UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PAR PHARMACEUTICAL, INC.,	
Plaintiff,	
v.	**Case No. _____**
UNITED STATES OF AMERICA et al.,	**Oral Argument Requested**
Defendants.	

PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Plaintiff Par Pharmaceutical, Inc. ("Par") hereby moves for a preliminary injunction as set forth below and for the reasons set forth in the accompanying Memorandum of Law in Support of Plaintiff's Motion for Preliminary Injunction ("Memorandum"). *See* Fed. R. Civ. P. 65(a). Par seeks to enjoin the government from applying provisions of the Federal Food, Drug and Cosmetic Act (the "Act"), 21 U.S.C. §§ 331(a), 331(d), 352(f)(1), 355(a), and regulations of the U.S. Food & Drug Administration ("FDA") interpreting the Act, 21 C.F.R. §§ 201.100, 201.128, and 202.1(*l*)(2), to criminalize Par's truthful and non-misleading speech to healthcare professionals about the FDA-approved, on-label use of Par's FDA-approved prescription drug, Megace® *ES*. The government's broad interpretation of these statutes and regulations as criminalizing Par's truthful and non-misleading speech is contrary to both the First Amendment and the Act.

In particular, Par's action seeks a declaration that (A) 21 C.F.R. §§ 201.100 and 201.128 are unconstitutional as applied to criminalize Par's truthful and non-misleading speech, or that those regulations are contrary to 21 U.S.C. § 352(f)(1) or 21 U.S.C. § 353(b)(2); and (B) 21 C.F.R. § 202.1(*l*)(2) is unconstitutional as applied to criminalize Par's truthful and non-

misleading speech, or that the regulation is contrary to 21 U.S.C. § 321(m). Par seeks a preliminary injunction against the enforcement of these provisions, which are currently causing irreparable harm to Par's First Amendment rights by chilling Par's protected speech.

The sworn declarations of John Ameres and Paul Campanelli, attached hereto as Exhibits A and B, respectively, attest to the truth of Par's allegations.

Par is entitled to a preliminary injunction because (1) Par "is likely to succeed on the merits" in proving that the government's interpretation of the Act and the FDA's regulations is contrary to the First Amendment and the Act; (2) Par is suffering and is likely to continue "to suffer irreparable harm" to its First Amendment rights "in the absence of preliminary relief"; (3) "the balance of equities tips in [Par's] favor"; and (4) "an injunction is in the public interest." *Mills v. District of Columbia*, 571 F.3d 1304, 1308 (D.C. Cir. 2009). Par has no adequate remedy at law.

Pursuant to Local Rule of Civil Procedure 7(m), Par has conferred with legal counsel for the defendants regarding this motion. The defendants object to this motion.

Because the preliminary injunction Par requests would present no monetary risk to the defendants, Par requests that bond be set at $1. *See* Fed. R. Civ. P. 65(c).

For the reasons set forth in the accompanying Memorandum and Complaint, Par prays that the Court grant this motion and preliminarily enjoin the defendants from enforcing the challenged provisions as applied until a final hearing on the merits.

Par requests oral argument on this motion because of the complex and significant legal arguments involved in this case.

Dated: October 14, 2011

Respectfully submitted,

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MEMORANDUM OF LAW IN SUPPORT OF PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

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October 14, 2011

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES AND REGULATIONS

OTHER AUTHORITIES

Par Pharmaceutical, Inc. ("Par") respectfully seeks a preliminary injunction preventing the federal government from enforcing certain regulations of the U.S. Food & Drug Administration ("FDA") that purport to criminalize Par's truthful and non-misleading speech to healthcare professionals. The speech at issue concerns the FDA-approved use of Par's FDA-approved prescription drug. As applied in the circumstances of this case, the FDA regulations violate the First Amendment and the Federal Food, Drug, and Cosmetic Act (the "Act").

INTRODUCTION

Par manufactures Megace® *ES*, a prescription drug that is FDA-approved for the treatment of anorexia, cachexia, or an unexplained significant weight loss in patients diagnosed with AIDS, collectively referred to as "AIDS-related wasting." Par seeks a declaratory judgment that it may speak truthfully about this FDA-approved (or "on-label") use of Megace® *ES* to physicians who could prescribe the drug for that use, even if those physicians are more likely to prescribe Megace® *ES* for uses that the FDA has not approved ("off-label uses"). It should be obvious that both the Act and the First Amendment give Par the right to speak about Megace® *ES* using an expressly on-label message to physicians who could use the drug for its on-label use. After all, that use is FDA-approved; Par's speech is truthful; and the government has no legitimate interest in criminalizing such speech. The FDA's regulations, however, impose extraordinarily broad and vague restrictions on manufacturer speech and threaten prosecution even for truthful, on-label speech that the government deems to intend or promote an off-label use. As a result, Par is deeply chilled from communicating to physicians and other healthcare professionals its truthful and valuable message about Megace® *ES*'s on-label use.

Par believes that such truthful and expressly on-label speech comports with all applicable statutes and regulations. If, however, the FDA's regulations prohibit this speech – as the

government appears to believe – then those regulations violate the First Amendment and the Act itself. Par's speech is truthful and relates to lawful activity, *i.e.*, the on-label use of Par's FDA-approved prescription drug. The government may believe that Par's marketing of the drug for its FDA-approved use could lead doctors to increase their prescription of Megace® *ES* for off-label uses. But off-label use of an FDA-approved prescription drug is entirely lawful and often necessary to appropriate patient care. Many off-label uses are widely medically accepted and reimbursed by the federal government under healthcare programs administered by the U.S. Department of Health and Human Services ("HHS"), of which the FDA is a part. 21 U.S.C. § 393(a).

Common sense dictates that the government cannot justify censoring a broad swath of truthful and valuable speech regarding lawful activity out of a desire to prevent other lawful activity. And it is absurd to think that the government may imprison a person for engaging in truthful speech about a lawful activity that the government itself subsidizes. Not surprisingly, nothing in the Act gives the FDA authority to impose such a sweeping and bizarre prohibition, and the First Amendment would preclude such a prohibition even if Congress or the FDA did purport to impose it.

BACKGROUND

A. The Federal Food, Drug, And Cosmetic Act

The Act prohibits the introduction or delivery for introduction into interstate commerce of any "new drug" that has not been approved by the FDA. 21 U.S.C. §§ 331(d), 355(a). To obtain FDA approval for a new drug, the manufacturer 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 for the uses

"prescribed, recommended, or suggested" in the drug's proposed labeling, and ensures that the proposed labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d).

If the FDA approves a new drug application, the approval extends to the uses "prescribed, recommended, or suggested" in the drug's FDA-approved "labeling." 21 U.S.C. § 321(p). 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," 21 U.S.C. § 321(p), which the manufacturer cannot lawfully sell absent FDA approval for the new use. 21 U.S.C. § 355(a). The Act defines "labeling" to mean "all labels and other 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). The Act defines "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). Violation of the Act's "new drug" provision is a criminal offense subject to imprisonment for up to three years as well as substantial fines and penalties. 21 U.S.C. §§ 331(a), 333(a), 355(a). Such a violation also may have severe collateral consequences, including, in the government's view, potential exclusion from participation in federal healthcare programs, such as Medicare, Medicaid, and programs for the military and veterans. 42 U.S.C. § 1320a-7.

The Act also prohibits the introduction or delivery for introduction into interstate commerce of an FDA-approved drug that is "misbranded." 21 U.S.C. §§ 331(a), 352. Misbranding, too, is a criminal offense subject to imprisonment and substantial fines and penalties, 21 U.S.C. §§ 331(a), 333(a), as well as potential exclusion from participation in the

Medicare and Medicaid programs. 42 U.S.C. § 1320a-7. The Act in Section 352 sets forth the circumstances in which a drug "shall be deemed to be misbranded." 21 U.S.C. § 352. As relevant here, a drug generally is misbranded "[u]nless its labeling bears . . . adequate directions for use." 21 U.S.C. § 352(f)(1). Section 352 authorizes the FDA to promulgate regulations exempting certain drugs from the requirement of "adequate directions for use" where the government finds the requirement "is not necessary for the protection of the public health." *Id.*

Section 353 of the Act separately exempts prescription drugs from the "adequate directions" requirement, and thus Section 352(f)(1) applies only to drugs that are dispensed directly to consumers without a prescription, *i.e.*, over-the-counter drugs. Section 353(b)(2) states in plain terms that "any drug dispensed by filling or refilling a written or oral prescription of a [licensed practitioner] shall be exempt" from Section 352(f)(1) of the Act. 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." *Id.*

Section 353(b)(4) further provides that a prescription drug "shall be deemed to be misbranded if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol 'Rx only.'" 21 U.S.C. § 353(b)(4)(A). Accordingly, as long as a prescription drug is dispensed with a label on the container bearing the symbol "Rx only" and the prescribing physician's directions to his or her patient, the Act does not require the manufacturer to provide additional directions for use by consumers.

B. Off-Label Use Of Approved Drugs Is Lawful, Widespread, And Often Medically Accepted And Subsidized By The Federal Government

Par wishes to speak to physicians about the FDA-approved, on-label use of its approved prescription drug in settings where physicians may prescribe the drug for both approved and

unapproved uses. There is nothing nefarious about a physician's prescription of an FDA-approved drug for an off-label use. Federal law does not regulate or restrict healthcare professionals from prescribing or administering any FDA-approved drug to treat any condition or disease, even if the FDA has not approved the use. "A physician may prescribe a legal drug to serve any purpose that he or she deems appropriate, regardless of whether the drug has been approved for that use by the FDA." *Wash. Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000). The "prescription of drugs for unapproved uses is commonplace in modern medical practice and ubiquitous in certain specialties." *Id.* In 2001, approximately 150 million prescriptions – 21% of all prescriptions – were written off-label. David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 Archives of Internal Med. 1021, 1021 (2006). Off-label use is thus an integral part of the healthcare system in the United States.

Indeed, in some specialties, such as oncology, the majority of patients receive off-label care. U.S. Gov't Accountability Office, GAO/T-HEHS-96-212, Prescription Drug: Implications of Drug Labeling and Off-Label Use 3 (1996). The minimum standard of care can even require doctors to prescribe drugs for off-label use where the FDA has not approved any drug to treat certain diseases or conditions. *See, e.g.*, 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") ("[O]ff-label uses or treatment regimens . . . may even constitute a medically recognized standard of care.").

Congress has recognized the importance and legitimacy of off-label uses of approved prescription drugs by authorizing the Medicare and Medicaid programs to reimburse States, healthcare professionals, hospitals, and patients for any off-label use that is "medically

accepted." 42 U.S.C. § 1396r-8(k)(6). Congress defined the phrase "medically accepted" to mean that either the FDA has approved the drug for the prescribed use, or, absent FDA approval, that the use is cited in one or more of three specified drug compendia: the American Hospital Formulary Service Drug Information, United States Pharmacopeia-Drug Information, or the DrugDex® Information System. *Id.*

The DrugDex® compendium, for instance, was first developed over 30 years ago, and "contains comprehensive evidence-based drug information including detailed information on dosing, pharmacokinetics, adverse effects, FDA-approved and off-label uses, comparative efficacy, and other critical information on the appropriate use of drugs." Letter from Thomson Microdex to CMS re: Formal Request for Change to Part B Compendia List – DrugDex®, at 2 (Feb. 13, 2008), *available at* http://ww.cms.hhs.gov/CoverageGenInfo/downloads/covdoc16.pdf. The drug information in DrugDex® is "referenced to the underlying studies and intended to provide the healthcare professional with both broad and in-depth review of all aspects of prescription drugs." *Id.* Thompson Microdex, the publisher of DrugDex®, utilizes editorial policies and procedures to ensure that the content of the compendium "remains unbiased and supports appropriate drug therapy." *Id.* DrugDex® cites megestrol acetate, the FDA-approved prescription drug at issue in this case, as medically acceptable for off-label use to treat adult patients suffering from wasting associated with cancer. *See infra* p. 10-11.

C. The FDA's Regulations Prohibit Manufacturers' Truthful And Non-Misleading Speech to Healthcare Professionals

Despite the legal and widespread medical acceptance of off-label uses, FDA regulations criminalize a manufacturer's speech whenever it expresses what the government calls an "objective intent" that an FDA-approved prescription drug should be used off-label. When such "objective intent" is expressed, the drug is criminally "misbranded" because, in terms of the

FDA's regulations, the drug's labeling does not bear adequate directions for the off-label use. 21 C.F.R. §§ 201.100(c)(1), 201.128. Because the manufacturer cannot alter the drug's labeling to provide directions for an off-label use without rendering the drug an unapproved "new drug" that cannot lawfully be sold, the regulations create a Catch-22 scenario in which the manufacturer can neither speak nor remain silent.

Not surprisingly, this perverse theory of criminality is not set forth in the Act. As described above, the Act *exempts* prescription drugs from the requirement that a drug's "labeling" must bear "adequate directions for use," as long as the drug's label affixed to the drug's container bears "the symbol 'Rx only'" and repeats the physician's "directions for use and cautionary statements, if any, contained in such prescription." 21 U.S.C. §§ 353(b)(2), (b)(4). The FDA's regulation nonetheless states that unless a prescription drug's labeling provides "adequate information for its use" by a physician, the labeling must contain "adequate directions for use" by a consumer. 21 C.F.R. § 201.100(c)(1); *see also* 21 C.F.R. § 201.5 (defining "adequate directions for use" to mean "directions under which the layman can use a drug safely and for the purposes for which it is intended"). The latter requirement, of course, is impossible to satisfy since a prescription drug by definition cannot be used safely by consumers without a physician's prescription. *See* 21 U.S.C. § 353(b)(1). In other words, by administratively substituting the word "information" for the word "directions," the FDA replaced the Act's express exemption of prescription drugs with a regulation imposing an obligation to supply adequate directions.

The regulatory requirement to supply adequate directions for an off-label use of an approved prescription drug is triggered when a manufacturer engages in what the regulations deem to be speech that expresses an objective intent that the drug be used off-label. In

particular, a drug is misbranded if its labeling does not bear "adequate information" under which medical professionals "can use the drug safely and for the purposes *for which it is intended, including all purposes for which [the drug] is advertised or represented.*" 21 C.F.R. § 201.100(c)(1) (emphasis added). In short, the FDA's regulations criminalize speech by rendering a drug misbranded if the manufacturer advertises or represents the drug for an off-label use.

The FDA's regulation, entitled "meaning of intended uses," provides that the phrase "intended uses" refers to a manufacturer's "objective intent," as demonstrated by the manufacturer's "expressions," including in "labeling claims, advertising matter, or oral or written statements." 21 C.F.R. § 201.128. A 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.* And, with regard to downstream sellers of a drug, the regulation provides that if a manufacturer merely "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.*

Thus, the government's byzantine regulatory scheme places pharmaceutical manufacturers in an impossible situation. In the government's view, a manufacturer's speech concerning exclusively the FDA-approved, *on-label* uses of an FDA-approved prescription drug may render the drug criminally misbranded if the manufacturer is deemed to be advertising or representing an off-label use. If a manufacturer speaks about the on-label use of its drug in a setting where the manufacturer knows that physicians prescribe the drug off-label, the

government interprets the FDA's "intended use" regulations to deem the manufacturer to be expressing an "objective intent" that physicians prescribe the drug off-label. The drug is then misbranded because its labeling does not provide physicians with "adequate information" for that off-label use. 21 C.F.R. § 201.100(c)(1). And, as discussed above, the manufacturer cannot avoid criminal liability by altering the drug's "labeling" to provide adequate information for the off-label use, because to do so would violate the Act's criminal prohibition against distributing a "new drug" with labeling that prescribes, recommends, or suggests an unapproved use. 21 U.S.C. §§ 321(p), 333(a), 355(a).

Significantly, the regulations do not specify the circumstances in which a manufacturer's on-label speech (*i.e.*, expressions limited to the FDA-approved uses of a drug) could be criminal based on the government's theory that the manufacturer nonetheless is expressing an "objective intent" that physicians prescribe the drug off-label. Thus, manufacturers, especially those whose drugs are commonly prescribed off-label, have no way of knowing when sales representatives are permitted to speak about the medical use indicated on the FDA-approved labeling to physicians who prescribe the drug off-label.

No regulation provides that a manufacturer must limit its communications to physicians who prescribe a drug exclusively (or even primarily) for its FDA-approved uses. And the regulations shed no light on what percentage of on-label prescriptions by a given doctor would suffice to permit the manufacturer to speak – without fear of prosecution – to physicians about the FDA-approved use of a life-saving product. Nor would any ratio requirement be practical. Doctors lawfully and commonly prescribe approved drugs off-label; the government, through its reimbursement policies, often encourages off-label prescriptions; and many physicians and facilities treat patients where it is medically appropriate (and even medically necessary) to use

drugs for both their approved and unapproved uses. Thus, the regulatory regime gives prosecutors unfettered discretion to charge that a manufacturer's speech expresses an "objective intent" that a drug be used off-label, based solely on the notion that the manufacturer knows that doctors prescribe the drug for off-label uses. This is untenable, as it exposes manufacturers to substantial criminal liability without notice or clear guidance as to which actions are prohibited.

D. Par Manufactures and Markets Megace® *ES*

Par produces and markets, among other products, the prescription drug Megace® *ES* (megestrol acetate oral suspension). Compl. ¶ 39. In July 2005, the FDA approved Megace® *ES* to treat 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." *Id.* 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. *Id.* Megace® *ES* provides important health benefits for patients suffering from AIDS-related wasting and can improve their appetite, caloric intake, body weight, and sense of well-being. *Id.* ¶¶ 41-42.

Physicians routinely prescribe Megace® *ES* for its on-label use to treat AIDS-related wasting. *Id.* ¶ 43. Physicians, in the exercise of their independent medical judgment, prescribe the drug even more frequently off-label to treat, *inter alia*, wasting in other patient populations, including geriatric and cancer patients who do not have AIDS. *Id.* Even before Par developed Megace® *ES*, physicians for decades commonly have prescribed earlier formulations of megestrol acetate for these off-label uses, including the drug's original formula that is branded as Megace® OS. *Id.* Megestrol acetate is widely viewed as one of the most effective treatments for wasting in non-AIDS geriatric and cancer patients. *Id.* ¶ 44. The DrugDex® compendium cites

megestrol acetate for off-label use to treat cancer-related wasting. DrugDex® Information System, DRUGDEX-EV 2345, at 21-22 (updated Mar. 2010). Off-label use of megestrol acetate to treat wasting in non-AIDS geriatric and cancer patients is "medically accepted," 42 U.S.C. § 1396r-8(k)(6), such that those uses are reimbursable under the Medicare and Medicaid programs. Compl. ¶¶ 47-48. Government websites also have commented on the appropriate medical off-label use of megestrol acetate to treat geriatric patients, including with elderly veterans receiving treatment for wasting at facilities operated by the U.S. Department of Veterans Affairs. *E.g.*, Nat'l Institutes of Health, U.S. Nat'l Library of Medicine, http://www.ncbi.nlm.nih.gov/pubmed/19390752; http://www.ncbi.nlm.nih.gov/pubmed/11193233; http://www.ncbi.nlm.nih.gov/pubmed/17722275.

E. Par Wishes To Engage In On-Label Speech To Physicians Who Reasonably May Prescribe Megace® *ES* For Its FDA-Approved Use

Par currently communicates with some physicians regarding the FDA-approved, on-label use of Megace® *ES* to treat AIDS-related wasting. Ex. A, Decl. of John Ameres ¶ 11 ("Ameres Decl."). As relevant here, Par engages in such speech not only in AIDS clinics, but also in other settings where physicians could encounter AIDS patients suffering from wasting, even though those physicians also may prescribe Megace® *ES* off-label. *Id.* For instance, Par speaks about on-label use of Megace® *ES* in long-term care facilities and oncology practices where physicians reasonably may encounter AIDS patients, and thus prescribe the drug on-label even though those physicians prescribe the drug off-label to treat wasting in non-AIDS geriatric and cancer patients. *Id.* Par markets Megace® *ES* in those settings 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. *Id.* ¶ 12. Par nonetheless is under a current fear of prosecution for engaging in this truthful speech regarding the FDA-approved, on-label use of Megace® *ES*. *Id.* ¶ 13.

But for the fear of prosecution, Par would engage in truthful speech about the on-label use of Megace® *ES* to a broader physician audience. *Id.* Par currently limits its marketing of Megace® *ES* to physicians who previously have prescribed earlier formulations of megestrol acetate oral suspension, based on prescriber data that Par purchases from a third-party vendor. *Id.* ¶¶ 11, 13. Also, 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®. *Id.* ¶ 13. Par also does not speak 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®. *Id.* But for the fear of prosecution, Par would speak about Megace® *ES* to those physicians in the long-term care and oncology settings where they may encounter AIDS patients. *Id.* In addition, but for the fear of prosecution, Par would speak to other physicians in long-term care and oncology settings without regard to those physicians' past prescribing practices. *Id.* As outlined below, Par wishes – without fear of prosecution – to engage in truthful and non-misleading speech in these additional settings regarding the FDA-approved, on-label use of Megace® *ES*.

Specifically, Par would inform healthcare professionals of the FDA-approved indication of Megace® *ES* to treat AIDS-related wasting. *Id.* ¶¶ 10-11. Par also would explain the health benefits of Megace® *ES* for patients suffering from AIDS-related wasting, including the potential to increase those patients' appetite, body weight, caloric intake, and sense of well-being. *Id.* ¶ 10. Further, Par would describe the drug's dosage, low viscosity, and bioavailability in the unfed condition – a common condition in patients suffering from wasting. *Id.* All of these

statements are within the FDA-approved labeling for Megace® *ES*. *See* Megace® *ES* Package Insert, http://www.megacees.com/PDF/Megace_ES_Portrait_PI.pdf.

Par also would provide healthcare professionals with other on-label product information about Megace® *ES*. Par would describe the on-label comparison between Megace® *ES* and Megace® OS, including the substantial difference in dosage between the two drugs. Ex. A, Ameres Decl. ¶ 10. Par also would discuss on-label use of Megace® *ES* in particular patient populations, including the elderly, as described in the drug's FDA-approved labeling. *Id.* Under the heading "Geriatric Use," the drug's labeling 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." Megace® *ES* Package Insert. The labeling further explains that clinical studies of megestrol acetate oral suspension to treat AIDS-related wasting 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.* Par also would provide physicians with on-label safety-related information regarding Megace® *ES*, including contraindications, warnings and precautions, adverse reactions, and drug interactions. Ex. A, Ameres Decl. ¶ 10.

Par has reviewed ample medical literature and other materials that support the marketing of its drug to doctors who do not treat primarily AIDS patients. Specifically, Par evaluated the incidence of AIDS in the long-term care and oncology settings, and determined – based on internal and external research and government data – that healthcare professionals in those settings reasonably may encounter AIDS patients. Compl. ¶¶ 50-56. In particular, data show a rising incidence of AIDS in long-term care facilities, with several key factors contributing to this

trend. For example, patients infected with HIV and AIDS are living longer and encountering more complications, including complex health problems usually associated with old age; also, the HIV infection rate has increased among individuals over 50 years of age. Centers for Disease Control and Prevention, *CDC HIV/AIDS Facts: HIV/AIDS Among Persons Aged 50 and Older*, Feb. 2008; *see also* materials cited at Compl. ¶¶ 52-54. Oncologists also are likely to encounter AIDS patients suffering from AIDS-related cancers, which encompass dozens of types of cancer. Nat'l Institutes of Health, Nat'l Cancer Institute, *AIDS-Related Cancers*, http://nci.nih.gov/cancertopics/typs/AIDS; *see also* materials cited at Compl. ¶ 56. Thus, short of limiting its marketing efforts to doctors who treat *exclusively* AIDS patients, long-term care and oncology are logical and appropriate settings to speak to physicians who reasonably may encounter AIDS patients and prescribe Megace® *ES* for its on-label use.

F. The FDA's Regulations Have A Chilling Effect On Par's Speech

Par fears that its truthful and non-misleading speech to healthcare professionals regarding the FDA-approved, on-label use of Megace® *ES* to treat AIDS-related wasting may lead to criminal prosecution and civil and administrative penalties. Ex. A, Ameres Decl. ¶ 13.

The FDA's regulations chill Par's on-label speech regarding Megace® *ES* because that speech could, in the government's view, render the drug criminally "misbranded." 21 U.S.C. §§ 331(a), 333(a), 352. Par cannot provide truthful information about the FDA-approved, on-label use of Megace® *ES* in settings where physicians prescribe the drug for off-label uses without exposing itself to criminal prosecution. The government views such expression as rendering the drug criminally misbranded under the theory that the regulatory regime deems on-label speech in such settings as expressing an "objective intent" that the drug be prescribed off-label. 21 C.F.R. §§ 201.100(c)(1), 201.128; *see also* 21 U.S.C. §§ 331(a), 333(a), 352.

Based on its truthful, written speech to healthcare professionals, Par also fears prosecution for unlawfully selling a "new drug" with "labeling" that prescribes, recommends, or suggests an unapproved use. 21 U.S.C. 331(d), 333(a), 355(a). Par does not propose to alter any "written, printed, or graphic matter" found on Megace® *ES* itself, its "containers or wrappers," or "accompanying" the drug in interstate commerce. 21 U.S.C. § 321(m), (k). Par's speech thus would not constitute "labeling" that would trigger the Act's new-drug provision. *See Kordel v. United States*, 335 U.S. 345, 348-50 (1948). And Par's speech is within the FDA-approved labeling for Megace® *ES*. Nonetheless, to the extent the regulations deem Par's written speech to relate to an off-label use based on the setting in which Par speaks, the written speech could fall within the FDA's expansive definition of "labeling" in the relevant regulation. 21 C.F.R. § 202.1(*l*)(2).

In connection with its ongoing investigation into Par's past marketing efforts, the government advised Par that if a manufacturer wishes to speak to healthcare professionals concerning on-label use of an FDA-approved prescription drug in a setting where off-label use also may occur, it first must confirm that there presently are a sufficient number of patients being treated for whom the drug could be prescribed on-label. Compl. ¶ 71. The government, however, has not provided any guidance to Par or other manufacturers regarding what, in the government's view, would constitute a sufficient number of on-label patients to permit Par to market its drug for its on-label uses in settings where off-label use is expected to occur. *Id.* Par is thus faced with the threat of criminal prosecution if it speaks to physicians about the FDA-approved, on-label use of its FDA-approved prescription drug because those physicians work in settings that treat patients who benefit medically from the drug's unapproved uses.

JURISDICTION

The Declaratory Judgment Act authorizes a district court to issue declaratory relief in "a case of actual controversy within its jurisdiction." 28 U.S.C. § 2201(a). Par raises federal questions giving rise to jurisdiction under 28 U.S.C. § 1331. And the dispute here is an "actual controversy," in that it is "definite and concrete, touching the legal relations of parties having adverse legal interests," as well as "real and substantial," "admitting of specific relief through a decree of a conclusive character." *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 239-41 (1937).

"[W]here threatened action by government is concerned," neither Article III nor the Declaratory Judgment Act requires a party to "expose himself to liability before bringing suit to challenge the basis for that threat – for example, the constitutionality of a law threatened to be enforced." *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 128-29 (2007). That is particularly true where, as here, a party seeks declaratory relief to avoid a chill on the exercise of its First Amendment speech rights. *See Seegars v. Gonzales*, 396 F.3d 1248, 1252-54 (D.C. Cir. 2005). Such a First Amendment challenge is ripe if (1) the challenged law "arguably chills" the plaintiff's speech; and (2) there is a "credible threat of prosecution," meaning that the plaintiff's "intended behavior is covered by the statute and the law is generally enforced." *Chamber of Commerce v. FEC*, 69 F.3d 600, 603 (D.C. Cir. 1995); *see also Seegars*, 396 F.3d at 1252 (same); *Babbitt v. United Farm Workers Nat'l Union*, 442 U.S. 289, 302 (1979) (a threat is "credible" unless the government has "disavowed any intention" of prosecuting and fear is "imaginary or wholly speculative"). That standard is easily satisfied here.

The FDA's "intended use" and "labeling" regulations so narrowly circumscribe a pharmaceutical manufacturer's expression that they expose Par to the threat of criminal and civil penalties based on its truthful and non-misleading speech to healthcare professionals regarding

the FDA-approved, on-label use of Megace® *ES* to treat AIDS-related wasting. Rather than risk prosecution, Par has refrained from speaking in many settings and to various audiences, including physicians who previously have prescribed appetite stimulants other than megestrol acetate oral suspension. Ex. A, Ameres Decl. ¶¶ 11-13. The harm thus is largely "one of self-censorship[,] a harm that can be realized even without an actual prosecution." *Virginia v. Am. Booksellers Ass'n*, 484 U.S. 383, 393 (1988). Accordingly, the Court should not be "troubled by the pre-enforcement nature of this suit." *Id.* This declaratory judgment action is a proper vehicle to vindicate Par's rights.

Second, the threat to Par of being prosecuted for speaking is real. The FDA regulations at issue are much more than "generally enforced." *Chamber of Commerce*, 69 F.3d at 603. The Department of Justice has aggressively prosecuted pharmaceutical manufacturers for alleged "off-label promotion." U.S. Accountability Office, GAO-08-835, Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses 2-3, 26-27 (2008). In recent months, the Justice Department also has stated unequivocally its intention to continue this aggressive prosecution of manufacturers, and also to prosecute individual manufacturer executives and employees. Press Release, U.S. Dep't of Justice, Novartis Pharmaceuticals Corporation to Pay $422.5 Million for Off-Label Drug Marketing (Sept. 30, 2010); Anna Edney, *Drugmaker CEOs May Be Targets for U.S. FDA in Off-Label Cases, Lawyer Says*, Bloomberg, Oct. 14, 2010. 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.

Further substantiating the threat, 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*. Compl. ¶ 70.

ARGUMENT

To obtain a preliminary injunction, a party must show that (1) it is likely to succeed on the merits; (2) it is likely to suffer irreparable harm in the absence of preliminary relief; (3) the balance of equities tips in its favor; and (4) the injunction is in the public interest. *See, e.g.*, *Gordon v. Holder*, 632 F.3d 722, 724 (D.C. Cir. 2011). Par satisfies each of these factors.

I. The Preliminary-Injunction Factors Of Irreparable Harm, Balance Of Equities, And Public Interest Weigh Heavily In Support Of Par's Request For Relief

Without this Court's intervention, the government's intrusion on Par's speech rights will cause immediate irreparable harm to Par. The "loss of constitutional freedoms, 'for even minimal periods of time, unquestionably constitutes irreparable injury.'" *Mills v. District of Columbia*, 571 F.3d 1304, 1312 (D.C. Cir. 2009) (quoting *Elrod v. Burns*, 427 U.S. 347, 373 (1976) (plurality)). Irreparable harm occurs whenever "First Amendment interests are either threatened or in fact being impaired at the time relief is sought." *Nat'l Treas. Employees Union v. United States*, 927 F.2d 1253, 1254-55 (D.C. Cir. 1991) (quoting *Elrod*, 427 U.S. at 373).

Here, the threat of enforcement of the FDA's regulations impedes and chills Par's ability to speak truthfully to healthcare professionals about the FDA-approved, on-label use of Megace® *ES*. Par currently engages in speech – marketing Megace® *ES* to physicians who may prescribe the drug for both on-label and off-label uses – that the government has indicated may constitute a crime. Compl. ¶¶ 66-67; Ex. A, Ameres Decl. ¶ 11. Par also refrains from engaging in such speech to many other healthcare professionals in an effort to avoid the government's allegation that marketing to a larger audience reflects an intent to expand the off-label market for

Megace® *ES*. Ex. A, Ameres Decl. ¶ 13. Thus, Par speaks about Megace® *ES* only to physicians who previously have prescribed earlier formulations of megestrol acetate oral suspension. *Id.* ¶¶ 11, 13. But for the fear of criminal prosecution under the FDA's regulations, Par would expand its marketing of Megace® *ES* to all healthcare professionals who reasonably may encounter AIDS patients in their practice, including many oncologists and healthcare professionals in long-term care facilities. *Id.* ¶ 13.

The balance of equities and the public interest also support preliminary relief where, as here, the moving party is likely to succeed on the merits of its First Amendment challenge. "These [two] factors merge when the Government is the opposing party." *Nken v. Holder*, 129 S. Ct. 1749, 1762 (2009). The government and the public have a strong interest in the enforcement of constitutional consumer-protection laws, but no legitimate interest in enforcing unconstitutional laws or regulations. By contrast, healthcare professionals, who are responsible for treating patients, unquestionably have a vital interest in access to truthful and non-misleading information about FDA-approved prescription drugs, so that their decisions about whether and how to prescribe those drugs can be "intelligent and well-informed." *Thompson v. Western States Med'l Ctr.*, 535 U.S. 357, 366 (2002) (quoting *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 765 (1976)).

II. Par Is Likely To Succeed On The Merits Of Its First Amendment Challenge

The FDA's regulations are unconstitutional as applied to criminalize Par's truthful and non-misleading speech to healthcare professionals about the FDA-approved, on-label use of Par's FDA-approved prescription drug. The FDA's regulations also conflict with the Act.

A. FDA Regulation Of Par's Speech Is Subject To Heightened Scrutiny

The government interprets the FDA's regulations to prohibit Par from engaging in truthful and non-misleading speech about the FDA-approved, on-label use of Megace® *ES* to

physicians who treat predominantly non-AIDS patients. That prohibition plainly is subject to First Amendment scrutiny. U.S. Const. amend. I, cl. 3 ("Congress shall make no law . . . abridging the freedom of speech . . . ."). "Both on [their] face and in [their] practical operation, [FDA's regulations] impose[] a burden based on the content of speech and identity of the speaker." *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2665 (2011). The regulations only prohibit speech that is deemed to promote an unapproved use of a drug, and only drug manufacturers are prohibited from engaging in such speech. Thus, the "Government's content-based burdens must satisfy the same rigorous scrutiny as its content-based bans. Lawmakers may no more silence unwanted speech by burdening its utterance than by censoring its contents." *Id.* at 2664 (quoting *United States v. Playboy Entm't Group, Inc.*, 529 U.S. 803, 812 (2000)).

To the extent the regulations impose criminal liability based on Par's failure to provide adequate directions or information for an unapproved use, the regulations violate the First Amendment's restriction against compelled speech. "There is certainly some difference between compelled speech and compelled silence, but in the context of protected speech, the difference is without constitutional significance, for the First Amendment guarantees 'freedom of speech,' a term necessarily comprising the decision of both what to say and what *not* to say." *Riley v. Nat'l Fed'n of the Blind of North Carolina, Inc.*, 487 U.S. 781, 796-97 (1988).

The FDA's regulations also do not prohibit only *conduct*, as the government previously has argued in an effort to evade First Amendment scrutiny. As an initial matter, the government's position that the regulations prohibit only conduct cannot be reconciled with its repeated characterization of the regulations as criminalizing "off-label *promotion*." U.S. Accountability Office, GAO-08-835, Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses 1-6, 20 tbl. 2 (2008) (emphasis added) (referring to numerous

prosecutions and regulatory actions alleging "off-label promotion"); *see also* U.S. Reply in Supp. of Mot. to Dismiss and for Summ. J. and Resp. to Cross-Mot. for Summ. J. at 6-7, 14, 20, 25, *Allergan, Inc. v. United States*, No. 09-1879 (JDB) (D.D.C. Mar. 29, 2010) (emphasizing distinction between what the government refers to as "promotion" and other speech, and arguing that only promotional speech about an off-label use creates a new intended use). Indeed, the government's theory of criminal liability is that a manufacturer is engaging in prohibited *promotion* of an off-label use of its drug.

Moreover, the regulations make it a crime to "*advertise[] or represent[]*" an off-label use without providing information about the off-label use in the drug's labeling. 21. C.F.R. § 201.100(c)(1) (emphasis added). The existence and content of Par's speech, along with the Catch-22 failure to make disclosures that are prohibited by law, are the *sine qua non* of a misbranding or new-drug offense. Crimes defined by the content of speech obviously are content-based. *See, e.g.*, *Sorrell*, 131 S. Ct. at 2664; *Western States*, 535 U.S. at 366-67; *cf. Whitaker v. Thompson*, 353 F.3d 947, 948-49 (D.C. Cir. 2004) (holding that speech may be used as evidence to show that an extract from the dwarf American palm was an unlawful and unapproved "drug" under 21 U.S.C. § 321(g)(1)(B)).

The FDA regulations are subject to strict scrutiny because they criminalize speech relating to the FDA-approved use of medicine. "A 'consumer's concern for the free flow of commercial speech often may be far keener than his concern for urgent political dialogue.' That reality has great relevance in the fields of medicine and public health, where information can save lives." *Sorrell*, 131 S. Ct. at 2664 (quoting *Bates v. State Bar of Ariz.*, 433 U.S. 350, 364 (1977)). Content-based restrictions on speech relating to FDA-approved medicine are

"presumptively invalid" and subject to strict scrutiny. *Id.*; *R.A.V. v. St. Paul*, 505 U.S. 377, 382 (1992).

The government's regulations are subject to strict scrutiny for the additional reason that they discriminate against pharmaceutical manufacturers, and no other speaker is prohibited from engaging in truthful speech about the off-label use of an approved drug, much less the speech at issue here – *i.e.*, speech about the FDA-approved, on-label use of a drug. Given the widespread off-label use of drugs, it is not surprising that the medical community, academics, and even the government engage in speech about the off-label use of drugs. *E.g.*, Compl. ¶¶ 51-56 (citing scientific studies and other materials discussing off-label uses). Some of that speech, including by the federal government, can be said to encourage off-label use of drugs, including megestrol acetate. *E.g.*, Nat'l Institutes of Health, U.S. Nat'l Library of Medicine, http://www.ncbi.nlm.nih.gov/pubmed/11193233 (discussing results of placebo-controlled study of megestrol acetate to treat wasting in elderly veteran patients at VA nursing home). Indeed, the NIH website contains a comprehensive and user-friendly collection of scientific journal articles discussing off-label uses of megestrol acetate to treat wasting in cancer and geriatric patients. *See* http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&cmd=link&linkname=pubmed_pubmed&uid=11193233. The government's regulations do not ban those speakers from promoting off-label use, even if they specifically intend to promote off-label use, and even if their speech has a dramatic effect on the prevalence of off-label use. Yet the government would consider it a crime for Par to make available the same off-label materials on its website, or even for Par's sales representatives to direct physicians to a website where the materials are discussed.

Laws that restrict speech by certain speakers, but not others, are subject to strict scrutiny and presumptively violate the First Amendment. *See, e.g.*, *Sorrell*, 131 S. Ct. at 2663

(invalidating law that "has the effect of preventing [pharmaceutical sales representatives] – and only [pharmaceutical sales representatives] – from communicating with physicians in an effective and informative manner"); *accord Citizens United v. FEC*, 130 S. Ct. 876, 898 (2010); *Playboy Entm't Group*, 529 U.S. at 812. In short, although the FDA has regulatory authority over drug manufacturers, the First Amendment requires that any regulations that take the form of discriminatory censorship must satisfy heightened scrutiny.

Par's speech in this case also does not fit the narrowly constructed mold of the lesser scrutinized, but still rigorously guarded, category of "commercial speech." *Central Hudson Gas & Elec. Co. v. Public Serv. Comm'n*, 447 U.S. 557, 564 (1980). The Supreme Court has defined this category as speech that "does no more than propose a commercial transaction," *Edenfield v. Fane*, 507 U.S. 761, 767 (1993), or, alternatively, as speech that is "related solely to the economic interests of the speaker and its audience." *Central Hudson*, 447 U.S. at 561 (citing *Va. State Bd. of Pharmacy*, 425 U.S. at 762). Par's speech does more than propose a commercial transaction. Par seeks to provide healthcare professionals with a variety of safety-related and other on-label information about Megace® *ES*, including contraindications, warnings and precautions, adverse reactions, and drug interactions – all truthful, scientific information that is pertinent to the safe use of the drug. Ex. A, Ameres Decl. ¶ 10. Par's speech also is not "related solely to the economic interests of the speaker and its audience." *Central Hudson*, 447 U.S. at 561. While communications with physicians generally relate to Par's interest in selling its drug, the interest of the physicians – Par's audience – is not economic in nature. Physicians may speak to pharmaceutical sales representatives for a variety of reasons, including to learn about new treatment options and discuss safety-related messages.

At a minimum, the speech here mixes core scientific speech with communication of some "commercial character" because it relates to a product Par manufactures and sells. *Riley*, 487 U.S. at 795-96. Where speech of a commercial character may be "inextricably intertwined" with "informative and perhaps persuasive speech," a court "cannot parcel out the speech, applying one test to one phrase and another test to another phrase," but rather must apply the test for "fully protected expression." *Id.*

B. Even Under Intermediate Scrutiny, The First Amendment Bars The FDA From Criminalizing The Speech At Issue

Even if the speech restrictions at issue are reviewed under the commercial speech doctrine, the FDA cannot constitutionally ban truthful speech about a lawful activity, particularly an activity that the government itself subsidizes and that other speakers, including the government, can and do freely discuss. *Cf. Sorrell*, 131 S. Ct. at 2667. A restriction on "commercial speech" is constitutional only if (a) the speech "concerns unlawful activity or is misleading," or (b) the restriction (1) furthers a "substantial" governmental interest; (2) does so "directly," and (3) does so without being "more extensive than is necessary to serve that interest." *Western States*, 535 U.S. at 367 (quoting *Central Hudson*, 447 U.S. at 564-66). The government shoulders the burden to justify the speech restriction under this test. *See id.* at 373; *Edenfield*, 507 U.S. at 770 ("It is well established that the party seeking to uphold a restriction on commercial speech carries the burden of justifying it.") (bracketing and citation omitted). As applied to Par's speech, the FDA regulations at issue fail intermediate scrutiny.

1. Par's Speech Concerns Lawful Activity And Is Non-Misleading

Because "[o]ffers to engage in illegal transactions are categorically excluded from First Amendment protection," *United States v. Williams*, 553 U.S. 285, 297 (2008), protected speech

must propose lawful activity. A manufacturer's truthful speech to physicians about an FDA-approved, on-label use of an FDA-approved prescription drug obviously concerns legal activity.

As an initial matter, as long as Par speaks to physicians who reasonably may encounter AIDS patients, Par's speech proposes an on-label use of Megace® *ES* and thus the speech proposes a lawful activity. Even if Par's speech within the drug's FDA-approved labeling were deemed to relate to an off-label use, the speech nonetheless proposes a lawful transaction. As discussed, physicians lawfully may (and routinely do) prescribe approved drugs to patients for off-label uses.

Moreover, Par seeks a declaration as to its right to engage in only truthful and non-misleading speech. The information that Par would provide to physicians from the FDA-approved labeling for Megace® *ES* is not false. It is a true statement of fact that the FDA has approved Megace® *ES* as safe and effective to treat AIDS-related wasting. Similarly, speech that is consistent with approved labeling is not misleading. To fall outside First Amendment protection as "misleading," commercial speech must be actually or inherently misleading, not just "potentially misleading." *Ibanez v. Florida Dep't of Bus. & Prof'l Regulation*, 512 U.S. 136, 146 (1994); *Wash. Legal Found. v. Friedman ("WLF II")*, 13 F. Supp. 2d 51, 66 (D.D.C. 1998). The FDA has acknowledged that even a manufacturer's blatant *off-label* speech is at most "potentially misleading." 62 Fed. Reg. 64,074, 64,079 (Dec. 3, 1997). The government similarly has conceded that "[i]t is *not* FDA's position that any statement by a manufacturer about the safety or effectiveness of an unapproved use is automatically false or misleading merely because the use has not yet been approved by FDA." U.S. Mem. in Supp. of Mot. to Dismiss and for Summ. J. at 34-35, *Allergan, Inc. v. United States*, No. 09-1879 (JDB) (D.D.C.

Jan. 7, 2010). *A fortiori*, where the manufacturer limits its speech to uses of a drug that the FDA *has approved*, the speech is neither potentially nor inherently misleading.

2. The First Amendment Prohibits FDA From Banning On-Label Speech

The government has little or no legitimate interest in punishing a manufacturer's speech about the FDA-approved use of a prescription drug. This analysis does not change when the manufacturer knows that physicians prescribe the manufacturer's drug for off-label uses, or when the manufacturer knows or intends that its on-label speech will increase the off-label use of a drug. Off-label use of approved prescription drugs is lawful, widespread, routine, may occur only upon the prescription of a licensed professional, and often is medically appropriate and even medically necessary. *See supra* pp. 4-6. All manufacturers of drugs that have common and medically accepted off-label uses know that some percentage of their drugs are prescribed for those perfectly lawful off-label uses. A manufacturer's knowledge or even intent that lawful conduct (*i.e.*, an off-label use) will result from lawful speech cannot – consistent with the First Amendment – make that speech a crime.

Any interest of the government in preventing off-label use is also illegitimate when the government itself endorses and subsidizes off-label uses as an integral and beneficial part of quality medical care. As discussed, HHS (of which the FDA is a part) subsidizes off-label uses of approved drugs under the Medicare and Medicaid programs where, as here, the uses are medically accepted. *See supra* pp. 4-6. The First Amendment prohibits the government from irrationally criminalizing speech about a lawful and medically beneficial activity that the government subsidizes.

Likewise, the government has no basis for imposing criminal penalties based on speculation that a manufacturer's speech about the *approved* use of a drug will have a greater

influence on off-label prescriptions than federal reimbursement for prescriptions for *unapproved* uses. To the contrary, the government's reimbursement for off-label label uses presumably has an even greater influence on off-label prescriptions. The impact of the government's encouragement of off-label use through its government insurance programs is particularly acute where, as here, some medical facilities face the threat of termination from the Medicare program if they fail to prescribe megestrol acetate (or another appetite stimulant) for an off-label use to treat patients. *See* Compl. ¶ 49. The First Amendment does not tolerate a system that incarcerates or otherwise punishes individuals based on the theory that their speech encourages off-label use when doctors and other members of the medical community remain free to encourage off-label use, and government policies themselves encourage such use.

Common sense also suggests that government subsidization of off-label uses has a pervasive influence on drug usage. In 2008, federally-funded healthcare programs, including Medicare and Medicaid, covered 37.2% of total pharmaceutical expenditures in the United States. Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2010*, at 372 tbl. 126 (2011), *available at* http://www.cdc.gov/nchs/data/hus/hus10.pdf. And surveys show that physicians are influenced more by drug reimbursement policies than by pharmaceutical marketing. PhRMA, *The Facts About Pharmaceutical Marketing & Promotion* 3-4 (2008), *available at* http://www.allianceforpatientaccess.org/news/080418%20Facts%20About%20Pharmaceutical%20Marketing.pdf (survey finding that 11% of physicians reported being strongly influenced by pharmaceutical sales representatives, whereas 35% of physicians reported being strongly influenced by insurance formularies that listed covered drugs); Tufts Ctr. for the Study of Drug Dev., *Outlook 2008*, at 5 (2008), *available at* http://csdd.tufts.edu/_documents/www/Outlook2008.pdf (survey with similar results).

For similar reasons, the FDA's regulations do not account for the fact that the government's own reimbursement policies provide a significant disincentive for manufacturers to seek FDA approval for new uses of approved drugs. Because federal subsidization increases a company's profits from an off-label use, the government can hardly justify imposing criminal penalties on manufacturers based on their knowledge of a widespread off-label use that the government itself helps to cause and sustain.

Moreover, off-label use of a drug may be so widely medically accepted that a manufacturer cannot conduct placebo-controlled clinical studies that are the standard prerequisites to obtain FDA approval for a new use of a previously approved drug. *See* Ex. B, Decl. of Paul Campanelli ¶ 14. In this case, 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 medically-accepted off-label use of megestrol acetate. *Id.*

In all events, the government's view of the regulations bans too much truthful and beneficial speech about the FDA-approved, on-label use of a potentially life-saving drug for AIDS patients. As discussed, Par wishes to market Megace® *ES* to any physician *who may treat AIDS patients*. The only way to avoid the risk of criminal liability, however, is for Par to limit its marketing to physicians *who only treat AIDS patients*. Because many doctors who may treat AIDS patients also treat non-AIDS patients, the FDA's regulations ban a wide swath of truthful speech to doctors who could prescribe the drug for its approved use. Such a regime hardly serves the community of AIDS patients, and it criminalizes individuals who are responsible for creating a life-saving medicine.

The regime also is Kafkaesque. Manufacturers have no way of knowing whether, under the FDA's regulations, they may speak to physicians who, for instance, prescribe the drug 20% on-label and 80% off-label, or to physicians with the reverse prescription ratio. And no ratio should be relevant as long as the approved use of a drug is potentially pertinent to a physician's medical practice. Thus, the First Amendment should not tolerate a ban on speech to doctors who do not currently treat patients for on-label use, but who previously have prescribed a drug on-label or reasonably might do so in the future. The government's contrary view of the First Amendment prevents countless doctors from hearing about the approved use of a critical drug for AIDS patients.

Because the regulatory regime leaves manufacturers in the dark as to what speech is criminal, the regulations pose heightened due process and First Amendment concerns. Vague penal statutes have a chilling effect on speech, risk arbitrary enforcement, and fail to give clear warning so that citizens can avoid criminal penalties. *Williams*, 553 U.S. at 292; *Reno v. Am. Civil Liberties Union*, 521 U.S. 844, 871-72 (1997). The regulations offer neither guidance nor standards – much less clear and binding standards – for when a manufacturer can communicate to healthcare professionals who may prescribe a drug for both approved and unapproved uses.

In *Western States*, 535 U.S. at 377, the Court invalidated under the First Amendment provisions of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Pub. L. No. 105-155, 11 Stat. 2325 (1997), that prohibited healthcare professionals from "advertis[ing] or promot[ing] the compounding of any particular drug, class of drug, or type of drug." 21 U.S.C. § 353a(c). "Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication to the needs of an individual patient." *Western States*, 535 U.S. at 360-61. In an effort to justify the ban on compounded drug

promotion, the government relied on "an interest in preserving the effectiveness and integrity of the [Act's] new drug approval process and the protection of the public health that it provides." *Id.* at 368 (bracketing and citation omitted). The government argued that if promotion of compounded drugs were allowed, compounded drugs could be produced and distributed on a large scale, effectively creating "a loophole that would allow unregulated drug manufacturing to occur under the guise of pharmacy compounding." *Id.* at 370-71.

The Court rejected that reasoning, holding that banning compounded drug promotion restricts far more speech than necessary. *Id.* at 371-72. Among other alternative approaches, the Court stated that the government's interests "could be satisfied by the far less restrictive alternative of requiring each compounded drug to be labeled with a warning that the drug had not undergone FDA testing and that its risks were unknown." *Id.* at 376. The Court further explained that the government's interests might already be achieved through "the requirement that compounding only be conducted in response to a prescription" by a physician exercising independent medical judgment, regardless of any promotional activities. *Id.* at 372. The Court held that "if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so." *Id.* at 371.

The same analysis applies with even greater force here. The government could require sales representatives, before meeting with doctors, to confirm that the FDA-approved use of a drug is potentially pertinent to the doctor's medical practice. Par currently engages in that practice. Compl. 59; Ex. A, Ameres Decl. ¶ 12. The government also could require manufacturers to disclose that the FDA has not approved the drug for any use not indicated on the label. What the government cannot do, however, is prohibit manufacturers from providing

truthful and non-misleading information to physicians who may a prescribe a drug for its approved use.

Indeed, the government's asserted interests in public safety and the integrity of the FDA approval process are at their lowest ebb when a manufacturer is engaged in speech about the FDA-approved, on-label use of its drug. Here, for example, Par already has sought and obtained FDA approval to market Megace® *ES* for its approved use to treat AIDS-related wasting, and thus the FDA already has determined that the drug is safe and effective for that use. To the extent the government seeks to limit the amount of off-label use of a drug, that interest is greatly diminished where, as here, the government reimburses that use through federal healthcare programs because it is medically appropriate or even medically necessary.

Also, as in *Western States*, the government's interests in public safety are significantly reduced because off-label use of a prescription drug can occur only when a licensed professional exercising independent judgment prescribes the drug for that off-label use. The First Amendment generally prevents the government from prohibiting dissemination of truthful information in order to influence the conduct of the listener. As the Supreme Court recently remarked:

> Those who seek to censor or burden free expression often assert that disfavored speech has adverse effects. But the fear that people would make bad decisions if given truthful information cannot justify content-based burdens on speech. The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good. These precepts apply with full force when the audience, in this case prescribing physicians, consists of sophisticated and experienced consumers.

Sorrell, 131 S. Ct. at 2670-71 (citations and internal quotation marks omitted); *see also, e.g.*, *Western States*, 535 U.S. at 374 (rejecting "the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of

the public from making bad decisions with the information"); *Va. State Bd. of Pharmacy*, 425 U.S. at 773 (government cannot restrict speech on based on the "effect upon . . . its recipients"); *Greater New Orleans Broad. Ass'n v. United States*, 527 U.S. 173, 194-95 (1999) (applying the "presumption that the speaker and the audience, not the Government, should be left to assess the value of accurate and non-misleading information about lawful conduct"); *Edenfield*, 507 U.S. at 767 (similar).

III. The FDA's Regulations Conflict With The Federal Food, Drug, And Cosmetic Act

The FDA's regulations fail First Amendment scrutiny, whether under the *Central Hudson* test for commercial-speech restrictions or, *a fortiori*, under strict scrutiny. At a bare minimum, though, the regulations give rise to grave constitutional doubt. Where, as here, there are "serious doubts" as to a statute's constitutionality, a court should construe the statute to avoid the constitutional problem absent "affirmative intention of Congress clearly expressed" to raise that serious constitutional question. *Edward J. DeBartolo Corp. v. Florida Gulf Coast Bldg. & Constr. Trades Council*, 485 U.S. 568, 584 (1988); *see also AFL-CIO v. FEC*, 333 F.3d 168, 175 (D.C. Cir. 2003) (stating that courts do not accord an agency deference "when its regulations create serious constitutional difficulties") (internal quotation marks omitted). Far from providing such a clear statement, the FDA's regulations violate the plain terms of the Act. At a minimum, the Act must be read consistent with Par's right to engage in truthful and non-misleading speech to healthcare professionals regarding the FDA-approved, on-label use of its FDA-approved prescription drug.

A. The FDA's "Intended Use" Regulations Conflict With The Act

Section 352(f)(1) states: "A drug . . . shall be deemed to be misbranded . . . [u]nless its labeling bears . . . adequate directions for use." 21 U.S.C. § 352(f)(1). That disclosure provision on its face requires manufacturers to speak. But the FDA's regulations, 21 C.F.R.

§§ 201.100(c)(1), 201.128, construe Section 352(f)(1) as a means to ban manufacturers from speaking. *See supra* pp. 6-10.

Naturally read, Section 352(f)(1) requires manufacturers to provide adequate directions for any use specified on the FDA-approved labeling. Nothing in the provision suggests that manufacturers should provide directions for some other "intended" use that differs from the uses specified on the approved labeling. The word "intended" does not appear in Section 352(f)(1), and Congress's use of the word "labeling" in the provision confirms that the disclosure requirement relates to any use specified in the FDA-approved labeling. Congress knew how to refer to an "intended" use in the Act when Congress meant to incorporate the concept of a manufacturer's intent. *See, e.g.*, 21 U.S.C. §§ 321(g) ("drug" means an article "intended for use" in treatment of disease or to affect bodily function), 321(h) (defining "device" based on "intended purposes"), 321(i) (defining "cosmetic" based on "intended" use), 321(s) (defining "food additive" based on "intended use").

Unlike those provisions, Congress in Section 352(f)(1) omitted any mention of intent. Moreover, Congress could not plausibly have meant to require that manufacturers alter a drug's FDA-approved labeling to provide directions for an unapproved use, because that would be illegal under the Act's "new drug" provision. 21 U.S.C. § 321(p). Simply put, Congress did not require manufacturer to do the legally impossible. The statute therefore does not authorize the FDA to declare a drug misbranded on the theory that, although the labeling contains adequate directions for the uses indicated on the labeling, the manufacturer must give adequate directions for some unapproved use.

In any event, Section 353 of the Act expressly provides that, with exceptions not relevant here, "any drug dispensed by filling or refilling a written or oral prescription of a [licensed

practitioner] *shall be exempt* from the requirements of [Section 352(f)(1)]." 21 U.S.C. § 353(b)(2) (emphasis added). The Section 353(b)(2) exemption from Section 352's adequate-directions requirement applies as long as a the drug's label bears "the directions for use and cautionary statements, if any, contained in such prescription." *Id.* The meaning of the statutory exemption is therefore plain: as long as the label affixed to a prescription drug's container repeats the physician's directions to his or her patient in the prescription, Congress did not require the manufacturer to provide any additional directions for consumer use. The Section 352 adequate directions requirement is thus limited to drugs provided to consumers without a prescription, *i.e.*, over-the-counter drugs. That conclusion is further confirmed by the Act's specific statement that a prescription drug is misbranded "if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol 'Rx only.'" 21 U.S.C. § 353(b)(4).

The FDA's regulations similarly support reading Section 352(f)(1) as limited to non-prescription, over-the-counter drugs. The FDA defines "adequate directions" under Section 352(f)(1) to mean "directions under which the *layman* can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5 (emphasis added). And, under the Act, a prescription drug by definition is "not safe for use except under the supervision of a [prescribing physician]." 21 U.S.C. § 353(b)(1). Accordingly, Section 353 and the FDA's definition of "adequate directions for use" make it categorically impossible for a prescription drug's labeling to bear adequate directions for use. Congress could not plausibly have imposed a disclosure requirement that is impossible to satisfy.

The FDA has nullified the statutory scheme by providing that a prescription drug is exempt from the Act's "adequate *direction*s for use" requirement only if the drug's labeling bears "adequate *information* for its use" by medical professionals. 21 C.F.R. § 201.100(c)(1)

(emphasis added). The FDA's regulations thus bizarrely posit that if a prescription drug's labeling does not bear "adequate information" for physicians, then the drug's labeling must bear "adequate directions" for consumers, even though under the Act and 21 C.F.R. § 201.5, it is impossible for a manufacturer to provide adequate directions to a laymen for a prescription drug. Even if the regulatory regime was coherent, the plain terms of the Act bar the FDA from reading Section 353(b)(2)'s prescription drug exemption out of existence. Congress "does not, one might say, hide elephants in mouseholes." *Whitman v. Am. Trucking Ass'ns, Inc.*, 531 U.S. 457, 468 (2001).

To be sure, the Fifth Circuit stated in *United States v. Evers*, 643 F.2d 1043 (5th Cir. 1981), that the Section 353(b)(2) exemption applies "only at the point at which the drug is actually prescribed and dispensed by a licensed physician." *Id.* at 1051. But *Evers* did not attempt to reconcile that statement with the language of the statute. Neither Section 352(f)(1) nor Section 353(b)(2) distinguish among different distributors or stages of distribution of a drug. Both provisions on their face apply at any point in the distribution process.

Moreover, *Evers* did not involve a challenge to the FDA's theory that a drug becomes misbranded if a manufacturer expresses an objective intent that a drug be prescribed for an off-label use. To the contrary, the court of appeals used the government's view of the statute to *reject* the government's creative misbranding charges against a doctor who the FDA claimed "did not provide adequate information to himself" for an off-label use of a prescription drug. *Id.* at 1053. The court of appeals criticized that government theory as "nonsensical" and contrary to what was "intended by the drafters of the statute." *Id.* Thus, *Evers* cannot be read to approve of the regulatory regime at issue here.

The FDA's lack of authority to impose an extra-statutory requirement on manufacturers does not mean prescription drugs can be manufactured and marketed without instructions for their use. In connection with obtaining FDA approval, the Act requires manufacturers to submit, and the FDA must approve, proposed labeling for a drug that includes instructions for all of the on-label uses being approved by the FDA. *See* 21 U.S.C. § 355(b)(1). Physicians have ready access to this information, including on the package insert for a drug.

Section 353(b)(2) specifically does not exempt prescription drugs from Section 352(a) of the Act, and thus prescription drugs are misbranded if their labeling is "false or misleading in any particular." 21 U.S.C. § 352(a). And the Act's new-drug provision prohibits manufacturers from altering a drug's labeling (as defined in *Kordell*) to prescribe, recommend, or suggest any off-label use. 21 U.S.C. § 321(p). Thus, a prescription drug's labeling still must provide instructions for all on-label uses, the labeling must not prescribe, recommend, or suggest any off-label use, and the labeling must not be false or misleading in any particular. And, as discussed above, the FDA remains free under the First Amendment to promulgate tailored regulations – for example, requiring disclosure by the manufacturer that the FDA has not approved a drug for any use not on the labeling.

B. The FDA's "Labeling" Regulation Conflicts With The Act

The Act defines "labeling" to mean "all labels and other 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). The FDA, however, defines "labeling" without regard to whether written materials accompany a drug. The FDA's regulation 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 broad definition of labeling thus encompasses any tangible materials distributed by the manufacturer that contain manufacturer-supplied drug information, irrespective of whether those materials accompany a drug under 21 U.S.C. § 321(m). This interpretation is manifestly inconsistent with the Act.

In construing the Act's definition of "labeling," the Supreme Court has adopted a "functional standard," holding that materials sent separately from a drug may be considered "labeling" if (1) the materials have a "textual relationship" to the drug; and (2) the materials and drugs were sent as part of an "integrated" transaction. *Kordel*, 335 U.S. at 348-50; *see also United States v. Urbuteit*, 335 U.S. 355, 358 (1948). By contrast, the FDA's expansive definition of "labeling" requires neither a "textual relationship" nor an "integrated" transaction to censor a manufacturer's speech. Instead, the FDA purports to regulate as "labeling" nearly any type of tangible material that contains "drug information" and is "disseminated by . . . the manufacturer." 21 C.F.R. § 202.1(*l*)(2). Thus, to the extent the government views Par's speech as being off-label, Par is exposed to a new-drug charge for suggesting an off-label use in the drug's labeling.

The government recently has asserted that 21 C.F.R. § 202.1(*l*)(2), which lists items that "are hereby determined to be labeling as defined in" 21 U.S.C. § 321(m), does not, after all, define the term "labeling" under 21 U.S.C. § 321(m). Instead, the government contends that the purpose of the regulation "is to limit the domain of the Act's prescription drug advertising requirements, by making clear what kinds of materials are *not* subject to those requirements. It

was never meant to suggest that the items in the list will be regulated as labeling." U.S. Reply in Supp. of Mot. to Dismiss and for Summ. J. and Resp. to Cross-Mot. for Summ. J. at 22-23, *Allergan, Inc. v. United States*, No. 09-1879 (JDB) (D.D.C. Mar. 29, 2010).

Whether or not the government's recent reading of the FDA's regulation is plausible, the government concedes that the regulation does not broaden the definition of labeling beyond what is set forth in the Act, as construed in *Kordel*. Thus, Par is entitled to a declaration that 21 C.F.R. § 202.1(*l*)(2) does not define materials to be "labeling," and that to be "labeling" under 21 U.S.C. § 321(m), materials must accompany a drug.

CONCLUSION

For the foregoing reasons, this Court should enter a preliminarily injunction preventing the federal government from enforcing the FDA's regulations that purport to criminalize Par's truthful and non-misleading speech to healthcare professionals about the FDA-approved use of Par's FDA-approved drug.

Dated: October 14, 2011

Respectfully Submitted,

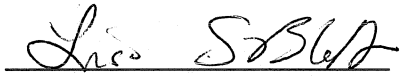

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Exhibit A

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PAR PHARMACEUTICAL, INC,	
Plaintiff,	
v.	**Case No. _____**
UNITED STATES OF AMERICA et al.,	
Defendants.	

DECLARATION OF JOHN AMERES

I, John Ameres, declare as follows,

1. I am over 18 years of age and competent to testify about the matters set forth herein. I submit the testimony below based on personal knowledge, except for that which I submit based on information and belief.

2. I am currently employed as Vice President, Marketing and Business Analytics at Strativa Pharmaceuticals (Strativa), the proprietary products division of Par Pharmaceutical, Inc. (Par).

3. In 1997, I graduated with a bachelor of arts degree in Chemistry and Business from the University of Scranton.

4. In August 1997, I joined Forest Laboratories as a sales representative. In February 1999, I moved into Forest's home office where for over six years I held various positions in product management, including specifically medical education, promotion, and forecasting. I left Forest Labs in June 2005 to join Par.

5. Before my current position, I held the following positions at Par: Director of Marketing, Director of Strategic Planning and Commercial Assessments, and Senior Director of Business Development. Since 2005, I have been involved with Par's Megace® *ES* product, which is marketed and sold through Strativa.

6. At Par, my primary responsibilities as Vice President, Marketing and Business Analytics, include developing the marketing strategy and managing all marketing activities for Strativa's branded products, including Megace® *ES* (indicated to treat AIDS-related wasting), Zuplenz (indicated to treat post-operative, post-chemotherapy, and radiation-induced nausea and vomiting), Nascobal (indicated to treat vitamin B12 deficiency), and Oravig (indicated to treat fungal infections of the mouth). Specifically, these duties include gathering and maintaining data on product usage within prescriber specialties, assessing market potential within the products' respective on-label markets, devising sales strategies based on prescriber data, and monitoring product marketability and sales.

7. The FDA approved Megace® *ES* in July 2005 as a prescription appetite stimulant indicated for the treatment of anorexia (loss of appetite), cachexia (severe malnutrition), or an unexplained significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS). Megace® *ES* is an advanced formulation of megestrol acetate oral suspension which was approved in 1993 under the brand name Megace®. Megace® and Megace® *ES* carry the same FDA-approved indication.

8. Megace® *ES* is the same chemical compound, megestrol acetate, as its predecessor Megace®. But Megace® *ES* employs a different formulation, using an advanced nanocrystal dispersion technology, which decreases the size of the particles containing the megestrol acetate molecule and increases the drug's bioavailability, particularly for patients who do not take the drug along with food. In other words, this means that Megace® *ES* is absorbed differently into the body and can be an effective treatment, especially when a patient has not eaten, an important benefit for patients who are suffering from wasting and frequently will not have eaten. By contrast, Megace® has limited absorption in patients who have not eaten.

9. In addition, Megace® *ES*'s formulation has made it effective in a lower dose than Megace®. The original formulation of megestrol acetate required a 800 mg dose administered as 20 mL to demonstrate efficacy, whereas Megace® *ES* is efficacious as a 625 mg dose administered as 5 mL (a teaspoon-sized volume) once daily. Megace® *ES* also has lower viscosity.

10. Par has developed a comprehensive marketing message for its sales representatives to educate physicians about the use of Megace® *ES* to treat wasting in AIDS patients. Par sales representatives speak to primary care physicians and other doctors regarding the benefits of Megace® *ES* to treat wasting in AIDS patients. The sales representatives are trained to educate doctors about Megace® *ES*'s formulation and its efficacy. The sales representatives also are trained to explain to physicians the dosing differences between Megace® *ES* and Megace®, since the dosing for Megace® *ES* (625 mg/day administered as 5 mL/day) is significantly different from that for Megace® (800 mg/day administered as 20 mL/day). This dosing issue is so significant that Megace® *ES*'s FDA-approved labeling contains a side-by-side chart illustrating the difference in dosages between the two drugs. The sales representatives also are trained to educate physicians about various on-label safety-related information, including contraindications, warnings and precautions, adverse reactions, and drug interactions.

11. Par currently markets Megace® *ES* only to physicians who, in the last 12 months, have prescribed earlier formulations of megestrol acetate oral suspension, including Megace® and generic versions of the drug, based on prescriber data that Par purchases from a third-party vendor. This includes physicians practicing in AIDS clinics, but also includes physicians in other settings, such as oncology and long-term care. Through my work in Par's marketing department, I have become aware that oncologists and long-term care physicians treat AIDS patients in the course of their medical practice, even though they may, at times, prescribe Megace® *ES* to treat wasting in non-AIDS patients as well as there are no currently FDA-approved drugs for wasting disorders not associated with AIDS. Within these practices, as with all practices, Par's sales representatives are trained to speak only about the approved use of Megace® *ES* to treat wasting in AIDS patients, and to clearly state Megace® *ES*'s FDA-approved indication.

12. Par currently markets Megace® *ES* only to physicians, including oncologists and physicians in long-term care facilities, who confirm that (1) Par sales representatives may only provide information that is consistent with the drug's FDA-approved labeling, and (2) information regarding the drug's FDA-approved indication to treat AIDS-related wasting is relevant to the physician's medical practice.

13. Based on the fear of criminal allegations or other enforcement action, Par significantly restricts its marketing of Megace® *ES*. In particular, Par does not specifically target healthcare providers for marketing of Megace ® *ES* who have not prescribed or dispensed megestrol acetate oral suspension in the last 12 months. Therefore, Par does not specifically identify for targeting and market Megace® *ES* to physicians based on past prescriptions of other anti-wasting drugs that have the same FDA-approved indication to treat AIDS-related wasting, such as Serostim® and Marinol®. Par also does not market Megace® *ES* to physicians based on past prescriptions 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 criminal allegations, Par would market Megace® *ES* to healthcare providers regardless of past prescribing or dispensing habits who may encounter AIDS-related wasting patients, including oncologists and prescribers practicing in the long-term care setting.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on this 12th day of October, 2011.

John Ameres

John Ameres

Exhibit B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PAR PHARMACEUTICAL, INC,

Plaintiff,

v.

UNITED STATES OF AMERICA, et al.,

Defendants.

Case No. _____

DECLARATION OF PAUL CAMPANELLI

I, Paul Campanelli, declare as follows,

1. I am competent to testify about the matters set forth herein. I submit the testimony below based on personal knowledge, except for that which I submit based on information and belief.
2. I am currently President of Par Pharmaceutical, the generic division at Par Pharmaceutical, Inc. (Par). I have worked at Par since 2001.
3. I graduated from Springfield College, Massachusetts, in 1984, with a Bachelor of Science.
4. After college, I went to work for Dr. Reddy's Laboratories Inc., a subsidiary of Dr. Reddy's Laboratories Ltd, a manufacturer of Active Pharmaceutical Ingredients (API) and Finished Dosage Drug Product, located in Ridgewood, New Jersey as a sales representative. Initially, my main duty at that company was selling API to pharmaceutical manufacturers. Toward the end of my time with Dr. Reddy's Laboratories Inc., my job shifted to licensing the company's New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDAs) to pharmaceutical manufacturers that would market and distribute the final pharmaceutical products. During my tenure at the company, I was promoted from sales representative to Sales Manager and eventually to Vice President of Business Development.
5. I left Dr. Reddy's Laboratories and joined Par in 2001 as a Senior Director. I was later promoted to Vice President, then to Senior Vice President, and later to Executive Vice President. Ultimately, Par promoted me to President of the Generic Drug Division in 2007.
6. From my date of hire, in 2001, until 2006, I reported directly to Scott Tarriff, Par's CEO at the time. Since his departure, I have reported to Patrick LePore, Par's current CEO.
7. Throughout my employment at Par, my primary area of responsibility has been the generic side of Par's business. However, from 2001 through 2004, I oversaw the work in securing approval for Par's modification of generic megestrol acetate oral suspension

(MAOS) through application of a new manufacturing process, nanocrystal dispersion (NCD), which created a new version of the drug. Originally named Megestrol Acetate NCD, Par later branded the drug as Megace® *ES*. I was responsible for participating in both the filing the 505(b)(2) application related to Megace® *ES* and communicating with the FDA related to that application. In addition, I was one of the people responsible for communicating with the FDA regarding other potential indications for Megace® *ES*.

8. Megace® *ES* is an appetite stimulant that is FDA-approved to treat anorexia, cachexia, and unintended significant weight loss in patients with a diagnosis of AIDS. It is a branded version of MAOS, which the FDA approved in 1993 with the same indication that Megace® *ES* now carries. The FDA gave Megace® *ES* the same indication as MAOS because the FDA determined that it works from the same active molecule and is bioequivalent to its predecessor product. The main differences between the two products is that Megace® *ES* is approved at a lower dose, is less viscous, and has a delivery system that makes it more bioavailable to patients who have not eaten. The FDA-approved label for Megace® *ES* includes the differences in bioavailability and dosing between Megace® *ES* and MAOS. A copy of the package insert for Megace® *ES*, as approved, is attached as Exhibit 1.

9. I am aware that Megace® *ES* is prescribed widely to treat wasting in non-AIDS oncology and geriatric patients, even though it is not indicated to treat wasting in these patient populations. I further understand that a significant percentage of Megace® *ES* prescriptions, like MAOS prescriptions, are written to treat these patient groups. Despite Par's diligent efforts, Par was not able to obtain indications for Megace® *ES* to treat oncologic and geriatric wasting, in large part because of the already widespread use of MAOS to treat wasting in those patient populations.

10. In 2002, Par began discussions with the FDA about seeking a new indication for Megace® *ES* to treat wasting in geriatric patients. In the initial meetings, Dr. Robert Perlstein of the FDA's Division of Metabolic and Endocrine Drug Products (DMEDP) indicated that the FDA was more interested in seeing improvement in patients' physical function as a notable study endpoint, rather than weight gain.

11. In September 2005, Par began a formal effort to set up studies for geriatric wasting. Throughout this time, I, along with other Par employees, including Michelle Bonomi, attended meetings with the FDA concerning Par's attempts to secure a geriatric indication. In certain of those meetings and on telephone calls with Ms. Bonomi, Dr. Perlstein made clear that he perceived significant hurdles to obtaining approval for a geriatric wasting indication. For example, Dr. Perlstein suggested that functional study endpoints, including patients' ability to walk, stand up, and perform other physical functions, would be required. These endpoints did not consider, however, whether patients, being elderly and likely suffering from other infirmities, could achieve the endpoints regardless of their appetite or nutritional state.

12. In addition, Dr. Perlstein, who had been part of the FDA's initial review and approval of MAOS in 1993, expressed concerns about the safety of elderly patients using the compound. Despite the years of safe use in that patient population, Dr. Perlstein was concerned that Bristol-Myers Squibb, the company that initially developed megestrol acetate as a treatment for AIDS wasting, had not conducted safety studies and felt such

studies needed to be conducted. Dr. Perlstein therefore asked Par to provide additional safety information. In the end, Dr. Perlstein suggested that Par pursue an oncology indication because the FDA's Oncology Division had a different risk threshold for study patients than DMEDP.

13. Realizing the FDA had effectively foreclosed a geriatric indication as an option, Par directed its efforts, as Dr. Perlstein suggested, to obtaining an oncology indication for Megace® *ES*. Throughout 2005 and 2006, Par was in regular contact with the FDA regarding the design of oncology-related studies. By early 2006, Par had designed randomized, placebo-controlled, double-blind studies for oncology patients, which were required for FDA approval.

14. By summer 2006, it became clear that requiring a placebo control for the Megace® *ES* studies was impeding enrollment because MAOS already was widely prescribed off label for oncologic wasting. The compound has been used to treat wasting in cancer patients since it was discovered to have an appetite stimulating effect in the 1970's (at which time it was in a tablet form indicated for and used to treat breast cancer). Ultimately, Par was unable to gain sufficient institutional review board (IRB) approval or enroll sufficient numbers of patients in those studies that were IRB-approved because many IRBs and physicians would not subject anorexic or cachectic patients to the risk of no treatment (*i.e.*, a placebo) when MAOS is an available and widely accepted treatment for non-AIDS cancer wasting. Some physicians told Par it would be unethical to administer a placebo to patients when such a widely accepted and effective treatment already was available. On August 21, 2006, Par submitted a letter informing the FDA that Par was closing its oncology studies.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on this 13th day of October, 2011.

Paul Campanelli

Exhibit 1

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEGACE® ES safely and effectively. See full prescribing information for MEGACE® ES.

MEGACE® ES (megestrol acetate) Oral Suspension

Initial U.S. Approval: 1993

INDICATIONS AND USAGE

Megace® ES oral suspension is a progestin indicated for the treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS) (1).

DOSAGE AND ADMINISTRATION

The recommended adult initial dosage of Megace® ES oral suspension is 625 mg/day (5 mL/day or one teaspoon daily). Shake container well before using (2).

DOSAGE FORMS AND STRENGTHS

Oral suspension containing 125 mg of megestrol acetate per mL (3).

CONTRAINDICATIONS

- History of hypersensitivity to megestrol acetate or any component of the formulation (4.1).
- Known or suspected pregnancy (4.2)(8.1).

WARNINGS AND PRECAUTIONS

- Women of childbearing potential should be advised to avoid becoming pregnant (5.2).
- Use with caution in patients with a history of thromboembolic disease (5.1).
- Clinical cases of overt Cushing's Syndrome have been reported in association with the chronic use of megestrol acetate. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic megestrol acetate in the stressed and non-stressed state (5.3).
- New onset and exacerbation of pre-existing diabetes have been reported (5.4).

ADVERSE REACTIONS

The most common adverse events occurring in > 5% of all patients receiving 800mg/20mL of megestrol acetate oral suspension in the two clinical efficacy trials were nausea, diarrhea, impotence, rash, flatulence, hypertension, and asthenia (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-828-9393, option 3 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Due to a significant decrease in indinavir exposure, administration of a higher dose of indinavir should be considered when coadministering with megestrol acetate (7.1, 12.3).

USE IN SPECIFIC POPULATIONS

- **Geriatrics:** In general, 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 therapy (8.5).
- **Nursing Mothers:** Because of the potential for adverse effects on the newborn, nursing should be discontinued if Megace® ES oral suspension is required (8.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 7/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Megace® ES oral suspension is indicated for the treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

1.1 Limitations of Use

Other Treatable Causes

Therapy with megestrol acetate for weight loss should only be instituted after treatable causes of weight loss are sought and addressed. These treatable causes include possible malignancies, systemic infections, gastrointestinal disorders affecting absorption, endocrine disease, renal disease or psychiatric diseases.

Prophylactic Use

Megestrol acetate is not intended for prophylactic use to avoid weight loss.

2 DOSAGE AND ADMINISTRATION

The recommended adult initial dosage of Megace® ES oral suspension is 625 mg/day (5 mL/day or one teaspoon daily). **Please refer to the table below for correct dosing and administration.** Shake the container well before using.

Table 1: Differences in Dosing between Megace® ES and Megace® Oral Suspension

	Megace® ES Oral Suspension	Megace® and other megestrol acetate oral suspensions
mg/mL	125 mg/mL	40 mg/mL
Recommended Daily Dose	625 mg	800 mg
Daily Volume Intake	5 mL (teaspoon)	20 mL (dosing cup)

3 DOSAGE FORMS AND STRENGTHS

Megace® ES is a milky white, lemon-lime flavored oral suspension containing 125 mg of megestrol acetate per mL. Megace ES does not contain the same amount of megestrol acetate as Megace oral suspension or any of the other megestrol acetate oral suspensions *(2)*.

4 CONTRAINDICATIONS

4.1 Hypersensitivity Reaction

History of hypersensitivity to megestrol acetate or any component of the formulation.

4.2 Pregnancy

Known or suspected pregnancy.

5 WARNINGS AND PRECAUTIONS

5.1 General

- Effects on HIV viral replication have not been determined.
- Use with caution in patients with a history of thromboembolic disease.

5.2 Fetal Effects

Megestrol acetate may cause fetal harm when administered to a pregnant woman. For animal data on fetal effects, *see NonClinical Toxicology: Impairment of Fertility (13.1)*. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

5.3 Adrenal Insufficiency

The glucocorticoid activity of megestrol acetate oral suspension has not been fully evaluated. Clinical cases of overt Cushing's Syndrome have been reported in association with the chronic use of megestrol acetate. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic megestrol acetate therapy in the stressed and non-stressed state. Furthermore, adrenocorticotropin (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic pituitary-adrenal suppression in patients treated with chronic megestrol acetate therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patient receiving or being withdrawn from chronic Megace® ES therapy who presents with symptoms and/or signs suggestive of hypoadrenalism (e.g., hypotension, nausea, vomiting, dizziness, or weakness) in either the stressed or non-stressed state. Laboratory evaluation for adrenal insufficiency and consideration of replacement or stress doses of a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognize inhibition of the hypothalamic-pituitary adrenal axis may result in death. Finally, in patients who are receiving or being withdrawn from chronic Megace® ES therapy, consideration should be given to the use of empiric therapy with stress doses of a rapidly acting glucocorticoid during stress or serious intercurrent illness (e.g., surgery, infection).

5.4 Diabetes

Clinical cases of new onset diabetes mellitus and exacerbation of pre-existing diabetes mellitus have been reported in association with the chronic use of megestrol acetate.

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

The following serious reactions and otherwise important adverse drug reactions are discussed in greater detail in other sections of the labeling:

- Hypersensitivity *[see Contraindications (4.1)]*
- Pregnancy *[see Contraindications (4.2)]*
- Fetal Effects *[see Warnings and Precautions (5.2)]*
- Thromboembolic Disease [*see Warnings and Precautions (5.1)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.3)]*

6.2 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse events which occurred in at least 5% of patients in any arm of the two clinical efficacy trials and the open trial for megestrol acetate oral suspension are listed below by treatment group. All patients listed had at least one post baseline visit during the 12 study weeks.

Table 2: Adverse Events

Percent of Patients Reporting Adverse Events							
	Trial 1 (N=236)				Trial 2 (N=87)		Open Label Trial
	Placebo				Placebo		
Megestrol Acetate mg/day	0	100	400	800	0	800	1200
No. of Patients	N=34	N=68	N=69	N=65	N=38	N=49	N=176
Diarrhea	15	13	8	15	8	6	10
Impotence	3	4	6	14	0	4	7
Rash	9	9	4	12	3	2	6
Flatulence	9	0	1	9	3	10	6
Hypertension	0	0	0	8	0	0	4
Asthenia	3	2	3	6	8	4	5
Insomnia	0	3	4	6	0	0	1
Nausea	9	4	0	5	3	4	5
Anemia	6	3	3	5	0	0	0
Fever	3	6	4	5	3	2	1
Libido Decreased	3	4	0	5	0	2	1
Dyspepsia	0	0	3	3	5	4	2
Hyperglycemia	3	0	6	3	0	0	3
Headache	6	10	1	3	3	0	3
Pain	6	0	0	2	5	6	4
Vomiting	9	3	0	2	3	6	4
Pneumonia	6	2	0	2	3	0	1
Urinary Frequency	0	0	1	2	5	2	1

Adverse events which occurred in 1% to 3% of all patients enrolled in the two clinical efficacy trials with at least one follow-up visit during the first 12 weeks of the study are listed below by body system. Adverse events occurring less than 1% are not included. There were no significant differences between incidence of these events in patients treated with megestrol acetate and patients treated with placebo.

Body as a Whole - abdominal pain, chest pain, infection, moniliasis and sarcoma

Cardiovascular System - cardiomyopathy and palpitation

Digestive System - constipation, dry mouth, hepatomegaly, increased salivation and oral moniliasis

Hemic and Lymphatic System - leukopenia

Metabolic and Nutritional - LDH increased, edema and peripheral edema

Nervous System - paresthesia, confusion, convulsion, depression, neuropathy, hypesthesia and abnormal thinking

Respiratory System - dyspnea, cough, pharyngitis and lung disorder

Skin and Appendages - alopecia, herpes, pruritus, vesiculobullous rash, sweating and skin disorder

Special Senses - amblyopia

Urogenital System - albuminuria, urinary incontinence, urinary tract infection and gynecomastia.

6.3 Postmarketing Experience

Postmarketing reports associated with megestrol acetate oral suspension include thromboembolic phenomena including thrombophlebitis, deep vein thrombosis, and pulmonary embolism; and glucose intolerance *[see Warnings and Precautions (5.1,5.4)]*.

7 DRUG INTERACTIONS

7.1 Indinavir

Due to the significant decrease in the exposure of indinavir by megestrol acetate, administration of a higher dose of indinavir should be considered when coadministering with megestrol acetate [See *Clinical Pharmacology (12.3*)].

7.2 Zidovudine and Rifabutin

No dosage adjustment for zidovudine and rifabutin is needed when megestrol acetate is coadministered with these drugs [See *Clinical Pharmacology (12.3*)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Warnings and Precautions (5.2)]*. No adequate animal teratology information is available at clinically relevant doses. Pregnant rats treated with low doses of megestrol acetate (0.02-fold the recommended clinical dose) resulted in a reduction in fetal weight and number of live births, and feminization of male fetuses.

8.3 Nursing Mothers

Because of the potential for adverse effects on the newborn, nursing should be discontinued if Megace® ES oral suspension is required.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of megestrol acetate oral suspension in the treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with AIDS did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, 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.

Megestrol acetate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Use in HIV Infected Women

Megestrol acetate has had limited use in HIV infected women.

All 10 women in the clinical trials reported breakthrough bleeding.

10 OVERDOSAGE

No serious unexpected side effects have resulted from studies involving megestrol acetate oral suspension administered in dosages as high as 1200 mg/day. Megestrol acetate has not been tested for dialyzability; however, due to its low solubility it is postulated that dialysis would not be an effective means of treating overdose.

11 DESCRIPTION

Megace® ES oral suspension contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone. Megestrol acetate is a white, crystalline solid chemically designated as 17-Hydroxy-6-methyl pregna-4,6-diene-3,20-dione acetate. Solubility at 37° C in water is 2 mcg per mL, solubility in plasma is 24 mcg per mL. Its molecular weight is 384.52.

The chemical formula is $C_{24}H_{32}O_4$ and the structural formula is represented as follows:

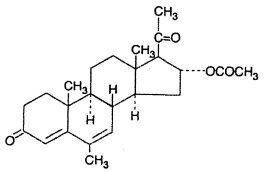

Figure 1: Megestrol Acetate Chemical Structure

Megace® ES is an oral suspension containing 125 mg of megestrol acetate per mL.

Megace® ES oral suspension contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial lime flavor, citric acid monohydrate, docusate sodium, hydroxypropyl methylcellulose (hypromellose), natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Several investigators have reported on the appetite enhancing property of megestrol acetate and its possible use in cachexia. The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at the present time.

12.3 Pharmacokinetics

Absorption and Distribution

Mean plasma concentrations of megestrol acetate after administration of 625 mg (125 mg/mL) of Megace® ES oral suspension are equivalent under fed conditions to 800 mg (40 mg/mL) of megestrol acetate oral suspension in healthy volunteers.

In order to characterize the dose proportionality of Megace® ES, pharmacokinetic studies across a range of doses were conducted when administered under fasting and fed conditions. Pharmacokinetics of megestrol acetate was linear in the dosing range between 150 mg and 675 mg after Megace® ES administration regardless of meal condition. The mean peak plasma concentration (C_{max}) and the mean area under the concentration time-curve (AUC) after a high fat meal were increased by 48% and 36%, respectively, compared to those under the fasting condition after 625 mg Megace® ES administration. This food effect is less than that seen for the original formulation, megestrol acetate 800 mg/20 mL, where a high fat meal significantly increased AUC and C_{max} of megestrol acetate to 2-fold and 7-fold, respectively, compared to those under the fasting condition. There was no difference in safety following administration in the fed state, therefore Megace® ES could be taken without regard to meals.

Plasma steady state pharmacokinetics of megestrol acetate was evaluated in 10 adult, cachectic male adult patients with acquired immunodeficiency syndrome (AIDS) and an involuntary weight loss greater than 10% of baseline who received single oral doses of 800 mg/day of megestrol acetate oral suspension for 21 days. The Mean (±1SD) C_{max} of megestrol acetate was 753 (±539) ng/mL. The mean AUC was 10476 (±7788) ng x hr/mL. Median T_{max} value was five hours.

In another study, 24 asymptomatic HIV seropositive male adult subjects were dosed once daily with 750 mg of megestrol acetate oral suspension for 14 days. Mean C_{max} and AUC values were 490 (±238) ng/mL and 6779 (±3048) hr x ng/mL, respectively. The median T_{max} value was three hours. The mean C_{min} value was 202 (±101) ng/mL. The mean % of fluctuation value was 107 (±40).

Metabolism and Excretion

The major route of drug elimination in humans is urine. When radio-labeled megestrol acetate was administered to humans in doses of 4 to 90 mg, the urinary excretion within 10 days ranged from 56.5% to 78.4% (mean 66.4%) and fecal excretion ranged from 7.7% to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%).

Megestrol acetate metabolites which were identified in urine constituted 5% to 8% of the dose administered. Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in urine and feces.

The mean elimination half-life of megestrol ranged from 20 to 50 hours in healthy subjects.

Specific Populations

The pharmacokinetics of megestrol acetate has not been studied in specific population, for example, pediatric, renal impairment, and hepatic impairment.

Drug Interactions

The effects of indinavir, zidovudine or rifabutin on the pharmacokinetics of megestrol acetate were not studied.

Zidovudine

Pharmacokinetic studies show that there are no significant alterations in exposure of zidovudine when megestrol acetate is administered with this drug.

Rifabutin

Pharmacokinetic studies show that there are no significant alterations in exposure of rifabutin when megestrol acetate is administered with this drug.

Indinavir

A pharmacokinetic study in healthy male subjects demonstrated that coadministration of megestrol acetate (675 mg for 14 days) and indinavir (single dose 800 mg) results in a significant decrease in the pharmacokinetic parameters (~32% for C_{max} and ~21% for AUC) of indinavir.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate at doses up to 0.01 to 0.1-fold the recommended clinical dose (13.3 mg/kg/day) based on body mass. No males were used in the dog and monkey studies. In female beagles, megestrol acetate (0.01, 0.1 or 0.25 mg/kg/day) administered for up to 7 years induced both benign and malignant tumors of the breast. In female monkeys, no tumors were found following 10 years of treatment with 0.01, 0.1 or 0.5 mg/kg/day megestrol acetate. Pituitary tumors were observed in female rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered in assessing the risk-to-benefit ratio when prescribing Megace® ES oral suspension and in surveillance of patients on therapy.

Megestrol acetate induced unscheduled DNA synthesis in primary cultures of human hepatocytes, but not in rat hepatocytes. Megestrol administered to mice increased the frequency of sister chromatid exchange and chromosomal aberrations in bone marrow cells after single intraperitonial doses of 16.25 and 32.50 mg/kg. Perinatal/postnatal (segment III) toxicity studies were performed in rats at doses up to 0.02 –fold the recommended clinical dose (13.3 mg/kg/day) based on body mass. In these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated females was impaired. Similar results were obtained in dogs. No toxicity data are currently available on male reproduction (spermatogenesis) *[see Warnings and Precautions (5.2)]*.

13.2 Animal Pharmacology and/or Toxicology

Long-term treatment with Megace® ES may increase the risk of respiratory infections. A trend toward increased frequency of respiratory infections, decreased lymphocyte counts and increased neutrophil counts was observed in a two-year chronic toxicity/carcinogenicity study of megestrol acetate conducted in rats.

14 CLINICAL STUDIES

Megestrol acetate oral suspension at a dose of 800 mg/20 mL is equivalent to 625 mg/5 mL of Megace® ES under the fed condition. The clinical efficacy of megestrol acetate oral suspension was assessed in two clinical trials as described below.

Trial 1

One was a multicenter, randomized, double-blind, placebo-controlled study comparing megestrol acetate (MA) at doses of 100 mg, 400 mg, and 800 mg per day versus placebo in AIDS patients with anorexia/cachexia and significant weight loss. Of the 270 patients entered on study, 195 met all inclusion/exclusion criteria, had at least two additional post baseline weight measurements over a 12 week period or had one post baseline weight measurement but dropped out for therapeutic failure. The percent of patients gaining five or more pounds at maximum weight gain in 12 study weeks was statistically significantly greater for the 800 mg (64%) and 400 mg (57%) MA-treated groups than for the placebo group (24%). Mean weight increased from baseline to last evaluation in 12 study weeks in the 800 mg MA-treated group by 7.8 pounds, the 400 mg MA group by 4.2 pounds, the 100 mg MA group by 1.9 pounds and decreased in the placebo group by 1.6 pounds. Mean weight changes at 4, 8 and 12 weeks for patients evaluable for efficacy in the two clinical trials is shown graphically. Changes in body composition during the 12 study weeks as measured by bioelectrical impedance analysis showed increases in non-water body weight in the MA-treated groups. In addition, edema developed or worsened in only 3 patients.

Greater percentages of MA-treated patients in the 800 mg group (89%), the 400 mg group (68%) and the 100 mg group (72%), than in the placebo group (50%), showed an improvement in appetite at last evaluation during the 12 study weeks. A statistically significant difference was observed between the 800 mg MA-treated group and the placebo group in the change in caloric intake from baseline to time of maximum weight change. Patients were asked to assess weight change, appetite, appearance, and overall perception of well-being in a 9 question survey. At maximum weight change only the 800 mg MA-treated group gave responses that were statistically significantly more favorable to all questions when compared to the placebo-treated group. A dose response was noted in the survey with positive responses correlating with higher dose for all questions.

Trial 2

The second trial was a multicenter, randomized, double-blind, placebo-controlled study comparing megestrol acetate 800 mg/day versus placebo in AIDS patients with anorexia/cachexia and significant weight loss. Of the 100 patients entered on study, 65 met all inclusion/exclusion criteria, had at least two additional post baseline weight measurements over a 12 week period or had one post baseline weight measurement but dropped out for therapeutic failure. Patients in the 800 mg MA-treated group had a statistically significantly larger increase in mean maximum weight change than patients in the placebo group. From baseline to study week 12, mean weight increased by 11.2 pounds in the MA-treated group and decreased 2.1 pounds in the placebo group. Changes in body composition as measured by bioelectrical impedance analysis showed increases in non-water weight in the MA-treated group (see Clinical Studies table). No edema was reported in the MA-treated group. A greater percentage of MA-treated patients (67%) than placebo-treated patients (38%) showed an improvement in appetite at last evaluation during the 12 study weeks; this difference was statistically significant. There were no statistically significant differences between treatment groups in mean caloric change or in daily caloric intake at time to maximum weight change. In the same 9 question survey referenced in the first trial, patients' assessments of weight change, appetite, appearance, and overall perception of well-being showed increases in mean scores in MA-treated patients as compared to the placebo group.

In both trials, patients tolerated the drug well and no statistically significant differences were seen between the treatment groups with regard to laboratory abnormalities, new opportunistic infections, lymphocyte counts, T4 counts, T8 counts, or skin reactivity tests *[see Adverse Reactions (6)]*.

Table 3: Megestrol Acetate Oral Suspension Clinical Efficacy Trials

Megestrol Acetate Oral Suspension Clinical Efficacy Trials						
	Trial 1 Study Accrual Dates 11/88 to 12/90				Trial 2 Study Accrual Dates 5/89 to 4/91	
Megestrol Acetate, mg/day	0	100	400	800	0	800
Entered Patients	38	82	75	75	48	52
Evaluable Patients	28	61	53	53	29	36
Mean Change in Weight (lb.) Baseline to 12 Weeks	0.0	2.9	9.3	10.7	-2.1	11.2
% Patients ≥5 Pound Gain at Last Evaluation in 12 Weeks	21	44	57	64	28	47
Mean Changes in Body Composition*:						
Fat Body Mass (lb.)	0.0	2.2	2.9	5.5	1.5	5.7
Lean Body Mass (lb.)	-1.7	-0.3	1.5	2.5	-1.6	-0.6
Water (liters)	-1.3	-0.3	0.0	0.0	-0.1	-0.1
% Patients With Improved Appetite: At Time of Maximum Weight Change	50	72	72	93	48	69
At Last Evaluation in 12 Weeks	50	72	68	89	38	67
Mean Change in Daily Caloric Intake: Baseline to Time of Maximum Weight Change	-107	326	308	646	30	464

*Based on bioelectrical impedance analysis determinations at last evaluation in 12 weeks.

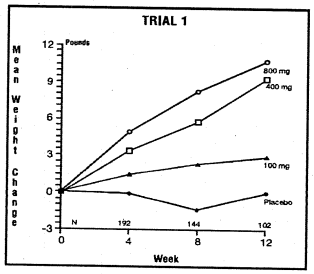

Figure 2: Mean Weight Change for Patients Evaluable for Efficacy in Trial 1

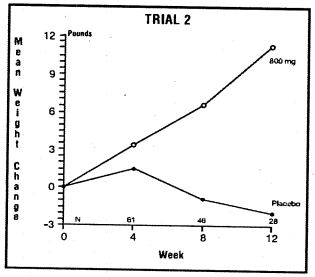

Figure 3: Mean Weight Change for Patients Evaluable for Efficacy in Trial 2

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Megace® ES oral suspension is a milky white, lemon-lime flavored oral suspension containing 125 mg of megestrol acetate per mL. Available in bottles of 150 mL (5 fl oz) NDC 49884-949-69.

16.2 Storage

Store Megace® ES oral suspension between 15° to 25° C (59° to 77° F) and dispense in a tight container. Protect from heat.

16.3 Safe Handling

Health Hazard Data

There is no threshold limit value established by OSHA, NIOSH, or ACGIH. Exposure or overdose at levels approaching recommended dosing levels could result in side effects described above *[see Warnings and Precautions (5) and Adverse Reactions (6)]*. Women at risk of pregnancy should avoid such exposure.

17 PATIENT COUNSELING INFORMATION

The prescriber should inform the patient about the product differences to avoid overdosing or underdosing of megestrol acetate. The recommended adult dosage of Megace® ES is one teaspoon (5 mL) once a day *[see table in Dosage and Administration (2)]*.

Patients using Megace® ES should receive the following instructions:

- This medication is to be used as directed by the physician.
- Megace® ES (625 mg/5 mL) does not contain the same amount of megestrol acetate as Megace® oral suspension or any of the other megestrol acetate oral suspensions. Megace® ES contains 625 mg of megestrol acetate per 5 mL (125mg/mL) whereas Megace® oral suspension and other megestrol acetate oral suspensions contain 800 mg per 20 mL (40 mg/mL).
- Report any adverse reaction experiences while taking this medication.
- Use contraception while taking this medication if you are a woman capable of becoming pregnant.
- Notify your physician if you become pregnant while taking this medication.

Manufactured by:
PAR PHARMACEUTICAL COMPANIES, INC.
Spring Valley, New York 10977

Revised: 07/10 OS949-52-1-05

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PAR PHARMACEUTICAL, INC.,

Plaintiff,

v.

UNITED STATES OF AMERICA et al.,

Defendants.

Case No. _____

[PROPOSED] ORDER GRANTING
PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

This matter is before the Court on the motion of plaintiff Par Pharmaceutical, Inc. ("Par") for a preliminary injunction. *See* Fed. R. Civ. P. 65. Par seeks to enjoin the government from applying provisions of the Federal Food, Drug and Cosmetic Act (the "Act"), 21 U.S.C. §§ 331(a), 331(d), 352(f)(1), and 355(a), and regulations of the U.S. Food and Drug Administration ("FDA") interpreting the Act, 21 C.F.R. §§ 201.100, 201.128, and 202.1(*l*)(2), to criminalize Par's truthful and non-misleading speech to healthcare professionals about the FDA-approved, on-label use of Par's FDA-approved prescription drug, Megace® *ES*. Par contends that the government's interpretation of these statutes and regulations as criminalizing Par's truthful and non-misleading speech is contrary to both the First Amendment and the Act.

Having considering the parties' arguments, this Court hereby ORDERS that Par's motion for a preliminary injunction is GRANTED. This Court's jurisdiction is proper under 28 U.S.C. §§ 1331 and 2201(a); venue is proper under 28 U.S.C. § 1391(e). This Court also finds that Par has carried its burden of establishing (1) that Par "is likely to succeed on the merits" in proving that the challenged regulations are contrary to the First Amendment and the Act itself; (2) that

Par is suffering and is likely to continue "to suffer irreparable harm" to its First Amendment rights "in the absence of preliminary relief"; (3) "that the balance of equities tips in [Par's] favor"; and (4) "that an injunction is in the public interest." *Mills v. District of Columbia*, 571 F.3d 1304, 1308 (D.C. Cir. 2009). Par also has no adequate remedy at law.

It is therefore hereby ORDERED that the named defendants, the United States, the U.S. Food & Drug Administration, Dr. Margaret Hamburg, Commissioner of Food and Drugs, and Kathleen Sebelius, Secretary of the Department of Health & Human Services, along with the named defendants' officers, agents, servants, employees, and attorneys, or any other persons who are in active concert or participation with them, or having actual or implicit knowledge of this Order by personal service or otherwise, are hereby preliminarily enjoined from enforcing 21 U.S.C. §§ 331(a), 331(d), 352(f)(1), and 355(a), and 21 C.F.R. §§ 201.100, 201.128, and 202.1(*l*)(2), against Par for engaging in truthful and non-misleading speech to healthcare professionals about the FDA-approved, on-label use of Megace® *ES*.

It is further ORDERED that the named defendants, the United States, the U.S. Food & Drug Administration, Dr. Margaret Hamburg, Commissioner of Food and Drugs, and Kathleen Sebelius, Secretary of the Department of Health & Human Services, along with the named defendants' officers, agents, servants, employees, and attorneys, or any other persons who are in active concert or participation with them, or having actual or implicit knowledge of this Order by personal service or otherwise, shall not take any action inconsistent with this Court's Order.

It is further ORDERED that bond be set at $1. *See* Fed. R. Civ. P. 65(c).

SO ORDERED.

_____

United States District Judge

October ___, 2011