IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

K-V PHARMACEUTICAL COMPANY,
2280 Schuetz Road
St. Louis, MO 63146,

and

THER-Rx CORPORATION,
2280 Schuetz Road
St. Louis, MO 63146,

Plaintiffs,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002,

UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES,
200 Independence Avenue, S.W.
Washington, DC 20201,

MARGARET A. HAMBURG, M.D.,
Commissioner of Food and Drugs,
U.S. Food and Drug Administration,
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002,

and

KATHLEEN SEBELIUS,
Secretary of Health and Human Services,
U.S. Department of Health & Human Services,
200 Independence Avenue, S.W.
Washington, DC 20201,

Defendants.

Case No. _____

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

INTRODUCTION AND SUMMARY

1. K-V Pharmaceutical Company ("KV") and its wholly-owned subsidiary, Ther-Rx Corporation ("Ther-Rx") (together, "Plaintiffs") bring this action under the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701-706, for temporary, preliminary, and permanent declaratory and injunctive relief to restore Plaintiffs' right under the Orphan Drug Act, a part of the Federal Food, Drug, and Cosmetic Act ("FDCA"), FDCA § 527(a), 21 U.S.C. § 360cc(a), to market exclusivity for the drug, Makena® (hydroxyprogesterone caproate injection).

2. This is a case where the U.S. Food and Drug Administration ("FDA") and the other Defendants have put the supposed financial interests of Medicaid, other third-party payers, and some patients above the medical interest of all patients for whom Makena is indicated. The patients are pregnant women with a singleton pregnancy who have a history of singleton spontaneous preterm birth and therefore are at heightened risk of another preterm birth, which threatens the lives of their unborn children. As a result of Defendants' action, it has become difficult or impossible for many of these women to obtain the one drug to treat their condition that FDA has approved as effective, safe, properly manufactured, and properly labeled. Instead, these women are being relegated to unapproved compounded versions of hydroxyprogesterone caproate injection (called "HPC" or "17P") of uncertain quality and potency and made from a bulk active pharmaceutical ingredient ("API") that the Defendants are allowing to be imported into the United States unlawfully.

3. Makena is the only drug approved by FDA to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

4. Plaintiffs challenge final action by FDA that effectively nullifies Plaintiffs' statutory right to market exclusivity by approving, inviting, encouraging, and permitting the

manufacture and distribution of unapproved, non-customized compounded drugs, which FDA, itself, has said are of a type made by a process "associated with serious health risks." The action by FDA challenged here has resulted in the raising of new barriers to women's access to Makena, and has undermined the major incentive provided by the Orphan Drug Act for the development of drugs to treat rare diseases and conditions. The challenged action also threatens the survival of Plaintiffs.

5. On information and belief based on extensive investigation, all or nearly all of the API used by compounders in the United States to compound 17P comes from factories that are located in China, the country where drug manufacturing facilities exporting to the United States are least likely to be inspected by FDA. At Plaintiffs' request, independent laboratories tested ten samples of Chinese API for compounded 17P and 24 samples of compounded 17P in finished dosage form. Of the API samples, the majority failed at least one of the specifications FDA set for Makena (primarily, presence of unknown impurities), and one contained no drug at all (instead, it contained glucose). Of the samples of finished dosage form, the majority failed at least one of the specifications set by FDA for Makena, primarily due to unacceptable potency and/or impurities in this injectable drug that is given to women with high-risk pregnancies. FDA conducted its own investigation and testing of compounded 17P and API for compounded 17P, and reported findings that it said did not raise safety concerns. FDA's investigation, however, was conducted under circumstances less likely to lead to representative results: compounders were advised by their trade association of FDA's investigation early in the investigation, which took many months; and so the compounders had opportunity to make special efforts to improve their products or to provide selected products. Even so, all sixteen samples of API that FDA tested, though meeting certain

other specifications, failed the limit for unidentified impurities that applies to Makena. FDA requirements would prohibit KV from using such API to make Makena.

6. Restoring Plaintiffs' right to market exclusivity under the Orphan Drug Act would not only benefit Plaintiffs. It also would protect the health of women at risk of preterm birth and their unborn children by removing the foundation for the barriers to their access to the one FDA-approved drug to treat their condition. It also would help preserve the effectiveness of the Orphan Drug Act in providing incentives for the development of additional drugs for rare diseases and conditions.

7. Under present circumstances, sales of Makena, on which KV is highly dependent, cannot generate the cash KV needs to satisfy its ongoing normal cash operating expenses and the material, near-term payment obligations the Company faces beginning in August 2012. Unless FDA publicly signals that it will stop the unlawful competition by non-customized compounded drugs (and thereby give KV's creditors a reason to believe that KV is likely to be able to meet its financial obligations if given more time), KV will not be able to attract new capital at a reasonable cost, and is likely to exhaust its working capital within three to six months and be forced to file for bankruptcy before then.

BACKGROUND

8. On February 3, 2011, the drug now named "Makena" became the first drug approved by FDA to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Each year, more than 130,000 women have the condition that Makena is approved to treat. Plaintiff KV invested and committed more than a quarter of a billion dollars to acquire, develop, and market Makena.

9. For a number of years before FDA approved Makena, women had been treated for a risk of preterm birth with versions of 17P that were "compounded" (*i.e.*, produced) by entities known as "compounding pharmacies" or "compounders." Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication customized to the needs of an individual patient. Compounded drugs generally are not reviewed or approved by FDA. Compounded versions of 17P were not and are not reviewed or approved by FDA; and, in general, their individual formulations, manufacturing processes, labeling, and adverse-event and treatment-failure histories were and are unknown to FDA. The facilities in which the compounding occurred and continues to occur generally were not and are not registered with or routinely inspected by FDA.

10. On March 17, 2011, in testimony before the Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies of the Senate Committee on Appropriations, the Commissioner of Food and Drugs, Defendant Margaret Hamburg, M.D., initially hailed the approval of Makena: "I think it is important and an advance that we have an FDA-approved drug to prevent pre-term pregnancy and all of its consequent serious medical concerns for both mother and infant. And while the drug has been available through compounding, . . . compounding as a practice has been associated with serious health risks, contamination . . . ." The Commissioner's statement is reported in *FY 2012 FDA Budget: Hearing Before the S. Subcomm. on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies of the S. Comm. on Appropriations*, 112th Cong. 10 (Mar. 17, 2011) (Lexis/Nexis).

11. The "serious health risks" referred to by Commissioner Hamburg are reflected in the results of an FDA survey reported in 2006, which FDA characterized as "suggest[ing] that

problems with the quality of compounded drugs occur throughout the country. . . . From 1990 to 2005, FDA learned of at least 240 serious illnesses and deaths associated with improperly compounded products. Because pharmacists are not required to report adverse events to FDA, there may be additional deaths and injuries of which the agency is unaware." The survey is reported in FDA, *2006 Limited FDA Survey of Compounded Drug Products* 2 (2006), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm.

12. FDA has also issued another report calling attention to special risks of compounding: FDA, *The Special Risks of Pharmacy Compounding* (May 31, 2007), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm107839.pdf. The report at page 1 includes comments by an official in FDA's Center for Drug Evaluation and Research ("CDER"):

> Steve Silverman, Assistant Director of CDER's Office of Compliance, says that poor practices on the part of drug compounders can result in contamination or in products that don't possess the strength, quality, and purity required. "And because patients who use these drugs may have serious underlying health conditions," he says, "these flawed methods pose special risks."

13. The Executive Director of the Missouri Board of Pharmacy has noted: "Literature in pharmacy is replete with incidents where consumers have been harmed or large scale compounding practices made the dispensing of sub-standard products of major significance." His statement appears in Kevin Kinkade, Mo. Bd. of Pharmacy, *Pharmacy Compounding: Report on Quality Assurance Initiatives in the State of Missouri and Issues Impacting Customer Protection* 2 (2005), *available at* http://pr.mo.gov/boards/pharmacy/Pharmacy-Compounding-Report-FY-2005.pdf.

14. On February 11, 2011, eight days after approving Makena, FDA confirmed to KV's predecessor, pursuant to the Orphan Drug Act, that, "as the first sponsor of this drug to obtain marketing approval, you are entitled to seven years of orphan-drug exclusive approval."

15. Yet, on March 30, 2011, under political pressure resulting in part from misleading press reports about Makena's list price, FDA issued an unprecedented press release (the "Statement") effectively approving, inviting, encouraging, and permitting—for the first time ever— direct nationwide competition between an entire class of unapproved compounded drug products (not customized to meet the medical needs of individual patients) and an approved orphan drug product. FDA's authorization of marketing of compounded 17P was, and is, without regard to whether the compounded products are customized to meet the needs of individual patients for whom Makena is indicated but medically inappropriate, and without regard to the quantity of compounded 17P introduced into commerce. Numerous compounded versions of 17P (not customized for individual patients) have entered, re-entered, or remained on the U.S. market, some manufactured on a commercial scale – in violation of the limits on compounding in section 503A of the FDCA, 21 U.S.C. § 353a, and the requirement in FDCA §§ 505(a) and 301(d), 21 U.S.C. §§ 355(a), 331(d), that any new drug be approved by FDA before it is introduced into interstate commerce. FDA also is permitting the importation into the United States of unapproved API for compounded 17P, in violation of Section 355(a) and FDCA § 801(a), 21 U.S.C. § 381(a).

16. Thus, FDA's Statement and the policy it sets forth effectively nullified, and continue to nullify, Plaintiffs' right, under the Orphan Drug Act, to seven years of market exclusivity for Makena.

17. On information and belief, FDA's Statement and policy are part of a plan, adopted by the Defendants, to make unapproved, unlawful, but cheaper, compounded versions of 17P

available in the marketplace, despite the statutory market exclusivity that applies to Makena – and to do so by allowing, indeed, encouraging, widespread violations of 21 U.S.C. §§ 353a and 355(a), despite the added risks that the products of those violations present to patients, and the erosion of the incentive for orphan drug development that the allowing of those violations causes. On March 30, 2011, within hours of the release of FDA's Statement, the Centers for Medicare & Medicaid Services ("CMS"), a unit of the Defendant Department of Health and Human Services ("DHHS"), issued its own statement, which effectively informed States and Medicaid payers that they can pay for non-customized compounded 17P despite the availability of FDA-approved Makena.

18. Under longstanding FDA policy, FDA generally does not take enforcement action against a compounder that compounds a drug that is customized to meet the special medical need of an individual patient for whom no drug approved by FDA is medically appropriate. Under that policy, FDA generally does take enforcement action against compounders that compound drugs that are not customized for such patients, especially where the compounding of such drugs amounts to commercial manufacturing. In 1997, Congress codified much of that FDA policy in 21 U.S.C. § 353a.

19. In reliance on FDA's Statement and policy and the statement issued by CMS the same day, some state Medicaid agencies have adopted policies that make it more difficult, and in some cases impossible as a practical matter, for pregnant women needing HPC injection to obtain access to Makena rather than compounded 17P. Thus, as a result of FDA's Statement and policy, without which CMS's statement could not have been issued and the state policies favoring non-customized compounded 17P over Makena could not have been adopted and implemented, the regulatory system has been turned upside down: the FDA-approved drug is now disfavored in comparison to unapproved versions (and in some States is placed effectively off limits), and

Medicaid beneficiaries are being subjected to the additional risks presented by compounded 17P (including the particular risks associated with ingredients from factories in China that are not identified in approved new drug applications and consequently are not routinely inspected by FDA, and the general risks inherent in the unapproved and varying processes used by compounders).

20. FDA issued its Statement in response to political pressure over the list price of Makena. FDA had no lawful reason to issue the Statement, and before issuing it FDA had not conducted any substantial investigation of the availability of Makena to patients.

21. The list price of a drug, however, is not the drug's final price, which reflects discounts and rebates that a drug's distributor negotiates with Medicaid and other third-party payers. Even uninsured patients do not pay the list price of Makena. Even before FDA's March 30, 2011 Statement, Plaintiffs had announced that they would provide Makena free to uninsured women whose household income was below a specified threshold, and at substantial discounts to other women on the basis of need. Since FDA's Statement, Plaintiffs have made that program even more generous, and have also reduced the list price of Makena by more than half.

22. The harm caused by FDA's Statement and the policy of non-enforcement against non-customized compounded 17P it sets forth extend far beyond the Plaintiffs and pregnant women who have the condition for which treatment with Makena is indicated. The Statement and policy threaten all those suffering from a rare disease or condition for which the development of new or better treatments might otherwise be stimulated by the Orphan Drug Act. Although the Statement asserts that it is limited to unique circumstances of Makena, unless the Statement and the policy it sets forth are held invalid and withdrawn, they will stand as an administrative precedent for similar action against other orphan drugs (and other drugs) that have statutory market

exclusivity but to the price of which FDA or those with political influence over FDA object. Unless they are held invalid and withdrawn, FDA's Statement and policy are likely to have a chilling effect on the development of drugs to treat rare diseases and conditions and on other private-sector activity that Congress intended the FDCA's market-exclusivity provisions to stimulate.

23. FDA's Statement and the general policy it sets forth violate four substantive provisions of the FDCA, and, under the APA, are arbitrary and capricious, an abuse of discretion, otherwise not in accordance with law, in excess of FDA's statutory authority and limitation, short of KV's statutory right, and without observance of procedure required by law.

THE PARTIES

24. Plaintiff KV, a pharmaceutical manufacturer and distributor, is the owner of Makena, and its orphan drug designation and regulatory approval by FDA. KV is a Delaware corporation, with its principal place of business at 2280 Schuetz Road, St. Louis, Missouri 63146. KV advertises, sells, and distributes its drugs in this District and nationwide, through its wholly-owned subsidiary, Ther-Rx.

25. Plaintiff Ther-Rx, a pharmaceutical distributor, is a wholly-owned subsidiary of KV, and markets, sells, and distributes Makena on behalf of KV. Ther-Rx is a Missouri corporation, with its principal place of business at 2280 Schuetz Road, St. Louis, Missouri 63146. Ther-Rx advertises, sells, and distributes KV's drugs in this District and nationwide.

26. Defendant FDA is an agency of the United States and a division of Defendant DHHS. FDA has the delegated responsibility to regulate, among other things, drugs sold within the United States. FDA's headquarters and principal place of business are at 10903 New

Hampshire Avenue, Silver Spring, Maryland 20903. Its governmental activities occur in this District and nationwide.

27. Defendant DHHS is a Department of the United States. Its headquarters and principal place of business are at 100 Independence Avenue, S.W., Washington, District of Columbia 20201. Its governmental activities occur in this District and nationwide.

28. Defendant Margaret A. Hamburg, M.D., is the Commissioner of Food and Drugs and the head of FDA. Plaintiffs sue her solely in her official capacity. Her governmental activities occur in this District and nationwide.

29. Defendant Kathleen Sebelius is the Secretary of Health and Human Services and the head of the DHHS. Plaintiffs sue her solely in her official capacity. Her governmental activities occur in this District and nationwide.

JURISDICTION, EXHAUSTION, AND VENUE

30. This Court has jurisdiction over Plaintiffs' claims pursuant to 28 U.S.C. § 1331. This action arises under the APA, 5 U.S.C. §§ 701-706. Plaintiffs' prayers for temporary, preliminary and permanent declaratory and injunctive relief are authorized by the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; the APA, 5 U.S.C. §§ 701-706; 28 U.S.C. § 1361; the All Writs Act, 28 U.S.C. § 1651; Rules 57 and 65 of the Federal Rules of Civil Procedure; and the inherent legal and equitable powers of this Court.

31. Immediate judicial review is warranted because: (a) FDA's Statement and the policy it sets forth effectively nullify Plaintiffs' statutory right to market exclusivity, and therefore constitute final agency action subject to immediate judicial review; (b) Plaintiffs have made exhaustive efforts to obtain relief from FDA, and those efforts have been unsuccessful; (c) Plaintiffs are suffering ongoing irreparable injury from FDA's unlawful nullification of KV's time-

sensitive and temporally limited right to market exclusivity and are at risk of running out of cash in less than three months; (d) Plaintiffs have no other adequate remedy in a court; and (e) FDA's Statement and policy are currently putting the health and safety of tens of thousands of patients and their fetuses at avoidable added risk.

32. Venue is proper in this Court under 28 U.S.C. § 1391(e) because at least one Defendant is an officer or agency of the United States and resides in the District of Columbia.

FACTS GIVING RISE TO THIS ACTION

FDA's Approval Process for New Drugs

33. Since 1938, a fundamental component of the FDCA has been its requirement, in 21 U.S.C. §§ 355(a) and 331(d), that—except in certain circumstances not pertinent to this case—FDA must approve a new drug before it is introduced into interstate commerce. Today, critical parts of the process of obtaining such approval are the conduct of studies showing that the new drug is effective and safe, the development of a controlled and reliable manufacturing process, and the drafting of labeling adequate to guide prescribing, as required by FDCA § 505(b), 21 U.S.C. § 355(b). Under FDCA § 505(*o*), 21 U.S.C. § 355(*o*), FDA may require additional studies as a condition of approval.

34. This premarket approval system is expensive and time-consuming for applicants, but ensures that new drugs consumed in the United States satisfy the FDCA's and FDA's rigorous standards for assessing effectiveness, safety, manufacturing processes, and product labeling. Under FDCA § 505(j), 21 U.S.C. § 355(j); 21 C.F.R. §§ 314.92-314.96, 314.105, pt. 320 (2012), even a generic form of an already approved drug must go through FDA's approval process, although, to obtain approval, a generic manufacturer generally need only show that its generic drug product is bioequivalent to the relevant branded drug product, that any differences between them

are acceptable, that the generic product will be properly manufactured under FDA's good-manufacturing-practice requirements, 21 C.F.R. pts. 210, 211 (2012), and that it will be properly labeled.

35. In addition to the premarket-approval requirements, sponsors of approved drugs are also subject to many post-approval requirements under, *e.g.*, 21 C.F.R. pts. 210, 211, §§ 314.70, 314.80, 314.81, 314.97, 314.98, 314.99, 314.540, 314.630 (2012).

The Orphan Drug Act

36. As relevant here, an orphan drug is one developed to treat a disease or condition that affects fewer than 200,000 people in the United States (an "orphan disease" or "orphan condition").

37. Prior to 1983, there often was insufficient incentive for pharmaceutical companies to try to develop drugs for orphan diseases or conditions. The markets for such drugs were small, yet the costs of development were still large because the approval standards applicable to drugs for such diseases or conditions were the same as those applicable to drugs with larger potential markets. In the Orphan Drug Act, Pub. L. No. 97-414, § 1(b)(4), 96 Stat. 2049, 2049 (1983), Congress found that, "because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss." Indeed, as stated in *Baker Norton Pharms., Inc. v. FDA*, 132 F. Supp. 2d 30, 31 (D.D.C. 2001), the incentives to develop drugs for rare diseases were so weak that, between 1973 and 1983, only ten products were developed to treat an orphan disease or condition.

38. In view of the relevant market dynamics, Congress concluded in section 1(b)(5) of the Orphan Drug Act that "some promising orphan drugs will not be developed unless changes are

made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs."

39. In response to this problem, Congress adopted the Orphan Drug Act, which amended the FDCA to provide incentives Congress believed necessary to encourage pharmaceutical companies to develop, obtain FDA approval for, and market orphan drugs. Congress did not change for orphan drugs the standards applicable to new drugs under section 355, including those as to effectiveness, safety, manufacturing processes, and labeling.

40. The most important incentive established by the Orphan Drug Act is that set forth in 21 U.S.C. § 360cc(a), which grants seven years of market exclusivity to the first drug approved by FDA to treat a particular orphan disease or condition.

Drug Compounding
and the Food and Drug Administration Modernization Act of 1997

41. Pharmacists sometimes create custom medications for patients who have a disease or condition for which an FDA-approved drug is indicated but for whom that drug is medically inappropriate. For example, a patient may be allergic to an inactive ingredient in the approved drug, or may need a different dosage form (*e.g.*, a liquid rather than a tablet). Drug compounding is a process by which a pharmacist combines, mixes, or alters ingredients to create a medication customized to the particular medical need of an individual patient, in the absence of an approved drug for the patient's disease or condition or where no approved drug is medically appropriate for that patient.

42. When Congress enacted the FDCA in 1938, compounding became unlawful because compounded drugs are "new drugs" under FDCA § 201(p), 21 U.S.C. § 321(p); and because, with exceptions not relevant here, 21 U.S.C. §§ 355(a) and 331(d) prohibit the introduction of new drugs into interstate commerce without FDA approval. Traditional

compounders of drugs customized for individual patients cannot recover the cost of obtaining FDA approval for their compounded drugs due to their individualized nature, and therefore generally do not obtain it.

43. Because compounded drugs have not been approved by FDA and generally are not regulated by FDA, they lack the degree of assurance that is provided by FDA approval and ongoing regulation that a drug product is effective and safe, properly manufactured, properly labeled with adequate directions for use, and properly monitored for adverse events.

44. Because compounding is sometimes necessary, however, FDA has not required new drug approval when pharmacists make and dispense customized compounded drugs for particular patients who cannot use an FDA-approved drug for their disease or condition. FDA has recognized that compounding can serve an important public purpose for which the health benefits outweigh the risks if the compounding is performed in response to a valid prescription in order to meet the special need of an individual patient for whom commercially available drugs are medically inappropriate. Such compounding is regulated by the States, as part of their regulation of the practice of pharmacy.

45. Starting in the 1980s, however, FDA began to see examples of "pharmacies" that were manufacturing "compounded" drugs on a commercial scale and selling them nationwide without prior FDA approval. In 1992, FDA promulgated an enforcement policy under which it would enforce the provisions of the FDCA and halt what were essentially drug-manufacturing operations in the guise of traditional compounding, but would not act against traditional compounding of drugs customized for individual patients.

46. In the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 127, 111 Stat. 2296, 2328-30 (1997), Congress codified much of FDA's 1992 enforcement

policy. It amended the FDCA by providing an exemption, codified at 21 U.S.C. 353a, for the products of traditional customized, patient-by-patient compounding from certain provisions that had made them unlawful; the amendment effectively excludes the products of non-customized compounding from the exemption. The amendment permits compounding in substantially the same traditional circumstances under which FDA's 1992 compliance policy withheld enforcement action against it. Thus, Congress gave traditional customized compounding a statutory basis as lawful conduct, and removed FDA's discretion to permit non-customized compounding.

47. Section 353a also prohibited the solicitation of prescriptions for, and the advertising of, compounded drugs. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court held those prohibitions unconstitutional. The Court did not address the other restrictions in Section 353a in that case, and has not addressed them subsequently.

FDA's Approval of Makena

48. Preterm birth in women with a singleton pregnancy who have a history of spontaneous preterm birth is an orphan condition. Petrini, *et al.*, *Estimated Effect of 17 Alpha-Hydroxyprogesterone Caproate on Preterm Birth in the United States*, 105 Obstetrics & Gynecology 267, 269 (Fig. 1) (Feb. 2005), *available at* http://mail.ny.acog.org/website/17PEffect.pdf, estimates that the annual patient population for HPC injection is a little over 130,000 women. Preterm birth—birth prior to 37 weeks of gestational age—is the leading cause of neonatal mortality, and is a major cause of early childhood mortality and morbidity, in the United States.

49. The March of Dimes reports at http://www.marchofdimes.com/mission/prematurity_costs.html that, in the United States, one in eight babies is born prematurely, and further reports, on the basis of a study by the Institute of

Medicine, that, in 2005, "[t]he average first-year medical costs, including both inpatient and outpatient care, were about 10 times greater for preterm infants ($32,325) than for full-term infants ($3,325)." The March of Dimes also reports, at http://www.marchofdimes.com/baby/loss_neonataldeath.html, that in 2006 about 19,000 babies died during their first month, and that preterm birth and its complications were the cause of about 25% of those neonatal deaths.

50. On May 6, 2006, Adeza Biomedical ("Adeza") submitted to FDA a New Drug Application ("NDA") for approval of Gestiva (later renamed "Makena") for prevention of preterm birth in women who have a singleton pregnancy and a history of prior preterm delivery. On June 5, 2006, FDA designated the NDA for priority review, a designation that, as explained in FDA, *Fast Track, Accelerated Approval and Priority Review, Accelerating Availability of New Drugs for Patients with Serious Diseases* (last updated May 28, 2010), *available at* http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm, is "given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists."

51. On January 25, 2007, FDA designated the drug as an orphan drug for its proposed indication.

52. Adeza's NDA was based, in part, on two studies conducted by the National Institute of Child Health and Human Development, part of the National Institutes of Health ("NIH"), and published in 2003 and 2007. On information and belief, the two studies together cost the NIH about $6 million.

53. It is not uncommon for the United States Government to help fund drug discovery and development costs, including the cost of clinical studies. For example, the Joint Economic

Committee of the Congress found that, of the 21 drugs with the highest therapeutic benefit to society between 1965 and 1992, public funding was instrumental for 15, and reported the finding in Office of the Chairman, Connie Mack, Joint Economic Committee, The Benefits of Medical Research and the Role of the NIH 27 (May 17, 2000), *available at* http://www.faseb.org/portals/0/pdfs/opa/2008/nih_research_benefits.pdf. Typically, pharmaceutical companies supplement research conducted by NIH with their own studies, as occurred with respect to Makena. Most of NIH's research would never result in drugs available to patients unless pharmaceutical companies were able to utilize that research as a foundation for a commercial product. Indeed, a grant program for clinical studies (*i.e.*, studies in human subjects) of orphan drugs exists under 21 U.S.C. § 360ee, and was expanded by the Rare Diseases Orphan Product Development Act of 2002, Pub. L. No. 107-281, § 3, 116 Stat. 1992, 1993 (2002).

54. On April 2, 2007, Cytyc Corporation purchased Adeza. In connection with that transaction, Adeza was merged with a subsidiary of Cytyc Corporation, and the surviving corporation's name was changed to "Cytyc Prenatal Products Corporation." On October 22, 2007, Hologic, Inc. acquired Cytyc Corporation, which became a subsidiary of Hologic, Inc.

55. On January 16, 2008, KV entered into an asset purchase agreement (the "2008 Agreement") with Cytyc Prenatal Products Corporation and Hologic, Inc. (together, "Hologic"). Under the terms of the 2008 Agreement, KV initially paid Hologic $7.5 million and agreed to additional future payments of $74.5 million (*i.e.*, $2.0 million upon the earlier to occur of a specified acknowledgement by FDA or FDA's approval of Makena, plus $72.5 million upon FDA's approval of Makena) for the acquired Makena assets (including the Makena NDA and Makena's orphan designation).

56. Under an amendment to the 2008 Agreement signed on January 8, 2010, in exchange for Hologic's agreement to make certain changes to the 2008 Agreement, KV agreed to increase these additional payments from $72.5 million to $190.0 million (beyond the previous payments of $7.5 million and $2 million, for a total of $199.5 million) for the Makena assets upon FDA approval and during a period extending to 21 months thereafter.

57. A second amendment to the 2008 Agreement, entered into on February 3, 2011, made certain changes to the payment dates. Hereinafter the asset purchase agreement, as amended by the first and second amendments, is referred to as the "Agreement."

58. Under the Agreement, Hologic remained obligated to pursue the approval of Makena, and remained the official sponsor of the Makena NDA pending at FDA until KV was substituted as the sponsor in February, 2011.

59. KV reimbursed Hologic for development expenses of $19 million incurred from the time the 2008 Agreement was signed until the NDA was approved by FDA on February 3, 2011. This sum included $10.2 million for the start of the post-approval clinical studies, which FDA required to meet certain milestones before it would approve the NDA for Makena. The $19 million sum also included $8.8 million for animal studies and other regulatory and chemistry/manufacturing expenses. The $19 million is in addition to the $199.5 million for acquisition of Makena.

60. During its review of the NDA, FDA made it clear that the NIH studies were not sufficient for approval, and that confirmatory clinical studies and certain other studies would be required. In particular, as a condition of approval, FDA required major, multi-year follow-on clinical studies of Makena involving at least 1,700 mothers and more than 500 infants. As noted

supra in paragraph 59, these studies began before the approval. KV reimbursed Hologic for its expenditures on these studies, and KV currently is funding them.

61. In addition to the $199.5 million in acquisition payments and $19 million in reimbursement for clinical studies and regulatory and chemistry/manufacturing expenses, KV has spent or expects to spend between $58 and $60 million for its own research on and development of Makena. This additional spending consists of research and development ("R&D") costs associated with data required by FDA for approval of this NDA. To meet the FDA post-approval commitments associated with the Makena NDA, KV has already incurred clinical and *in vitro* study costs of approximately $7 million, and estimates that over the next four to five years it will incur additional clinical and *in vitro* study costs of $34 to $35 million. KV estimates that it has thus far spent $6 million in internal personnel costs for R&D employees working on the Makena program, and will incur additional R&D personnel costs of $11 to $12 million.

62. Thus, KV's payments for research and development with respect to Makena consist of the $19 million in reimbursement to Hologic and $58 to $60 million for its own research and development – for a total of $77 million to $79 million. In sum, KV has paid or will pay approximately 93% of the total research and development cost to obtain approval for this orphan drug indication (the other 7% was paid by NIH).

63. KV's overall acquisition and R&D costs to bring Makena to the market (excluding operational costs for manufacturing, marketing, etc.) are summarized in the following chart:

Acquisition payments to Hologic	$199.5 million total: $ 7.5 million paid 1/2008; $ 2.0 million paid 5/2008; $ 70.0 million paid 1/2010; $ 12.5 million paid 2/2011; $ 12.5 million paid 2/2012 $ 95.0 million outstanding.
R&D reimbursements	$ 19.0 million from 1/2008 through 2/2011.
KV out-of-pocket costs or commitments	$ 58 to 60 million total: $ 7 million for clinical and *in vitro* study costs from 2/2011-present; $ 34 to 35 million for clinical and *in vitro* study costs of over next 4-5 years for required studies; $ 17-18 million in internal personnel costs for R&D employees working on Makena.
Grand Total	**$276.5 million to $278.5 million**

64. Thus, KV has invested or committed well over a quarter of a billion dollars with respect to Makena. The cost of the NIH studies is a very small, indeed, immaterial, percentage of that amount.

65. Plaintiffs did not receive a free ride on the NIH studies. The price that KV paid for the rights to Makena, as a result of the arms-length negotiations with Hologic, was based on the developmental status of, and the anticipated revenues from, Makena. The value, and the cost to KV, of those rights did not depend on who had paid for the NIH studies.

66. FDA formally approved Makena on February 3, 2011.

67. In a letter dated February 11, 2011, FDA confirmed that, "as the first sponsor of this drug to obtain marketing approval" for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of spontaneous preterm birth, Hologic is "entitled to seven years of orphan-drug exclusive approval . . . The seven year exclusive approval began on February 3, 2011." Under the Agreement, this entitlement is now owned by KV, which shares its benefit with Ther-Rx.

Reports on Makena's Pricing

68. Shortly after Makena was approved, various news outlets reported in very heated terms that Makena would have a list price of $1,500 per injection, or up to $30,000 for a course of treatment.

69. The "list price" for a drug, however, does not determine or reflect what patients, Medicaid, private insurers, or others ultimately pay for it. The list price is a pre-negotiation price (*i.e.*, before applicable discounts and rebates are negotiated with Medicaid programs, private insurers, and other private payers). Medicaid, for example, is entitled to a minimum of a 23.1% rebate under law. It is standard industry practice for both public and private payers to negotiate substantial price reductions – using upfront discounts and end-of-quarter or -year rebates – to reach a mutually agreeable net effective price. The list price merely establishes a starting point for negotiating with payers to reach a final price.

70. Moreover, few of the press reports took into account Plaintiffs' programs to ensure that women who could not afford Makena have access to it. Plaintiffs have confirmed that they are and will be providing Makena to all eligible uninsured patients at a significantly reduced cost, and free of charge to eligible uninsured patients whose annual gross household income is below a specified amount. In addition, Plaintiffs will subsidize co-pay amounts set by payers for insured patients, and will require no co-payment from insured patients who meet certain eligibility and income criteria. Under Makena's patient-financial-assistance program, an uninsured patient with an annual gross household income of less than $60,000 will not pay anything for Makena, and an uninsured patient with an annual gross household income of $115,000 will pay $20.00 per injection of Makena. On the basis of U.S. Census data, Plaintiffs estimate that approximately 85%

of all patients have a household income that would qualify them to pay $20.00 or less out of pocket per injection of Makena.

71. Moreover, in a press release dated April 1, 2011, Plaintiffs announced:

> Effective immediately, Ther-Rx has:
>
> - Reduced the list price of Makena by nearly 55 percent, to $690 per injection;
> - Will offer supplemental rebates that, in conjunction with the list price reduction and the standard Medicaid rebate of 23.1 percent, will result in a substantially reduced cost per injection for state Medicaid agencies compared to list price. This will help ensure that every woman who is prescribed Makena – regardless of her ability to pay – has the comfort of knowing a medication that has been rigorously reviewed by FDA for safety and efficacy is available to her;
>
> . . .
>
> - Expanded the Company's patient assistance program for patients who are prescribed this important medication by removing income caps to qualify for financial assistance. . . .

This press release is *available at* http://www.kvpharmaceutical.com/news_center_article.aspx?articleid=341. (The element omitted from the quotation did not become operative, and has been terminated.)

72. The press reports also did not take into account the fact that orphan drugs generally are more expensive than other types of drugs. An orphan drug necessarily is expensive, as compared to other approved drugs and to compounded drugs, because (a) to be approved by FDA, an orphan drug must satisfy the same standards as non-orphan drugs, and consequently the costs of developing the orphan drug and securing FDA approval are not necessarily less than the corresponding costs as to a drug for a larger patient population; but (b), due to the smallness of an orphan drug's patient population, recovery of those costs and any profit must be drawn from fewer patients; and (c) compounders do not incur any of the substantial costs for meeting FDA's

approval requirements and the substantial ongoing costs of compliance with FDA's post-approval requirements.

73. Even the original list price of a course of treatment with Makena (up to $30,000) was substantially below the cost of treatment with some other orphan drugs against whose orphan drug exclusivities Defendants have not taken any action. Some orphan drugs have a list price of more than $200,000 annually. In addition, Jonathan D. Rockoff, *Pfizer's Future: A Niche Blockbuster*, Wall St. J. (Aug. 30, 2011), *available at* http://online.wsj.com/article/SB10001424053111903352704576538683370950462.html#printMode, reports the following costs of treatment with recently approved orphan drugs:

(a) Xalkori, sold by Pfizer, Inc.: $115,200 per year;

(b) Herceptin, sold by Roche Holdings, A.G.: $50,400 per course of treatment (sales in 2010: $6.8 billion); and

(c) Zelboraf, sold by Roche Holdings, A.G. and Daiichi Sankyo Corp.: $56,400 for six months of treatment.

FDA's website shows the following approved orphan indications for these drugs:

(a) Xalkori (crizotinib): treatment of ALK positive non-small cell lung cancer, *available at* http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=310610;

(b) Herceptin (trastuzumab): treatment of HER2-overexpressing advanced adenocarcinoma of the stomach, including gastroesophageal junction, *available at* http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=292409; and

(c) Zelboraf (vemurafenib): treatment of patients with IIb to Stage IV melanoma positive for the BRAF(v600) mutation, *available at* http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=325310.

74. Although the Defendants have no authority to consider a drug's price in decision-making about a drug under the FDCA, the press reports about Makena's price led to pressure by Members of Congress on the Defendants to do something to make HPC injection available at a price lower than the initial list price of Makena.

FDA's March 30, 2011 Statement

75. On March 30, 2011, FDA issued a press release (the "Statement") addressing Makena, which ended: "In order to support access to this important drug, at this time and under this unique situation, FDA does not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products."

76. The Statement is contrary to the relevant facts.

(a) Although it purports to "support access" to HPC injection, FDA has never made any determination that access to Makena has been or is impaired in any way; and, in fact, since it was launched in the market on March 14, 2011, Makena has been, and still is, available to eligible women in adequate supply on a national basis. Moreover, since it was launched, it has been, and is, available at a cost to patients, subsidized by KV, that makes it affordable or even free to them.

(b) FDA characterizes Makena's pricing as presenting a "unique situation," when in fact, as illustrated in paragraphs 72-73, *supra*, the price of Makena does not present a "unique situation."

77. In the Statement, FDA effectively revoked and nullified Plaintiffs' statutory right to a period of seven years of market exclusivity by assuring compounders that they could, with FDA's approval, manufacture, distribute in interstate commerce, and sell, even in commercial quantities, unapproved, non-customized compounded 17P, on a general and nationwide basis, to reduce the risk of preterm birth in women with a history of spontaneous preterm birth, despite the commercial availability of Makena, an approved orphan drug with statutory market exclusivity for that indication. FDA has never made, and there never has been a factual basis for it to make, any determination, in the Statement or elsewhere, to support a conclusion that access to Makena was impaired in any way, or that supplies of Makena were not, are not, or will not be sufficient to satisfy the market demand for HPC injection.

78. The Statement also failed to apply to compounders of 17P four of the restrictions on compounding set forth in 21 U.S.C. § 353a and in FDA's own CPG 460.200: (a) the requirement that there be a medical necessity for the use of a compounded drug instead of an FDA-approved drug; (b) the prohibition on regularly compounding copies of commercially available FDA-approved drugs; (c) the limitations on preparing compounded drugs in advance of receiving a prescription; and (d) the statutory cap on out-of-state sales of compounded drugs in the absence of a memorandum of understanding between FDA and a State. Thus, the Statement and the policy it sets forth approve, authorize, invite, encourage, and permit the manufacture, distribution in interstate commerce, and sale of non-customized "compounded" 17P on a commercial scale, but

outside the FDCA's and FDA's systems for protecting the public with respect to drugs manufactured, distributed, and sold in interstate commerce on a commercial scale.

79. The Statement also does not subject the compounders of 17P to any of the approval and post-approval requirements that apply to KV with respect to Makena, despite the fact that much of the "compounded" 17P on the market is non-customized, manufactured on a commercial scale, and distributed in interstate commerce.

80. FDA's Statement is not the exercise of case-by-case enforcement discretion as to past conduct, but, rather, addresses future conduct and announces a general policy that is binding on FDA personnel as long as it has not been revoked, and that approves, authorizes, invites, encourages, and permits an unlimited and unknown number of "compounders" to distribute nationwide during Plaintiffs' exclusivity period and for an unlimited time thereafter non-customized 17P intended to be used for the same orphan indication for which Makena is approved. This approval, authorization, invitation, encouragement, and permission extend to the commercial manufacture in unlimited quantities of non-customized 17P in facilities not registered with, approved by, or routinely inspected by, FDA. The compounded versions of this drug for injection (which therefore must be, among other things, sterile in order to be safe) have unknown compositions not approved by FDA, are, in general, of unknown effectiveness and safety, are manufactured by unknown processes not approved by FDA, lack FDA-approved labeling information for prescribers, are not subject to required reporting of adverse events, and are used to treat women with a condition that threatens the lives of their fetuses. Indeed, surveys by FDA and the Missouri Board of Pharmacy during the last several years have found that approximately 11.6% to 33% of compounded drugs fail to meet specifications in quality testing. The data

summarized in paragraph 5 *supra* show that many versions of compounded 17P present avoidable elevated risks of lack of effectiveness and lack of safety.

81. The Statement also makes no mention of (a) the factual circumstances of any particular compounders, (b) any need to prioritize use of FDA's enforcement resources, or (c) any prospect that any of the compounded products allowed to be marketed will ever come into compliance with the FDCA.

82. The Statement also is based on an impermissible factor, a desire to nullify Plaintiffs' statutory market exclusivity in order to make HPC injection available at a price lower than the price of Makena, in response to political pressure.

83. On information and belief, FDA's Statement was coordinated with a statement issued the same day by CMS. CMS's statement effectively authorized and encouraged state Medicaid agencies to pay for compounded 17P in substitution for Makena.

84. In conjunction with CMS's statement, FDA's Statement affirmatively solicits and facilitates violations of the FDCA and the flow of Medicaid and private money to pay for those violations. Thus, FDA's Statement is an abdication of FDA's enforcement responsibilities under the FDCA, including its responsibilities to respect and protect orphan drug exclusivity and to protect patients.

85. FDA's Statement suggests that FDA may act against a compounder if FDA learns, after the fact, that "the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products." Thus, FDA's approach to these products is akin to the unsatisfactory situation that existed before the enactment of the drug approval process in the FDCA in 1938—in which FDA had to catch up with

drug safety and quality problems after the fact rather than preventing them through the approval process.

86. Some state Medicaid programs have interpreted FDA's Statement and CMS's statement as authorizing the total displacement of Makena by compounded 17P. For example:

(a) Under the Georgia Department of Community Health's Makena Position Statement, *available at* http://dch.georgia.gov/vgn/images/portal/cit_1210/48/42/169845946Makena.pdf, the Medicaid Division of the Georgia Department of Community Health started requiring "prior authorization for any prescription for Makena™." Physicians wishing to prescribe Makena "will be required to demonstrate the medical necessity of the manufactured product, Makena™, over the compounded CHC product to obtain a prior authorization."

(b) Montana's Medicaid program now also requires a prescribing physician seeking approval for a patient to receive Makena to demonstrate that the patient has a medical need for Makena as compared to compounded 17P.

(c) The Louisiana Department of Health & Hospitals has announced that "Medicaid will . . . cover the average costs of the compounded version of the drug, and we urge medical professionals to use it in their patients for whom it is indicated."

87. These actions by state Medicaid agencies, which are made possible by FDA's Statement, which called forth unlimited manufacturing and distribution of non-customized compounded 17P, stand the law on its head by requiring doctors to provide proof that the FDA-approved drug is medically necessary in comparison to unapproved compounded versions produced by whatever processes and practices compounders choose to use.

88. Never before has FDA publicly approved, authorized, invited, encouraged, or permitted widespread non-customized compounding to replace an FDA-approved drug. Indeed, just two weeks before FDA's Statement, FDA spokesperson Jeff Ventura specifically reiterated in connection with Makena that compounding copies of an approved commercially available drug regularly or in inordinate amounts is prohibited.

89. Many (possibly, all) compounders of 17P use active ingredient manufactured in China. None of the Chinese manufacturing establishments whose output of active ingredient for 17P is exported to the United States is identified in an approved NDA for HPC.

90. In GAO, DRUG SAFETY[:] Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program 24 (GAO-08-970 Sept. 2008), *available at* http://www.gao.gov/new.items/d08970.pdf, the Government Accountability Office ("GAO") reported: "The country with the lowest proportion of [drug manufacturing] establishments inspected [by FDA] was China . . . ."

91. A Table in GAO, DRUG SAFETY[:] FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed 17 (Table 2) (GAO-10-961 Sept. 2010), *available at* http://www.gao.gov/new.items/d10961.pdf, shows that, as of fiscal year 2009, 88% of the drug manufacturing establishments in China in FDA's inventory may never have been inspected, the highest such percentage for any country. That GAO report also notes at page 18: "Unless a foreign establishment is listed on an application for a new drug, FDA is still unlikely to select the establishment for inspection." No such applications are submitted for compounded 17P.

92. FDA stated in FDA, Pathway to Global Product Safety and Quality 16 (July 7, 2011) (footnote omitted), *available at*

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OC/GlobalProductPathway/UCM262528.pdf: "Perhaps the most serious challenge on the horizon for FDA is that growing access to the global marketplace will also expose Americans to a set of economically-motivated harms including counterfeiting, fraud, and other intentional adulterations. Recent, highly-public incidents involving adulterated heparin and melamine-tainted baby formula underscore how serious the potential danger can be. . . . The U.S. has seen a steady increase in the number of counterfeiting incidents. The World Health Organization estimated that between 5% and 8% of all of [sic] pharmaceuticals worldwide were counterfeit in 2003." The heparin and melamine-tainted baby formula referred to were produced in China.

93. Problems with compounding, as a process, in the United States have been extensively documented, as reflected in paragraphs 11-13, *supra*.

94. FDA has issued further public statements on Makena on November 8, 2011 and June 15 and 29, 2012; CMS also issued a further statement on Makena on June 15, 2012. None of these statements has announced an intent to take enforcement action against unlawful compounded 17P that is not customized to meet the special needs of individual patients who have the condition for which Makena, a drug that has statutory market exclusivity, is indicated but for whom Makena is medically inappropriate.

Harm to Plaintiffs and the Public Interest

95. KV is reliant almost entirely on the success of Makena to meet its future cash operating needs and to make obligatory debt payments. Makena is KV's most significant drug by far, and was expected to account for the vast majority of KV's projected revenue over the remaining Makena exclusivity period. KV's survival as a going concern is primarily dependent on KV's ability to obtain relief from FDA's March 30, 2011 Statement and the policy it sets forth, and

the resulting actions by CMS and state Medicaid agencies, which could not have occurred without FDA's approval of widespread distribution of compounded 17P not customized for individual patients for whom Makena is medically inappropriate. KV can survive only if it generates future revenues from sales of Makena that will be sufficient to meet KV's future needs, including recovery of its costs for the acquisition of Makena and its R&D and operating expenses. Unless KV is able to immediately generate significantly higher market share and revenues from Makena than the current levels, the company will not be able to meet its cash obligations, and will run out of cash in less than three months from the date of this Complaint.

96. Absent declaratory and injunctive relief, Plaintiffs will be effectively deprived of their statutory market exclusivity; and, consequently, will be unable to survive as going concerns. As a result of FDA's Statement, Makena is being, and will continue to be, widely displaced in the market by compounded 17P. Competition from compounders of non-customized versions of 17P, who do not bear the large costs of complying with FDA's approval and quality-manufacturing and other post-approval requirements, has undercut, and will continue to undercut, Plaintiffs' sales of Makena. If such unfair competition continues, it will destroy Plaintiffs. Consequently, FDA's Statement has caused, is causing, and will continue to cause, severe, immediate, and irreparable harm to Plaintiffs.

97. FDA's Statement and policy are continuing to deprive Plaintiffs of their first-mover advantage. The loss of that advantage is irreparable harm.

98. In addition, absent declaratory and injunctive relief, the health and safety of women with high-risk pregnancies and their unborn children will continue to be subjected to the significant avoidable risks posed by compounded 17P as compared to Makena. Compounding generally has a history of producing products that have high rates of failure in quality testing and

adverse outcomes for patients, as described in paragraphs 11-13, *supra*. In particular, compounded 17P, with API manufactured in China, has failure rates, referred to in paragraph 5, *supra*, that would be unacceptable to FDA as to an approved product, and should be unacceptable as to an unapproved product.

99. In addition, absent declaratory and injunctive relief, FDA's Statement and the policy it sets forth will continue to reduce the effectiveness of the incentive provided by orphan drug exclusivity for the development of orphan drugs. FDA's reduction of that incentive is contrary to congressional intent and to the public interest in the effectiveness of that incentive.

100. In addition, absent declaratory and injunctive relief, FDA's Statement and the policy it sets forth will continue to violate the public interest in federal agencies' compliance with the statutes they administer.

101. Plaintiffs have no adequate remedy at law to make themselves whole for the injury to their business resulting from FDA's Statement.

102. Plaintiffs need temporary, preliminary, and permanent declaratory and injunctive relief.

FIRST CAUSE OF ACTION
Violation of 21 U.S.C. § 360cc

(APA, 5 U.S.C. §§ 558(c), 706(2)(A), (B), (C), & (D);
21 U.S.C. § 360cc; U.S. Const.amend. V)

103. Plaintiffs reallege and incorporate by reference Paragraphs 1-102.

104. FDCA § 527, 21 U.S.C. § 360cc (entitled "Protection for drugs for rare diseases or conditions"), prohibits FDA, during the seven-year period of an approved orphan drug product's market exclusivity, from approving (formally or in any other way), authorizing, inviting, encouraging, or generally permitting the introduction into interstate commerce of any compounded

versions of that same drug product for the same orphan indication as to which the approved drug has been designated an orphan drug, except where the compounded version is customized to meet the medical need of an individual patient for whom the approved product is not medically appropriate (and thus the approved orphan drug would not be used by that patient in any event). Such action by FDA would nullify orphan drug exclusivity, and thereby would defeat the statutory incentive Congress created for orphan drugs in section 360cc.

105. FDA's Statement and the policy it sets forth violate section 360cc(a) by effectively nullifying Makena's statutory seven-year period of market exclusivity by giving *de facto* approval to compounded versions of 17P that are intended for use to treat the same indication for which Makena is designated as an orphan drug and is approved, and that are not customized to meet the medical needs of individual patients who have the condition for which Makena is indicated but for whom Makena is not medically appropriate.

106. FDA has no authority to consider cost in determining whether there is sufficient access to an orphan drug, and FDA has made no determination that patients for whom Makena is indicated have insufficient access to it, either as a matter of quantities available or as a matter of cost.

107. FDA's Statement and the policy it sets forth effectively nullify Makena's statutory seven-year period of market exclusivity by publicly approving, authorizing, inviting, encouraging, and permitting violations of 21 U.S.C. §§ 353a and 355(a), and by stimulating such violations that would not occur but for FDA's Statement and policy.

108. In issuing its Statement "to support access to" HPC injection, FDA failed to comply with the procedural requirements of 21 U.S.C. § 360cc(b); 21 C.F.R. § 316.36 (2012); 5 U.S.C. § 558(c); and the Due Process Clause of the Fifth Amendment to the U.S. Constitution.

109. FDA's Statement and the policy it sets forth are arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law, contrary to constitutional right, in excess of statutory jurisdiction, authority, or limitation, short of statutory right, and without observance of procedure required by law, in violation of 5 U.S.C. § 706(2)(A), (B), (C), and (D).

SECOND CAUSE OF ACTION
Violation of 21 U.S.C § 353a

(APA, 5 U.S.C. § 706(2)(A) & (C); 21 U.S.C. § 353a)

110. Plaintiffs reallege and incorporate by reference Paragraphs 1-109.

111. The prohibitions on advertising and solicitation of prescriptions by drug compounders contained in FDCA § 503A, 21 U.S.C. § 353a, which were held unconstitutional in *Western States*, 535 U.S. at 372-74, are severable from the other provisions of Section 353a, which remain in effect.

112. FDA's Statement and the policy it sets forth are contrary to Section 353a's express limitations on compounding. Among other things:

(a) the Statement and policy approve, authorize, invite, encourage, and permit compounding of 17P without verification that the patients who will receive the compounded 17P have a medical need for compounded 17P rather than Makena;

(b) the Statement and policy approve, authorize, invite, encourage, and permit regular compounding of non-customized17P and compounding of non-customized 17P in inordinate amounts, to substitute for Makena;

(c) the Statement and policy approve, authorize, invite, encourage, and permit compounding of 17P before a compounder has received a prescription and without the compounder having a pre-existing relationship with a prescribing physician or other licensed practitioner and that physician's or practitioner's patient; and

(d) the Statement and policy approve, authorize, invite, encourage, and permit compounding of 17P in disregard of the limitation set forth in Section 353(b)(3)(B).

113. FDA's Statement and the policy it sets forth are arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law, in excess of FDA's authority, and in excess of statutory jurisdiction, authority, or limitation, in violation of 5 U.S.C. § 706(2)(A) and (C).

THIRD CAUSE OF ACTION
Violation of 21 U.S.C. § 355(a) and 301(d)

(APA, 5 U.S.C. § 706(2)(A) & (C); 21 U.S.C. §§ 355(a), 331(d))

114. Plaintiffs reallege and incorporate by reference Paragraphs 1-113.

115. FDA's Statement and the policy it sets forth approve, authorize, invite, encourage, and permit the introduction, and delivery for introduction, into interstate commerce of unapproved new drugs—unapproved versions of 17P not customized to meet the medical need of patients who have the condition for which Makena is indicated but for whom Makena is medically inappropriate—in violation of FDCA §§ 505(a) and 301(d), 21 U.S.C. §§ 355(a) and 331(d).

116. FDA's Statement and the policy it sets forth are arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law, in excess of statutory authority, and without observance of procedure required by law, in violation of 5 U.S.C. § 706(2)(A) and (C).

FOURTH CAUSE OF ACTION
Violation of 21 U.S.C. § 381(a)

(APA, 5 U.S.C. § 706(2)(A), (C), & (D); 21 U.S.C. §§ 355(a), 381(a))

117. Plaintiffs reallege and incorporate by reference Paragraphs 1-116.

118. FDCA § 201(g)(1), 21 U.S.C. § 321(g)(1), provides in relevant part: "The term ''drug'' means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any

supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." Under 21 C.F.R. § 210.3(b)(3) (2012), the term "component" means "any ingredient intended for use in the manufacture of a drug product . . . ." Under 21 C.F.R. § 210.3(b)(4) (2012), the term "drug product" means "a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. . . ." Within the scope of these definitions, compounded 17P is a "drug" and a "drug product," and API for compounded 17P is a "component" and a "drug."

119. Under FDCA §§ 201(p), 21 U.S.C. § 321(p), compounded 17P and API for compounded 17P are unapproved new drugs, which are barred from interstate commerce by FDCA §§ 505(a) and 301(d), 21 U.S.C. §§ 355(a) and 331(d).

120. FDCA § 801(a), 21 U.S.C. § 381(a), provides in mandatory terms for FDA to refuse importation of any drug that appears to be unapproved in violation of 21 U.S.C. § 355: "The Secretary of the Treasury shall deliver to the Secretary of Health and Human Services, upon his request, samples of . . . drugs . . . which are being imported or offered for import into the United States . . . . If it appears from the examination of such samples or otherwise that . . . such article is . . . in violation of section 355 of this title . . . then such article shall be refused admission [with an exception not relevant here]."

121. The foreign-manufactured API for compounded 17P appears to be—and, indeed, is—an unapproved new drug and, when imported or offered for import into the United States, appears to be—and, indeed, is—in violation of Section 355.

122. Such API for compounded 17P cannot lawfully be introduced or delivered for introduction into interstate commerce or lawfully be imported into the United States.

123. Since March 30, 2011 and continuing to the present, Defendants have been, and are, allowing the import of such API for compounded 17P. Such allowance by Defendants violates Section 381(a) and has been and is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

124. Defendants' March 30, 2011 Statement announcing implicitly that they would allow such imports has been and is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

125. FDA's allowance of such imports injures Plaintiffs by facilitating unlawful competition with KV's product, Makena, by compounders of non-customized 17P.

PRAYER FOR RELIEF

WHEREFORE, the Plaintiffs pray that this Court, pursuant to 28 U.S.C §§ 1361, 2201-02, 1651, and Rules 57 and 65, Fed. R. Civ. P., and the inherent power of this Court:

1. Temporarily declare:

(a) That FDA's March 30, 2011 Statement and its June 15, 2012 statement and the policy of non-enforcement against the compounding of 17P not customized to meet the special needs of patients who have the condition for which Makena is indicated but for whom Makena is medically inappropriate, which those statements set forth and maintain, are unlawful, in that they violate 21 U.S.C. §§ 360cc(a), 353a, and 355(a).

(b) That FDA's allowance of the importation of unapproved API for compounded 17P not so customized violates 21 U.S.C. § 381(a).

(c) That FDA has a duty under 21 U.S.C. § 360cc(a) to protect Makena from

the kind of approval of non-customized compounded 17P that FDA's March 30, 2011 Statement announced and FDA's June 15, 2012 statement maintains and the unlawful competition that has resulted from those statements; and that, to the extent that FDA's CPG 460.200 fails to make protection of orphan drug exclusivity a significant factor in case evaluation, it is unlawful.

(d) That, because FDA's March 30, 2011 Statement approved, invited, and called forth the unlawful competition with Makena by compounded 17P not customized to meet the special needs of patients who have the condition for which Makena is indicated but for whom Makena is medically inappropriate, FDA has a duty to terminate that unlawful competition forthwith.

2. Temporarily order:

(a) That Defendants immediately suspend FDA's March 30, 2011 Statement and June 15, 2012 statement, announce that those statements are suspended, and not maintain or implement the policy of non-enforcement as to non-customized compounding of 17P set forth and maintained in those statements.

(b) That Defendants cease and desist from permitting the importation into the United States of unapproved API for compounded 17P.

(c) That, within two (2) business days, Defendants issue a new public statement communicating (i) their intent to enforce, in appropriate cases and with priority to compounding that is regular or in inordinate amounts, 21 U.S.C. §§ 360cc(a), 353a and 355(a) against compounders of 17P not customized to meet the special needs of patients who have the condition for which Makena is indicated but for whom Makena is medically inappropriate, and (ii) that shipments of unlawful compounded 17P not so customized must cease immediately.

(d) That, within ten (10) business days, Defendants report to the Court, under seal if and to the extent necessary and with a redacted version publicly filed, the actions they have taken to terminate shipments of unlawful compounded 17P not customized to meet the special needs of patients who have the condition for which Makena is indicated but for whom Makena is medically inappropriate.

3. Preliminarily and permanently declare:

(a) That the distribution in interstate commerce of compounded 17P beyond the scope of the traditional practice of pharmacy, *i.e.*, the distribution in interstate commerce of a compounded version of 17P that is not customized for an individual patient who has the condition for which Makena is indicated but for whom Makena is medically inappropriate, is unlawful.

(b) That FDA's March 30, 2011 Statement, and FDA's June 15, 2012 statement, and the policy of non-enforcement against compounded 17P not so customized, which those statements set forth and maintain, are unlawful, in that they violate 21 U.S.C. §§ 360cc(a), 353a, 355(a), and 331(d), and are not a lawful exercise of enforcement discretion; and therefore the Statement and policy are arbitrary, capricious, an abuse of discretion, otherwise not in accordance with law, in excess of statutory jurisdiction, authority, or limitation, short of statutory right, and without observance of procedure required by law.

(c) That Defendants have a duty under 21 U.S.C. § 360cc(a) to protect Makena from the kind of approval of non-customized compounded 17P that FDA's March 30, 2011 Statement announced and FDA's June 15, 2012 statement maintains and the unlawful competition that has resulted from those statements; and that, to the extent that FDA's CPG 460.200 fails to make protection of orphan drug exclusivity a significant factor in case evaluation, it is unlawful.

(d) That 21 U.S.C. § 360cc(a) requires Defendants to enforce 21 U.S.C. §

355(a), in light of 21 U.S.C. § 353a, to the extent necessary to protect an orphan drug's exclusivity.

(e) That, because FDA's March 30, 2011 Statement approved, invited, and called forth the unlawful competition with Makena by compounded 17P not so customized, Defendants have a duty to terminate that unlawful competition forthwith.

(f) That FDA cannot make findings as to access to or availability of an approved orphan drug, *e.g.*, Makena, without complying with the procedural and substantive provisions of 21 U.S.C. § 360cc(b) and 21 C.F.R. § 316.36 (2012); 5 U.S.C. § 558(c); and the Due Process Clause of the Fifth Amendment to the U.S. Constitution.

(g) That, in considering (i) whether the holder of an approved application for an orphan drug, *e.g.*, Makena, can assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated an orphan drug, or (ii) whether such persons otherwise have adequate access to the drug, FDA may not consider the list price, or any other price, or the cost, of the drug.

(h) That the foreign-manufactured API for compounded 17P appears to be—and is— an unapproved new drug under 21 U.S.C. § 355.

(i) That such API for compounded 17P cannot lawfully be introduced or delivered for introduction into interstate commerce or lawfully be imported into the United States.

(j) That, since March 30, 2011 and continuing to the present, Defendants have been, and are, allowing the import of such API for compounded 17P, and that such allowance has been and is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

(k) That FDA's March 30, 2011 Statement announcing implicitly that DFDA would allow such imports was and is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

4. Permanently declare that, under 21 U.S.C. § 360cc, KV is entitled to seven years of marketing exclusivity for Makena, and that that seven-year period is to be calculated as running from February 3, 2011 to March 30, 2011, and from the date of the grant of temporary, preliminary, or final declaratory and/or injunctive relief, whichever is first, until the date that is six years and 310 days from that date.

5. Preliminarily and permanently order:

(a) That Defendants withdraw FDA's March 30, 2011 Statement and June 15, 2012 statement, announce that those statements are withdrawn, and not maintain or implement the policy of non-enforcement as to non-customized compounding of 17P set forth in the March 30, 2011 Statement.

(b) That Defendants take sufficient enforcement actions to stop the unlawful competition with Makena by compounded 17P not customized to meet the special needs of patients who have the condition for which Makena is indicated but for whom Makena is medically inappropriate.

(c) That Defendants report to the Court quarterly for one year and semi-annually for the following two years, under seal if and to the extent necessary and with a redacted version publicly filed, the actions they have taken to terminate shipments of non-customized compounded 17P.

(d) That Defendants not permit the entry into the United States of, and not release into domestic commerce, any future shipments of, foreign-manufactured API for use in compounding non-customnized 17P, except such API that is from an establishment that is identified in an approved NDA for hydroxyprogesterone caproate injection, and that is in compliance with that approved NDA.

(e) That Defendants DHHS and Secretary Sebelius take all actions necessary and appropriate to implement the relief awarded by the Court, including, but not limited to, withdrawal of CMS's March 30, 2011 statement relating to payment for 17P.

6. Provide such other and further relief as the Court finds just and proper.

Respectfully submitted,

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Attorneys for Plaintiffs K-V Pharmaceutical Company and Ther-Rx Corporation

Dated: July 5, 2012.

CERTIFICATE OF SERVICE

I hereby certify that on this 5th day of July, 2012, the foregoing Complaint for Declaratory and Injunctive Relief was served:

Via hand-delivery on:

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c/o Civil Process Clerk
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/s/ Michael V. Pinkel
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