EXHIBIT B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

K-V PHARMACEUTICAL COMPANY *et al.*, Plaintiffs, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	No. 1:12-cv-01105-ABJ

BRIEF OF *AMICI CURIAE* ALERE WOMEN'S AND CHILDREN'S HEALTH, LLC, AND INTERESTED PHYSICIANS IN SUPPORT OF DEFENDANTS

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PRELIMINARY STATEMENT

Plaintiffs' drug, Makena, is a recent, branded version of a pharmaceutical compound, commonly referred to as 17 α -hydroxyprogesterone caproate (commonly known as "17P" or, alternatively "17HPC"), which has been on the market for more than 50 years. Largely on the basis of two studies funded by the National Institutes of Health ("NIH"), Plaintiffs' predecessor obtained from the Food and Drug Administration ("FDA") a new drug approval ("NDA") for 17P to treat a relatively rare condition in certain pregnant women at risk for pre-term birth. Before the NDA was granted, *amicus* Alere Women's and Children's Health, LLC, a Delaware limited liability company ("Alere") had been administering a compounded, preservative-free version of 17P for administration to pregnant women for this condition. Even after Makena's approval, some doctors continued to prescribe the compounded version of the drug for certain patients for various reasons, including concern over the preservative in Makena—benzyl alcohol—which has been associated in some studies with serious medical complications in newborns.

Plaintiffs were afraid that sales of compounded 17P would threaten their ability to recoup the $200 million premium they paid for Makena's NDA, and they undertook a false and misleading publicity campaign designed to eliminate compounding. As the Government notes in its brief, Plaintiffs falsely told physicians and pharmacists that prescribing or compounding preservative-free 17P was categorically prohibited under the Food, Drug, and Cosmetic Act ("FDCA") and that FDA was obligated to take enforcement action against a physician or pharmacist that continued to do so. To correct the public record, FDA issued a press release that made clear that Plaintiffs' NDA did not make compounding illegal in all circumstances, and further announced that FDA did not intend to take enforcement action against compounding practices for 17P that did not raise health or safety concerns. FDA has subsequently clarified

that only compounding within the limits of traditional pharmacy practice, as specified in statute and FDA policy guidance, is permitted and that FDA retains the option to take enforcement action against any pharmacy that fails to adhere to those limits.

Plaintiffs ask this Court to order FDA to issue yet another press release signaling a more aggressive enforcement policy, and then to assume ongoing supervision of FDA's enforcement activities in a manner reminiscent of a court putting a public agency into receivership. Plaintiffs plainly intend to use this further press release in yet another campaign to put a complete stop to the compounding of preservative-free 17P. Contrary to the picture Plaintiffs would like to paint, compounding is a well established feature of traditional pharmacy practice and has been recognized as permitted under specified circumstances under the FDCA by Congress, FDA, and even the Supreme Court. Compounding, on the instructions of the physician and where there is a need for the compounded version for an individual patient, is also consistent with the basic principle of the FDCA that the federal government does not seek to regulate the practice of medicine or physicians' exercise of their medical judgment. The decision of many doctors, including the *Amici* Physicians, to prescribe for a given patient a compounded version of 17P that does not contain benzyl alcohol as a preservative is an appropriate exercise of their professional medical judgment that is permitted under the FDCA.

No authority remotely supports Plaintiffs' extreme and unprecedented request for this Court to take over supervision of FDA's enforcement activities at the request of a private party. The decision regarding whether any particular instances of compounding exceed the scope of permissible traditional pharmacy practice is one that quintessentially requires the exercise of FDA's technical expertise. Likewise, the decision to take enforcement action against any compounding that may violate the FDCA requires FDA to weigh competing policy goals and

enforcement priorities. Moreover, in addition to the general presumption against judicial review of an agency's non-enforcement decisions, the FDCA contains a specific provision precluding private enforcement of the Act. Plaintiffs' suit is a patent attempt to do just that.

Finally, even if the Court had authority to hear Plaintiffs' case and to grant the extraordinary relief Plaintiffs request, the balance of equities weighs decisively against granting Plaintiffs any equitable relief. To begin, Plaintiffs' own filings before another court contradict the stated basis for Plaintiffs' request for relief from this Court. Whereas Plaintiffs' suit for injunctive relief before this Court characterize FDA's public statements as having affirmatively encouraged nationwide distribution of uncustomized compounded 17P in unlimited quantities, *see* Plaintiffs' Injunction Mem. (ECF No. 2) 15, Plaintiffs have taken precisely the opposite position in a newly filed action in the United States District Court for the Northern District of Georgia. In that suit, challenging an alleged policy to deny coverage for Makena under Georgia's Medicaid program, Plaintiffs repeatedly characterize FDA's statements as making increasingly clear that the FDCA's statutory limits apply to the compounding of 17P and that FDA may take enforcement action against compounding that is inconsistent with those limitations. Plaintiffs should not be permitted to seek equitable relief based on a factual assertion of harm that is contradicted by Plaintiffs' own filings in another judicial forum. Even apart from Plaintiffs' inconsistency, the public interest weighs heavily in favor of the continued availability of a preservative-free version of 17P, which studies indicate raise no safety or efficacy concerns, and which is within the financial means of patients. Plaintiffs' interest is to charge monopoly prices that will allow them to recover the $200 million premium they paid for an NDA that was largely publicly funded. Saving Plaintiffs from their miscalculation about the monopoly prices they would be able to charge is not a public interest that warrants equitable relief. And

Plaintiffs' waging of a false and misleading publicity campaign to intimidate pharmacists and physicians constitutes unclean hands that should independently preclude equitable relief.

For all the foregoing reasons, further explained below, Plaintiffs' request for injunctive relief should be denied.

STATEMENT OF PERTINENT FACTS

Alere

Alere delivers a wide spectrum of obstetrical care services, including risk assessment to identify women at risk for pregnancy complications, home-based obstetrical programs and nursing services to manage and monitor pregnant women who have medical or pregnancy-related problems that could harm the health of the mother or baby, and neonatal programs for early infant care management. Alere is a subsidiary of Alere Inc., a diversified healthcare company with a wide range of product and service offerings.

Alere contracts with hospitals, physicians, and third-party payors including Medicaid and private health insurance companies for the provision of its services to patients for whom the services are deemed appropriate. Among the services offered by Alere is an at-home nursing service designed to manage the risk of preterm birth for suitable patients. Preterm birth is defined as birth occurring before the 37th week of pregnancy. *See* Centers for Disease Control and Prevention: Premature Birth, http://www.cdc.gov/features/prematurebirth (last visited July 24, 2012). Over 500,000 preterm births occur each year in the United States, representing approximately 12.5% of all births, and that rate has been increasing in recent years. *Id.* The causes of preterm birth are not clearly understood and can happen to any woman, but certain factors may increase the risk for early delivery, including carrying twins, triplets, or more, or having had a preterm birth in the past. Preterm birth is a serious, and often fatal, medical event. As summarized by the Centers for Disease Control and Prevention (*id.*):

> [P]reterm delivery is the most frequent cause of infant deaths. Some premature babies require special care and spend weeks or months hospitalized in a neonatal intensive care unit (NICU). Those who survive may face lifelong problems such as [i]ntellectual disabilities, [c]erebral palsy, [b]reathing and respiratory problems, [v]ision and hearing loss, and [f]eeding and digestive problems.

Alere's preterm management home nursing service provides initial and ongoing education regarding preterm labor identification, interventions, and medication regimens; identifies warning signs of preterm labor through weekly physician-prescribed assessments; provides physician-ordered administration services for physician-prescribed medication for the prevention of preterm labor, including both compounded 17P and Makena; monitors compliance with the prescribed treatment regimen; and assists in the identification of other concomitant high risk pregnancy conditions. Over the past nearly 30 years since introducing its preterm management home nursing service, Alere has managed over 750,000 high-risk obstetrical cases.

The *Amici* Physicians[1]

The *Amici* Physicians are respected practicing specialists in obstetrics and gynecology; some hold academic appointments in that specialty as well. In their practices, the *Amici* Physicians regularly see and treat women at risk of preterm birth. The *Amici* Physicians use a range of treatment modalities to manage that risk, including prescribing 17P. All of the *Amici* Physicians have prescribed compounded 17P for some of their patients and have utilized Alere's 17P administration service for that treatment. For the reasons stated below, the *Amici* Physicians believe it is vital, from a public health standpoint, to maintain the availability of compounded 17P for the prevention of preterm birth.

[1] The *Amici* Physicians are identified in Appendix 1.

17P

Currently, the drug most commonly prescribed by physicians for the prevention of preterm birth is 17P. 17P is a synthetic steroid progestin hormone that is an ester derivative of 17α-hydroxyprogesterone formed from caproic acid (hexanoic acid) and is similar to the naturally occurring steroid hormone progesterone. 17P works by relaxing the uterus and slowing down contraction signals. Studies to date have not reported serious side effects from 17P for either mother or baby; the most common problems are soreness, irritation, itching, bruising, swelling or pain that can occur at the injection site.

17P is not a recently discovered drug, nor was it invented or developed by Plaintiffs or their predecessors. To the contrary, 17P was developed some six decades ago and was first approved by FDA for marketing in the U.S. in 1956 under the brand name Delalutin. As originally approved, the drug was indicated for use, not in preventing preterm birth, but rather for other medical conditions, including the treatment of uterine cancer and amenorrhea.[2] The drug remained on the market for nearly 45 years, until 2000, when the drug's marketer, Bristol Myers Squibb, requested, and FDA granted, withdrawal of the drug from the market. 65 Fed. Reg. 55,264 (Sept. 13, 2000). FDA subsequently advised that Delalutin was not withdrawn from the market for reasons of safety or effectiveness.[3] 75 Fed. Reg. 36,419, 36,420 (June 25, 2010).

As noted in the Declaration of Michael Jozwiakowski submitted with Plaintiff's motion papers, in June 2003, several years after the withdrawal of Delalutin from the market, a landmark

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[2] Specifically, the last version of the approved labeling for Delalutin stated that it was approved for the following indications in non-pregnant women: (1) the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); (2) the management of amenorrhea (primary or secondary); (3) abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; (4) as a test for endogenous estrogen production (Medical D&C); and (5) the production of secretory endometrium and desquamation. *See* 75 Fed. Reg. at 36,419.

[3] It is Alere's understanding that other drug treatments became available for the conditions that Delalutin had been approved to treat and effectively rendered Delalutin obsolete, resulting in a decrease in sales to the point that it was no longer commercially feasible to maintain on the market.

study conducted by the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development, part of the NIH, was published in the New England Journal of Medicine. Jozwiakowski Decl. ¶ 5 [ECF No. 2-3]; *see* Paul J. Meis, et al., *Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate*, 348 New. Eng. J. Med. 2379 (June 12, 2003), *available at* http://www.nejm.org/doi/pdf/10.1056/nejmoa035140. This study, known as the "Meis Study" after its principal investigator, showed that weekly treatments with 17P beginning between the 16th week and 20th week and 6th day of gestation significantly reduced the rate of preterm delivery before 37 weeks, 35 weeks, and 32 weeks of gestation among a cohort of 310 women who were pregnant with a singleton and who had a history of singleton spontaneous preterm birth. A follow-up study of the children born to women who were treated with 17P injection during their pregnancies demonstrated no increased risks for birth defects for fetuses. Jozwiakowski Decl. ¶ 5; *see* Allison Northen, et al., *Follow-up of Children Exposed in Utero to 17-Alpha-Hydroxyprogesterone Caproate Compared with Placebo*, 110 Obstetrics & Gynecology 865 (Oct. 2007), *available at* http://journals.lww.com/greenjournal/fulltext/2007/10000/follow_up_of_children_exposed_in_utero_to_17.21.aspx.

Based on that publication, physicians, including *Amici* Physicians, increasingly prescribed 17P for patients at risk of preterm birth. Although Delalutin had been withdrawn from the market, the drug was lawfully available from licensed compounding pharmacists. Indeed, as noted in the Declaration of Michael Jozwiakowski submitted with Plaintiff's motion papers, the 17P used in the NIH studies was not supplied by the previously FDA-approved marketer, but rather was custom-manufactured by two contract manufacturers. Jozwiakowski Decl. ¶ 5 & Exs. 2, 3.

In 2006, on the basis of the NIH studies, Plaintiffs' predecessor submitted a New Drug Application to FDA for an identical formulation of 17P for use "to reduce the risk of preterm birth in women with singleton pregnancy who have a history of singleton spontaneous preterm birth." *Id.* ¶ 4. FDA approved that application and granted a request for "orphan drug" status to Makena in February 2011. *Id.* ¶ 4 & Ex. 2. The approved instructions for use direct that the drug be administered beginning between the 16th week and 20th week and 6th day of gestation.

While FDA specifically approved Makena for patients with a singleton pregnancy and a history of a singleton preterm birth, and specified when in the gestation cycle the use of the drug is approved to begin, physicians are free to prescribe, and frequently do prescribe, 17P for other patients who the physician concludes may be at risk for preterm birth, including those who exhibit symptoms of that condition, those who are carrying multiple fetuses, and those who are diagnosed before the 16th gestational week or after the 20th week. Indeed, the 130,000 patients referenced by Plaintiffs in their papers represent only about a quarter of the approximately 500,000 annual cases of preterm birth in the U.S. Thus, while the population of patients who meet the specific indications for use for which FDA granted Orphan Drug Approval for Makena may fall below the statutory threshold for orphan drug status (i.e., 200,000), the population of patients who potentially would benefit from 17P is much larger.

Alere's 17P Administration Service

As noted above, since the publication of the Meis Study, 17P has been increasingly prescribed by physicians and utilized by women across the United States for prophylaxis against recurrent spontaneous preterm delivery. As Delalutin had been withdrawn from the market, 17P was obtainable only from compounding pharmacies. Obtaining compounded 17P and scheduling its weekly administration, however, posed certain challenges for patients and providers. To

address these challenges, Alere introduced, and since 2003 has continuously offered, a 17P home nurse administration care management program to provide weekly maternal assessment and administration of compounded 17P in the patients' homes. From inception, the comprehensive program has included the administration of physician-prescribed, patient-specific, unit dose vials of 17P compounded by a contracted compounding pharmacy. Following FDA's market approval of Makena, Alere also has offered administration of Makena in its 17P administration program.

Treatment with 17P (compounded or Makena) entails weekly deep intramuscular injection of 250mg/ml of the drug per physician order. As with all of the preterm management nursing services provided by Alere, Alere's provision of nursing services in executing physicians' prescribing orders and administering physician-prescribed 17P is conducted in accordance with the laws and regulations administered by state boards of nursing relating to administration of prescribed medications and the laws and regulations of home health agencies where applicable.

From the outset, the formulation of compounded 17P that Alere has administered has been preservative-free. In this regard, the product differs from Makena, which contains the preservative benzyl alcohol. The individual doses of compounded, preservative-free 17P administered by Alere's nurses are, and have always been, compounded by an independent compounding pharmacy in response to an individual physician's prescription for an individual patient. The compounding pharmacy maintains strict quality-control procedures and documentation to assure sterility and potency of the compounded product, as required by USP General Chapter 797 compendial standards for pharmaceutical compounding of sterile preparations. Among other steps, the compounding pharmacy submits the compounded 17P

prescribed by a physician to an independent laboratory for testing to assure purity and potency, quarantines the compounded 17P pending confirmation that it conforms to the applicable quality standards, immediately reports any nonconforming test results to Alere, and destroys any nonconforming 17P. Once these quality assurance procedures have been completed, the pharmacy has responsibility for delivery of the compounded product to the patient's home.

Alere's 17P administration service using compounded preservative-free 17P has been an unqualified success, as is made abundantly clear in a careful independent study by Dr. Baha Sibai and others, to be published in the August issue of the peer-reviewed *American Journal of Perinatology* and currently available on-line ("Sibai Study"). *See* B. Sibai, et al., *Pregnancy Outcomes of Women Receiving Compounded 17 α-Hydroxyprogesterone Caproate for Prophylactic Prevention of Preterm Birth 2004 to 2011*, Am. J. of Perinatology (forthcoming Aug. 2012), *available at* https://www.thieme-connect.de/DOI/DOI?10.1055/s-0032-1311979. The Sibai Study entailed a comprehensive review of outcome data from over 5,000 patients who received a course of injections of compounded preservative-free 17P and a detailed comparison of those outcomes to the outcomes reported for the 310 subjects in the pioneering Meis Study. As the report of the Sibai Study summarizes (*id.*):

> Rates of preterm delivery at <37 weeks were not remarkably different between the populations. Rates of delivery at <35 and <32 weeks were lower in the home administration sample as compared with the NICHD study group. Rates of miscarriage, stillbirth, neonatal death, and total perinatal mortality were also lower in the current study sample.

The report also notes:

> Presently, there is no evidence that the FDA-approved product is safer or more effective than compounded 17P. In fact, since the 2003 NICHD-MFMU publication, compounded 17P has been the only α-hydroxyprogesterone caproate product available for patients outside of the research setting until the availability of the FDA-branded Makena™ in February 2011. Indeed, there are vastly

more data available from women receiving compounded 17P than Makena™.[4]

Likewise, in Alere's own recent statistical study of outcomes from treatments of patients receiving Alere's compounded preservative-free 17P administration services over a five-year period,[5] Alere found a 47% reduction in the rate of spontaneous preterm deliveries prior to 37 weeks, as compared to the Meis Study placebo group; a 55% reduction in the rate of all preterm deliveries prior to 35 weeks; and a 71% reduction in the rate of all preterm deliveries prior to 32 weeks. On average, 19.3 weeks of pregnancy were gained between the start of the administration nursing service and delivery, with an average of 17 injections of compounded 17P administered per patient.

In short, the aspersions cast by Plaintiffs against compounded 17P are not borne out by the evidence. Rather, as the Sibai Study concluded, "there is no evidence that the FDA-approved product is safer or more effective than compounded 17P." *Id.*

Physicians' Preference For Compounded Preservative-Free 17P

Although Alere now offers both the administration of Makena and the administration of compounded preservative-free 17P, the decision to prescribe and choice of formulation rests entirely with the prescribing physician, based on the patient's needs and the physician's medical judgment. Alere carefully documents that choice with respect to each patient.

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[4] Other peer-reviewed research reinforces the conclusions reached in the Sibai Study regarding the compounded preservative-free 17P administered by Alere. *See, e.g.,* Brad Lucas et al., *Pregnancy Outcomes of Managed Medicaid Patients Prescribed Home Administration of 17P*, 29 Am. J. of Perinatology 489 (2012); Victor H. Gonzalez-Quintero et al., *Rates of preterm delivery in women receiving nurse administered 17P in a home vs. office setting*, 206 Am. J. of Obstetrics & Gynecology S82 (Jan. 2012) Andrei Rebarber et al., *Using 17 alpha-hydroxyprogesterone caproate to impact rates of recurrent preterm delivery in clinical practice*, 23 J. Maternal Fetal Neonatal Med. 1139 (Oct. 2010).

[5] An integral part of Alere's 17P administration program has been the prospective collection of comprehensive historic, demographic, clinical, safety, and outcome data for each patient receiving the 17P injections.

One factor that may influence a physician's choice is that, as noted above, Makena, unlike the compounded 17P administered by Alere when prescribed, contains 2% benzyl alcohol as a preservative. Many physicians, including *Amici* Physicians, have concerns about possible health risks from the use of benzyl alcohol as a preservative in pharmaceutical products administered to newborns as well as to pregnant women. The risk posed by the direct administration of a drug containing benzyl alcohol to a newborn has been summarized as follows in a well-respected journal's *A Guide to Pharmaceutical Excipients (Inert Ingredients)*:

> The link between benzyl alcohol and neonatal cardiovascular collapse, "the gasping baby syndrome," is perhaps the most widely publicized adverse reaction related to the use of inert ingredients. This relationship was discovered in 1982 after a series of neonates died or developed a severe illness associated with gasping respirations, metabolic acidosis, and hematologic abnormalities. These cases were linked to the use of intravenous flush solutions and medications containing benzyl alcohol. As a result, both the FDA and the American Academy of Pediatrics now recommend that benzyl alcohol containing products should be avoided whenever possible in infants. In older patients, benzyl alcohol use has been associated with hypersensitivity reactions, including contact dermatitis, nausea, and angioedema.

2 Pediatric Pharmacotherapy No. 9, at 1-2 (Sep. 1996), *available at* http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news/1995-2000/199609.pdf (citing J. Gershanik et al., *The Gasping Syndrome and Benzyl Alcohol Poisoning*, 307 New Eng. J. of Med. 1384 (1982); Centers for Disease Control, *Neonatal Deaths Associated with Use of Benzyl Alcohol*, 31 MMWR 290 (1982); Committee on Fetus and Newborn, Committee on Drugs, American Academy of Pediatrics, *Benzyl Alcohol: Toxic Agent in Neonatal Units,* 72 Pediatrics 356 (1983)).

Based on the clinical evidence, many authorities have concluded that pharmaceutical products containing benzyl alcohol should never be used with newborns. *See also, e.g.*, C. Anderson et al., *Benzyl Alcohol Poisoning in a Premature Newborn Infant*, 148 Am. J. Obstetrics

& Gynecology 344, 345 (1984) (case study and literature review, concluding "The use of benzyl alcohol-preserved bacteriostatic saline is dangerous and discontinuance of this agent in newborn infants is recommended."); D. Jardine & K. Rogers, *Relationship of Benzyl Alcohol to Kernicterus, Intraventricular Hemorrhage, and Mortality in Preterm Infants*, 63 Pediatrics 153 (1989) ("Studies have now shown a significant decrease in the incidence of intraventricular hemorrhage and death as well as cerebral palsy and developmental delay among preterm infants since the discontinuation of benzyl alcohol from use in nurseries.").

It is not presently known whether, and to what degree, benzyl alcohol passes through the placenta to the fetus; thus, it is not known whether, and to what extent, use of benzyl alcohol as a preservative in a drug poses a risk to a fetus when administered to a pregnant woman. *See, e.g.*, S. Moll, *A Low-Molecular-Weight Heparin Preparation Contraindicated During Pregnancy*, 184 Am. J. Obstetrics & Gynecology 344, 1046 (2001) ("Benzyl alcohol cannot be cleared by the immature liver of the premature infant and therefore accumulates, leading to metabolic acidosis and hyperventilation. Several deaths have occurred. In a pregnant woman treated with preparations of benzyl alcohol-containing drugs, the alcohol is cleared by the mother's liver and is therefore unlikely to cause damage to the fetus. Because benzyl alcohol may cross the placenta, however, the package insert of benzyl alcohol-containing vials contains the warning that it should not be used during pregnancy.").

The uncertainty over the potential adverse effects on a fetus of administering drugs that contain benzyl alcohol to pregnant women has led FDA to require, on the labeling of some pharmaceutical products such as heparin (a commonly-used blood-thinning medication), contraindications and warnings relating to use by pregnant women.[6] This uncertainty also has

[6] *See, e.g.*, Heparin Sodium Injection, http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm219000.htm (last visited July 24, 2012) ("If available, preservative-free Heparin Sodium Injection is recommended when heparin

caused many medical professionals, including the *Amici* Physicians, to avoid where practicable the use, with pregnant women, of parenteral pharmaceutical drugs containing benzyl alcohol. *See, e.g.*, Sibai Study ("Benzyl alcohol, although not contraindicated in pregnancy, is generally avoided, if possible, in sterile preparations for pregnant patients due to concerns about the risk for serious adverse events and death, particularly in pediatric patients."). Consistent with this trend, Alere has found that, even for patients who meet Makena's specific approved indication for use, many treating physicians determine that there is a medical reason to prescribe the compounded preservative-free formulation of 17P, rather than Makena.

The *Amici* Physicians are well aware that the FDA has approved Makena as safe for the indicated use. That approval, however, is not a guarantee that the drug is without risk of adverse effects for every patient, or any particular patient, any more than FDA's determination that Makena is effective for the indicated use guarantees that the drug will work as intended for every patient who receives it. Most approved prescription drugs—indeed, even most over-the-counter drugs —carry some risk of adverse effects in some patients.[7] The *Amici* Physicians stress that it

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therapy is needed during pregnancy. There are no known adverse outcomes associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration; however, the preservative benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants."); PROCRIT, http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088988.pdf ("Dangers of giving PROCRIT to newborns, infants, and pregnant or breastfeeding women. Do not use PROCRIT from multi-dose vials in newborns, infants, pregnant or breastfeeding women because the PROCRIT in these vials contains benzyl alcohol. Benzyl alcohol has been shown to cause brain damage, other serious side effects, and death in newborn and premature babies. PROCRIT that comes in single-dose vials does not contain benzyl alcohol. *See* "Who should not take PROCRIT?"); LOVENOX - enoxaparin sodium injection, http://www.pdr.net/drugpages/productlabeling.aspx?mpcode=73081210#section-8.4 (last visited July 24, 2012) ("Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed.");Bacteriostatic Sodium Cloride: Injection, http://editor.appharma.com/PIs/Sodium_Chloride_0_9Pct_Bacterio_45765D_Apr_08.pdf ("Pregnancy Category C. Animal reproduction studies have not been conducted with Bacteriostatic 0.9% Sodium Chloride Injection, USP. It is also not known whether Bacteriostatic 0.9% Sodium Chloride Injection containing additives can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Bacteriostatic 0.9% Sodium Chloride Injection containing additives should be given to a pregnant woman only if clearly needed.").

[7] Indeed, FDA's determination that a drug is safe for use does not preclude FDA from later withdrawing approval of the drug based on adverse effects that became apparent after initial approval.

is ultimately their responsibility to appreciate those risks, as well as the potential benefits, of various treatment options and to make informed expert medical judgments about the patient's best interests in the light of those risks and benefits. In many instances, the medical judgment of many physicians, including *Amici* Physicians, is that compounded preservative-free 17P is preferable to Makena because of the potential risk posed by Makena's inclusion of benzyl alcohol as a preservative.

As a separate matter, many physicians, including the *Amici* Physicians, prescribe 17P for pregnant women who do not fall within the parameters set forth in Makena's approved indication for use (i.e., singleton pregnancy and a history of singleton preterm birth) or its approved instructions for use (treatment to begin between the 16th week and 20th week and 6th day of gestation).[8] For example, some patients do not have a history of a singleton preterm birth, but present with other risk factors. Other patients are pregnant with multiple fetuses. Still other patients may not be diagnosed as needing medication for preterm labor until after the 20th gestation week. Indeed, for economic and other reasons, many Medicaid patients do not even obtain prenatal care until late in their pregnancies.

As noted above, the estimated 130,000 patients who meet the approved indications for use of Makena represent only about a fourth of the total of 500,000 preterm births every year in the United States. For the other 370,000 potential patients, there is no FDA-approved

[8] Several peer-reviewed studies indicate the potential benefits of administering 17P to such patients. *See, e.g.*, Lucas, et al., *supra*, 29 Am. J. of Perinatology 489 (initiating home-based 17P administration at 21-26.9 weeks of gestation yields results that are comparable to results from initiating administration at 16-20.9 weeks in terms of gestational age at birth and NICU utilization); H.Y. How et al., *Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter?*, 197 Am. J. of Obstetrics & Gynecology 260 (Sep. 2007) (same) . Likewise, Alere's own patient statistics show that many patients other than those with singleton pregnancies and a history of a singleton preterm birth have benefitted from administration of compounded preservative-free 17P. For example, Alere's most recent analysis of patients who received administration of compounded 17P over a five-year period but who would not have fallen within the parameters set forth in Makena's approved indication for use (i.e., singleton pregnancy and a history of singleton preterm birth) or its approved instructions for use (treatment to begin between the 16th week and 20th week and 6th day of gestation) shows results equal to or better than those obtained in the Meis Study in terms of the number of preterm births by the 32nd and 37th weeks, and comparable results at the 35th week.

commercially available drug for the prevention of preterm birth, although physicians are free to prescribe either Makena or compounded 17P in their medical judgment. If compounded 17P were eliminated from the U.S. market, as Plaintiffs effectively seek, only Makena, with benzyl alcohol, would be available for physicians to prescribe off-label even for those 370,000 patients who, at present, do not meet the approved indication for Makena or whose pregnancy is beyond the temporal range set forth in Makena's instructions for use.

For all these reasons, Alere and the *Amici* Physicians strongly believe it is medically appropriate and, from a public-health standpoint, vital that physicians continue to have the option of treating patients with compounded preservative-free 17P.

Plaintiffs' Inequitable Conduct

Although it is perhaps understandable that Plaintiffs, seeking to maximize profits, would like to achieve and maintain an absolute monopoly on 17P, it is regrettable that, in seeking that outcome, Plaintiffs have engaged in tactics going well beyond the initiation of this lawsuit and have engaged in acts of blatant intimidation and deception of the medico-pharmacological community. Specifically, Alere has received multiple reports from physicians, including *Amici* Physicians, who have been visited by Plaintiffs' sales representatives and advised—falsely—that physicians are at risk of *malpractice suits* if they continue to prescribe compounded 17P. Likewise, Plaintiffs mounted a public-relations campaign designed to convince pharmacists—again, falsely—that FDA would no longer permit the compounding of versions of 17P following the approval of Makena. While an *amicus* brief does not afford Alere the opportunity to develop a record in this regard, we do not believe Plaintiffs' conduct should go without note.

Plaintiffs' inequitable conduct extends as well to their activities before the courts. Plaintiffs' complaint and motion for injunctive relief before this Court take, as their fundamental

premise, the assertion that FDA has "*approved and encouraged* … nationwide distribution, during KV's exclusivity period and for Makena's approved indication, of *unlimited quantities of uncustomized 17P*." Plaintiffs' Injunction Mem. 15 (emphasis added); *see id.* at 21 (asserting that FDA has "announce[d], as a matter of general applicability and future effect, that FDA will permit unlimited market entry of compounded versions of 17P during KV's exclusivity period"). Plaintiffs have taken precisely the opposite position, however, in a newly filed action in the United States District Court for the Northern District of Georgia. In their Georgia suit, Plaintiffs challenge an alleged policy of the Georgia Department of Community Health to deny coverage for Makena under the Georgia Medicaid program. In that context, Plaintiffs state in unequivocal terms that FDA's public statements "leave no room for doubt" that the FDCA's statutory limits on compounding apply to 17P. Complaint ("*Cook* Complaint") 24, *K-V Pharmaceutical Co. v. Cook*, No. 12-cv-2491 (N.D. Ga. July 17. 2012) (attached as Appendix 2). In that suit, in contrast to this, Plaintiffs characterize FDA as becoming increasingly "direct in its statements" about compounded 17P, culminating in a Q&A about Makena published on June 29, 2012, in which FDA stressed that it "may take enforcement action against pharmacies that compound large volumes of drugs that are essentially copies of commercially available products." *Id.* at 6. In Plaintiffs' own words, FDA's June 29 public statement "got right to the point" in making clear that prescribing the compounded version of 17P rather than Makena is appropriate only where "the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product." Memorandum in Support of Application for Preliminary Injunction ("*Cook* Injunction Mem.") 8-9, *K-V Pharmaceutical Co. v. Cook*, No. 12-cv-2491 (N.D. Ga. July 17. 2012) (attached as Appendix 3) (quoting June 29 FDA Q&A).

Plaintiffs' statements in the *Cook* filings severely undercut the position taken in the instant action.

ARGUMENT

I. COMPOUNDING IS AN ACCEPTED AND VITAL PART OF THE HEALTH CARE SYSTEM, BUT PLAINTIFFS' SUIT POSES A DIRECT THREAT TO THAT PRACTICE, WHICH IS CRITICAL TO PATIENT HEALTH

A. Compounding is a Critical Part of the Medical System

Drug compounding is the long-standing pharmacy practice by which a pharmacist "combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient." *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 361 (2002). Compounding is as old as pharmacy itself and central to the practice of the modern profession. As the Supreme Court recently observed, drug compounding is "a traditional component of the practice of pharmacy" essential to allowing "patients with particular needs [to] obtain medications suited to those needs." *Id.* at 361, 369. Even with the growth of mass pharmaceutical production, compounding has remained a vital tool in medical practice.[9] Today, most pharmacy schools continue to teach compounding, most states require that pharmacists have sufficient education and equipment to perform basic compounding services,[10] and most hospitals administer compounded drugs. *See Western States Med. Ctr. v. Shalala*, 69 F. Supp. 2d 1288, 1291 (D. Nev. 1999). FDA continues to recognize drug compounding by pharmacies as "a valuable medical service that is an integral part of our modern health care system." *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect*

[9] Virtually every pharmacy in the United States compounds, and "[e]stimates of the proportion of prescriptions that are compounded range from 1% to 10% of all prescriptions." Jesse M. Boodoo, *Compounding Problems and Compounding Confusion: Federal Regulation of Compounded Drug Products and the FDAMA Circuit Split*, 36 Am. J. Law & Med. 220, 223 (2010) ("Today, at least thirty million prescriptions are compounded each year.").

[10] Some states consider compounding to be so vital as to require licensed pharmacies to offer compounding services. *See, e.g.*, W. Va. Code St. R. § 15-1-19.4 (2009).

Patients: Hearing on Oversight Before the Senate Comm. on Health, Education, Labor, & Pensions, 108th Cong. (2003) (statement of Steven Galson, MD, MPH, Deputy Director, Center of Drug Evaluation and Research, FDA) ("Galson Testimony"), http://www.fda.gov/NewsEvents/Testimony/ucm115010.htm.

The goal of a compounding pharmacist is to mix, modify, and make safe customized pharmaceutical forms. The compounding process typically involves creation or modification of drugs through customization of dose, delivery vehicle, binding agents, and flavor. While the API involved in compounding is often commercially available, the unique forms of final compounded products are typically not. *See id.*

Compounding serves a number of significant medical needs. For example, a pharmacist might compound a liquid or suppository dosage form for a patient with difficulty swallowing, a lower dose form of an adult medication for a young patient, or a higher dose form of a pain medication for a hospice patient near the end of life. *See id.*; *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Hearing on Oversight Before the Senate Comm. on Health, Education, Labor, & Pensions*, 108th Cong. (2003) (statement of Daniel A. Herbert, President-elect, American Pharmaceutical Association) ("Herbert Testimony"), http://www.pharmwatch.org/comp/hearing.pdf. A hospital pharmacy might compound several sorts of intravenous admixtures, "ranging from simple fluid replacement to the delivery of complicated, individualized chemotherapy regimens." Herbert Testimony at 55. As in the present case, compounding may involve taking a recognized active ingredient and formulating it "without a dye or preservative" to meet the needs of particular patients. Galson Testimony.

These examples reflect the nature of modern compounding and the critical role of compounding in the treatment of disease. Compounding works, often indispensably, to address the health care needs of patients who fall partially or completely outside the range of commercially-imposed drug formulations. *See Western States Med. Ctr.*, 535 U.S. at 369 (noting the Government's position "that eliminating the practice of compounding drugs for individual patients would be undesirable because compounding is sometimes critical to the care of patients with drug allergies, patients who cannot tolerate particular drug delivery systems, and patients requiring special drug dosages"). Large-scale manufacturers cannot, nor can they reasonably be expected to, produce all necessary varieties of medications in a cost-effective manner. *See* Herbert Testimony. In view of these factors, FDA considers "traditional forms of pharmacy compounding" to be "an integral part of our modern health care system" and "an important component of our pharmaceutical armamentarium." Galson Testimony.[11] The Supreme Court has similarly recognized an important governmental interest "in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs." *Western States Med. Ctr.*, 535 U.S. at 369.

B. Approval of a New Drug Subject to the Orphan Drug Act does not Preclude Compounding Permitted under the Established Exception to Section 355

For years, compounding pharmacists have safely, effectively, and legally compounded 17P at an affordable price. These many doses of 17P, like the many millions of doses of other compounded drugs created each year, represent ordinary compounds—not unapproved "new drugs" subject to the NDA provisions of the FDCA. *See* 21 U.S.C. § 355(a). Although on its

[11] *See also* FDA, Compliance Policy Guide § 460.200 ("CPG") (May 2002), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM118050.pdf (recognizing and approving of fact "that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner").

face the FDCA might appear to subject compounded drugs to the new drug approval requirements, FDA has long recognized an effective exception to those requirements for traditional pharmacy compounding. While the precise contours of this exception have not always been clear, its existence has never seriously been questioned. *See Western States Med. Ctr.*, 535 U.S. at 369 (noting that "it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process," and recording the Government's position that subjecting compounds to NDA requirements would undesirably "eliminate the practice of compounding").

FDA formalized its position that traditional pharmacy compounding should be exempt from § 355's NDA requirements in 1992, when FDA issued Compliance Policy Guide § 7132.16 (Mar. 16, 1992). Congress later codified the compounding exception at 21 U.S.C. § 353a. *See Western States Med. Ctr.*, 535 U.S. at 364 (section 353a "exempts compounded drugs from the FDCA's 'new drug' requirements and other requirements provided the drugs satisfy a number of restrictions"). As plaintiffs acknowledge, "Section 353a makes traditional customized compounded drugs lawful by exempting them from the FDCA's new-drug-approval requirements . . . if the compounding pharmacist complies with certain restrictions." Plaintiffs' Injunction Mem. 6. Because the Supreme Court struck down the advertising restrictions that Section 353a had imposed on compounders, *Western States Med. Ctr.*, 535 U.S. at 377, the remainder of Section 353a was also drawn into doubt, *see Western States Med. Ctr. v. Shalala*, 238 F.3d 1090, 1097-98 (9th Cir. 2001) (finding remaining provisions of § 353a not severable). In response, FDA readopted the policies of § 353a as a matter of FDA enforcement discretion. *See* CPG § 460.200. Thus, the long-recognized exception for traditional pharmacy compounding from the scope of the FDCA's "new drug" requirements remains intact.

As drug products excepted from NDA requirements, compounded drugs within the limits of traditional compounding practices are not implicated by the ODA, 21 U.S.C. §§ 360aa-ee. In 1983, Congress enacted the ODA to encourage the development of drugs to treat rare diseases.[12] Once a product is designated an "Orphan Drug," the ODA provides that FDA may no longer "approve another application under section 355 of this title [*i.e.*, a "new drug" application] . . . for such drug for such disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of approval of the approved application." 21 U.S.C. § 360cc(a). Although Plaintiffs reference this provision as providing "market exclusivity," *see* Plaintiffs' Injunction Mem. 22, the ODA's text in fact protects only against FDA's approval of another NDA for the same drug for the same disease, during the seven year period. As one court has observed, FDA "enforce[s] this market exclusivity by refusing to approve any application for the 'same drug' used for the same therapeutic purpose as the first-approved drug until the seven-year period of exclusivity expires." *See Mutual Pharm. Co. v. Ivax Pharm., Inc.*, 459 F. Supp. 2d 925, 930 (C.D.Cal. 2006). Because traditional compounding (within the limits set by Congress and FDA policy) is outside of the NDA requirements, and because the ODA only protects the manufacturer of an orphan drug from the issuance of a further NDA for the same drug and same indication, the ODA's protective scope does not circumscribe pharmacists' ability to engage in such compounding.

Although Plaintiffs criticize this as a "literal reading" of the ODA, it is entirely appropriate to apply the statute according to its terms. "[C]ourts must presume that a legislature says in a statute what it means and means in a statute what it says there. When the words of a

[12] The legislative history of the ODA reflects that Congress was particularly concerned with the development of drugs that "are not profitable," for which "[i]t is difficult to conduct human clinical trials to prove their effectiveness," which are not patentable, and which may "cause more adverse side effects, on average, than drugs for common diseases." Subcommittee on Health and the Environment of the Committee on Energy and Commerce, *Preliminary Report on the Survey on Drugs for Rare Diseases*, 1982 U.S.C.C.A.N. 3579, 3580.

statute are unambiguous, then, this first canon is also the last: judicial inquiry is complete." *Connecticut Nat'l Bank v. Germain*, 503 U.S. 249, 253-54 (1992) (internal quotation omitted). And, even if policy considerations could overcome the statute's clear text, a plain reading of the ODA's "literal" language does not conflict with the statute's intended purpose, or create an absurd result. To the contrary, because compounding is "a traditional component of the practice of pharmacy" essential to allowing "patients with particular needs [to] obtain medications suited to those needs," *Western States Med. Ctr.,* 535 U.S. at 361, 369, the Court should not presume that Congress intended the ODA to eliminate *sub silentio* otherwise permissible compounding.

Here, it is Plaintiffs' reading that conflicts with the statute by granting a monopoly far broader than the one Congress afforded. Congress gave orphan drugs limited seven-year protection against a *direct* new drug competitor: the protection extends only to a prohibition against FDA issuing another NDA "for such drug for such disease or condition." 21 U.S.C. § 360cc(a)(2).[13] Plaintiffs seek much broader protection. For example, as discussed above, of the approximately 500,000 preterm births every year in the United States, only an estimated 130,000 involve patients who meet the approved indications for use of Makena. For some percentage of the remaining 370,000 women who are at risk for preterm births, doctors either prescribe Makena off label, or prescribe compounded 17P. If Plaintiffs were successful in eliminating the availability of compounded 17P, Plaintiffs would have assured themselves a virtual monopoly for treating these patients, even though they do not suffer from "such disease or condition" for which Makena was approved and to which the ODA protections apply. 21 U.S.C. § 360cc(a)(2).

[13] It is apparent that Congress intentionally offered a degree of protection to Orphan Drugs distinctly weaker than that available through the patent system. *Cf.* Robert Rogoyski, *The Orphan Drug Act and the Myth of the Exclusivity Incentive*, 7 Colum. Sci. & Tech. L. Rev. 4, 7-9 (2006); 35 U.S.C. § 271.

C. Plaintiffs' Broader Arguments Pose a Direct Threat to Compounding and to the Thousands of Patients Who Benefit from the Practice

Plaintiffs' arguments must be rejected for the additional reason that they would drive a stake in the heart of traditional compounding, to the great detriment of patients. Plaintiffs seek to paint this as a narrow challenge to compel FDA to enforce a statutorily guaranteed monopoly. Even stated in those terms, the suit would constitute an impermissible usurpation of FDA's enforcement discretion. *See infra*, 26-31. Moreover, Plaintiffs' arguments are, in fact, much broader, and cut at the core of the authority of pharmacies to engage in traditional compounding.

To begin, Plaintiffs argue for a broad reading of § 355 of the FDCA in which traditional compounding would be subject to the requirement to obtain an NDA. *See* Plaintiffs' Injunction Mem. 33. Although the compounding statute exempts traditional compounding, 21 U.S.C. § 353a, in the Ninth Circuit (and perhaps elsewhere in the future), the compounding provision has been held unconstitutional *in toto*. *See Western States Med. Ctr.*, 238 F.3d at 1097-98. In those jurisdictions, the permissibility of compounding is established only in FDA's guidance policy. CPG § 460.200 (May, 2002). If Plaintiffs were correct that Section 355 subjects traditional pharmacy compounding to the "new drug" requirements, and if Plaintiffs were also right that FDA lacks the authority to announce a categorical policy of non-enforcement against the introduction of a new drug without an NDA, then FDA's compounding guidance is invalid, as was FDA's original compounding guidance issued in 1992. In other words, if the court were to adopt Plaintiffs' arguments, it would cast into legal doubt the compounding of drugs that has saved or improved millions of lives over the past decades.

Another aspect of Plaintiffs' arguments would significantly narrow the discretion of physicians to prescribe compounded drugs based on differences between the FDA-approved and compounded versions. Here, as noted above, FDA-approved Makena and the preservative-free

version of compounded 17P are significantly different because the omitted preservative, benzyl alcohol, has been associated with serious health risks and has caused considerable concern among doctors. Yet, according to Plaintiffs, Makena and compounded 17P are "essentially copies." *See* Plaintiffs' Injunction Mem. 27-28. Plaintiffs' narrow reading of the compounding statute would deprive compounding of almost all of its present and historic usefulness. In many instances, compounding entails only slight changes to commercially-available forms, such as the flavor. *See* Galson Testimony, *supra*. The differences between Makena and compounded 17P are much more substantial than that, yet Plaintiffs would have this Court issue a categorical declaration that the omission of benzyl alcohol does not satisfy the requirements of Section 353a or FDA's enforcement policy respecting compounding. Such a declaration would cast significant doubt over other traditional compounding practices.

Plaintiffs' construction is also inconsistent with FDA's long-standing deference to doctors' practice of medicine. The FDCA does not provide, nor has FDA ever claimed, authority to regulate the practice of the medicine or restrict the manner in which a physician may use, prescribe, or adapt legally available pharmaceuticals. *See* S. Rep. No. 74-361, at 3 (1935) (FDCA was "not intended as a medical practices act and [should] not interfere with the practice of the healing art"); S. Rep. No. 74-646, at 1 (1935) (enactment of the FDCA was not intended to permit FDA to interfere with medical practice as between physician and patient). [14] In the

[14] *See also* FDA, "Off-Label" and Investigational use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (last visited July 24, 2012) (noting that "[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment"); 37 Fed. Reg. 16, 503, 16,504 (Aug. 15, 1972) ("The physician is . . . responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him."). The FDCA does not provide, nor has FDA ever claimed, authority to regulate the practice of the medicine or restrict the manner in which a physician may use, prescribe, or adapt legally available pharmaceuticals. *See* S. Rep. No. 74-361, at 3 (1935) (FDCA was "not intended as a medical practices act and [should] not interfere with the practice of the healing art"); S. Rep. No. 74-646, at 1 (1935) (enactment of the FDCA was not intended to permit FDA to interfere with medical practice as between physician and patient).

compounding provision, this deference to physicians' medical judgment is enshrined in the statute. It allows a drug to be compounded if the difference between the compounded and FDA-approved drug "produces for th[e] patient a significant difference, *as determined by the prescribing practitioner*." 21 U.S.C. § 353a(b)(2) (emphasis added).[15] As explained above, many prescribing practitioners (including the *Amici* Physicians) have concluded, based on their own discretion, and consideration of their patients' interests and concerns, that absence of benzyl alcohol preservative and elimination of its attendant risk is a sufficiently "significant difference" to warrant prescribing compounded 17P. Yet, Plaintiffs would have the Court override those doctors' medical judgment and rule, as a matter of law, that this difference is not enough to bring compounded 17P within the limits of the compounding exception to the NDA requirement. That argument, if accepted, would mark a sea change in the historical deference to physicians' medical judgment under the FDCA and would severely circumscribe the availability of compounded drugs.

II. PLAINTIFFS' SUIT IS AN IMPERMISSIBLE ATTEMPT TO PRIVATELY ENFORCE THE FDCA, WHICH IMPROPERLY ASKS THE COURT TO USURP FDA'S EXERCISE OF ITS POLICYMAKING DISCRETION

Plaintiffs' suit impermissibly seeks a judicial decree dictating FDA's enforcement policy under the FDCA. There is a strong presumption against judicial review of an agency's decision not to initiate enforcement action, *Heckler v. Chaney*, 470 U.S. 821, 831 (1985), and that is especially apposite here, where the Plaintiffs are effectively seeking a judicially mandated press release, which (history suggests) they will use in an attempt to deter doctors from prescribing compounded 17P even within the legitimate scope of their medical practice. But even apart from

[15] CPG § 460.200 contemplates the compounding of "products . . . that are essentially copies of commercially available FDA-approved drug products." Where such "essential[] copies" are at issue, FDA will weigh in reaching an enforcement decision, among other non-determinative factors, "whether there is documentation of the medical need for the particular variation of the compound."

the general rule against judicial review of agency enforcement discretion, Plaintiffs' attempt to compel enforcement of the FDCA's compounding provisions is precluded by the FDCA itself. As the Supreme Court has recognized, Congress specifically precluded private enforcement of the FDCA. Because the agency must balance competing policy goals in deciding whether to undertake enforcement action, Congress conferred exclusive authority on FDA to enforce the FDCA. Plaintiffs seek, through this lawsuit, to usurp the agency's policy-making authority. The Court must reject that request.

In *Heckler v. Chaney*, the Supreme Court made clear that "an agency's decision not to prosecute or enforce, whether through civil or criminal process, is a decision generally committed to an agency's absolute discretion" and that there is a "presumption . . . that judicial review is not available." 470 U.S. 821, 831 (1985). As the Government comprehensively explains, Plaintiffs' attempts to distinguish *Chaney* are unconvincing. S*ee* Memorandum in Support of Defendants' Motion to Dismiss and in Opposition to Plaintiffs' Motion for Injunctive Relief ("Gov't Mem.") 20-40 (ECF No. 7). *Chaney* involved the same statute at issue here, and also concerned a general pronouncement that the agency would not enforce the FDCA against sales of a particular drug for a particular use. Nor, contrary to Plaintiffs' contentions, is this a situation in which Congress has mandated a particular course for the agency, without room for discretion. The enforcement actions Plaintiffs seek to compel require policy determinations that can only be made by the agency.

Chaney's presumption against judicial review of non-enforcement decisions is even stronger in this case because adjudicating Plaintiffs' suit would require the Court to exercise policy discretion that the FDCA reserves for FDA. Plaintiffs attempt to paint a picture in which the policy judgments have been made by Congress (or already determined by FDA), and the

Court is merely called upon to force FDA to take obligatory enforcement steps. But, as demonstrated above, the factual circumstances of this case are much more complicated, and any decision to take enforcement action against the compounding of 17P would require FDA first to make numerous complex policy determinations. Plaintiffs ask this Court to make those policy determinations in the first instance.

Plaintiffs, for example, would have this Court determine the proper construction of the FDCA's requirements that compounded versions that are "essentially copies" of approved drugs not be produced "regularly or in inordinate amounts," and that the differences be medically significant for the patient. As discussed above, the decision to prescribe the preservative-free version of compounded 17P is consistent with the FDCA's compounding provision because some prescribing doctors have determined, in their medical judgment, that the omission of benzyl alcohol is a significant difference for some patients' health. Plaintiffs ask this Court to determine, in the first instance, the application of these terms, whereas the construction of these ambiguous terms is a policy question for the agency. *See Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 980 (2005) ("[A]mbiguities in statutes within an agency's jurisdiction to administer are delegations of authority to the agency to fill the statutory gap in reasonable fashion.").

Similarly, the decision whether to exclude imports of the API for compounding 17P under § 381(a) requires the exercise of discretion on the part of FDA, contrary to Plaintiffs' assertions. Section 381(a) provides that "[i]f it appears" to FDA that the imported "article is adulterated, misbranded, or in violation of section 355 . . . then such article shall be refused admission." 21 U.S.C. § 381(a). Plaintiffs do not contend that FDA has already made a determination that the imported bulk drug product that is the API for compounded 17P is

"adulterated, misbranded, or in violation of section 355." *Id.* Rather, Plaintiffs ask this Court to make that determination in the first instance.

There is, in fact, strong reason to believe that FDA would *not* regard API imported for the compounding of 17P as misbranded or in violation of Section 355. The FDCA's compounding provisions specifically contemplate and authorize the use in compounding of bulk drug products that have no NDA, as long as the drug product does not "appear[] on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of drug products have been found to be unsafe or not effective." 21 U.S.C. § 353a(b)(1)(C). The API for 17P does not appear on the list of unsafe drug products. S*ee* 21 C.F.R. § 216.24. Nor has the API been withdrawn or removed because it was unsafe or ineffective. In fact, FDA specifically advised that Delalutin, which had the same API as 17P, was *not* withdrawn from the market for reasons of safety or effectiveness. 75 Fed. Reg. 36,419, 36,420 (June 25, 2010). Because the API can be used for the purpose of compounding 17P that is perfectly legal under Section 353a and FDA's policy guidance, Plaintiffs' contention that importation of the API is categorically prohibited by Section 381(a) lacks foundation. At the very least, the foregoing demonstrates that FDA has *not determined* that the API imported for purposes of compounding is "adulterated, misbranded or in violation of section 355," and making such a determination will require the exercise of the agency's policy-making expertise.

In addition to the general presumption against judicial review of agency decisions not to enforce, the FDCA contains an explicit statutory prohibition against attempts by private individuals to enforce the Act. "The FDCA leaves no doubt that it is the Federal Government rather than private litigants who are authorized to file suit for [FDCA] noncompliance."

Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 349 (2001). Congress specified that "*all* . . . proceedings for the enforcement, or to restrain violations, of [the FDCA] shall be *by and in the name of the United States*." 21 U.S.C. § 337(a) (emphasis added). Plaintiffs seek to circumvent this limitation by asking the Court, at the request of a "private litigant," to force the United States to bring a proceeding to enforce the FDCA. But the rationale behind the bar on private enforcement precludes such end-run tactics. FDA is given the discretion not only to determine *how* to enforce the FDCA, but *whether* to initiate enforcement action at all.

Congress specifically put at FDA's "disposal a variety of enforcement options that allow it to make a measured response" when it perceives that there has been a violation of the FDCA. *Buckman*, 531 U.S. at 349. "FDA may respond . . . by seeking injunctive relief, and civil penalties; seizing the [offending articles]; and pursuing criminal prosecutions." *Id.* (internal citations omitted). The "flexibility" afforded FDA "is a critical component of the statutory and regulatory framework." *Id.*

The bar against private enforcement and the flexibility afforded FDA to choose how to respond to suspected violations each reflect Congress's recognition that FDA must "pursue[] difficult (and often competing) objectives." *Id.* For example, FDA must "regulat[e] the marketing and distribution of [drugs and] medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals." *Id.* at 350. The compounding provision is one example of that recognition of the health care professional's discretion, to prescribe a compounded drug when the physician believes some ingredient of the FDA-approved drug would be harmful to the patient, as many physicians believe is the case with benzyl alcohol.

The discretion afforded FDA in deciding how to respond to a purported violation also includes the decision whether to bring any enforcement action at all. FDA must use its authority "to achieve a somewhat delicate balance of statutory objectives." *Id.* at 348. FDA might consider, for example, the need to get a new product "on the market within a relatively short period of time." *Id.* at 350. Likewise, it might weigh the desire for "competition among predicate devices and . . . health care professionals' ability to prescribe appropriate off-label uses." *Id.* at 351.[16] For example, if off-label use of a product were the only available treatment for a particular situation, FDA could appropriately weigh the effect of removing that product when deciding whether to bring an enforcement action. *Id.* at 347-51. Indeed, Congress recognized that FDA could decline to prosecute or enjoin what FDA determined to be "minor violations" of the Act. 21 U.S.C. § 336. In other words, the FDCA affords FDA not only discretion *which* enforcement mechanism to utilize, but also "complete discretion *not* to employ the enforcement provisions of the [FDCA]." *Community Nutrition Institute v. Young*, 818 F.2d 943, 950 (D.C. Cir. 1987) (emphasis added).

III. PLAINTIFFS CANNOT SATISFY THE REQUIREMENTS FOR EQUITABLE RELIEF

The granting of equitable relief is committed to the discretion of the Court on the basis of, among other factors, whether equitable relief is in the public interest. *Sea Containers Ltd. V. Stena AB*, 890 F.2d 1205, 1208 (D.C. Cir. 1989). "In litigation involving the administration of regulatory statutes designed to promote the public interest, this factor necessarily becomes crucial." *Virginia Petroleum Jobbers Ass'n v. Federal Power Com'n*, 259 F.2d 921, 925 (D.C.

[16] One aspect of the "competition" among drugs or devices to which the Court referred in *Buckman* is plainly the desirable effect that competition has on prices. Here, it is clear that price competition is exactly what Plaintiffs oppose. Their charges of hundreds of dollars, originally $1,500 per does and currently up to $690, for a drug that has long been available for $10-$20 per dose demonstrates the critical value that competition can play in ensuring patients' access to critical drugs.

Cir. 1958). "The interests of private litigants must give way to the realization of public purposes." *Id.*

As a threshold matter, Plaintiffs' have failed to demonstrate the need for the relief they seek. Plaintiffs' assertion that FDA has "approved and encouraged … nationwide distribution, during KV's exclusivity period and for Makena's approved indication, of unlimited quantities of uncustomized 17P," Plaintiffs' Injunction Mem. 15, is a blatant mischaracterization of FDA's public statements. Indeed, Plaintiffs own filings in their Georgia action against the state Medicaid program takes precisely the opposite position. There, Plaintiffs state unequivocally that FDA's public statements "leave no room for doubt" about the limits the FDCA imposes on compounding 17P. *Cook* Complaint ¶ 47. As their Georgia filings demonstrate, when it suits Plaintiffs' interests, they are able to understand perfectly well the significance of FDA's statement in its June 29 Q&A, which stressed that FDA "may take enforcement action against pharmacies that compound large volumes of drugs that are essentially copies of commercially available products." *Id.* ¶ 5. In Plaintiffs' own words, FDA's June 29 public statement "got right to the point" in emphasizing that prescribing a compounded version of 17P is appropriate only where "necessary for the particular patient" in order to "provide a significant difference for the patient as compared to the FDA-approved commercially available drug product." *Cook* Injunction Mem, 8-9 (quoting June 29 FDA Q&A). Because FDA has "highlighted" the lawful limits on compounding, *id.* at 9, as well as the possibility that FDA "may take enforcement action," *Cook* Complaint ¶ 5, Plaintiffs have failed to establish the alleged policy of categorical nonenforcement of the FDCA that is the premise of their request for equitable relief.

Moreover, the public interest weighs against Plaintiffs' proposed injunction. In the FDCA, Congress recognized a strong public interest in maintaining and protecting public access

to compounded drug products. 21 U.S.C. § 353a(b)(1)(D). *See Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 33 (D.D.C. 2006) (public interest factor favored denying injunction which would hinder access to drug "hundreds of thousands of Americans rely on"). And, as noted, Congress has specifically authorized FDA to decline, based on its own gauge of the public interest, to prosecute or enjoin "minor violations" of the Act. 21 U.S.C. § 336. The aggressive enforcement posture that Plaintiffs ask the Court to compel FDA to take could easily drive physicians and pharmacists to abandon compounding 17P altogether, including within the limits of the FDCA. Even assuming that some compounding activity by some entities qualifies as "violations" of the Act, FDA could permissibly determine that the public's access to preservative-free formulations of compounded 17P as an alternative to Makena was more important than Plaintiffs' ability to earn hundreds or thousands of dollars on each administration of the drug. "A faithful and coherent interpretation of the FDCA . . . outweighs the purely financial harm to the[] drug compan[y]." *Mylan Labs., Inc. v. Leavitt*, 484 F. Supp. 2d 109, 124 (D.D.C. 2007).

If Plaintiffs' proposed injunction is denied—and, indeed, even if Plaintiffs are forced into bankruptcy as a result—the public will face no resultant harm. The alleged harm identified by Plaintiffs is their inability to charge up to $690 (originally $1,500) per dose of a drug that has been on the market since 1960 and that was already available to the public for $20 or less per dose before Plaintiffs obtained their NDA on the basis of government funded studies. Plaintiffs' ability to charge such unjustified monopoly profits for public research is not the public interest for which the FDCA exists. Rather, the FDCA's purpose is to ensure the availability of safe and efficacious drugs to the public. For a number of years before Plaintiffs obtained their NDA, pharmacists were providing compounding versions of 17P that were safe, efficacious, and cost-effective. Pharmacists will continue to do so even if Plaintiffs were to enter bankruptcy

proceedings. Indeed, Plaintiffs' bankruptcy is unlikely even to deprive the public of access to the FDA-approved form of 17P, insofar as certain physicians or patients might prefer it. Another pharmaceutical company could be expected to purchase the Makena NDA out of bankruptcy, for a price that omits a premium Plaintiffs paid apparently based on unsustainable projections of monopoly profits. That company would then be able to offer FDA approved Makena at a price more reflective of the true cost of the drug and complying with FDA regulatory requirements.

There exists no public interest in repaying Plaintiffs' inflated purchase price, which almost exclusively reflects Plaintiffs' erroneous predictions of their own ability to charge monopolist pricing for Makena. Plaintiffs inaccurately attempt to cast their financial position as a unique consequence of its investment in Orphan Drugs. In reality, Plaintiffs' position is the product of the premium they chose to pay a predecessor for the NDA it obtained largely on the basis of publicly funded NIH research. Denying Plaintiffs' proposed injunction would discourage wasteful bets on Orphan Drug status as a means of capturing markets and diseases already well-served by compounds. Denying the injunction would not undermine the actual aim of the ODA—*i.e.,* the development of truly necessary drugs for untreated rare diseases.

Also critical here is the highly unusual nature of the equitable relief Plaintiffs seek. Among other things, Plaintiffs request Orders that FDA issue a court-ordered press release indicating its intent to eradicate compounding of 17P and that, within ten days of decision, FDA report to the Court the particular actions it takes to stop compounding of 17P. Plaintiffs' Injunction Motion 3. In this Court, "[t]he power to issue a preliminary injunction, especially a mandatory one, should be sparingly exercised." *Dorfmann v. Boozer*, 414 F.2d 1168, 1173 (D.C. Cir.1969) (internal quotations and citations omitted). Because Plaintiffs are "seeking affirmative relief that would alter the status quo by requiring the FDA" to take mandatory action, the Court

must review Plaintiff's "request for injunctive relief with even greater circumspection than usual in determining whether the 'extraordinary writ of preliminary injunction' is warranted." *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d 30, 36 (D.D.C. 2000) (Roberts, J.) (quoting *Boozer*, 414 F.2d at 1173).

Finally, Plaintiffs come to the Court with unclean hands and should not now be heard to seek equitable relief. The unclean hands doctrine "closes the doors of a court of equity to one tainted with inequitableness or bad faith relative to the matter in which he seeks relief." *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 814 (1945). The doctrine applies whether the inequitable conduct "is due to conduct which technically constitutes fraud, or which is unconscionable." *Cochran v. Burdick*, 89 F.2d 831, 834 (D.C. Cir. 1937).

Prior to the initiation of this lawsuit, as the Government notes in its brief, Plaintiffs undertook a well-financed campaign to convince pharmacists, with use of blatantly false and misleading statements, that "FDA will no longer exercise enforcement discretion with regard to compounded versions of Makena." *See* Govt. Mem. Ex. 1 (March 30, 2011 FDA Statement). Indeed, the FDA March 2011 statement of which Plaintiffs complain was necessary precisely to counteract Plaintiffs' own misleading campaign to thwart entirely lawful compounding. *See id.* (noting that Plaintiffs' public statement "is not correct"); *see also* Govt. Mem. 9-10.[17] In addition, Alere has received multiple reports from physicians who have been visited by Plaintiffs' sales representatives and advised—again falsely—that physicians are at risk of *malpractice suits* if they continue to prescribe compounded 17P. The inconsistent positions

[17] Plaintiffs falsely and misleadingly told pharmacies that performed compounding: "FDA has stated that it views compounded drugs to be 'new drugs' . . . and as such, they may not be introduced into interstate commerce without FDA approval. Although FDA will exercise its enforcement discretion with respect to certain pharmacy compounding practices, this discretion does not extend to compounding of copies or essentially copies of commercially available FDA-approved products. Therefore, although compounding of [17P] injection may have, in the past, been subject to FDA enforcement discretion, continuing to compound this product after FDA-approval of Makena renders the compounded product subject to FDA enforcement for violating certain provisions of the [FDCA]." Ther-Rx cease-and-desist letter of February 17, 2011, http://freepdfhosting.com/a78b282680.pdf.

Plaintiffs have taken in this action and in their papers before the Georgia court are further evidence of Plaintiffs' unclean hands. Plaintiffs' Georgia filings demonstrate that Plaintiffs fully understand that, contrary to Plaintiffs' allegations here, FDA has not "approved and encouraged . . . nationwide distribution . . . of unlimited quantities of uncustomized 17P." Plaintiffs' Injunction Mem. 15. Rather than needing a new statement by FDA to correct the record, Plaintiffs seek a judicial imprimatur on their campaign against even lawful compounding of 17P.

"Equity does not require blamelessness with respect to other matters, but it does require that one seeking relief must have acted fairly and without fraud or deceit as to the controversy at issue." *Monument Realty LLC v. Wash. Metro.Area Transit Auth.*, 540 F. Supp. 2d 66, 82 (D.D.C. 2008). Plaintiffs have acted with notable dishonesty with respect to 17P, its compounders, and the physicians who prescribe its compounded form. Plaintiffs' case should fail for this reason alone. *See Steele v. Isikoff*, 130 F. Supp. 2d 23, 34 (D.D.C. 2000) ("To aid a party in such a case would make th[e] court the abetter of iniquity.") (quoting *Synanon Found., Inc. v. Bernstein*, 503 A.2d 1254, 1264 (D.C. 1986)).

CONCLUSION

For the foregoing reasons, Plaintiffs' motion for injunctive relief should be denied and Defendants' motion to dismiss should be granted.

Respectfully submitted,

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By: _____

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