No. 15-5166

IN THE
UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

SPECTRUM PHARMACEUTICALS, INC.,
Plaintiff-Appellant,

v.

SYLVIA MATTHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, et al.
Defendants-Appellees,

SANDOZ, INC.,
Intervenor-Defendant-Appellee.

Appeal from the United States District Court for the District of Columbia in Case No. 1:15-cv-00631-RCL, Judge Royce C. Lamberth

AMICUS CURIAE BRIEF OF THE NATIONAL ORGANIZATION FOR RARE DISORDERS IN SUPPORT OF THE OPENING BRIEF OF APPELLANT SPECTRUM PHARMACEUTICALS, INC.

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July 28, 2015

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CERTIFICATE OF INTEREST

Pursuant to Federal Rule of Appellate Procedure 26.1 and Circuit Rule 26.1, counsel for *amicus curiae* certifies the following:

1. The full name of every party or *amici* represented by me is: National Organization For Rare Disorders.

2. The name of the real party-in-interest (if the party named in the caption is not the real party-in-interest) represented by me is: Not Applicable.

3. All parent corporations and any publicly-held companies that own 10 percent or more of the stock of the party or *amici* represented by me are: None.

4. The names of all law firms and the partners and associates that appeared for the party or *amici* now represented by me in the trial court or agency or are expected to appear in this Court are:

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Date: July 28, 2015

/s/ Jonathan M. Ettinger
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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Pursuant to Circuit Rule 28(a)(1) the undersigned counsel certifies as follows:

(A) Parties and *Amici*: Except for the following parties, intervenors, and *amici* appearing before the district court and in this Court are listed in the Briefs for Appellants and Appellees: National Organization for Rare Disorders.

(B) Rulings Under Review: References to the ruling at issue appear in the Brief for Appellants.

(C) Related Cases: Related cases appear in the Brief for Appellant

Date: July 28, 2015

/s/ Jonathan M. Ettinger
Jonathan M. Ettinger

STATEMENT PURSUANT TO FEDERAL RULE OF APPELLATE PROCEDURE 29(C)(5)

No party or party's counsel authored this brief in whole or in part or contributed money intended to fund preparing or submitting this brief. Moreover, no person other than the *amicus curiae*, their members, and their counsel contributed money intended to fund preparing or submitting this brief.

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GLOSSARY

In accordance with D.C. Circuit Rule 28(a)(3), the table below identifies the abbreviations used in this brief.

ANDA	Abbreviated New Drug Application
FDA	Food and Drug Administration
FFDCA	Federal Food Drug and Cosmetic Act
Hatch-Waxman Amendments	Drug Price Competition and Patent Term Restoration Act of 1984
NIH	National Institutes of Health
NORD	National Organization for Rare Disorders
ODA	Orphan Drug Act
RTU vials	Ready-to-use vials
sNDA	supplemental New Drug Application

STATEMENT OF IDENTITY AND INTEREST OF *AMICUS CURIAE*

The National Organization for Rare Disorders ("NORD"), founded in 1983, is a unique federation of over 230 patient advocacy groups and voluntary health organizations dedicated to helping all people with rare diseases and assisting the organizations that serve them. For more than 30 years, NORD has been an advocate for the 30 million Americans affected by one of more than 7,000 known rare diseases. The organization is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and service.

NORD's founders played an active role in the creation of the Orphan Drug Act ("ODA"), and preserving the integrity of the ODA is a primary function of the organization. The ODA is a successful model of how to incentivize the development of treatments and is responsible for prolonging and saving thousands of lives. Analysis of data in the United States shows that years of life lost to rare diseases declined at an annual rate of 3.3% after the ODA due to the development and deployment of new treatments. Frank Lichtenberg, *The Impact of New (Orphan)Drug Approvals on Premature Mortality From Rare Diseases in the United States and France, 1999-1997*, 14 The European Journal of Health Economics, 41-56 (2013). Without these new drug approvals, years of life lost would have increased at a rate of about one percent. *Id.*

INTRODUCTION

In this action, Appellees seek to maintain the approval of a generic version of the orphan drug FUSILEV under the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Amendments"), yet in a manner inconsistent with the ODA. This brief will address the singular importance of market exclusivity authorized under the ODA to the development of new treatments and cures and the potentially erosive threat that the District Court's order poses to the future working of the ODA. It is the position of NORD that the Food and Drug Administration ("FDA") has approved Appellee Sandoz Inc.'s generic levoleucovorin without regard to facts at its disposal that make it clear that the approval contravenes valid orphan drug exclusivity protecting FUSILEV's colorectal cancer indication.

SUMMARY OF ARGUMENT

The decision of the District Court to uphold FDA's approval of Sandoz's abbreviated new drug application ("ANDA") for a generic version of FUSILEV at a strength that is twenty to thirty times more than is needed for the non-exclusive methotrexate indications flies in the face of the ODA's market exclusivity protections for orphan drug indications. The District Court erred for two reasons. First, nothing in the ODA permits FDA to disregard distinguishing characteristics between an exclusive and a non-exclusive orphan drug indication in a manner that

may facilitate approval of generic competition for the latter yet broadly undermine the protections afforded by statute to the former. Second, read in the context of the overall statutory scheme of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), it is implausible that Congress intended Section 360cc(a) to be read to limit FDA review to "the use for which generics are labeled." *Spectrum Pharms., Inc. v. Burwell*, No. 15-631(RCL), slip op. at 9 (D. DC Jun. 5, 2015) *citing Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002). FDA's decision to ignore the distinguishing characteristics between an exclusive and a non-exclusive use of an orphan drug product will greatly reduce the incentives, which Congress carefully constructed in the ODA, to promote the development of orphan drugs. NORD respectfully asks this Court to reverse the District Court's decision.

ARGUMENT

I. The Integrity of the Orphan Drug Act is Critical to the Health and the Prospects for Treatment or Cure of Tens of Millions of Americans.

A. The Orphan Drug Act Has Had Tremendous Beneficial Influence on the Search For Treatments and Cures for Rare Diseases and Conditions.

Nearly 30 million Americans suffer from a rare disease or condition. *Impact of the Orphan Drug Tax Credit on Treatments for Rare Diseases* ("NORD White Paper") (June 2015) at i.[1] Congress has defined a rare disease or condition as one

[1] Available at http://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc

that affects fewer than 200,000 patients in the United States. 21 U.S.C. §360bb(a)(2)(A). Many rare diseases are serious or life threatening, including Huntington's Disease, ALS (Lou Gehrig's Disease), and muscular dystrophy. *H.R. Rep. No. 97-840*, Cong. Rec. Vol. 128 (1982).

Despite the debilitating nature of many of these diseases, rare diseases are much less likely to have an approved treatment option when compared to more common diseases. NORD White Paper at 1. Only four percent of rare diseases have an approved treatment. *Id.* at i. As such, millions of Americans lack treatment options. Because investigational treatments for rare diseases can often languish without a sponsor willing to fund further research and development, these treatments are referred to as "orphan drugs." Significantly, the high cost of drug development coupled with limited patient populations act as market barriers to the development of new orphan drugs; the total cost to bring a new drug to market is estimated to be between $1.5 and $2.6 billion. *Id.* at 3. However, for orphan drug manufacturers, the opportunity to recover their initial investment in research and development is diminished by a limited pool of potential patients, and spreading the cost of developing a new drug over small patient populations can result in a per-patient cost of tens of thousands of dollars. *Id.* As a result, prior to 1983, many promising discoveries never received the substantial investment required to

develop the clinical evidence necessary for FDA review and approval of new, safe, and effective orphan drugs. *Id.*

In 1983, Congress enacted the ODA to lower the economic barriers and spur innovation in the development of new drugs for patients who suffer from rare diseases. *See generally* 21 U.S.C. §360aa-360ee; *H.R. Rep. No. 97-840*. The ODA "created financial incentives, including grants, for the developers of new drugs for people with rare diseases. Under this system, developers of promising drugs or biologics can, prior to submitting applications for approval of those products, apply to receive 'orphan drug status' designation for their products. If products so designated are subsequently shown to be safe and effective and receive marketing approval, their developers receive market exclusivity for seven years." *FDA's Efforts on Rare and Neglected Diseases: Hearing Before the U.S. Senate Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, Committee on Appropriations*, 111th Cong. 111 (June 23, 2010) (statement of Jesse L. Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health, Food and Drug Administration) ("Goodman, Senate Testimony")[2]; Pub. L. 97-414.

[2] Available at http://www.fda.gov/NewsEvents/Testimony/ucm216991.htm

The ODA's market exclusivity provision is one component of the ODA's carefully designed statutory structure to encourage investment in orphan drugs at different stages of development. Congress recognized that "the determination that a drug is for a rare disease or condition, and therefore lacks the potential for an adequate return on investment, can occur at different stages of a drug's development." *H.R. Rep. No. 97-840* at 8. Under the ODA, there are three major provisions to spur the development of orphan drugs: the Orphan Drug Grant Program, the Orphan Drug Tax Credit, and market exclusivity. *Id.*; *see also* NORD White Paper at 7. The Orphan Products Grant Program and the Orphan Drug Tax Credit both reduce a drug developer's upfront costs in researching and testing a drug. *See* 21 U.S.C. §360ee; 26 U.S.C. §45C. These two provisions, which reduce the cost of making an initial investment, are intentionally paired with the ODA's market exclusivity provision, which protects the sponsor of an approved orphan drug against competition from a generic version of the same drug for the protected orphan indication for seven years after the reference drug's approval. 21 U.S.C. §360cc.

B. Orphan Drug Exclusivity is a Critical Incentive to Promote Rare Disease Research and the Development of Novel Orphan Drugs to Treat and Cure Rare Diseases.

Of all of the incentives created by the Orphan Drug Act of 1983, it is the seven years of orphan drug exclusivity that has been most effective in spurring

interest in rare disease research and orphan product development over the years. HHS Office of the Inspector General, OEI-09-00-00380, *The Orphan Drug Act: Implementation and Impact* (2001).[3] Market exclusivity, in the case of orphan drugs, prohibits FDA from approving another drug application for "such drug for such disease or condition" for seven years from the date of approval of the orphan indication. 21 U.S.C. §360cc(a)(2). Because of the length of time it takes to complete the FDA approval process, drugs often reach the market with relatively few years of patent protection remaining. NORD White Paper at 8. To minimize the effect of this on orphan drugs, market exclusivity increases the economic incentives for developing orphan drugs by extending the time orphan drug developers have to recover their investment once a drug is approved. Orphan drug exclusivity is key to providing sufficient return on investments to make orphan drug development profitable and viable.

In combination with the other provisions of the ODA, market exclusivity has been "extremely successful in changing the landscape and success rate of orphan drugs and improving the lives of many patients" by spurring innovation, rare disease research, and drug development. Goodman, Senate Testimony. Prior to the enactment of the ODA, an estimated thirty-four orphan drugs had been approved.

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[3] Available at https://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf

NORD White Paper at i. Since 1983, more than 2,150 medical therapies have been officially designated as "orphans", Goodman, Senate Testimony, of which about 495 of these therapies have been approved for market, *Orphan Drug Designations and Approvals*, U.S. Food and Drug Administration, (July 27, 2015, 7:15 pm), http://www.accessdata.fda.gov/scripts/opdlisting/oopd, despite the fact that there are almost 7,000 identified rare diseases and disorders. Janet Woodcock, M.D., *The More We Know About Rare Diseases, The More Likely We Are To Find Safe And Effective Treatments*, FDA Voice (Oct. 23, 2014), http://blogs.fda.gov/fdavoice/index.php/tag/rare-diseases/.

Under the ODA, orphan drug exclusivity is virtually absolute. The ODA only contemplates abbreviating or ending such exclusivity to permit the approval and marketing of the same drug for the same use before the end of the natural seven-year term of the exclusivity under very narrow circumstances:

> (i) the withdrawal of the approved product from market;
>
> (ii) the FDA's withdrawal of orphan drug designation or approval of the drug;
>
> (iii) the failure of the sponsor to "assure the availability of sufficient quantities of an orphan drug to meet the needs of patients"; or

(iv) the demonstration of a subsequent sponsor of the "clinical superiority" of their version of "a previously approved [orphan] drug for the same use or indication."

21 C.F.R. 316.31; 21 C.F.R. 316.36.

None of these exceptions apply to the current case.

II. FDA's Approval of Sandoz's Generic Levoleucovorin Undermines Orphan Drug Exclusivity Protecting the Use of FUSILEV Against Colorectal Cancer.

A. FDA is Aware that Sandoz Secured Approval of Generic Levoleucovorin to Treat Colorectal Cancer in Violation of the Orphan Drug Act.

The FDA is well aware of clear evidence that the approval of the Sandoz ANDA violates the orphan drug exclusivity protecting FUSILEV's colorectal cancer indication. The District Court recognized that Spectrum submitted a supplemental New Drug Application ("sNDA") and that the FDA reviewed this application based upon data and information that the large ready-to-use vials ("RTU vials") were for use against colorectal cancer and not for the drug's methotrexate indications. *Spectrum Pharms.*, No. 15-631(RCL), slip op. at 5. Similarly, the RTU vials are not appropriate for use under the unprotected methotrexate indications; the 175 and 250 milligram (mg) vials are much larger than the 7.5 mg individual doses called for by the methotrexate indications. *Id.*, slip op. at 5-6. The FDA acknowledges that FUSILEV's "approved [methotrexate

indications do] not require single-use vials larger than 50 mg." Joint Appendix ("JA") 65.

Additionally, as the District Court notes, Sandoz filed its ANDA to secure FDA approval of generic levoleucovorin under FUSILEV's colorectal cancer indication and the use of the RTU vials. *Spectrum Pharms.*, No. 15-631 (RCL), slip op. at 5. Sandoz has since acknowledged that it sought approval for the higher strength vials of its generic levoleucovorin in an attempt to supply the market demand for the larger size vial. JA 165. Based on the strength required, this market demand is clearly unrelated to the approved methotrexate indications. *See* JA 65.

B. FDA Must Act on Its Knowledge of the Violation of the Orphan Drug Act To Protect Exclusive Orphan Drug Uses and Withdraw Approval of Sandoz's Generic Levoleucovorin.

The FDA cannot disregard the available evidence to approve a generic drug that expressly undermines the legal protection of a valid orphan drug exclusivity, when approval of the appropriate strength vials of the generic drug for previously-protected indications of use is a simple and obvious alternative. It is notable that, unlike Sandoz, three other generic drug sponsors have submitted ANDAs for approval not of the RTU vials, but of the smaller vials and labeling for the unprotected methotrexate indications of use.

The District Court, in relying on the decision of the Fourth Circuit in *Sigma Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002), creates an overbroad

standard under which FDA is permitted to be willfully blind to any and all evidence that indicates an ANDA approval is being sought for an indication that is protected by orphan drug exclusivity. *Spectrum Pharms.*, No. 15-631(RCL), slip op. at 9 ("the evidentiary basis for the agency's approval must be… the use for which the generics are labeled"). The District Court couches its argument in a fear that an "intended- or foreseeable-use test" will be administratively burdensome for FDA and will greatly limit the approval of low cost generic drugs. *See Spectrum Pharms., Inc.*, No. 15-631(RCL), slip op. at 10. Although under other circumstances the District Court's concerns might be well founded, in this case, where FDA's own statements and empiric evidence clearly indicate a distinction in dosage between the protected and non-protected indication, a rule of law that permits FDA to be willfully blind to a generic drug's intended use undermines the purposes, efficacy, and operation of the ODA.

There can be a clear line between instances in which FDA records indicate there is a specific difference in how two indications of a drug are dosed or delivered and instances in which FDA would be left to speculate if and how frequently an orphan drug will be used for off-label uses. The District Court mischaracterized Spectrum's argument as an "intended- or foreseeable-use test." *Id.* FDA can take into consideration distinguishing characteristics between an

orphan drug's exclusive indication and a non-exclusive indication without engaging in an inefficient and speculative analysis.

In the case at the bar, FDA has acknowledged that the higher strength formulation of FUSILEV was intended for the colorectal indication. *See* JA 65 (FDA statement that the methotrexate indications do "not require single-use vials larger than 50 mg."). The dosage for which Sandoz sought approval in the ANDA is far greater than what is needed for the methotrexate indications for which the generic was approved. *Id.* In this limited circumstance, when two indications have such distinct characteristics, FDA can consider these differences without having to "glean knowledge, intent, or even the relative strength of multiple simultaneously-held intents." *See Spectrum Pharmaceuticals*, No. 15-631(RCL), slip op. at 10.

The Fourth Circuit in *Sigma Tau Pharmaceuticals, Inc.*, 288 F.3d at 148, correctly points out that there is an inherent tension between the incentive-structure of the ODA and the goals of the Hatch-Waxman Amendments, which sought to increase the number of low cost generic drugs by establishing a simpler generic drug approval procedure. *See* Pub. L. No. 98-417, 98. NORD recognizes that permitting the approval of generic drug is an important yet competing policy goal. However, just as the Fourth Circuit criticized Sigma Tau for putting all of the weight on orphan drug development, so does the District Court put all of the weight on generic drug approval by permitting FDA to ignore the factual

distinctions between the colorectal and methotrexate indications. Unlike *Sigma Tau*, this case does not require FDA to review market data and evidence that cannot be effectively analyzed in the pre-approval context. *Sigma Tau*, 288 F.3d at 147. However, by permitting FDA to be willfully blind to a drug's intended use, the District Court gives no weight to the importance of orphan drug development.

In some circumstances, willful blindness may serve a necessary practical purpose —FDA cannot hope to ferret out intent of all sponsors in all situations. However, where FDA policy, information in its files, or decisions the agency has made, either confirm or imply intent to usurp an exclusive indication, then FDA should take it into consideration what they know. They should not be able to engage in willful blindness and ignore some distinguishing characteristics that separate the second indication from the first indication. In this case, an ANDA should be limited to the original "no longer protected" labeling and the physical characteristics of the original orphan product. Allowing marketing beyond that undercuts the ODA.

C. It is Implausible that Congress Intended to Broadly Undercut the Orphan Drug Act In Order to Facilitate Approval of Generic Drugs For Non-Orphan Protected Indications.

While the District Court is correct that the FDA may "properly grant … approval" of a drug for an indication of use that is not protected by orphan drug exclusivity, it is mistaken that the FDA may limit its inquiry to "the use for which

the generics are labeled" without careful regard to how such uses, labeling, and other information submitted by the generic sponsor impinges and interrelates with drug uses protected under the Orphan Drug Act. *Spectrum Pharms.*, No. 15-631, slip op. at 9 *citing Sigma Tau*, 288 F.3d at 145.

Reading a statutory phrase "in its most natural sense…. may not be as clear as it appears when read out of context." *King v. Burwell*, 576 U.S. ____, slip. op. at 11 (U.S. Jun. 25, 2015). "The words of a statute must be read in their context and with a view to their place in the overall statutory scheme." *Id.* at ____ (slip. op. at 15) (internal citation omitted). "A provision that may seem ambiguous in isolation is often clarified by the remainder of the statutory scheme… because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law." *Id. quoting United Sav. Assn. of Tex. v. Timbers of Inwood Forest Associates, Ltd.*, 484 U.S. 365, 371 (1988).

Labeling carve-outs for indications of use protected by orphan drug exclusivity are common, and allow generic drugs to reach market for other, unprotected indications of use. However, in the present case, the District Court erred because it disregards the necessity imposed by section 360cc(a) on the FDA to account fully for evidence, not of generic sponsor intent as characterized by the District Court but of the distinguishing characteristics of the protected and non-protected indications of an orphan drug.

To achieve this statutory result, FDA must act under section 360cc(a) to look beyond an ANDA's label in the limited circumstances when distinctions between a drug's exclusive and non-exclusive indications will result in a generic manufacturer circumventing the ODA's market exclusivity requirements. Any other reading of the statute would substantially dilute Congress's intended purpose to improve the ability of orphan drug manufacturers to recoup their investments after a drug had been approved. Its reading would create a statutory scheme in which Congress helped reduce a drug manufacturer's costs of development, but drastically limited the manufacturers ability to recoup any private investment that was made.

In contrast, the District Court permits FDA to ignore distinctions between an exclusive and non-exclusive use of an orphan drug, and in doing so, permits Sandoz to substantially dilute the value of Spectrum's market-exclusivity for FUSILEV's colorectal indication. The Court should reject this interpretation of the statute because it creates the exact problem the ODA was intended to address. *See New York State Dept. of Social Servs. v. Dublino*, 413 U.S. 405, 419-420 (1973) ("We cannot interpret federal statutes to negate their own stated purposes"). For FDA to ignore its own documents indicating the larger vials of FUSILEV were intended solely for the colorectal indication, which involves no speculation and is readily at FDA's disposal, only serves as a disincentive for a drug manufacturer to

research and seek regulatory approval for a new orphan indication of a drug. Congress was clear that the ODA was intended to spur innovation and decrease market barriers to the research and development of new therapies for rare disorders. *See* H.R. Rep. No. 97-840 at 5 ("The purpose of the Orphan Drug Act is to facilitate the development of drugs for rare diseases or conditions. The legislation accomplishes this goal by … offering exclusive marketing rights on un-patentable orphan drugs for a period of seven years.").

III. Appellees' Approach Would Diminish Incentives to Pursue Rare Disease Research and Develop Novel Orphan Drugs to Treat and Cure Rare Diseases.

Left uncorrected, the District Court will have created a damaging and novel discount factor in the fiscal decisions and planning of entrepreneurial scientists, startup companies, and venture capitalists, which is all critical to initiating and supporting programs of scientific discovery and clinical study of rare diseases. More broadly, the District Court effectively invites the global industry of generic competitors to exploit this detrimental decision and adopt new business and regulatory strategies to undercut the integrity of orphan drug exclusivities, once any protection of the first approved indications of such orphan drugs has lapsed.

This would be especially threatening to development programs focused on identifying promising new rare disease uses of existing drugs. In addition to the repurposing of drugs originally approved for common diseases, FDA's regulations make clear, "A drug that shows promise in multiple, different rare diseases or

conditions may be eligible for multiple designations, one for each disease or condition." FDA Orphan Drug Rule, 78 Fed. Reg. 35117 (June 12, 2013). The case in hand would also undermine Federal interagency initiatives at FDA and the National Institutes of Health ("NIH") to encourage drug repurposing, which is playing an increasingly important role in the development of rare disease therapies.[4]

These are real, unnecessary, and legally unfounded risks to add to the already challenging environment in which scientists, physicians, and patients struggle daily to improve our scientific understanding of rare diseases, organize and finance clinical studies, and recruit volunteer patients to undergo the necessary experimentation to demonstrate the safety and effectiveness of new treatments or cures. The consequences for future orphan drug development could be substantial and hazardous, potentially jeopardizing support for fundamental scientific research into the basis and pathogenesis of rare diseases, the identification and preclinical testing of promising molecules as potential treatments or cures, and the

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[4] *See e.g.* FDA Office Of Orphan Product Development, A Valuable Resource For Drug Developers: The Rare Disease Repurposing Database (RDRD) available at: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm; NIH Nat'l Ctr. For Advancing Translational Sciences, Discovering New Therapeutic Uses For Existing Molecules, available at: http://www.ncats.nih.gov/ntu.

organization and funding of expensive and arduous clinical trials in sometimes extraordinarily small patient populations worldwide.

CONCLUSION

FDA's decision to approve Sandoz's generic version of FUSILEV in a dosage that was clearly intended for use to treat an orphan indication that is protected by an exclusivity period is in contradiction to the ODA and would have the effect of reducing the incentives to invest in orphan drugs. For the foregoing reasons, *amicus* NORD respectfully request that the Court reverse.

Respectfully submitted,

NATIONAL ORGANIZATION FOR RARE DISORDERS

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CERTIFICATE OF COMPLIANCE

I certify that the foregoing brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 3,966 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14-point Times New Roman.

/s/ *Jonathan M. Ettinger*
Jonathan M. Ettinger

CERTIFICATE OF SERVICE

I hereby certify that on this 28th day of July 2015, I caused the forgoing document to be electronically filed with the Clerk of the Court using the CM/ECF system that will send an electronic copy to the registered participants identified on the Notice of Electronic Filing, and further certify that a paper copy will be sent to those indicated as non-registered participants as of the date hereof.

_/s/ *Jonathan M. Ettinger*_____