "contrary to constitutional right" and "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," as applied to Par's truthful and non-misleading speech to healthcare professionals. 5 U.S.C. § 706(2)(A), (B).

84. Par has no adequate remedy at law.

85. Par therefore seeks entry of a judgment declaring that the FDA's "intended use" regulations – 21 C.F.R. §§ 201.100 and 201.128 – violate the First Amendment as applied to Par's truthful and non-misleading speech to healthcare professionals regarding what the government deems to be off-label use of an FDA-approved drug, and enjoining defendants from enforcing the regulations to prohibit Par's speech.

COUNT III

(The FDA's Definition Of "Labeling" Is Unconstitutional As Applied To Truthful, Non-Misleading Speech Regarding Off-Label Uses)

86. Par re-alleges and incorporates herein by reference paragraphs 1 through 85.

87. To the extent Par's truthful and non-misleading speech is deemed to relate to an off-label use of its drug, the First Amendment nevertheless safeguards that speech.

88. Based on the government's interpretation of the Act and the FDA's definition of "labeling," Par's truthful and non-misleading written speech to healthcare professionals about the FDA-approved use of its drug, if deemed to relate to an off-label use, would render Megace® *ES* a "new drug" that cannot lawfully be sold, since Par would have "prescribed, recommended, or suggested" an unapproved use in the drug's "labeling," as the FDA has defined that term in 21 C.F.R. § 201.1(l)(2). *See* 21 U.S.C. §§ 321(p), 331(d), 355(a).

89. The Act prohibits a manufacturer of an FDA-approved drug from introducing the drug into interstate commerce if the manufacturer has "prescribed, recommended, or suggested" an unapproved, off-label use for the drug in its "labeling." 21 U.S.C. §§ 321(p), 331(d), 355(a). The Act defines "labeling" to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m).

90. The FDA's regulation defines "labeling" more broadly to encompass all tangible materials distributed by a manufacturer containing manufacturer-supplied drug information. 21 C.F.R. § 201.1(1)(2). Par's communications with healthcare professionals regarding on-label use of Megace® *ES* could fall within the FDA's expansive definition of labeling, even though those communications do not constitute labeling under 21 U.S.C. § 321(m).

91. Such a criminal prohibition of speech would violate the First Amendment, as applied to Par's truthful and non-misleading speech to healthcare professionals regarding Megace® *ES*.

92. The FDA's "labeling" regulation is "contrary to constitutional right" and "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," as applied to Par's truthful and non-misleading speech to healthcare professionals. 5 U.S.C. § 706(2)(A), (B).

93. Par has no adequate remedy at law.

94. Par therefore seeks entry of a judgment declaring that the FDA's definition of "labeling" in 21 C.F.R. § 201.1(1)(2) violates the First Amendment as applied to a manufacturer's truthful and non-misleading speech to healthcare professionals regarding off-label use of an FDA-approved drug, and enjoining defendants from enforcing the regulation to prohibit Par's speech.

COUNT IV

(The FDA's "Intended Use" Regulations Are Invalid As A Matter Of Statutory Interpretation)

95. Par re-alleges and incorporates herein by reference paragraphs 1 through 94.

96. The Act expressly exempts prescription drugs from the requirement that a drug's "labeling" must bear "adequate directions for use," 21 U.S.C. § 352(f)(1), as long as the drug's

“label” bears, among other information, “the directions for use and cautionary statements, if any, *contained in such prescription.*” 21 U.S.C. § 353(b)(2) (emphasis added). The Act further provides that a prescription drug is misbranded “if at any time prior to dispensing the label . . . fails to bear, at a minimum, the symbol ‘Rx only.’” 21 U.S.C. § 353(b)(4).

97. The FDA has promulgated a regulation providing that the Section 353(b)(2) exemption applies only if a prescription drug’s “labeling” bears “adequate information for its use.” 21 C.F.R. § 201.100(c)(1).

98. Par therefore seeks entry of a judgment declaring that 21 C.F.R. § 201.100(c)(1) is invalid as a matter of statutory interpretation, and “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law,” 5 U.S.C. § 706(2)(A), because it conflicts with 21 U.S.C. § 353(b)(2)’s express exemption of prescription drugs from the “adequate directions for use” requirement under 21 U.S.C. § 352(f)(1), and enjoining defendants from enforcing the regulation to prohibit Par’s speech.

COUNT V

(The FDA’s Definition Of “Labeling” Is Invalid As A Matter Of Statutory Interpretation)

99. Par re-alleges and incorporates herein by reference paragraphs 1 through 98.

100. The Act defines a drug’s “labeling” to mean all “written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” 21 U.S.C. §§ 321(m), (k).

101. The FDA has defined “labeling” more broadly to encompass all tangible materials distributed by a manufacturer containing manufacturer-supplied drug information. 21 C.F.R. § 201.1(l)(2).

102. Par therefore seeks entry of a judgment declaring that 21 C.F.R. § 201.1(l)(2) is invalid as a matter of statutory interpretation, and “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law,” 5 U.S.C. § 706(2)(A), because it conflicts with 21 U.S.C. §§ 321(m)’s definition of a drug’s “labeling,” and enjoining defendants from enforcing the regulation to prohibit Par’s speech.

PRAYER FOR RELIEF

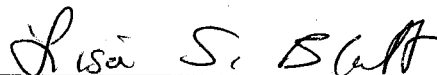
WHEREFORE, Plaintiff Par Pharmaceutical, Inc. requests that the Court:

- A. Declare that the FDA’s “intended use” regulations – 21 C.F.R. § 201.100(c)(1) and 21 C.F.R. § 201.128 – violate the First Amendment as applied to prohibit Par’s truthful and non-misleading speech to healthcare professionals concerning the FDA-approved, on-label use of its FDA-approved prescription drug;
- B. Declare that a manufacturer cannot be deemed to intend an off-label use merely because the manufacturer sells a drug with knowledge that physicians will prescribe the drug for an off-label use, as set forth in 21 C.F.R. § 201.128;
- C. To the extent that Par’s speech about the FDA-approved, on-label use of its drug is deemed to relate to an off-label use, declare that the FDA’s “intended use” regulations – 21 C.F.R. § 201.100(c)(1) and 21 C.F.R. § 201.128 – violate the First Amendment as applied to prohibit Par’s truthful and non-misleading speech to healthcare professionals concerning off-label use of its FDA-approved prescription drug;
- D. To the extent that Par’s speech about the FDA-approved, on-label use of its drug is deemed to relate to an off-label use, declare that the FDA’s definition of “labeling,” 21 C.F.R. § 201.1(l)(2), violates the First Amendment as applied to

prohibit Par's truthful and non-misleading speech to healthcare professionals concerning off-label use of its FDA-approved prescription drug;

- E. Declare that 21 C.F.R. § 201.100(c)(1) is invalid as a matter of statutory interpretation because it is contrary to 21 U.S.C. § 353(b)(2);
- F. Declare that the FDA's definition of "labeling," 21 C.F.R. § 201.1(l)(2), is invalid as a matter of statutory interpretation because it is contrary to 21 U.S.C. § 321(m);
- G. Enter a preliminary injunction preventing defendants from taking any action during the pendency of this litigation to enforce the FDA's unconstitutional and invalid regulations against Par based on Par's truthful and non-misleading speech to healthcare professionals, and thus to protect Par's First Amendment rights from ongoing harm while the litigation is pending;
- H. Enter a permanent injunction preventing defendants from taking any action to enforce the FDA's unconstitutional and invalid regulations against Par based on Par's truthful and non-misleading speech to healthcare professionals;
- I. For such costs and reasonable attorneys' fees to which it might be entitled by law; and
- J. For such other relief as this Court may deem just and appropriate.

Respectfully Submitted,



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Dated: October 14, 2011