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. _____

VERIFIED COMPLAINT FOR DECLARATORY, INJUNCTIVE, AND OTHER RELIEF

Plaintiff Spectrum Pharmaceuticals, Inc. ("Spectrum") hereby brings this Verified Complaint against Defendants Sylvia Mathews Burwell, solely in her official capacity as Secretary of the Department of Health and Human Services ("HHS"), and Steven Ostroff, M.D., solely in his official

capacity as Acting Commissioner of Food and Drugs, head of the Food and Drug Administration ("FDA" or the "agency"), and alleges as follows:

INTRODUCTION

1. This is an action to hold unlawful and set aside FDA's decision to grant final approval to 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), paving the way for Sandoz to market a purported generic version of Spectrum's FUSILEV® (levoleucovorin) for injection ("FUSILEV").

2. 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 cancer drug methotrexate, and one of which involves palliative treatment of patients with advanced metastatic colorectal cancer. In deciding to approve 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 exclusivity rights for that indication, which extend until April 29, 2018. As a result, Sandoz's drug will only be labeled for the two methotrexate indications. However, Sandoz's drug was approved solely in vial sizes that are appropriate ***only*** for the carved-out colorectal cancer indication, not for the two remaining approved indications. This discrepancy between the Sandoz drug's labeling and its vial sizes poses an increased risk of dosing errors and product contamination from multiple uses of a vial designed for single use. FDA's decision to approve Sandoz's drug therefore violates FDA's own regulations governing labeling carve-outs. FDA's conduct is arbitrary and capricious and violates the Administrative Procedure Act ("APA").

3. FDA's actions pose a substantial and imminent harm to prospective patients who will be placed on Sandoz's drug. Because Sandoz's drug is only available in vial sizes appropriate for an

indication for which it is not approved, it poses a palpable risk of dosing errors and product contamination from multiple uses of a vial designed for single use. FDA's actions will also irreparably harm Spectrum. Upon information and belief, Sandoz is poised to flood the market with its drug at any moment. Absent immediate injunctive relief, Sandoz's drug will immediately overtake FUSILEV®'s market share, drive down prices, interfere with Spectrum's ability to invest in pipeline products and support existing products, and irreparably harm both Spectrum and the public at large.

PARTIES

4. Plaintiff Spectrum Pharmaceuticals, Inc. is a Delaware company with its principal place of business at 11500 S. Eastern Avenue #240, Henderson, NV 89052. Spectrum is a commercial-stage biotechnology company with fully integrated commercial and drug development operations, with particular focus in oncology and hematology. Spectrum holds an approved NDA for FUSILEV®.

5. Defendant Sylvia Mathews Burwell, who is being sued in her official capacity only, is the Secretary of HHS and is responsible for administering and enforcing the Food, Drug, and Cosmetic Act, 21 U.S.C. § 321, *et seq.* Defendant Burwell maintains an office at 200 Independence Avenue, S.W., Washington, D.C. 20201.

6. Defendant Stephen Ostroff, M.D., who is being sued in his official capacity only, is the Acting Commissioner of Food and Drugs and is responsible for supervising the activities of FDA, an administrative agency within HHS. Defendant Ostroff maintains offices at 10903 New Hampshire Avenue, Silver Spring, MD 20993.

JURISDICTION AND VENUE

7. Jurisdiction in this Court is grounded upon and proper under 28 U.S.C. § 1331, in that

this is a civil action arising under the laws of the United States; 28 U.S.C. § 1346, in that this case involves claims against the federal government; 5 U.S.C. § 702, in that Spectrum is seeking judicial review of an agency action from which it has suffered a legal wrong, has been adversely affected, and has been aggrieved; 28 U.S.C. § 1361, in that this is an action to compel an officer of the United States to perform his duty; 28 U.S.C. §§ 2201-2202, in that there exists between Spectrum and the Defendants an actual, justiciable controversy as to which Spectrum requires a declaration of its rights by this Court as well as preliminary and permanent injunctive relief to prohibit the Defendants from violating laws and regulations; and 21 U.S.C. § 355(q) and other sources of law, in that the conduct complained of constitutes final agency action.

8. Venue is proper in this Court under 28 U.S.C. §§ 1391(b) and (e) because this is a civil action in which the Defendants are officers of the United States acting in their official capacities and one of the Defendants maintains her office and conducts business in this judicial district. Moreover, a substantial part of the events giving rise to the claims herein occurred within this judicial district.

9. Spectrum has standing to bring the present lawsuit because it is suffering and faces additional actual injury as a result of FDA's decisions and because it is within the zone of interest of the relevant statutory provisions.

NATURE OF THE CASE

I. Statutory and Regulatory Background

A. New Drug Approval Process

10. The Food, Drug, and Cosmetic Act ("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).

11. When a drug is approved under an NDA, the drug and any related 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

12. Congress passed the Orphan Drug Act of 1983 ("ODA") 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 ODA 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 ODA'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).

13. 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 CFR Part 316, 316.3(b)(10). To obtain designation, a sponsor must submit a request for the designation before the submission of an NDA or supplement. 21 U.S.C. § 360bb(a)(1).

14. Orphan drug designation entitles the drug sponsor to certain benefits, including 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

15. 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.

16. In order 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).

17. 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. Ex. 1 (FDA Letter to Dexmedetomidine Hydrochloride Injection NDA Holder/ANDA Applicant, Docket

No. FDA-2014-N-0087 (Aug. 18, 2014) at 7).[1]

18. 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). This is referred to as 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.*

II. Factual Background

A. Spectrum's FUSILEV®

19. Spectrum is a biotechnology company with a primary focus in hematology and oncology. Spectrum currently has only five drug products on the market, all developed and approved for orphan indications. Since 2006, Spectrum has devoted over $150 million to developing, patenting, and marketing FUSILEV®. FUSILEV® is Spectrum's most successful product, accounting for more than 50% of its revenues in any given year. Revenues from FUSILEV® are used to recover Spectrum's past research and development investment into FUSILEV® and to fund Spectrum's investment in promising new oncology and hematology drugs, many also for orphan indications.

20. Spectrum's FUSILEV® is comprised of levoleucovorin, a *levo*-isomeric form of leucovorin, which traditionally has been used to treat or prevent toxic effects of the cancer medicine

[1] Available at http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-0087-0025.

methotrexate. 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. 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. FUSILEV® is reconstituted and injected into a vein through an IV by a health care provider.

1. The Methotrexate Indications

21. 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.

Ex. 2 (FUSILEV® Package Insert). Both of these indications will be referred to collectively herein as the "Methotrexate Indications." Sales of FUSILEV® for the Methotrexate indications constitute a very small percentage of sales of FUSILEV®— upon information and belief, the Methotrexate Indications account for less than 5% of total sales of levoleucovorin.

22. The Orange Book indicates that both of the Methotrexate Indications were protected by orphan exclusivity until March 7, 2015.

2. The Colorectal Indication

23. 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"). 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).

24. On December 22, 2010, Spectrum submitted another supplemental NDA seeking approval of two new, larger vial sizes of FUSILEV® in a ready-to-use ("RTU") dosage form. The larger vial sizes were intended for use solely with the forthcoming Colorectal Indication, which requires larger doses than the previously-approved Methotrexate Indications. 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. Ex. 4, (Cover Letter to December 22, 2010 Supplemental NDA).

25. This correlation between the larger vial sizes and the Colorectal Indication is clear from FDA's own review documents for the supplemental NDA seeking larger vial sizes.[2] 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**

[2] 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." 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. Ex. 2. In contrast, the Colorectal Indication has two standard dosing regimens that involve individual doses exceeding 7.5 mg. *Id.* 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.

cancer indication." Ex. 5, Food and Drug Administration, *Supplemental New Drug Application S-011 for FUSILEV (NDA #20140) - Medical Review(s)* (Apr. 23, 2011) (emphasis added).

26. 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*.

27. 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." Ex. 5. 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.*

28. 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." 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.* at 2 (emphasis added).

29. 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.

30. FDA approved the applications in reverse order. On April 20, 2011, FDA approved a liquid single use, RTU dosage form of FUSILEV® at these two new larger vial 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"). Ex. 7 (April 20, 2011 Approval Letter).

31. 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.

Ex. 2 (FUSILEV® Package Insert). The Orange Book indicates that the Colorectal Indication is protected by orphan drug market exclusivity until April 29, 2018.

32. There can be no doubt that the single-use 175 mg vial and 250 mg vial sizes are

appropriate only for the Colorectal Indication. In fact, FDA has recognized that the Methotrexate Indications do "not require single-use vials larger than 50 mg." Ex. 3. The most frequently used dosing regimens for the Methotrexate Indications typically use only about 7.5 mg levoleucovorin per individual dose. In contrast, the two dosing regimens listed in the FUSILEV® Package Insert for the Colorectal Indication exceed 7.5 mg. Ex. 2. Specifically, for the Colorectal Indication, per the Package Insert, FUSILEV® is dosed daily at either 10 mg/m^2 or 100 mg/m^2. *Id*. Assuming a body surface area of 1.5 m^2, this translates into individual doses of 15 mg and 150 mg respectively. According to the National Comprehensive Cancer Network guidelines for metastatic colorectal cancer, doses of 200 mg/m^2 are included in most current chemotherapy regimens. Ex. 8, National Comprehensive Cancer Network, *Clinical Practice Guidelines in Oncology: Colon Cancer, Version 2.2015* at COL-C 6-8 (Oct. 3, 2014).

33. Spectrum ultimately decided not to market the 175 mg and 250 mg vial configurations. 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.

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

34. Several years ago, Sandoz submitted an ANDA seeking permission to market a purported generic version of FUSILEV®. *See* Ex. 9. In order 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. However, its ANDA sought approval for only the 175 mg and 250 mg vial configurations appropriate for the treatment of colorectal cancer.

35. In a separate paragraph IV notification that Spectrum has received, the generic

applicant did not improperly select the RTU dosage form for its RLD, as Sandoz has with its ANDA. Instead, the other generic applicant appropriately selected the 50 mg lyophilized powder dosage form as its RLD. This demonstrates a recognition by other generic applicants that the 50 mg lyophilized powder should be selected as the RLD in order to correctly align the Methotrexate Indications with the applicable FUSILEV dosage form.

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

37. On February 24, 2015, FDA denied Spectrum's Citizen Petitions. Ex. 10 (FDA Denial of Spectrum's Citizen Petitions). That same day, FDA tentatively approved Sandoz's ANDA.

38. 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. Ex. 11. 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.

39. Sandoz's drug is approved only for the Methotrexate Indications, but yet is available only in the 175 mg and 250 mg vial sizes that are only appropriate for the Colorectal Indication.

40. The denial of Spectrum's Citizen Petition means that Spectrum has exhausted its

administrative remedies.

C. Sandoz's Drug, As Approved, is Less Safe and Effective Than FUSILEV®

41. FDA's own regulations prohibit it from permitting a generic manufacture to carve out an indication in a way that renders the resulting generic drug "less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7). And yet that is exactly what has happened here.

42. First, the Sandoz drug poses a heightened risk of medication errors. Although the Sandoz drug is only labeled for the Methotrexate Indications, it is available in vial sizes well in excess of what is needed to treat most patients for those conditions. As noted, the 50 mg vial is the appropriate size for the vast majority of patients being treated for the Methotrexate Indications. The increased volume (and thus increased amount of levleucovorin) in the 175 mg and 250 mg RTU vials may contribute to dosing errors due to confusion between levoleucovorin and leucovorin, which are both approved for similar indications and can be interchanged. Additionally, leucovorin is commonly supplied in a liquid RTU form, where levoleucovorin has been available only in the lyophilized powder form. A healthcare provider who sees these larger vials of RTU product in an unfamiliar product configuration—knowing that leucovorin is administered at double the dose of levoleucovorin—might reasonably assume that the generic RTU vials contain leucovorin and administer an overdose. There is no acceptable justification for permitting any increase in the risk of medication errors associated with the generic 175 mg and 250 mg RTU vials approved for use with the carved-out labeling.

43. Second, because the 175 mg and 250 mg single use vials are tentatively approved for

the Methotrexate Indications, there is a palpable risk that they will be used for multiple administrations. For example, if a methotrexate patient requires a levoleucovorin dose of 7.5 mg —as is standard for most patients—and if the provider 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. In the case of the 250 mg vial, if only 7.5 mg were used in the treatment of a methotrexate patient, then 242.5 mg—97% of the total vial— would go to waste. Faced with this problem, providers will be under enormous financial and administrative pressure to inappropriately use the excess product in the vials to treat additional patients.

44. Indeed, despite numerous well-documented contamination outbreaks, many clinicians continue to reuse single-dose vials for multiple patients. 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. Ex. 12, Schaefer et al., *Infection Control Assessment of Ambulatory Surgical Centers*, 303 JAMA 2273, 2276 (June 9, 2010). *See also* Ex 16 (M. Cohen and J. Smetzer, ISMP Medication Error Report Analysis, 48 Hosp. Pharm. 803 (2013)), Ex. 17 (FDA Drug Shortages – Leucovorin Calcium Lyophilized Powder for Injection). It is well-established that reusing a single-use vial multiple times to extract more than one dose can result in pathogens being introduced into the vial. Ex. 12. If these pathogens are then transmitted to subsequent patients dosed from the same vial, those patients can develop severe and sometimes life-threatening infections.

45. For both of these reasons, the Sandoz product (as tentatively approved) is less safe and effective than FUSILEV®, rendering it ineligible for a labeling carve-out. 21 C.F.R. § 314.127(a)(7).

46. But the Court need not take Spectrum's word for it. FDA has expressly acknowledged that single-use vials containing excess drug volumes create the foregoing safety risks. 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.").

47. 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).

III. FDA's Conduct is Unlawful, Arbitrary and Capricious

48. FDA's decision to approve Sandoz's ANDA violates the FDCA and applicable regulations, including but not limited to 21 U.S.C. § 355(j); 21 U.S.C. § 360cc; 21 C.F.R. § 316.31(a); 21 C.F.R. §314.127(a)(7).

49. FDA acted arbitrary, capriciously, and contrary to law when it approved Sandoz's ANDA for vial sizes that are only appropriate for the Colorectal Indication despite the fact Spectrum has the exclusive right to that indication until April 29, 2018. FDA regulations prohibit labeling "carve-outs" unless 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." 21 C.F.R. § 314.127(a)(7). Allowing Sandoz to carve-out the Colorectal Indication from its 175 mg and 250 mg vial sizes renders its product unsafe for the Methotrexate Indications for which the Sandoz drug is approved. As noted above, this poses palpable safety risks because of the increased likelihood of dosing errors and

multiple uses of a single-use formulation.

50. FDA's approval of Sandoz's ANDA reflects a failure to engage in reasoned decision making.

51. FDA's approval of Sandoz's ANDA was not in accordance with federal law and therefore violates 5 U.S.C. § 706(2)(A).

52. FDA's approval of Sandoz's ANDA also constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

IV. FDA's Actions Will Cause Immediate and Irreparable Harm to Patients and Spectrum

53. FDA's approval of Sandoz's ANDA opens the door for Sandoz to flood the market with its "generic" version of FUSILEV® immediately.

54. It is well known in the pharmaceutical industry that generic drugs quickly take over the market soon after their launch.

55. FDA's approval of Sandoz's ANDA poses a very real imminent risk to the public. As noted, marketing Sandoz's drug for use in the Methotrexate Indications in vial sizes well in excess of what is needed to treat most patients for those conditions will result in an increased risk of dosing errors and the use of single-dose vials for multiple administrations.

56. FDA's approval of Sandoz's ANDA also threatens Spectrum with grave irreparable harm. By approving Sandoz's ANDA in 175 mg and 250 mg vial sizes, which are only appropriate for the Colorectal Indication, FDA has deprived Spectrum of the orphan drug marketing exclusivity to

which it is statutorily entitled for the Colorectal Indication, which extends until April 29, 2018.

57. FDA's actions will cause irreparable reputational harm to Spectrum absent entry of a temporary restraining order and/or preliminary injunction. Providers and patients typically do not distinguish between harms caused by brand name drugs and generics based on them. Any injuries or fatalities resulting from the misuse of the 175 mg and 250 mg vial sizes of will be unfairly imputed to FUSILEV®, which would lead to reputational harm for the product and possibly to Spectrum. These adverse effects on business reputation, goodwill, and relationships with physicians and patients constitute irreparable harm sufficient to warrant injunctive relief.

58. Providers submit reimbursement claims under a Healthcare Common Procedure Coding System ("HCPCS") (pronounced "hic-pix") code established by the federal government. *See* 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[3], 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 fall within the same J-code as FUSILEV®. *Id.* Given that the net price of Sandoz's generic levoleucovorin product is likely to be lower than FUSILEV®, but both drugs will be reimbursed at the same rate, healthcare providers will be incentivized to use Sandoz's drug over

[3] HCPCS Code: J0641 ("Injection, levoleucovorin calcium, 0.5 mg").

FUSILEV®. *See id.* ¶ 7.

59. The impact on Spectrum would be commercially devastating. *See generally* Ex. 15, Turgeon Decl. Revenues from FUSILEV® comprise over 50% of Spectrum's total revenues, funding Spectrum's operations and permitting the company to invest in promising new oncology and hematology drugs, particularly those to address unmet needs for additional orphan indications. Spectrum would lose the value of its investment if a generic levoleucovorin product were permitted to prematurely enter the market. *See id.* ¶¶ 6-10.

60. 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. And because the foregoing losses never can be recovered from FDA, Spectrum will be irreparably harmed unless FDA's conduct is enjoined promptly.

61. Conversely, neither FDA nor Sandoz will suffer any significant hardship if approval of Sandoz's ANDA is enjoined. Because FDA may not lawfully approve an ANDA prior to April 29, 2018 for the Colorectal Indication, Sandoz cannot claim a legitimate interest in sales before that date.

62. The intent of Congress will be served by an Order directing FDA to rescind its approval of Sandoz's ANDA. In addition, such an Order will serve the public interest by protecting patient safety, and requiring FDA to comply with its obligations.

63. FDA's denial of Spectrum's Citizen Petitions and approval of Sandoz's ANDA constitutes final agency action for which Spectrum has no other adequate remedy within the meaning of 5 U.S.C. § 704.

Count I
(Administrative Procedure Act: Violation of the FDCA and Applicable Regulations)

64. Spectrum re-alleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 63 of the Verified Complaint as though set forth fully herein.

65. FDA's denial of Spectrum's Citizen Petitions and decision to approve Sandoz's ANDA was unlawful and in violation of the FDCA and the agency's own regulations, policies and procedures.

66. FDA's denial of Spectrum's Citizen Petitions and decision to approve Sandoz's ANDA constitutes final agency action for which Spectrum has no other adequate remedy within the meaning of 5 U.S.C. § 704.

67. FDA's denial of Spectrum's Citizen Petitions and decision to approve Sandoz's ANDA was not in accordance with federal law and therefore violates 5 U.S.C. § 706(2)(A).

68. FDA's denial of Spectrum's Citizen Petitions and decision to approve Sandoz's ANDA constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

69. Both Spectrum and the patient population will be irreparably harmed unless FDA is enjoined from approving – or, alternatively, required to withdraw its approval of – Spectrum's ANDA and extend Spectrum's exclusivity period.

70. There is no mechanism by which Spectrum can be made whole for the injury that would result from the entry into the marketplace of an unlawful levoleucovorin product and/or the premature termination of Spectrum's exclusivity period. Spectrum is without an adequate remedy at

law because of the unique nature of the harm.

71. The intent of Congress will be served by an Order directing FDA to withdraw its approval of Sandoz's ANDA. In addition, the public interest will be served by such an Order.

Count II
(Administrative Procedure Act: FDA's Conduct Was Arbitrary, Capricious, an Abuse of Discretion and Contrary to Law)

72. Spectrum re-alleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 71 of the Verified Complaint, as though set forth fully herein.

73. The APA prohibits FDA from implementing the FDCA in a manner that is arbitrary, capricious, or an abuse of discretion. 5 U.S.C. § 706(2)(A).

74. FDA's denial of Spectrum's Citizen Petitions and decision to approve Sandoz's ANDA was not based on reasoned decision or rational basis, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

75. FDA's denial of Spectrum's Citizen Petitions and decision to approve Sandoz's ANDA was premised on agency determinations that represented abrupt departures from long-standing agency practice and treated similarly-situated entities differently. FDA's conduct was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

76. FDA's denial of Spectrum's Citizen Petitions and decision to approve Sandoz's ANDA violates FDA's own regulations and governing statute, in violation of the APA.

77. FDA's denial of Spectrum's Citizen Petitions and decision to approve Sandoz's ANDA

constitutes final agency action for which Spectrum has no other adequate remedy within the meaning of 5 U.S.C. § 704.

78. Both Spectrum and the patient population will be irreparably harmed unless FDA is required to withdraw its approval of Sandoz's ANDA.

79. 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 product. Spectrum is without an adequate remedy at law because of the unique nature of the harm.

80. The intent of Congress will be served by an Order directing FDA to withdraw its approval of Sandoz's ANDA. In addition, the public interest will be served by such an Order.

PRAYER FOR RELIEF

WHEREFORE, plaintiff respectfully prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that FDA's decision to approve Sandoz's ANDA was arbitrary, capricious, and contrary to law under the APA and the FDCA;

B. A declaration pursuant to 28 U.S.C. § 2201 that FDA's denial of Spectrum's Citizen Petitions was arbitrary, capricious and contrary to law under the APA and the FDCA;

C. Temporary, preliminary and permanent injunctive relief enjoining, requiring FDA to rescind or—at the very least—stay its approval of Sandoz's ANDA;

D. An order awarding plaintiff's costs, expenses and attorneys' fees pursuant to 28 U.S.C. § 2412; and

E. Such other and further relief as the Court deems just and proper.

Respectfully submitted,

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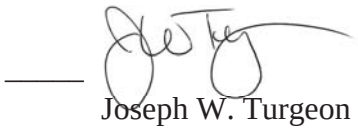
Attorneys for Plaintiff Spectrum Pharmaceuticals, Inc.

Dated: April 27, 2015

VERIFICATION

I, the undersigned, having read the allegations of the foregoing Verified Complaint, hereby declare under penalty of perjury and pursuant to 28 U.S.C. § 1746 that the factual allegations asserted in the Verified Complaint are true and correct based on my personal knowledge and on information derived from the business records of Spectrum Pharmaceuticals, Inc. I further declare that matters asserted upon information and belief are believed to be true and correct.

Executed this 27 day of April, 2015.



Joseph W. Turgeon