IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

SPECTRUM PHARMACEUTICALS, INC. 11500 S. Eastern Avenue #240, Henderson, NV 89052, Plaintiff, v. SYLVIA MATHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, 200 Independence Avenue, S.W. Washington, DC 20201, and STEPHEN OSTROFF, M.D., in his official capacity as ACTING COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, 10903 New Hampshire Avenue, Silver Spring, MD 20993, Defendants.	Civil Action No. _____

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF'S MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

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Dated: April 27, 2015

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INTRODUCTION

Plaintiff Spectrum Pharmaceuticals, Inc. ("Spectrum") seeks a TRO or preliminary injunction to prevent an unlawful labeling carve-out that threatens to deprive Spectrum of its statutorily-mandated Orphan Drug Act exclusivity. FDA recently approved an application submitted by Sandoz, Inc. ("Sandoz") under Section 505(j)(1) of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(1), for permission to market a purported generic version of Spectrum's FUSILEV® (levoleucovorin) for injection ("FUSILEV"). FDA's approval reflects an unlawful labeling carve-out and therefor was arbitrary, capricious, and unlawful under the Administrative Procedure Act ("APA").

Spectrum's FUSILEV® is an FDA-approved injectable drug used to treat three different conditions, two of which relate to counteracting the effects of the drug methotrexate, and one of which involves palliative treatment of patients with advanced metastatic colorectal cancer. In approving Sandoz's drug, FDA permitted Sandoz to "carve out" this latter colorectal cancer indication from the drug's labeling in order to sidestep Spectrum's orphan drug exclusivity for that indication, which extends until April 29, 2018. As a result, Sandoz's drug is only approved and labeled for the two methotrexate indications. However, Sandoz's drug was approved solely in large vial sizes that are appropriate ***only*** for the carved-out colorectal cancer indication, not for the two methotrexate indications. This discrepancy between the Sandoz drug's labeling and its large vial sizes poses an increased risk of dosing errors and the potential for product contamination if the generic version of FUSILEV® is used for multiple administrations even though it is designed only for single use. FDA's approval of Sandoz's drug therefore violates FDA's labeling carve-out regulation, which prohibits a labeling carve-out that will render the

purported generic drug less safe than the brand name drug upon which its approval is based. Notably, FDA has offered no explanation as to why such large vial sizes are needed.

The four factors governing injunctive relief strongly favor issuance of an injunction in this case. Spectrum's likelihood of success is strong. FDA's own regulations prohibit labeling carve-outs that result in approval of a generic drug that is less safe than the brand name drug on which it is based. And FDA itself has said that single-use vials containing excess drug – precisely the situation presented here – present very real safety concerns, particularly in the form of dosing errors and product contamination that can result from multiple uses of a vial designed for single use. Granting an injunction will promote the public interest by protecting patients from potentially severe – and entirely unnecessary – safety risks associated with the discrepancy between the Sandoz drug's approved indications and the approved vial sizes. In the absence of immediate injunctive relief, Spectrum will suffer irreparable injury. Because the Sandoz product will be placed in the same reimbursement code as FUSILEV® and undoubtedly will cause price decreases, providers will have an enormous incentive to substitute the Sandoz product for FUSILEV® – particularly in the first few months following its entry into the marketplace. Absent immediate injunctive relief, Sandoz's drug will immediately overtake FUSILEV®'s market share, drive down prices, and have a devastating effect on Spectrum's ability to invest in R&D for pipeline products and otherwise support commercial operations. The requested injunctive relief will cause no undue hardship to FDA or to Sandoz, since it simply preserves the status quo pending briefing on the merits.

STATEMENT OF FACTS

1. Statutory Background

A. The New Drug Approval Process

The FDCA requires all new prescription drugs to obtain FDA approval before they can enter the marketplace. 21 U.S.C. § 355(a). Manufacturers of brand name ("pioneer" or "innovator" drugs) must demonstrate the safety and effectiveness of their products in order to gain FDA approval. Typically, that is done by conducting pre-clinical and clinical studies and submitting the resulting data to FDA in a new drug application ("NDA"). 21 U.S.C. § 355(b)(1).

When a drug is approved under an NDA, the drug and any applicable patents are listed in an FDA publication called *Approved Drug Products with Therapeutic Equivalence Evaluations* (34th Ed. 2014), known as the "Orange Book." The Orange Book also lists the date on which the NDA was approved as well as the dates on which any periods of exclusivity expire, including orphan drug exclusivity. A searchable electronic copy of the Orange Book is available on FDA's website at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

B. Orphan Drug Exclusivity

Congress passed the Orphan Drug Act of 1983 in order to promote the development of "orphan drugs" – drugs that treat rare diseases or disorders that affect only small patient populations. Pub. L. No. 97-414, 96 Stat. 2049 (1983). In pursuit of this objective, the Orphan Drug Act amended the FDCA to provide research assistance, grants, tax incentives, and – most importantly – market exclusivity to companies that undertake development of orphan drugs. 21 U.S.C. §§ 360aaee. In promulgating the regulations to implement these new provisions of the FDCA, FDA interpreted the Orphan Drug Act's "main purpose" as "stimulat[ing] innovation in developing treatments for patients with rare disease and conditions and to foster the prompt

availability of therapeutically superior drugs." 56 Fed. Reg. 3338 (Jan. 29, 1991) (Orphan Drug Regulations Proposed Rule).

To fulfill this objective, the statute requires FDA to grant orphan drug designation to a drug that meets certain criteria, including that the drug treats a "rare disease or condition," *i.e.*, any disease or condition which either (i) affects less than 200,000 persons in the United States; or (ii) affects more than 200,000 persons in the United States for which there is no reasonable expectation that the cost of developing and making available the drug for such disease or condition in the United States will be recovered from sales of such drug in the United States. 21 U.S.C. § 360bb(a)(2); 21 C.F.R. Part § 316.3(b)(10).

When FDA approves a designated orphan drug for the designated indication, the drug sponsor receives a number of benefits, the most significant of which is a seven-year period of market exclusivity. With limited exceptions not applicable here, during this exclusivity period, FDA may not approve another application for the same drug for such disease or condition to anyone but the original NDA holder. 21 U.S.C. § 360cc.

C. Generic Drug Approval Process and Labeling Carve-outs

Following a period of marketing exclusivity and, if applicable, patent protection afforded to a pioneer drug, FDA may permit generic pharmaceutical manufacturers to sell generic drugs containing the same active ingredient as the pioneer drug (which is known as the "reference listed drug" or "RLD"). Generic drugs are approved by means of an Abbreviated New Drug Application ("ANDA"). 21 U.S.C. § 355(j)(1). ANDAs generally do not contain new clinical data. Instead, an ANDA relies on FDA's finding of safety and efficacy for a previously approved RLD. 21 U.S.C. § 355(j)(2). In essence, the agency's previous determination that the RLD is safe and effective is fully extrapolated to the generic product, based on the demonstration

that the generic is "the same as" the RLD. *See id.* § 355(j)(4). As such, the ANDA approval process allows an ANDA applicant to rely on FDA's previous finding of safety and efficacy for an RLD rather than requiring the ANDA applicant to independently demonstrate the safety and efficacy of the proposed generic drug through rigorous pre-clinical and clinical studies.

To rely on an RLD's finding of safety and efficacy, the ANDA applicant must identify the RLD and submit to FDA one of four specified certifications set out in 21 U.S.C. § 355(j)(2)(A)(vii) for each patent listed with the RLD in the Orange Book. These certifications are:

> (I) that such patent information has not been filed (a paragraph I certification);
>
> (II) that such patent information has expired (a paragraph II certification);
>
> (III) the date on which such patent will expire (a paragraph III certification); or
>
> (IV) that such patent is invalid or will not be infringed by the manufacture, use or sale of the proposed generic drug (a paragraph IV certification).

The ANDA applicant must then show that its proposed drug product is the "same as" the RLD in all key respects (including active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling), and that its product is bioequivalent to the RLD. 21 U.S.C. § 355(j)(2)(A)(ii)-(v). The statute also requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." 21 U.S.C. § 355(j)(2)(A)(i). FDA has acknowledged that this language reflects Congress's intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. Verified Complaint, Ex. 1 (FDA Letter to Dexmedetomidine Hydrochloride Injection NDA Holder/ANDA Applicant, Docket No. FDA-2014-N-0087 (Aug. 18, 2014) at 7).

Notably, FDA's regulations allow a generic drug's labeling to differ from the labeling for the innovator product so that the generic's labeling excludes those parts of the innovator drug's labeling that "are protected by patent, or by exclusivity." 21 C.F.R. § 314.127(a)(7). The regulation, which enumerates a list of exceptions, refers specifically to "exclusivity under 505(j)(5)(F)," but does not refer to orphan drug exclusivity. Excluding parts of the innovator drug's labeling is called a labeling "carve-out." However, FDA's regulations make clear that labeling carve-outs are permitted only where the omissions "do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." *Id.* When a proposed labeling carve-out renders the generic product less safe than the reference product, FDA may not approve the ANDA. *Id.*

2. Factual Background

A. Spectrum's FUSILEV®

Spectrum is a mid-size biotechnology company with a primary focus in hematology and oncology. Verified Compl. ¶ 19. Spectrum currently has only five drug products on the market, all for orphan indications. *Id.* As such, preserving the benefit of the orphan drug exclusivity that Spectrum has been awarded – exclusivity earned by meeting the requirements of a statutory scheme designed to incentivize development of orphan drugs – is especially important to the company. Spectrum has invested over $150 million of dollars in FUSILEV®. *Id.* FUSILEV® is by far Spectrum's most successful product, comprising over 50% of the company's annual revenue. *Id.* Revenues from FUSILEV® are used to fund Spectrum's investment in promising new oncology and hematology drugs, including additional orphan/rare diseases, which have a limited population from which to recoup that investment. *Id.*

FUSILEV® is comprised of levoleucovorin, a *levo*-isomeric form of leucovorin, a similar drug that traditionally has been used to treat or prevent toxic effects of the cancer medicine methotrexate. *Id.* ¶ 20. Unlike leucovorin, levoleucovorin does not contain the inactive *dextro*-isomer, which preclinical studies have demonstrated may compete with the active *levo*-isomer for uptake at the cellular level. *Id.* Because it does not contain the inactive *dextro* form, the dosage of FUSILEV® is one-half that of leucovorin, and patients are spared the administration of an inactive substance. *Id.* FUSILEV® is reconstituted and injected into a vein by a health care provider. *Id.*

i. The Methotrexate Indications

On March 7, 2008, FDA approved FUSILEV® for injection, in the form of a lyophilized (*i.e.*, freeze-dried) powder in a 50 mg single-use vial (the "50 mg vial") for the following indications:

- Rescue after high-dose methotrexate therapy in osteosarcoma; and
- Diminishing the toxicity and counteracting the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

Verified Compl., Ex. 2 (FUSILEV® Package Insert). Both of these indications will be referred to collectively herein as the "Methotrexate Indications." The Orange Book indicates that the Methotrexate Indications were protected by orphan exclusivity until March 7, 2015. Verified Compl. ¶ 22.

ii. The Colorectal Indication

On October 29, 2010, Spectrum submitted a supplemental NDA seeking approval of a new indication for the palliative treatment of patients with advanced metastatic colorectal cancer (the "Colorectal Indication"). Verified Compl. ¶ 23. Specifically, FUSILEV® is used in

combination chemotherapy with fluorouracil to treat the symptoms of colorectal cancer that has metastasized (spread to other parts of the body). *Id.*

On December 22, 2010, Spectrum submitted another supplemental NDA seeking approval of two new, larger sizes of FUSILEV® in a liquid ready to use ("RTU") form in order to support the Colorectal Indication, which requires larger doses than the previously-approved Methotrexate Indications. Verified Compl., Ex. 3 (Official record of FDA responses to questions posed by Spectrum in advance of Feb. 23, 2009 meeting to discuss various issues regarding FUSILEV) ("The approved [Methotrexate Indications do] not require single-use vials larger than 50 mg."). The proposed labeling submitted with this supplemental NDA was based on the proposed labeling for the Colorectal Indication. Verified Compl., Ex. 4 (Cover Letter to December 22, 2010 Supplemental NDA). In other words, Spectrum proposed approval of the larger vial sizes in conjunction with approval of the Colorectal Indication, and it was understood by both Spectrum and FDA that the larger vial sizes would be used for the Colorectal Indication.

This is clear from FDA's own review documents for the supplemental NDA seeking larger vial sizes.[1] In the Medical Review, FDA states:

> This CMC supplement proposes a new dosage form (injection) of Fusilev in 2 new strengths, solutions of 175 mg/17.5 mL and 250 mg/25 mL, **to support the new colorectal cancer indication**.

[1] Indeed, the single-use 175 mg vial and 250 mg vial sizes are only appropriate for the Colorectal Indication. FDA has recognized that the Methotrexate Indications do "not require single-use vials larger than 50 mg." Verified Compl., Ex. 3. In fact, the most frequently used dosing regimens for the Methotrexate Indications typically use only about 7.5 mg levoleucovorin per individual dose. Verified Compl. ¶ 32. In contrast, the dosing regimens listed in the Package Insert for the Colorectal Indication has two standard dosing regimens that involve individual doses exceeding 7.5 mg. Verified Compl. Ex. 2. Specifically, for the Colorectal Indication, FUSILEV® – which is dosed by the patient's weight – is dosed daily at either 10 mg/m2 or 100 mg/m2. *Id.* Assuming a body surface area of 1.5 m2, this translates into individual doses of 15 mg and 150 mg respectively.

Verified Compl. Ex. 5, Food and Drug Administration, *Supplemental New Drug Application S-011 for FUSILEV (NDA #20140) - Medical Review(s)* (Apr. 23, 2011). Indeed, FDA explicitly stated that the indication for the RTU dosage form is "[u]se in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer," with no mention of the methotrexate indications. *Id*. In the one instance from the Medical Review where FDA does mention the methotrexate indications, the Agency associates them with the 50 mg lyophilized powder dosage form:

> The existing formulation (for injection) consists of a sterile lyophilized powder equivalent to 50 mg of levoleucovorin, which supports the high dose methotrexate indication, for which Fusilev gained initial approval in 2008.

Id. In contrast, the medical reviewer makes no comment on using the larger vial sizes with the methotrexate indications, and in fact states that the lyophilized powder dosage form "supports" the methotrexate indications. *Id.*

The link between the larger vial sizes in RTU form and the Colorectal Indication also was acknowledged by FDA's Division of Medication Error Prevention and Analysis (DMEPA), which was responsible for the "evaluation of the container labels, carton and insert labeling." Verified Compl. Ex. 6, Food and Drug Administration, *Supplemental New Drug Application S-011 for FUSILEV (NDA #20140) - Other Review(s)* at 1 (Mar. 21, 2011). DMEPA stated:

> This supplement provides for a new dosage form (injection) in two new strength presentations (175 mg/17.5 mg and 250 mg/25 mL). **These proposed strengths support an efficacy supplement for using Fusilev in combination with 5-Fluorouracil in the treatment of colorectal cancer.**

Id. Furthermore, it is clear that DMEPA's review was based on a version of the FUSILEV label that included the CRC indication. In one of its recommendations, DMEPA requests that the

following change be made to the "Highlights and Dosage and Administration" section of the FUSILEV label:

> DMEPA recommends clearly stating the name of the medication, 5-Fluorouracil (5-FU), for the 22 hour infusion in the first paragraph and the 46 hour infusion in the second paragraph of each presentation of these dosing regimens. The current presentation of these statements without the medication name along with the dose of the continuous infusion could be interpreted as 5-FU or Fusilev.

Id. at 2. Of course, the administration of 5-fluorouracil as part of FUSILEV's dosing regimens is required only for the CRC indication.

FDA approved the supplemental NDAs in reverse order. On April 20, 2011, FDA approved the two larger vial sizes proposed in the second of the two supplemental NDAs. Specifically, FDA approved a single use, RTU liquid dosage form of FUSILEV® at these two new larger sizes: (1) FUSILEV® Injection, 17.5 mL solution at 10 mg/mL levoleucovorin concentration, equivalent to 175 mg levoleucovorin (the "175 mg vial"); and (2) FUSILEV® Injection, 25 mL solution at 10 mg/mL levoleucovorin concentration, equivalent to 250 mg levoleucovorin (the "250 mg vial"). Verified Compl., Ex. 7.

Nine days later, on April 29, 2011, FDA approved the Colorectal Indication as a supplemental indication for FUSILEV®:

- Use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer.

Verified Compl., Ex. 2. The Orange Book indicates that the Colorectal Indication is protected by orphan drug market exclusivity until April 29, 2018. Verified Compl. ¶ 31.

Spectrum ultimately decided not to market the 175 mg and 250 mg vial configurations. *Id.* ¶ 33. Because the FUSILEV® 175 mg and 250 mg RTU vials are not commercially available, oncologists routinely use multiple 50 mg vials to achieve the appropriate dose for colorectal

cancer patients. *Id.* Sales of FUSILEV® for the Methotrexate Indications account for less than 5% of total sales. Verified Compl. ¶ 21.

B. Sandoz's ANDA and Spectrum's Citizen Petition

Several years ago, Sandoz submitted an ANDA seeking permission to market a purported generic version of FUSILEV®. Verified Compl. ¶ 34; Ex. 9. To avoid Spectrum's orphan exclusivity for the Colorectal Indication (which runs until April 29, 2018), Sandoz sought permission to market its drug solely for the Methotrexate Indications. *Id.* However, its ANDA sought approval for *only* the large 175 mg and 250 mg vial configurations that are appropriate for the Colorectal Indication. Sandoz did not seek approval for a 50 mg vial, which is the appropriate and approved vial size for the Methotrexate Indications.

On September 30, 2014, Spectrum submitted a Citizen Petition with FDA requesting that the agency refuse to approve any ANDA for a generic version of FUSILEV® to treat the Methotrexate Indications in vial sizes that would only be appropriate for the Colorectal Indication until the expiry of the relevant orphan drug exclusivity, April 29, 2018. Verified Compl. ¶ 36.

On February 24, 2015, FDA denied Spectrum's Citizen Petition and tentatively approved Sandoz's ANDA. Verified Compl., Ex. 10 (FDA Denial of Spectrum's Citizen Petitions).

On March 6, 2015, shortly before FDA approved Sandoz's ANDA, the Federal Circuit temporarily enjoined Sandoz from launching its drug pending consideration of a request for an injunction pending appeal in a patent infringement case. FDA issued a final approval of Sandoz's drug on March 9, 2015. Verified Compl., Ex. 11. Although Sandoz's drug is only approved for the Methotrexate Indications, it was approved in the larger (175 mg and 250 mg) vial sizes appropriate only for the carved-out Colorectal Indication. *Id.* The Federal Circuit's

injunction was lifted on April 8, 2015. Since that time, Spectrum has devoted substantial efforts to trying to resolve this dispute without the Court's intervention, including through intensive settlement discussions with Sandoz. Those efforts fell apart on April 23, 2015. Verified Compl. ¶ 38.

C. Sandoz's Drug, As Approved, is Less Safe and Effective Than FUSILEV® for the Treatment of Methotrexate Rescue Patients

As labeled, the Sandoz drug poses a heightened risk of medication errors. Although the Sandoz drug is only labeled for the Methotrexate Indications, it is solely available in vial sizes well in excess of what is needed to patients for those conditions. Verified Compl. ¶ 39. As noted, the 50 mg vial is the appropriate dosage size for the vast majority of patients being treated for the Methotrexate Indications. *E.g.*, Verified Compl., Ex. 3. The much-larger 175 mg and 250 mg Sandoz vials are likely to contribute to dosing errors. Verified Compl. ¶ 42. A healthcare provider who sees these substantially greater product sizes in the liquid form—knowing that leucovorin is routinely supplied in a liquid form and is administered at double the dose of levoleucovorin—might reasonably assume that the generic RTU vials contain leucovorin and administer an overdose. *Id.*

In addition, because the 175 mg and 250 mg single-use vials are approved only for the Methotrexate Indications, there is a palpable risk that they will be used for multiple administrations, increasing the risk of infections considerably. *Id.* ¶ 43. For example, if a methotrexate patient requires a levoleucovorin dose of 7.5 mg —as is standard for most patients—and if the hospital pharmacy only has the "generic" 175 mg vial in stock, then 167.5 mg of product would be unused after the patient's dose is withdrawn from the vial. In other words, over 95% of the 175 mg vial would go to waste. The 250 mg vial would involve even

more waste – 97% of the vial. Faced with this problem, providers will be under enormous financial and administrative pressure to use the excess product in the vials to treat additional patients. *Id.* Indeed, despite numerous well-documented contamination outbreaks, many clinicians reuse single-dose vials for multiple patients. *Id* ¶ 44.[2]

Lest there be any doubt, FDA has expressly acknowledged that single-use vials containing excess drug volumes create the foregoing safety risks. Verified Compl., Ex. 13 (Draft Guidance) at 2 (excess volume in a single-use vial "may result in medication errors and may lead to misuse of leftover drug product …."); *see also id.* at 3 ("even when appropriately labeled, single-dose vials that contain significantly more drug than is required for a single dose may result in the misuse of the leftover drug product."). For that reason, FDA has cautioned: "***Single-dose vials should not contain a significant volume beyond what would be considered a usual or maximum dose for the expected use of the drug product***." *Id*. at 4 (emphasis added).

D. The Need for Immediate Judicial Intervention

Three days before FDA approved Sandoz's ANDA, the Federal Circuit temporarily enjoined Sandoz from launching its drug while it considered a patent appeal filed by Spectrum. The Federal Circuit lifted the temporary injunction on April 8, 2015. Since then, Spectrum has been working diligently to try to protect its rights without invoking this Court's assistance. Among other things, Spectrum entered into intensive settlement discussions with Sandoz, which fell apart on April 23, 2015. Upon information and belief, Sandoz is poised to launch its drug at

[2] In one 2010 study piloted by the Centers for Medicare & Medicaid Services published in the Journal of the American Medical Association, 28% of medical facilities in the survey used drugs in single-dose vials for multiple patients. Verified Compl., Ex. 12, M. Schaefer et al., *Infection Control Assessment of Ambulatory Surgical Centers*, 303 JAMA 2273, 2276 (June 9, 2010).

any moment. Spectrum therefore has no choice but to seek this Court's assistance in protecting its orphan drug rights.

As noted above, FDA's actions pose a substantial and imminent harm to patients, primarily through the increased risk of dosing errors and infections. FDA's actions also will irreparably harm Spectrum. Any reputational harm associated with overdoses and infections resulting from Sandoz's drug may be ascribed to FUSILEV® and Spectrum. Verified Compl. ¶ 57. Introduction of a low-cost purported generic also will have an immediate and devastating effect on Spectrum's sales of FUSILEV®, which comprise over 50% of the company's total revenues. *Id.* ¶ 19. Such losses will have a devastating effect on Spectrum's support for existing products and investment in pipeline products, including additional treatments for rare diseases, for which there are few potential patients to recoup development costs. Verified Compl., Ex. 15 ¶ 10. There is no mechanism by which Spectrum can be made whole for the injury that would result from the entry into the marketplace of Sandoz's drug. Judicial intervention therefore is necessary to prevent devastating harm.

ARGUMENT

The standards governing issuance of a TRO or preliminary injunction are well known. *See Morgan Stanley DW Inc. v. Rothe*, 150 F. Supp. 2d 67, 72 (D.D.C. 2001). The movant must show: "(1) a substantial likelihood of success on the merits, (2) that it would suffer irreparable injury if the injunction is not granted, (3) that an injunction would not substantially injure other interested parties, and (4) that the public interest would be furthered by the injunction." *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998) (citation omitted). All four of these factors mandate entry of injunctive relief here.

I. PLAINTIFF HAS A STRONG LIKELIHOOD OF SUCCESS ON THE MERITS.

The APA provides that a court "shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). It is well settled that an agency acts unlawfully when it violates its governing statute or its own regulations. *See Nat'l Envtl. Dev. Ass'ns Clean Air Project v. E.P.A.*, 752 F.3d 999, 1009 (D.C. Cir. 2014). It is "axiomatic . . . that an agency is bound by its own regulations." *Id.* (citing *Panhandle Eastern Pipe Line Co. v. F.E.R.C.*, 613 F.2d 1120, 1135 (D.C. Cir. 1979)). "Although it is within the power of [an] agency to amend or repeal its own regulations, [an] agency is not free to ignore or violate its regulations while they remain in effect." *Nat'l Envtl. Dev. Ass'ns Clean Air Project*, 752 F.3d at 1109 (citing *U.S. Lines, Inc. v. Fed. Mar. Comm'n*, 584 F.2d 519, 526 n. 20 (D.C. Cir. 1978)).

Agency action also is arbitrary and capricious where, as here, it deviates from agency precedent without reasoned explanation. *See, e.g.*, *Lone Mtn. Processing, Inc. v. Sec'y of Labor*, 709 F.3d 1161, 1164 (D.C. Cir. 2013) (finding action arbitrary and capricious where agency "failed to even mention or discuss, let alone distinguish" prior orders); *Friedman v. Sebelius*, 686 F.3d 813, 828 (D.C. Cir. 2012) (finding agency decision arbitrary and capricious because "it failed to explain its departure from the agency's own precedents"). Along the same lines, an agency may not treat similarly-situated entities differently without adequate justification. *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997) ("an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so.").

Judicial review of agency action requires a "searching and careful" inquiry into the basis for the agency's decision. *Zotos Int'l, Inc. v. Young*, 830 F.2d 350, 352 (D.C. Cir. 1987). The reviewing court may give deference to an agency's scientific judgments to the extent they are

consistent and reasonable, but the court does "not hear cases merely to rubber stamp agency actions. To play that role would be tantamount to abdicating the judiciary's responsibility under the [APA]." *Natural Res. Def. Council, Inc. v. Daley*, 209 F.3d 747, 755 (D.C. Cir. 2000) (quotation omitted). In other words, while courts defer to an agency's substantiated scientific judgments, the emphasis is very much on "substantiated." Mere assertions of agency expertise will not do; the agency must show its work.

FDA fails all of these tests. FDA acted arbitrarily and capriciously in approving Sandoz's drug to treat the Methotrexate Indications in the larger vial sizes that are only appropriate for the "carved-out" Colorectal Indication. The discrepancy between approved indication and the larger vial sizes is not only an end-run around Spectrum's orphan drug exclusivity; in addition, it renders the Sandoz drug less safe than FUSILEV®, making it ineligible for a labeling carve-out under FDA's own regulations. 21 C.F.R. § 314.127(a)(7).

FDA regulations prohibit labeling carve-outs if the omissions "render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." *Id.* FDA's decision to permit Sandoz to carve out the Colorectal Indication but make its product available only in the larger vial sizes appropriate for the carved-out indication renders the resulting drug product less safe than FUSILEV®. As a result, FDA's decision to permit the labeling carve-out violates its own regulation. *Id.*

First, the labeling carve-out poses a heightened risk of medication errors. Although the Sandoz drug is only labeled for the Methotrexate Indications, it is available solely in vial sizes well in excess of what is needed to treat most patients for those conditions. Verified Compl. ¶ 39. FDA itself has recognized that the Methotrexate Indications do "not require single-use vials larger than 50 mg." Verified Compl., Ex. 3. The larger RTU vials used by Sandoz may

contribute to dosing errors due to confusion between levoleucovorin and leucovorin, which are approved for similar indications and can be interchanged. Verified Compl. ¶ 42.[3] Leucovorin is also currently available on the market in a liquid RTU form, whereas levoleucovorin is not. *Id.* A healthcare provider who knows that leucovorin is administered at double the dose of levoleucovorin and who sees RTU vials in sizes more than three times the standard dose of levoleucovorin might reasonably assume that the generic RTU vials contain leucovorin and administer an overdose. *Id.*

Second, because the 175 mg and 250 mg single-use vials contain well more drug than necessary for the approved Methotrexate Indications, there is a palpable risk that providers will administer the drug from a single vial to multiple patients, which substantially increases the risks of infection. Verified Compl. ¶¶ 43-44. For example, if a methotrexate patient requires a levoleucovorin dose of 7.5 mg—as is standard for most patients—and if the provider has even the smaller "generic" 175 mg vial in stock, then 167.5 mg of product would be unused after the patient's dose is withdrawn from the vial. In other words, over 95% of the 175 mg vial would go to waste. The 250 mg vial creates even more waste – 97%. Faced with this problem, providers will be under enormous financial and administrative pressure to use the excess product in the vials to treat additional patients. *Id.* ¶ 43. Unfortunately, clinical experience makes clear that clinicians often reuse single-dose vials for multiple patients despite the well-documented risks of infection. Verified Complaint ¶ 44.

[3] Indeed, there have been reports of health care providers confusing levoleucovorin and leucovorin. Verified Compl. Ex. 16 (M. Cohen and J. Smetzer, ISMP Medication Error Report Analysis, 48 Hosp. Pharm. 803 (2013)). FDA also has acknowledged the "potential for dosing errors when interchanging leucovorin and levoleucovorin (Fusilev)." *Id.*, Ex. 17 (FDA Drug Shortages – Leucovorin Calcium Lyophilized Powder for Injection).

But this Court need not take Spectrum's word for it. FDA itself has recognized that excess volume in a single-use vial "may result in medication errors and may lead to misuse of leftover drug product . . . ." Verified Compl., Ex. 13 at 2. *See also id.* at 3 ("even when appropriately labeled, single-dose vials that contain significantly more drug than is required for a single dose may result in the misuse of the leftover drug product."). FDA further has indicated that "volumes remaining that could provide a second dose, or would encourage pooling for a second dose, would be considered excessive." *Id.* As a result, FDA has expressly cautioned:

> ***Single-dose vials should not contain a significant volume beyond what would be considered a usual or maximum dose for the expected use of the drug product***.

Id. at 4 (emphasis added). Rather, "[w]ith regard to a drug product's vial fill size, FDA recommends that it should be appropriate for the labeled use and dosing of the product." *Id*.

In denying Spectrum's Citizen Petition, FDA tried to downplay its earlier statement that the Methotrexate Indications do "not require single-use vials larger than 50 mg." Specifically, the agency contended that its "records indicate that the referenced comments were made specific to the context of a drug shortage and a request for expedited review related to the shortage." Verified Compl., Ex. 10. But the context does not change the fact that the agency acknowledged that the Methotrexate Indications do not require single-use vial sizes larger than 50 mg. If anything, the context actually supports Spectrum's argument. At the time of the discussion, there was a shortage of leucovorin, which had become a popular drug for treating colorectal cancer. Both Spectrum and FDA wanted to address that shortage, and the "expedited review" under discussion was focused on approving the two larger vial sizes for use in connection with the as-yet-unapproved Colorectal Indication. As the agency noted:

> Spectrum plans to supplement NDA 20-140 with a new presentation of levoleucovorin: Fusilev Injection. Would the Agency consider an expedited review of this supplement as

> a way to address the current leucovorin drug shortage as a public health issue as referenced in 21CFR 314.70(b)(4)?

In response, FDA stated in part:

> We would consider an expedited review should the shortage of leucovorin persist. However, the approved indication does not require single use vials larger than 50 mg.

Thus, it is quite clear that FDA tied the larger vial size solely to the Colorectal Indication. Indeed, it was the agency itself – not Spectrum – that linked the CRC indication to the prospect of developing "single use vials larger than 50 mg." FDA's effort to recast that statement now must fail. *See, e.g., Lone Mountain Processing, Inc.*, 709 F.3d at 1164 ("an agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored . . . .") (citations omitted).

FDA also asserted in its Citizen Petition Response that doses larger than 50mg are occasionally required for the Methotrexate Indications, citing one example requiring at 75 mg dose and another requiring an 85-90 mg dose. Verified Compl., Ex. 10. But FDA failed to explain why a patient being treated for one of the Methotrexate Indications would need a vial size of 175mg or even 250mg. At most – according to FDA's own analysis – an average adult patient being treated for the Methotrexate Indications would not require a dose of over 90mg. Such a patient could easily be accommodated with two 50 mg vials (as is the current practice with FUSILEV®) rather than with a 175mg vial, where nearly half of the vial's contents (85mg) would go to waste. Of course, the same is true to an even a greater extent for the 250mg vials, where 160 mg would be wasted. FDA offers no explanation as to why such large vial sizes would be needed for the Methotrexate Indications, especially in light of FDA's clear pronouncements about the safety risks inherent in using larger vial sizes than necessary for the intended use. Verified Compl., Ex. 13 at 2-3. That failure is fatal.

Finally, in its petition response, FDA notes that the Fusilev 175 mg and 250 mg vial sizes were approved prior to the approval of the supplement to add the CRC Indication, suggesting that these vial sizes were somehow appropriate for the Methotrexate Indications. But that position is belied by FDA's own pronouncements during approval of the larger vial sizes. Verified Compl. Ex. 5 ("This CMC supplement proposes a new dosage form (injection) of Fusilev in 2 new strengths, solutions of 175 mg/17.5 mL and 250 mg/25 mL, to support the new colorectal cancer indication."); *id*. (the only indication given for the RTU dosage form is "[u]se in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer," the methotrexate indications are not stated); Ex. 6 ("This supplement provides for a new dosage form (injection) in two new strength presentations (175 mg/17.5 mg and 250 mg/25 mL). **These proposed strengths support an efficacy supplement for using Fusilev in combination with 5-Fluorouracil in the treatment of colorectal cancer.").**

FDA also ignores the fact that the supplemental NDA for the larger vials was expressly tied by Spectrum to the supplemental NDA for the Colorectal Indication. Verified Compl., Ex. 4 (Cover Letter to December 22, 2010 Supplemental NDA).

In short, FDA has not – indeed cannot – offer any rationale for why the 175 mg and 250 mg vials should be approved in the Sandoz ANDA.

II. THE PUBLIC INTEREST FAVORS THE REQUESTED RELIEF.

The public interest plainly favors granting an injunction here. Absent judicial intervention, FDA's actions will usher into the marketplace a drug that creates very real public safety concerns. First, as discussed above, the Sandoz drug poses a heightened risk of medication errors; the larger vials used by Sandoz may confuse providers into thinking that they

contain leucovorin, which is approved for similar indications and can be interchanged with levoleucovorin. *See supra* at 17-18. Second, because the 175 mg and 250 mg single use vials contain well more drug than necessary for the approved Methotrexate Indications, there is a palpable risk that they will be used for multiple administrations. *Id.* FDA has expressly acknowledged both of these risks. Verified Compl., Ex. 13 at 2 (excess volume in a single-use vial "may result in medication errors and may lead to misuse of leftover drug product ….). And, as noted above, FDA has provided absolutely no explanation for why a dose of more than 90 mg would ever be needed for an average-sized adult patient being treated for the Methotrexate Indications.

The public also has an unmistakable interest in seeing that laws are faithfully executed by public officials. *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("there is a strong public interest in meticulous compliance with the law by public officials"); *see also, e.g., O'Donnell Constr. Co. v. District of Columbia*, 963 F.2d 420, 429 (D.C. Cir. 1992); *Nobby Lobby, Inc. v. City of Dallas*, 970 F.2d 82, 93 (5th Cir. 1992) (approving district court conclusion that "the public interest always is served when public officials act within the bounds of the law and respect the rights of the citizens they serve"). This public interest overrides any countervailing public interest in the availability of a cheaper purported generic drug. *See Mova Pharm. Corp.*, 140 F.3d at 1066 (upholding district court's decision that the public's interest in the "faithful application of the laws" tipped public interest prong in favor of requested preliminary injunction, notwithstanding the public's interest in the availability of generic drugs).

The public interest simply is not served by the capricious approval of generic drugs, where questions remain about the processes and standards used to evaluate such products.

III. SPECTRUM WILL SUFFER IRREPARABLE INJURY ABSENT IMMEDIATE RELIEF.

Unless enjoined by this Court, FDA's conduct will cause substantial, imminent, and irreparable injury to Spectrum. After the Federal Circuit's injunction was lifted on April 8, 2015, Spectrum worked diligently to try to protect its rights without invoking this Court's assistance, including through intensive settlement discussions with Sandoz. Those efforts have all failed within the last few days, and now the only thing that can protect Spectrum from suffering irreparable harm due to FDA's conduct is judicial intervention. Sandoz's product will flood the market almost immediately. Spectrum will, in turn, suffer severe irreparable harm, both reputational and commercial in nature.

First, Sandoz's entry on the market will cause irreparable reputational harm to Spectrum. Providers and patients typically do not distinguish between harms caused by brand name drugs and generics based on them. Verified Compl. Ex. 15, Turgeon Decl. ¶ 6. As a result, any injuries or fatalities resulting from the misuse of the 175 mg and 250 mg vial sizes of may be unfairly imputed to FUSILEV®, which will lead to reputational harm for both the product and Spectrum. Verified Compl. ¶ 57. These adverse effects on business reputation, goodwill, and relationships with physicians and patients constitute irreparable harm sufficient to warrant injunctive relief. *Patriot, Inc. v. Dep't of Hous. and Urban Dev.*, 963 F. Supp. 1, *5 (D.D.C. 1997) (asserting that damage to business reputation supports finding of irreparable harm); *see also Tate Access Floors v. Interface Architectural Res., Inc.*, 132 F. Supp. 2d 365, 378 (D. Md. 2001) (finding irreparable harm based in part on the "loss of long-term relationships with major customers, beyond the short-term loss of individual sales"), *aff'd*, 279 F.3d 1357 (Fed. Cir. 2002).

Second, entry of Sandoz's drug into the market will have an immediate and precipitous effect on Spectrum's sales, market share, and pricing of FUSILEV® – all of which will irreparably undermine Spectrum's ability to support existing product lines and invest in new ones. The health care reimbursement scheme virtually guarantees this result. As noted more fully in the attached Declarations, providers submit reimbursement claims under a Healthcare Common Procedure Coding System ("HCPCS") (pronounced "hic-pix") code established by the federal government. Verified Compl. Ex. 14, Grabowski Decl. ¶ 6. For most drugs, the amount that physicians and certain other providers are reimbursed by Medicare for a drug within a particular HCPCS is based on the average sales prices for all drugs within that code, plus 6%. *Id.* ¶ 7. Currently, FUSILEV® has its own HCPCS code and is reimbursed under this methodology. *Id.* ¶ 8. Like many injectable drugs, the HCPCS code for FUSILEV® is called a "J-code" because the first digit of the code is "J." As FUSILEV® is the only drug within its J-code, physicians and certain other providers are reimbursed based on the average sales price for FUSILEV® during the relevant time period, plus 6%. *Id.* If Sandoz's product is allowed onto the market, it will be assigned to FUSILEV®'s J-code. *Id.* The presence of Sandoz's drug will cause price to be much lower for FUSILEV®: healthcare providers will be strongly incentivized to use Sandoz's drug over FUSILEV®, because physicians will be reimbursed at a rate much higher than they are paying for the drug. *Id.* This will lead to a rapid decline in Spectrum's revenues regardless of whether Spectrum decides to lower its price. *Id.* ¶¶ 8-9; Turgeon Decl. ¶ 9. For this reason, it is expected that in the first few months after approval of Sandoz's drug, there will be a veritable "feeding frenzy" of healthcare providers administering Sandoz's drug and obtaining reimbursement based on FUSILEV®'s pricing. *See* Verified Compl. Ex. 14, Grabowski Decl. ¶ 7. Periodically, the average sales price in the FUSILEV® J-code will be

recalculated, meaning that the reimbursement rate will drop and Spectrum will be required to lower its price so that providers are not losing money by administering FUSILEV®. *See id.*

Spectrum is a mid-size pharmaceutical company. FUSILEV® sales account for more than 50% of the company's total revenues. Verified Compl. ¶ 19. Sales lost because of Sandoz's entry into the market will have a commercially devastating effect on the company's operations. Verified Compl. Ex. 15, Turgeon Decl. ¶¶ 9-10. Spectrum currently has 14 different products at various stages of development that would treat a wide range of cancers, including leukemia, lymphoma, prostate cancer, and breast cancer. *Id.* ¶ 10. Without the revenues from the sales of FUSILEV®, Spectrum may be forced to postpone or halt development of these potentially life-saving drugs. *Id.* It is well settled that these types of harm constitute irreparable harm sufficient to warrant a TRO. As this Court has explained, "[i]t is not at all difficult to foresee that [a pioneer drug company's] market position would collapse as soon as one or more generic drugs became available. [The innovator] would lose its head start in the market and its continued viability would be at issue. It could never recoup from FDA any losses that would occur. . . . These are the kinds of circumstances in which irreparable harm has been found." *CollaGenex Pharms., Inc. v. Thompson*, No. 03-1405 (RMC), 2003 WL 21697344, at *10 (D.D.C. July 22, 2003) (citing cases); *see also In re Cardizem Antitrust Litig.*, 200 F.R.D. 326, 340-41 (E.D. Mich. 2001) (describing predictable pattern of pioneer market share loss of up to 90% upon entry of competing generics); *Sanofi-Synthelabo v. Apotex, Inc.*, 488 F. Supp. 2d 317, 342-44 (S.D.N.Y. 2006) (describing sequence of events whereby generic drugs erode market share of pioneer drugs and noting that "irreversible price erosion . . . is a legitimate basis for a finding of irreparable harm"), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006); *Merrill Lynch, Pierce,*

Fenner & Smith, Inc. v. Bradley, 756 F.2d 1048, 1054 (4th Cir. 1985) (noting that "customers cannot be unsolicited").

Because the foregoing losses can never be recovered from FDA, Spectrum will be irreparably harmed unless FDA's conduct is enjoined promptly. *See Bayer HealthCare, LLC v. U.S. Food and Drug Admin.*, 942 F. Supp. 2d 17, 26 (D.D.C. 2013) (finding irreparable harm where the innovator drug company would "experience a decline in market share, price erosion, loss of customer good will, and loss of research and development funding as a result of [a generic's] entry into the market"); *see also Clarke v. Office of Fed. Hous. Enterprise Oversight*, 355 F. Supp. 2d 56, 65-66 (D.D.C. 2004) (holding that economic losses constitute irreparable injury where they are unrecoverable due to government immunity); *Nat'l Med. Care, Inc. v. Shalala*, 1995 WL 465650, at *3 (D.D.C. June 6, 1995) ("[T]he policy considerations behind the judiciary's general reluctance to label economic injuries as 'irreparable' do not come into play in APA cases: even if the Plaintiffs ultimately prevail on the merits, they cannot bring an action to recover the costs of their compliance with the Defendant's unlawful retroactive rule, and thus will not be able to alleviate their economic damage through subsequent litigation."); *Woerner v. Small Bus. Admin.*, 739 F. Supp. 641, 650 (D.D.C. 1990) (finding irreparable injury where government is immune from damage suits to recover for economic losses); *Informatics Corp. v. United States*, 40 Fed. Cl. 508, 518 (1998) (finding irreparable harm where, absent the injunction, movant could recoup only the bid preparation costs and not lost profits).

IV. INJUNCTIVE RELIEF WILL NOT BURDEN DEFENDANTS' OR SANDOZ'S LEGITIMATE INTERESTS.

Neither FDA nor Sandoz can contend that it will be burdened if a TRO is issued, because neither has any legitimate interest in engaging in action that is contrary to the APA and the

FDCA. Granting this motion would merely preserve the status quo by preventing Sandoz's drug from overtaking the market pending further consideration by this Court. *See Anderson v. Davila*, 125 F.3d 148 (3d Cir. 1997); *Dist. 50, United Mine Workers v. International Union, United Mine Workers*, 412 F.2d 165, 168 (D.C. Cir. 1969) ("The usual role of [an] injunction is to preserve the *status quo*."). At worst, entry of a TRO would delay Sandoz's entry into the generic market, but for good reason – to enable appropriate review of FDA's decision to approve a generic that does not meet statutory standards for approval. Indeed, because FDA may not lawfully approve an ANDA before April 29, 2018 for the Colorectal Indication, Sandoz cannot claim a legitimate interest in sales before that date. As a result, any resulting burden to Sandoz is far outweighed by the risk to patients and Spectrum if injunctive relief is denied.

CONCLUSION

For all the foregoing reasons, Plaintiff's motion for a TRO and/or preliminary injunction should be granted.

Respectfully submitted,

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Dated: April 27, 2015