USV PHARMACEUTICAL CORP. v. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 72-666. Argued April 17, 1973—Decided June 18, 1973

Petitioner sells drug products containing citrus bioflavonoid, an extract from fruit skins, as a principal active ingredient. In the 1950's new drug applications (NDA's) were filed and became effective for seven products, and two were sold without any NDA. After the enactment of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, these products, together with a large number of other bioflavonoid products were examined by the Food and Drug Administration (FDA) for effectiveness. Based upon National Academy of Sciences-National Research Council (NAS-NRC) reports and its own evaluation, FDA gave notice of opportunity for hearing on its proposal to withdraw approvals of NDA's for all drugs containing these compounds, alone or in combination with other drugs. Petitioner then brought suit in the District Court, seeking a declaratory judgment that its drugs are exempt from the efficacy requirements under § 107.(c)(4), the so-called "grandfather" clause. FDA refused a stay pending the judicial proceedings and went forward with its administrative action. Petitioner submitted no evidence of "adequate and well-controlled investigations" as required by § 505 (d) to support its claims of effectiveness, and FDA withdrew petitioner's NDA's. Section 107 (c) (4) exempts from the effectiveness requirements any drug which on the day preceding the 1962 enactment (1) was commercially used or sold in the United States, (2) was not a "new drug" as defined in the 1938 Act, and (3) "was not covered by an effective application" for a new drug under the 1938 Act. The District Court found that two of the products had never been covered by effective NDA's and that, while seven had been covered, their applications had later been withdrawn by petitioner. It concluded that petitioner's drugs were not covered by effective applications, and hence were exempt from the effectiveness criterion. The Court of Appeals reversed on the merits. It held that petitioner's drugs were not entitled to an exemption, that an applicant could not withdraw an NDA once

it became effective, that the drugs were "covered by an effective application," and that although "me-too" drugs (similar drugs) of other manufacturers would be exempt, petitioner's "me-too's" were not exempt. *Held:*

1. "Any drug" is used in § 107 (c) (4) in the generic sense, which means that the "me-too's" whether the products of the same or of different manufacturers "covered" by an "effective" NDA are not exempt from the efficacy requirement of § 201 (p). Pp. 663–665.

2. Prescription drugs on the market are subject to the 1962 efficacy requirements, for if the 1962 amendments are to be comprehensively meaningful, § 107 (c) (4) cannot be read so as to provide a loophole to permit the marketing of drugs previously subject to new drug regulation without demonstrating by the new statutory standards that they have the claimed efficacy. Pp. 665–666.

3. The congressional purpose was to exempt only those drugs that never had been subject to the new drug regulation, and therefore any drug for which an NDA had once been effective does not fall within the exempt category. Pp. 666–668.

461 F. 2d 223, affirmed.

DOUGLAS, J., delivered the opinion of the Court, in which all Members joined, except BRENNAN, J., who took no part in the consideration or decision of the case, and STEWART, J., who took no part in the decision of the case.

Joel E. Hoffman argued the cause for petitioner. With him on the briefs were *Robert L. Wald, Selma M. Levine, Philip Elman,* and *Philip J. Franks.*

Deputy Solicitor General Friedman and *Andrew L. Frey* argued the cause for respondents. With *Mr. Frey* on the briefs were *Solicitor General Griswold, Assistant Attorney General Kauper, Deputy Solicitor General Wallace, Howard E. Shapiro,* and *Peter Barton Hutt.**

**Lloyd N. Cutler, Daniel Marcus,* and *William T. Lake* filed a brief for Pharmaceutical Manufacturers Assn. as *amicus curiae* urging reversal.

Bruce J. Terris, Joseph Onek, and *Peter H. Schuck* filed a brief

MR. JUSTICE DOUGLAS delivered the opinion of the Court.

Petitioner sells a line of drugs containing, as a principal active ingredient, citrus bioflavonoid, which is an extract from fruit skins. The drugs are sold in capsules, syrup, and tablets. In the 1950's new drug applications (NDA's) were filed and became effective for seven of them; two, however, were sold without any NDA. In 1961 the Food and Drug Administration (FDA) advised petitioner that two of the products, when distributed under the existing labels, were not new drugs. These drugs were recommended for a wide variety of ailments from bleeding, to hypertension, to ulcerative colitis. After the 1962 amendments to the Federal Food, Drug and Cosmetic Act of 1938, 52 Stat. 1040, as amended 76 Stat. 780, these products, together with a large numbe of other bioflavonoid products, were examined by FDA for drug effectiveness. The National Academy of Sciences-National Research Council (NAS–NRC) panels reviewed them. One panel on metabolic disorders concluded that the "use of these materials as hemostatic agents for capillary fragility is felt to be unjustifiable and not proved." A panel on hematologic disorders found there was no proof that these products were efficacious for any medical use.

Based upon the NAS–NRC reports and its own evaluation, FDA gave notice of opportunity for hearing on its proposal to withdraw approvals of NDA's for all drugs contal to withese compounds, alone or in combination with other drugs. Petitioner thereupon brought suit in the District Court, asking for a declaratory judgment that its drugs are exempt from the efficacy requirements under

for American Public Health Assn. et al. as *amici curiae* urging affirmance.

Thomas D. Finney, Jr., Thomas Richard Spradlin, and *Daniel F. O'Keefe, Jr.,* filed a brief for the Proprietary Assn. as *amicus curiae.*

§ 107 (c)(4). The administrative proceedings went forward, FDA refusing a stay pending the judicial proceedings. Petitioner submitted no evidence of "adequate and well-controlled investigations" as required by § 505 (d) of the Act, 21 U. S. C. § 355 (d), to support its claims of effectiveness. The Commissioner made findings and withdrew petitioner's NDA's.

In the District Court petitioner contended that the drugs were exempt from regulation by reason of § 107 (c)(4) of the 1962 amendments, which provides:

> "In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201 (p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

The District Court found that two of the products had never been covered by effective NDA's and that, while seven had been covered, their applications had later been withdrawn by petitioner. It found that the products were "safe" for use in treating abnormal capillary permeability and fragility. It therefore concluded that, as of the day the 1962 amendments became effective, petitioner's products were not new drugs, were not covered by effective applications within the meaning of § 107 (c)(4), and hence were exempt from the effectiveness criterion added to the regulatory provisions of §§ 505 and 201 (p), 21 U. S. C. §§ 355 and 321 (p). In so ruling,

the District Court necessarily determined that it, and not FDA, had jurisdiction to decide exemption questions.

The Court of Appeals agreed that the District Court alone had jurisdiction but reversed on the merits.[1] 461 F. 2d 223. It held that none of petitioner's bioflavonoid drugs were entitled to exemption under § 107 (c)(4). As to the seven for which NDA's had been filed, it held that an applicant could not withdraw an NDA once it became effective. It concluded that even if the drugs were generally recognized as safe on the day preceding the effective date of the 1962 Act, they were "covered by an effective application" within the meaning of § 107 (c)(4)(C) and thus were not exempt from the 1962 amendments. As to the "me-too" drugs, those specific drugs for which petitioner had not filed an NDA, the Court of Appeals held that although the "me-too's" of other manufacturers competing with petitioner's bioflavonoids would be exempt, petitioner's "me-too's" were not exempt because the NDA's covering the pioneer drugs prepared by petitioner covered all of its products similar in formula and labeling. While the Government agrees that peti-

[1] Unlike the situation in *CIBA Corp.* v. *Weinberger, ante,* p. 640, the order of the Commissioner withdrawing petitioner's NDA's had not become final prior to the District Court's assuming jurisdiction. In fact, the Court of Appeals for the District of Columbia Circuit reversed the Commissioner's decision, 151 U. S. App. D. C. 284, 466 F. 2d 455; and the proceedings on remand are now pending before the Commission. Thus, petitioner was not barred from proceeding in the District Court. Cf. *CIBA Corp.* v. *Weinberger, supra.* Our decision today is not meant to indicate that the District Court, had it concluded that its jurisdiction was concurrent with that of FDA, would not have abused its discretion in refusing to stay this action pending the outcome of administrative proceedings. Cf. *Weinberger* v. *Bentex Pharmaceuticals, Inc., ante,* p. 645. The Court of Appeals below found it unnecessary to consider whether petitioner had failed to exhaust its administrative remedies. 461 F. 2d, at 226.

tioner's "me-too" products should be accorded the same treatment as the "me-too's" of other manufacturers who had never filed NDA's, the parties are at odds on other issues.[2]

The resolution of the questions presented turns essentially on the meaning of § 107 (c)(4), quoted above. But as background for the problem of construction, references should be made to other 1962 amendments. Section 201 (p) [3] was amended to redefine a "new drug" as one not generally recognized by experts as both safe and effective for use under the conditions prescribed or one that has not been used to a material extent and for a material time. Section 505 (a) was amended to require affirmative approval of FDA, where previously it

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[2] There lurks in the case a question whether a drug could have been unsafe prior to the 1962 amendments because it was ineffective in treating the conditions for which its use was recommended by the label. That question, however, was not presented in the petition for certiorari.

[3] "The term 'new drug' means—

"(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal 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, except that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

"(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal 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).

had provided that an NDA would automatically become effective unless a contrary order were issued.[4] Section 505 (d) [5] was amended to require disapproval of an appli-

[4] Section 505 (c) provides:

"Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

"(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

"(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) . . . on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs." 21 U. S. C. § 355 (c).

[5] That section provides:

"If the Secretary finds, after due notice to the applicant in accordance with subsection (c) . . . and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) . . . , do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence

cation if there is "a lack of substantial evidence that the drug will have the effect it purports or is represented to have." Section 505 (e) was amended to require that any previous approval of an application be withdrawn whenever it appears from new information or otherwise that there is a lack of substantial evidence of the drug's effectiveness.

There remained the problem of the application of the new drug efficacy provisions to drugs already on the market. Without transitional protection all drugs—except those marketed prior to the 1938 Act whose labeling had not been changed and which were exempt from the "new drug" provision of § 201 (p)—would have been in violation of the amended Act unless generally recognized as effective. Even NDA's which were outstanding would have become ineffective because FDA had not approved them under the new criteria. Section 107 (c) (2) of the amendments therefore provides that applications which were effective on the day before the enactment date of the 1962 amendments should be deemed "approved." Section 107 (c) (2) thus eliminated the

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that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) . . . , the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U. S. C. § 355 (d).

necessity to review and approve every application already on file.

Section 107 (c)(3) provides that drugs covered by NDA's already on file whose labeling remains unchanged are not affected by the amended provisions of § 505 (b) or by approvals or refusals under § 505 (d) insofar as the effectiveness of the drugs is concerned, so long as the application is not withdrawn or suspended under § 505 (e). It also provides that the new effectiveness requirement in the withdrawal provision would not apply until two years after the amendments were adopted, or until the NDA approval were withdrawn for reasons other than lack of the drug's effectiveness, whichever came first. It seems apparent that by reason of § 107 (c)(3) the industry was assured it could continue to market previously approved NDA's unless and until the NDA was withdrawn and that before such withdrawal they would be given a minimum of two years within which to submit "substantial evidence" to support the claims for their products.

Section 107 (c)(4) exempted drugs from the new effectiveness requirements so long as their composition and labeling remained unchanged. This exemption, however, applies only to a product that, on the day before the 1962 amendments became effective, (A) was used or sold commercially in the United States, (B) was generally recognized by the experts as safe; and (C) was not "covered" by an "effective" application.

The first question is, which "me-too" copies of an NDA drug are subject to the efficacy requirements to the same extent as the NDA product itself? Are only the "me-toos" of the same manufacturer "covered" by an effective application within the meaning of § 107 (c)(4)(C) and thus not exempt from § 201 (p) or are no "me-too's" exempt whoever manufactures them? It seems clear that § 107 (c) was designed in general to make the new

1962 requirements applicable to drugs then on the market after a two-year grace period. Section 107 (c)(4) created an exception from this general policy. Senator Eastland explained these "transitional provisions," stating: "Established drugs which have never been required to go through new drug procedures will not be affected by the new effectiveness test insofar as their existing clauses are concerned." [6] It is true that an NDA covers a particular product or products that it names and that § 505 when applied to an NDA is personal to the manufacturer who files it. Section 505, in other words, addresses itself to drugs as individual products. But we agree with the Government that "any drug" when used in § 107 (c)(4) is used in the generic sense, which means that the "me-too's," whether products of the same or of different manufacturers "covered" by an "effective" NDA, are not exempt from the efficacy requirements of § 201 (p). If that were not true, then, as the Court of Appeals said, the "me-too's" of one manufacturer covered by an NDA of another manufacturer would be exempt from regulation, while the "me-too's" of the manufacturer holding the NDA could be regulated. That seems to be a reading of § 107 (c)(4) that is discriminatory and needlessly so. For it is avoided by taking "any drug" in that subsection as a generic term. The transitional nature of § 107 (c) works in that direction. A reading to exclude all "me-too" drugs from the word "covered" as used in § 107 (c)(4) would create a hiatus in the regulatory scheme for which there seems to be no cogent reason. We find no persuasive reason to resolve the ambiguities in favor of the manufacturers so that pre-existing pioneer drugs would be subject to the new efficacy requirements but the "me-too's" which often do equal service for them would escape

[6] 108 Cong. Rec. 17366.

the thrust of the 1962 amendments. That resolution of the ambiguities would largely leave pre-1962 drugs of unproved effectiveness untouched by the 1962 amendments and perpetuate a competitive contest in the marketing of ineffective pre-1962 drugs. FDA would, of course, have authority to pursue that category of drugs under the misbranding provisions of the Act. But that slow, cumbersome method is utterly unsuited to the need. We decline to attribute such a self-defeating purpose to the Congress. After all, the 1962 regulatory scheme proposes administrative control through an expert agency in lieu of the more cumbersome 1938 devices, as a result of which, "good medical practice is hampered, and the consumer is misled until, perhaps years later, the Government has gathered the necessary evidence to sustain its burden of proving the violation in court." [7]

Petitioner, focusing on prescription drugs,[8] contends that the construction of § 107 (c)(4) urged by the Government would make the exemption meaningless. Prescription drugs, as FDA points out, are not likely to have come on the market subsequent to 1938 without being a "new drug" for some time. But the over-the-counter (OTC) drugs, known as the proprietaries, are often made up of old, established ingredients. Such products, coming on the market for the first time between 1938 and 1962, might never have been subject to new drug regulation. If so, they would be entitled to the exemption provided by § 107 (c)(4). Senator Kefauver, the main

[7] H. R. Rep. No. 2464, 87th Cong., 2d Sess., p. 3.

[8] Prescription drugs, as defined by § 503 (b), 21 U. S. C. § 353 (b), include any drug for human use which (A) is habit forming; (B) "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug"; or (C) is limited to prescription use in the application under § 505.

sponsor of the 1962 Act, deplored the absence in an earlier bill of the failure to submit proprietaries on the market to tests of efficacy. He said:

> "Effectiveness, as well as safety, should apply to new proprietary drugs, but proprietaries now on the market are not to be subject under the present bill to the provisions requiring them, upon notice by the FOA [*sic*], to support their claims for effectiveness. I think they should be so required. That is a matter which can be remedied in conference or by other legislation." [9]

It can be inferred from this statement that prescription drugs on the market were to be subjected to the efficacy requirements. If the 1962 amendments are to be comprehensively meaningful, we decline to read § 107 (c) (4) so as to provide a loophole so that the manufacturers can go on marketing drugs previously subject to new drug regulation without demonstrating by the new statutory standards that they are effective as claimed.

The second question presented by this case is whether an applicant could have withdrawn or "deactivated" an NDA prior to the 1962 amendments so that its drug was no longer "covered by an effective application" and thus is now exempt from efficacy regulation by reason of § 107 (c)(4). Petitioner in 1961 had stated in a letter to the Director of New Drug Branch of the Bureau of Medicine in FDA that "[i]t is our recollection that the C. V. P. class of products were no longer considered to be new drugs . . . ." Petitioner in 1961 also stopped filing supplemental information as required by regulation with regard to the products for which NDA's had become effective. It claims that these acts were sufficient to

[9] 108 Cong. Rec. 17368.

withdraw the NDA's and to bring its products within the exemption.

Initially, we repeat that the legislative history indicates that it was Congress' purpose to exempt only those drugs that never had been subject to the new drug regulation.[10] Quite obviously, any drug for which an NDA once had been effective does not fall within that category.

Congress rejected an approach that would have exempted from the efficacy requirements of the 1962 amendments all drugs then marketed which had become generally recognized as safe. It now would be irrational for us to construe § 107(c)(4) of the amendments to exempt a drug merely because the manufacturer had taken some formal steps totally unrelated to the drug's effectiveness to indicate that the drug was no longer a "new drug" under the pre-1962 standards. The result would be that some drugs for which an NDA had been filed would be subject to the efficacy requirements and some would not, even though one could not differentiate between the drugs on the grounds of effectiveness. For example, 43 NDA's had been filed with respect to bioflavonoids and related compounds. There is no reason to believe that any product is more or less effective than another. According to the Solicitor General, the "state of activity, inactivity, or withdrawal" of the applications varied from one to the next when the 1962 amendments became effective. It would be totally inconsistent with the statutory scheme and the policy underlying the 1962 amendments, as well as patently unjust, to conclude that some manufacturers could continue to market their bioflavonoid products, but others could not. We cannot attribute such

[10] See S. Rep. No. 1744, 87th Cong., 2d Sess., pt. 2, p. 8; H. R. Rep. No. 2464, 87th Cong., 2d Sess., 12; H. R. Rep. No. 2526, 87th Cong., 2d Sess., 22-23; 108 Cong. Rec. 17366.

an intention to Congress and, accordingly, cannot agree with petitioner that its NDA's had been withdrawn prior to 1962 so that its bioflavonoid products were no longer "covered by an effective application."

Affirmed.

MR. JUSTICE BRENNAN took no part in the consideration or decision of this case. MR. JUSTICE STEWART took no part in the decision of this case.