UNITED STATES COURT OF APPEALS

FOR THE FIFTH CIRCUIT

No. 99-30425

UNITED STATES OF AMERICA,

Plaintiff-Appellant,

VERSUS

SAGE PHARMACEUTICALS, INC.,
JIVN REN CHEN,

Defendants-Appellees.

Appeal from the United States District Court
For the Western District of Louisiana

April 20, 2000

Before HIGGINBOTHAM and PARKER, Circuit Judges and JACK, District Judge.[*]

JANIS GRAHAM JACK, District Judge.

This is an enforcement action brought by the United States against Sage Pharmaceuticals, Inc., a manufacturer of prescription and over-the-counter drugs, and its president, Jivn Ren Chen (collectively, Sage). The United States sought to enjoin the

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[*]District Judge of the Southern District of Texas, sitting by designation.

distribution of adulterated drugs and unapproved new drugs in violation of the Federal Food, Drug, and Cosmetic Act (FDCA).[1] Following a three day bench trial, the district court entered an order enjoining Sage from distributing drugs until compliance with Current Good Manufacturing Practice (CGMP) regulations had been established to the satisfaction of the Food and Drug Administration (FDA). The district court, however, declined to enjoin Sage from introducing into interstate commerce unapproved new drugs Palgic D and Palgic DS. The United States appeals from this portion of the district court's order. Because we conclude that the district court's denial of an injunction constitutes an abuse of discretion, we reverse.

I. Facts and Procedural History

Sage is a pharmaceutical manufacturer located in Shreveport, Louisiana. Sage manufactured Menogen and Menogen H.S., prescription drugs indicated in the treatment of moderate to severe vasomotor symptoms (hot flashes) associated with menopause in those patients not improved by estrogen alone, and Palgic D and Palgic

[1] See 21 U.S.C. §§ 331(a), 351(a)(2)(B) (dealing with adulterated drugs and current good manufacturing practices); §§ 331(d), 355(a)(addressing unapproved new drugs); and § 332(a)(providing for injunctions against violations of § 331). The text of the provisions relevant to this appeal is set out in Part II of this opinion.

DS, prescription drugs used for the symptomatic relief of seasonal and perennial allergic rhinitis and vasomotor rhinitis. Although Sage made and sold Palgic and Palgic DS since 1995 and Menogen and Menogen H.S. since 1997, none of the Menogen or Palgic series of drugs was the subject of approved new drug or abbreviated new drug applications. Prior to the initiation of this lawsuit, the FDA conducted five CGMP inspections[2] of Sage from March of 1995 to October of 1997. The FDA conducted a sixth inspection during the trial court proceedings in July of 1998. FDA inspectors reported a substantial number of CGMP violations during their investigations of Sage. These purported violations of CGMP regulations prompted the FDA to recommend that the United States institute enforcement proceedings against Sage. The new drug charge which forms the basis of this appeal was added to the CGMP violations in the United States' complaint against Sage.

[2]In addition to determining the safety and efficacy of new drugs as it authorizes new drug applications, the FDA also inspects facilities used to manufacture, pack, and store drugs to ensure that the drugs are not adulterated by the manufacture, package, or storage in improper conditions. See 21 U.S.C. § 374(a). The FDA's CGMP regulations set forth the minimum requirements for all aspects of drug manufacturing, including component control, production and process control, packaging and labeling control, and maintenance of required records and reports. See 21 C.F.R. Parts 210, 211.

At trial, the government demonstrated that Sage distributed adulterated drugs in violation of the FDCA by failing to comply with CGMP regulations. The district court enjoined Sage from distributing certain drugs until compliance with the CGMP regulations was established to the FDA's satisfaction. As to the new drug charge, the district court fashioned a conditional injunction order stating that "Sage agrees not to sell Palgic D and Palgic [DS][3] unless other manufacturers are currently selling products 'substantially similar' to Palgic D and Palgic [DS]." [4] The determination of whether other manufacturers are selling Palgic-like drugs was to be made by the trial court, effectively removing the FDA from the approval process. The United States moved to alter or amend the judgment on October 7, 1998, asking the court to enjoin Sage from selling unapproved new drugs in contravention of the FDCA. After denial of this motion by the trial court, the United States filed its notice of appeal.

II. Applicable Law

Although this court reviews the denial of a permanent injunction for an abuse of discretion, "[t]he district court abuses

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[3]Sage previously ceased the manufacture and distribution of Menogen and Menogen H.S. in August of 1997 pursuant to a consent permanent injunction entered in a private lawsuit.

[4]Although the district court's order is labeled a "Settlement Order," no formal agreement was reached between the parties. It appears from the record that the district court attempted to facilitate a settlement between the parties, perhaps in an attempt to save jobs in the community.

its discretion . . . if it relies on erroneous conclusions of law when deciding to grant or deny the permanent injunction." Peaches Entertainment v. Entertainment Repertoire Assocs., 62 F.3d 690, 693 (5th Cir. 1995). This court reviews the district court's conclusions of law under the *de novo* standard. Id.

The FDCA, 21 U.S.C. §§ 301 et. seq., as enacted in 1938, heralded a new system of drug regulation requiring pre-market approval before a drug could be sold. United States v. Generix Drug Corp, 460 U.S. 455, 458, 103 S.Ct. 1298, 1301 (1983). The FDCA prohibits the sale of unapproved new drugs[5] in interstate commerce: "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application [to the FDA] is effective with respect to such drug." 21 U.S.C. § 355(a). A drug manufacturer or distributor obtains FDA approval by submitting a new drug application (NDA) or abbreviated

[5]The term "new drug" means --
(1) Any drug...the composition of which is such that such drug is not generally recognized among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof;...or (2) Any drug...the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.
21 U.S.C. § 321(p).

new drug application (ANDA)[6] in accordance with the statute and FDA regulations. See 21 U.S.C. § 355(b)-(b)(1); 21 C.F.R. § 314.50 (detailing contents of NDA). The United States enforces the FDCA by, among other things, seeking injunctive relief against manufacturers and distributors which violate its terms. See 21 U.S.C. § 332(a).

In 1962, the FDCA was amended to require NDAs to show that a drug is not only safe, but also effective for its intended uses. See Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 612-14, 93 S.Ct. 2469, 2474-75 (1973). The amendments also required the FDA to act affirmatively to approve an NDA, instead of allowing it to become effective through inaction. Hynson, Wescott, 412 U.S. at 613, 93 S.Ct. at 2475. The 1962 amendments applied retroactively to drugs already on the market with approved NDAs based upon safety alone.[7] Id. In order to expedite review of the effectiveness of drugs with approved NDA's based solely upon their safety, the FDA instituted the Drug Efficacy Study Implementation

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[6]An alternative to the NDA is available for generic drugs. A generic version of an approved pioneer drug may obtain FDA approval by filing an ANDA. 21 U.S.C. § 355(j).

[7]All new drugs require an approved NDA or ANDA before marketing unless they are generally recognized among experts as safe and effective for their labeled uses (the "GRASE" exception) or fall within a limited grandfather clause exempting certain drugs from the additional effectiveness requirements. Hynson, Westcott, 412 U.S. at 613-615, 93 S.Ct. 2475-76. Neither exception to the amendments is applicable to the Palgic drugs.

(DESI) Program. See Hynson, Westcott, 412 U.S. at 615-16 & n.7, 93 S.Ct. at 2476 & n.7. Under the DESI program, the FDA and the National Academy of Sciences-National Research Council (NAS-NRC) convened expert panels to consider the efficacy of classes of drugs already on the market with approved NDA's at the time of the 1962 amendments for supplemental NDA approval. Hynson, Westcott, 412 U.S. at 614-15, 93 S.Ct. at 2475-76. If the FDA concurred with the panel's determination under the DESI review, a notice was published in the federal register and a supplemental NDA was approved for the drug. Florida Breckenridge, Inc. v. Solvay Pharmaceuticals, Inc., 174 F.3d 1227, 1229 (11th Cir. 1999), withdrawn at the request of the court.

The DESI program was the basis for a short-lived policy under which the FDA permitted the continued sale of some drugs without effective NDAs. Hoffman-LaRoche, Inc. v. Weinberger, 425 F.Supp. 890, 892-93 (D.D.C. 1975). However, this policy was challenged in 1975 as inconsistent with the FDCA, which requires pre-market approval before a drug is sold. Hoffman-LaRoche, 425 F.Supp. at 894. In response to the Hoffman-LaRoche decision, the FDA in 1976 adopted its Compliance Policy Guide 7132c.02 (CPG) wherein it acknowledges the presence of unapproved drugs on the market. The CPG "reaffirm[s] that all products marketed as drugs under the DESI program are new drugs, and therefore, require an approved NDA or ANDA for marketing." CPG 7132c.02 § 440.100 at 134, quoted in Florida Breckenridge, 174 F.3d at 1229. The CPG also sets forth

the FDA's priorities for enforcing the statutory prohibition against selling unapproved new drugs. CPG 7132c.02 § 440.100 at 134.

III. Analysis

Sage concedes the following: (1) the Palgic drugs are new drugs within the meaning of the FDCA; (2) for which Sage has not obtained FDA approval by submitting a NDA; and (3) which Sage was manufacturing and distributing, until shortly after the institution of this enforcement action by the United States. Section 355(a) of the FDCA clearly mandates FDA approval before any drug can be sold or otherwise introduced into interstate commerce. See 21 U.S.C. 355(a). "[T]here is no magical exception that allows [a drug company] to opt out of the FDA approval process." Florida Breckenridge, 174 F.3d at 1233. By manufacturing and distributing Palgic D and Palgic DS without FDA approval, Sage clearly violated the statute.

Notwithstanding its admitted violations of the FDCA, Sage argues that it should be permitted to sell the Palgic drugs because the FDA's Compliance Policy Guide ("CPG") provides that the agency enforce the FDCA on a "class-wide basis" against all manufacturers of unapproved new drugs. Sage points to other pharmaceutical companies selling Palgic-like drugs without FDA approval, some under the same Palgic trade name, which have not come under government scrutiny.

Sage asserts that FDA policy embodied in its CPG 7132c.02

allows the sale of unapproved new drugs in certain categories unless the FDA takes affirmative steps to remove the entire category from the market. The policy guide, adopted after the successful challenge of FDA procedure in Hoffman-LaRoche, acknowledges the continued marketing of new drugs without approval and "reaffirm[s] that all products marketed as drugs under the DESI program are new drugs" which require an approved NDA or ANDA for marketing. CPG 7132c.02 § 440.100 at 134. The policy provides that the FDA must proceed to remove such new drugs from the market. Id. Confronted with limited resources and a multitude of unapproved drugs already on the market, the FDA outlined its strategy and priorities for removal of drugs from the market: "The District Offices will then initiate regulatory action against any violative products on the market in accordance with the Compliance Program regarding that specific category of drugs." Id. at 135. Notwithstanding the priorities for enforcement listed in the CPG, the FDA clearly reserves the right to include a new drug charge in an enforcement proceeding against a manufacturer of "a drug subject to this policy which become[s] violative under another provision of the act." Id. at 136.

The FDCA's comprehensive scheme of drug regulation is designed to ensure the nation's drug supply is safe and effective. See United States v. Dotterweich, 320 U.S. 277, 280, 64 S.Ct. 134, 136 (1943). Congress has determined that the best way to meet the FDA's goals is to prohibit the sale of drugs before they are

rigorously tested and subjected to the careful scrutiny of federal regulators. See Hyson, Westcott, 412 U.S. at 623, 93 S.Ct. at 2480 (discussing addition in 1938 of the pre-market approval requirement for drugs sold in commerce). The FDA's policy of adding a new drug charge to a CGMP proceeding fosters efficiency and minimizes the risk of duplicative litigation.

Here, Sage's violations of the CGMP regulations led to the initiation of an enforcement action to which a new drug charge was added. The sale of the Palgic drugs without approval came to the attention of the FDA following the repeated violations of production standards at Sage.[8] The policy clearly permits the FDA to address the unapproved status of a particular drug outside the established priorities in the same enforcement proceeding as other violations of the FDCA. It would be inefficient to expect the government to address the problems at Sage in a piecemeal fashion, enforcing the CGMP regulations and drug approval provisions of the FDCA in separate proceedings.

Nevertheless, Sage argues for the first time on appeal that the government's action against it violates the Administrative Procedure Act (APA) as it is arbitrary and capricious because the

[8]The three day trial in the district court focused on Sage's repeated and pervasive violations of the CGMP requirements. As the FDA's District Director testified, those violations included "validation problems, not properly validating their manufacturing process or qualifying their equipment, stability issues as far as the drug products are concerned...[record keeping] issues, and laboratory controls."

government has not taken similar action against its competitors. See Allergan, Inc. v. Shalala, 6 FDC Law Rep. (CCH) ¶38,375 (D.D.C. November 10, 1994)(action to compel FDA to treat similarly situated companies alike by continuing enforcement action against Allergan's competitor), vacated as moot, August 14, 1995. The Supreme Court has held, however, that the APA prohibits review of the FDA's enforcement decisions, at least when the FDA declines to enforce the Act against a manufacturer. Heckler v. Chaney, 470 U.S. 821, 835, 105 S.Ct. 1649, 1658 (1985) (holding that the FDA's decision not to seek an injunction is left entirely to the discretion of the FDA and cannot be reviewed under APA). Assuming arguendo that Heckler permits review of the FDA's recommendation that the United States seek enforcement against Sage, a claim that the FDA's action is arbitrary and capricious is not a defense to an enforcement proceeding. See Heckler, 470 U.S. at 825, 105 S.Ct. at 1652. (review sought under APA of FDA's failure to enforce FDCA's prohibition of allegedly misbranded drugs used in executions by lethal injection).

Sage also argues for the first time on appeal that the FDA's decision to enforce the FDCA against Sage, while ignoring similarly situated companies manufacturing the same drugs, constitutes an equal protection violation. To prevail on a claim of selective prosecution, Sage must show that others similarly situated have not been subject to enforcement proceedings by the government and that there was an impermissible basis for the decision to institute

enforcement action against Sage, "'such as race, religion, or other arbitrary classification.'" United States v. Armstrong, 517 U.S. 456, 464, 116 S.Ct. 1480, 1486 (1996)(quoting Oyler v. Boles, 368 U.S. 448, 456, 82 S.Ct. 501, 506 (1962)). Sage does not assert, nor does the record establish, that the United States had an improper motive for initiating this enforcement proceeding. Instead, the record clearly supports the government's contention that the enforcement action was prompted by Sage's repeated violations of the CGMP violations. Therefore, Sage cannot show an equal protection violation.

In sum, the plain language of the statute provides that Sage must not sell new drugs without FDA approval. Sage cannot show any legitimate justification for avoiding the clear mandate of the FDCA.

IV. Conclusion

For the foregoing reasons, the district court's judgment denying an injunction against Sage is reversed. This action is remanded to the district court with directions to modify its judgment to enjoin Sage from manufacturing or distributing Palgic D or Palgic DS without FDA approval in accordance with the FDCA, 21 U.S.C. § 355(a).

REVERSED AND REMANDED.