FDA "NEW DRUG" APPROVAL PROCEDURES: THE IMPACT OF JUDICIAL INTERVENTION ON PUBLIC AND PHARMACEUTICAL COMPANY INTERESTS

The use of generic drug products[1] as a substitute for their more expensive brand name[2] counterparts is being encouraged through legislative action in many states.[3] However, whether the public can

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[1] When an innovative pharmaceutical company introduces to the market a new drug ingredient which has been approved by the FDA, all subsequent drug products using this particular ingredient are generic drug products. Knapp, *Issues of Generic Substitution*, 34 FOOD DRUG COSM. L.J. 98 (1979).

Dorland's Illustrated Medical Dictionary defines generic as "nonproprietary; denoting a drug name not protected by a trademark, usually descriptive of its chemical structure." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 639 (25th ed. 1974).

Stedman's Medical Dictionary defines a generic name as follows:

> 2. In the drug and commercial fields, generic names are synonomous with, albeit a misnomer for, nonproprietary names. Nonproprietary names apply to individual substances regardless of manufacturer, whereas proprietary or trademark names usually apply to preparations (which usually incorporate several substances) and are often limited to use by one manufacturer. Nonproprietary names, like trademarks, are almost always coined designations and are derived in many different ways. Nonproprietary names often have an "official" connotation, since they are recognized or recommended by governmental agencies (e.g., Federal Food and Drug Administration) as well as by quasi-official organizations (National Formulary, U.S. Pharmacopeia, U.S. Adopted Names Council, or the World Health Organization); similar names coined without official sanction are sometimes referred to as trivial names.

STEDMAN'S MEDICAL DICTIONARY 576 (23d ed. 1976).

[2] Brand names are used by manufacturers to distinguish their drug products from other identical products. Thus, one FDA approved drug product may be marketed by several different companies under several different brand names. LAWYERS' MEDICAL CYCLOPEDIA § 3A.5a, at 61 (Supplementary Service 1980); THE MERCK MANUAL 1948-49 (13th ed. 1977). Brand name drug products are often referred to as proprietary drug products. *Dorland's Illustrated Medical Dictionary* defines proprietary as:

> any chemical, drug, or similar preparation used in the treatment of diseases, if such article is protected against free competition as to name, product, composition, or process of manufacture by secrecy, patent, trademark, or copyright, or by any other means.

DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 1266 (25th ed. 1974).

[3] Pharmadyne Laboratories, Inc. v. Kennedy, 466 F. Supp. 100, 106 (D.N.J. 1979), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979). Judge H. Curtis Meanor acknowledged that approximately 31 state legislatures have enacted generic drug substitution laws. *Id.* New Jersey's code provides that if a prescription form for a brand name drug is marked, "substitution possible," the pharmacist is obliged to consult a list of approved interchangeable drugs and to fill the prescription with a less expensive generic drug equivalent. N.J. STAT. ANN. §§ 24:6E-1, -6,-7 (West Cum. Supp. 1980-1981). *See generally* Knapp, *Issues of Generic Substitution*, 34 FOOD DRUG COSM. L.J. 98 (1979); McCarey, *Generic Substitution Policy*, 34 FOOD DRUG COSM. L.J. 103 (1979); Ruggieri, *Manufacturers' View of Generic Substitution Legislation*, 34 FOOD DRUG COSM. L.J. 108 (1979); LAWYERS' MEDICAL CYCLOPEDIA § 3A.5a, at 61-62 (Supplementary Service 1980).

rely on a generic drug product being as safe and effective as the drug it replaces is questionable.[4] The Food and Drug Administration (FDA) is responsible for approving drugs as safe and effective for marketing.[5] This FDA pre-market clearance applies only to "new drugs."[6] Thus, the issue arises: is a generic drug product a "new drug" which must be approved by the FDA for marketing?[7]

The growing conflict on this issue is evident from recent case law.[8] Generic drug companies contend that generic drugs are not new drugs.[9] Specifically, they interpret the new drug definition in 21 U.S.C. § 321(p)[10] to require that an FDA approved brand name drug and its alleged generic drug equivalent have identical active ingredients in order to be classified as an old drug.[11] Such a determination renders bioavailability (ability of drug to be absorbed by a person's bloodstream), bioequivalence (ability of two or more drugs to be absorbed equally into one's bloodstream), and quality control problems irrelevant.[12]

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[4] United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699, slip op. at 6 (D.N.J. Jan. 20, 1981); United States v. Generix Drug Corp., 498 F. Supp. 288, 291 (S.D. Fla. 1980). *See* LAWYER'S MEDICAL CYCLOPEDIA § 3A.5a at 61 (Supplementary Service 1980); Knapp, *Issues of Generic Substitution*, 34 FOOD DRUG COSM. L.J. 98 (1979); Ruggieri, *Manufacturers' View of Generic Substitution Legislation*, 34 FOOD DRUG COSM. L.J. 108 (1979).

[5] Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301-92 (1976 & Supp. I 1977).

[6] *Id.* § 355(a). Section 355 states:

> No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an [NDA] filed pursuant to subsection (b) of this section is effective with respect to such drug.

Id.

The FDA considers the term "new drug" synonymous with "new drug product." For the remainder of this comment, the term "drug" will mean a "drug product" unless specified otherwise. *See* Premo Pharmaceutical Laboratories, Inc. v. United States, 475 F. Supp. 52, 54-55 (S.D.N.Y. 1979); Pharmadyne Laboratories, Inc. v. Kennedy, 466 F. Supp. 100, 103 (D.N.J. 1979); notes 98-100 *infra* and accompanying text. For statutory definition of "new drug," see notes 29 & 46 *infra*.

[7] Premo Pharmaceutical Laboratories, Inc. v. United States, 629 F.2d 795, 798 (2d Cir. 1980); United States v. Articles of Drug (Lannett Co.), 585 F.2d 575, 577-79 (3d Cir. 1978); United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699, slip op. at 2 (D.N.J. Jan. 20, 1981); United States v. Generix Drug Corp., 498 F. Supp. 288, 290 (S.D. Fla. 1980); Pharmadyne Laboratories, Inc. v. Kennedy, 466 F. Supp. 100, 101 (D.N.J. 1979), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979).

[8] *See* note 7 *supra*.

[9] Premo Pharmaceutical Laboratories, Inc. v. United States, 629 F.2d 795, 799 (2d Cir. 1980); United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699, slip op. at 7 (D.N.J. Jan. 20, 1981); United States v. Generix Drug Corp., 498 F. Supp. 288, 291 (S.D. Fla. 1980).

[10] For definition of new drug, see notes 29 & 46 *infra*.

[11] *See* note 9 *supra*.

[12] United States v. Articles of Drug (Lannett Co.), 585 F.2d 575, 578, 580, 582, 584 (3d Cir. 1978); United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699, slip op. at 7 (D.N.J. Jan. 20, 1981); Pharmadyne Laboratories, Inc. v. Kennedy, 466 F. Supp. 100, 102 (D.N.J. 1979), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979). For detailed definitions of

The FDA counters that drug ingredients are trade secrets making exact duplication uncertain; that the Code requires both the inactive and the active ingredients to be the same; and that regardless of ingredient exactness, bioinequivalence between two drugs may possibly be enhanced by the manufacturing process and the sources from which the drugs are obtained.[13]

The legislative history of the present Federal Food, Drug, and Cosmetic Act[14] began when President Theodore Roosevelt signed the Food and Drugs Act of 1906,[15] which banned the manufacture and interstate commerce of adulterated or misbranded drugs.[16] Any person who violated the Act could be found guilty of a misdemeanor and any product that was examined and failed to meet the requisite safety standards was subject to seizure through libel actions.[17]

In *United States v. Johnson*[18] the 1906 Act was narrowly construed by the Supreme Court, thereby severely limiting it from protecting the public in the manner intended.[19] The Court held that the Act's drug labeling provisions prohibited false statements about the drug's ingredients, but did not prohibit false therapeutic claims.[20]

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bioavailability and bioequivalence, see *Bioavailability and Bioequivalence Requirements*, 21 C.F.R. § 320.1(a) & (e) (1980); LAWYERS' MEDICAL CYCLOPEDIA § 3A.5a, at 62 (1980 Supplemental Service); THE MERCK MANUAL 1782, 1783 (13th ed. 1977); *See* Cabana, *Bioavailability/Bioequivalence*, 32 FOOD DRUG COSM. L.J. 512 (1977).

[13] Plaintiff's Post Hearing Memorandum in Support of Government's Motion for Preliminary Injunction at 43, United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699 (D.N.J. Jan. 20, 1981). *See* United States v. Articles of Drug (Lannett Co.), 585 F.2d 575, 580 (3d Cir. 1978); United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699, slip op. at 3, 5, 6 (D.N.J. Jan. 20, 1981); United States v. Generix Drug Corp., 498 F. Supp. 288, 290-91 (S.D. Fla. 1980); Pharmadyne Laboratories, Inc. v. Kennedy, 466 F. Supp. 100, 104 (D.N.J. 1979), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979).

[14] 21 U.S.C. §§ 301-92 (1976 & Supp. I 1977). For discussion on legislative background, see S. REP. No. 321, 96th Cong., 1st Sess. 1 (1979); 40 Fed. Reg. 26,142 (1975); Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185 (1971); Note, *The Drug Amendments of 1962: How Much Regulation?*, 18 RUTGERS L. REV. 101 (1963). For history of FDA regulation of me-too drugs, see Benfield, *Life After* Lannett: *Open Season for "Me-Too" Drugs?*, *34* FOOD DRUG COSM. L.J. 212, 213-17 (1979). For case law discussion on prior law, see Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); United States v. Articles of Drug (Lannett Co.), 585 F.2d 575 (3d Cir. 1978); Hoffman-LaRoche, Inc. v. Weinberger, 425 F. Supp. 890 (D.D.C. 1975).

[15] Ch. 3915, 34 Stat. 768 (1906).

[16] *Id.* §§ 1-2. An adulterated drug would be one which was sold under a recognized name in the United States Pharmacopoeia or National Formulary, but which failed to meet the standards of strength, quality or purity set forth within. *Id.* § 7. A drug was misbranded if it was "an imitation of or offered for sale under the name of another product," if the contents of the drug as originally produced were altered in any manner, or if the product's label failed to indicate any certain quantities such as alcohol or narcotics. *Id.* § 8.

[17] *Id.* §§ 1, 2, 10.

[18] 221 U.S. 488 (1911).

[19] *Id.* at 497-98.

[20] *Id.*

The outcome from this ruling could have been the creation of a new and legal market for the sale of false cures for any imaginable disease.[21] In light of this possibility, President Taft asked Congress for appropriate protective legislation.[22] Congress responded with the Food and Drugs Act Amendment of 1912,[23] which declared as misbranded any drug that was not effective in aiding in the cure of the disease for which it was labeled.[24] While the 1912 Act's labeling provisions appeared to protect the public's rights, enforcement of the Act had a major drawback. A successful action by the government required that it show the therapeutic claim to be both false and fraudulent.[25] The fraud requirement in the Act was difficult to prove since it involved an intent to deceive.[26]

Spurred by the Elixir of Sulfanilamide disaster which resulted in approximately one hundred deaths when a chemist tested the wonder drug for flavor, fragrance, and appearance but neglected to test for safety,[27] Congress substantially revised the government's authority in the control of drugs by passing the Federal Food, Drug, and Cosmetic Act of 1938.[28] This Act defined a "new drug" as one not generally recognized among experts as safe.[29] Prior to a new drug receiving

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[21] *Id.* at 501 (Hughes, J., dissenting).

[22] S. REP. No. 321, 96th Cong., 1st Sess. 1, 2 (1979). President Taft had urged Congress saying:

> There are none so credulous as sufferers from disease. The need is urgent for legislation which will prevent the raising of hopes of speedy cures of serious ailments by misstatement of facts as to worthless mixtures on which the sick will rely while their disease progresses unchecked.

Id.

[23] Ch. 352, 37 Stat. 416 (1912).

[24] *Id.* § 8.

[25] *Id.* The amended statute reads as follows:

> Third. If its package or label shall bear or contain any statement, design, or device regarding the curative or therapeutic effect of such article or any of the ingredients or substances contained therein, which is false *and* fraudulent.

Id. (emphasis added).

[26] S. REP. No. 321, 96th Cong., 1st Sess. 1, 2-3 (1979).

[27] *Id.* at 3; United States v. Premo Pharmaceutical Laboratorties, Inc., No. 80-699, slip op. at 4 (D.N.J. Jan. 20, 1981); 40 Fed. Reg. 26,142 (1975).

[28] Ch. 675, 52 Stat. 1040 (1938).

[29] A new drug was defined as:

> (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 of drugs, as safe 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 enactment of this Act 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
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> (2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so

pre-market clearance, the Act required that a New Drug Application (NDA) be submitted which would set forth the drug's safety.[30] An NDA would become effective automatically after sixty days unless the FDA took action to deny approval on grounds of insufficient evidence of safety.[31] Further, if an approved drug were subsequently found to be unsafe, its NDA could be suspended after due notice and an opportunity for hearing.[32] To enforce the decision concerning a drug which violated the Act, the government could sue to enjoin, prosecute, seize or condemn.[33] An old drug previously subjected to the 1906 Act could escape the NDA requirement.[34] However, if the government believed that an old drug was unsafe, it could, through court action and upon meeting the burden of proof that the drug was unsafe, have the drug removed from the market.[35]

The FDA's implementation of the 1938 Act was slowed because of limited resources with which to review NDA's and an ever increasing number of the applications. Consequently, the FDA established a practice whereby products which were identical, related or similar to approved NDA's were considered marketable as old drugs.[36] Such an identical, related or similar drug is commonly referred to as a "me-too" drug.[37] The manufacturer would either not submit an NDA after concluding one was unnecessary since an NDA was already in effect for the drug it was copying, or would receive an advisory

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recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Id. § 201(p).

[30] *Id.* § 505. The statute provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) is effective with respect to such drug." *Id.* § 505 (a). Although the statute does not express the terminology, new drug application or NDA, such reference is now acceptable. 40 Fed. Reg. 26,142 (1975).

[31] Ch. 675, § 505(c)-(d), 52 Stat. 1040 (1938). The FDA could get the 60 day period extended to 180 days upon notice to the manufacturer that additional investigation was needed. *Id.* § 505(c). If an NDA was disapproved, the manufacturer was entitled to due notice and the opportunity for a hearing as to the lack of evidence of the drug's safety. *Id.* § 505(d).

[32] *Id.* § 505(e). The 1938 Act gave the Secretary of Agriculture the authority to suspend a drug's application. *Id.* Presently, the Secretary of Health, Education and Welfare has such authority.

[33] *Id.* §§ 301-04.

[34] *Id.* § 201(p)(2).

[35] S. REP. No. 321, 96th Cong., 1st Sess. 1, 4 (1979).

[36] 40 Fed. Reg. 26,142-43 (1975). *See* Benfield, *supra* note 14, at 213.

[37] Note 36 *supra*. *See* Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 614 (1972). A "me-too" drug product, often referred to interchangeably with a generic drug product, is distinguishable. A generic drug product contains an FDA approved drug ingredient while a me-too drug product is a copy of the FDA approved drug product. Thus, a me-too is always a generic, but a generic is not necessarily a me-too.

opinion from the FDA that an NDA was not required for that particular drug.[38]

There were estimates that from five to thirteen me-too drugs were on the market for every FDA approved drug. Since the law did not require manufacturers to register their drug products with the FDA and no general census of the products on the market existed, the FDA could not effectively regulate me-too drugs except through occasional random proceedings.[39] Furthermore, the safety of these me-too drugs was questionable.[40]

Moved by the thalidomide tragedy, Congress passed the Drug Amendment of 1962.[41] Thalidomide, which prior to the Amendment was marketed in Europe and prescribed for use by pregnant women, could result in the birth of grossly deformed babies.[42] Fortunately, since the drug was not approved by the FDA, its use in America was restricted.[43] It was, however, distributed for experimental purposes and a survey revealed that of 3,879 users, nine gave birth to a malformed child.[44] With respect to new drugs, the 1962 Amendment made three important changes: first, the assumption that the NDA was approved unless the FDA notified the manufacturer to the contrary was reversed so that an NDA required affirmative approval by the FDA;[45] second, the weakness of the 1938 Act in not requiring a showing of a drug's efficacy before approval was modified so that a "new drug" had to be proven effective as well as safe;[46] and third, the

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[38] *See* note 36 *supra*.

[39] *See* note 36 *supra*.

[40] *See* notes 65-138 *infra* and accompanying text.

[41] Pub. L. No. 87-781, 76 Stat. 780 (codified at 21 U.S.C. §§ 301-92 (1976)).

[42] S. REP. No. 321, 96th Cong., 1st Sess. 1, 7 (1979). *See* Pharmadyne Laboratories, Inc. v. Kennedy, 466 F. Supp. 100, 105 (D.N.J. 1979), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979).

[43] Pharmadyne Laboratories, Inc. v. Kennedy, 466 F. Supp. 100, 105 (D.N.J. 1979), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979). If the United States had marketed thalidomide, it was estimated the result would have been 10,000 deformed American babies. *Id.* at 105 n.9.

[44] S. REP. No. 321, 96th Cong., 1st Sess. 1, 7 (1979).

[45] Pub. L. No. 87-781, § 104(a), 76 Stat. 780 (codified at 21 U.S.C. § 355(a) (1976)). The FDA has 180 days or such additional time as is agreed upon to approve the application or give notice and the opportunity for a hearing as to the approvability of the drug application. *Id.* § 104(b) (codified at 21 U.S.C. § 355(c) (1976)). The significance of the 180 day period is supported by evidence that the median time for an FDA approval for a new drug in 1979 was 23 months. S. REP. No. 321, 96th Cong., 1st Sess. 1, 12 (1979).

[46] Pub. L. No. 87-781, § 102(a), 76 Stat. 781 (codified at 21 U.S.C. § 321(p)(1) 1976)) provides:

> (p) The term "new drug" means—
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> (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

manufacturer was required to prove through substantial evidence that its drug was safe and effective.[47]

The 1962 Amendment included transitional provisions that drugs which had pre-1962 NDA approvals were assumed approved unless the FDA asked for proof of effectiveness,[48] in which case the manufacturer had a two-year grace period to show by substantial evidence its product's effectiveness.[49] If the FDA found there was insufficient proof, the NDA could be removed.[50] A grandfather clause exempted pre-1962 drugs which had never been subjected to NDA requirements and were generally recognized as safe for use under the efficacy standard.[51] Me-too drugs which met this grandfather clause requirement, however, were not automatically exempt, because the FDA reasoned that the efficacy ruling and resulting marketability of these drugs were dependent upon the FDA's decision for the drug being copied.[52]

The implementation of the efficacy provisions for pre-1962 drugs was an overwhelming task. The FDA already had all it could handle in processing current NDA's, without having to find the resources to review the effectiveness of the thousands of pre-1962 NDA's. The first step toward review was not taken until 1964 when the FDA requested that all manufacturers of pre-1962 approved NDA's submit evidence in support of their efficacy claims. In 1966 a contract was entered into with the National Academy of Science-National Research Council

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> 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 conditons of its use; or
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> (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.

Id. § 321(p).

[47] Pub. L. No. 87-781, § 102(c), 76 Stat. 781 (codified at 21 U.S.C. § 355(d) (1976)). "Substantial evidence" is defined in terms of adequate and well controlled studies by experts. *Id.*

[48] *Id.* § 107(c)(2) (codified at 21 U.S.C. § 301 (1976)).

[49] *Id.* § 107(c)(3)(B) (codified at 21 U.S.C. § 355 (1976)).

[50] Ch. 675, § 505(e), 52 Stat. 1040 (1938).

[51] Pub. L. No. 87-781, § 107(c)(4), 76 Stat. 789 (codified at 21 U.S.C. § 355 (1976)). The grandfather clause, § 107(c)(4), is usually applied only to drugs introduced between 1938 and 1962, because pre-1938 drugs have their own grandfather clause, § 201(p) (codified at 21 U.S.C. § 321(p) (1976)), which exempts all such drugs from new drug status.

[52] 40 Fed. Reg. 26,142, 26,144 (1975); Note, *Drug Efficacy and the 1962 Drug Amendment*, 60 GEO. L.J. 185, 203 (1971). Four Supreme Court decisions supported the FDA treatment. U.S. Pharmaceutical Corp. v. Weinberger, 412 U.S. 655 (1973); Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645 (1973); Ciba Corp. v. Weinberger, 412 U.S. 640 (1973); Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973).

(NAS-NRC) to handle the enormous retrospective review. Decisions by the NAS-NRC panel which was comprised mainly of physicians affiliated with academic institutions were purely advisory, for only the FDA had statutory authority to determine efficacy. In 1968 the NAS-NRC released its findings to the FDA classifying drugs as "probably effective," "possibly effective," "effective, but" and "effective." Relying on these findings, the FDA published Drug Efficiency Study Implementation (DESI) notices in the Federal Register for those drug products which were considered ineffective and therefore were having their NDA approvals removed subject to the manufacturer's continued lack of efficacy evidence and a hearing.[53] Despite rigorous court challenges by manufacturers, the Supreme Court in 1973 reinforced the authority of the FDA to determine drug status as new or old and to apply DESI notices for approved drugs to their me-too copies.[54]

The 1975 case of *Hoffman-LaRoche, Inc. v. Weinberger*[55] signaled a turning point in the FDA's interpretation of the Food, Drug, and Cosmetic Act. Hoffman-LaRoche sought a declaration that the FDA's policy of allowing new drugs into the marketplace without first receiving an approved NDA violated the statutory requirements in the Act and therefore the FDA should be enjoined from such practice.[56] Based on this premise, Hoffman-LaRoche challenged the existing approval procedures for me-too drugs. The FDA would request Abbreviated New Drug Applications (ANDA) instead of full NDA's for me-too drugs of NDA-approved drugs which were covered by a DESI notice. Most important was the fact that the me-too drug could be marketed while waiting for the decision on its ANDA.[57] Specifically, Hoffman-LaRoche reacted to a competitor making a me-too of one of its NDA

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[53] 40 Fed. Reg. 26,142, 26,143-44 (1975); Note, *supra* note 52, at 207-10. *See* Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); American Pub. Health Ass'n v. Veneman, 349 F. Supp. 1311, 1314 (D.D.C. 1972).

[54] *See* note 52 *supra*.

[55] 425 F. Supp. 890 (D.D.C. 1975).

[56] *Id.* at 891. Hoffman-LaRoche claimed violations of 21 U.S.C. §§ 331 (introduction of drug into interstate commerce in violation of § 355), and 355 (requirement that new drug submit an NDA).

[57] 425 F. Supp. at 892. *See* 40 Fed. Reg. 26,142, 26,145 (1975) where the Commissioner of Food and Drugs stated:

> It is not feasible from an administrative standpoint to handle all abbreviated NDA's expeditiously, in view of the lack of resources available to the agency. Many of the drug products involved have been determined to be safe and effective when labeled in accordance with the applicable DESI notice and present no bioavailability or special manufacturing problems. To require that an abbreviated NDA be approved prior to the marketing of such drug products would necessarily disrupt the distribution of important human prescription drugs, reduce competition in a way directly contrary to the public interest, and serve no public health purpose.

Id.

approved drugs. Then, while Hoffman-LaRoche started suit against the competitor for infringement of its patent, and prior to FDA approval of the competitor's ANDA, the competitor placed the me-too drug on the market.[58] Hoffman-LaRoche argued that clear statutory directives, coupled with congressional intent for public safety, dictated that a drug cannot be marketed prior to FDA approval of its NDA or ANDA.[59]

The FDA countered that its resources were taxed, that the need to police the distribution of me-too drugs was minimal, and that proving such drugs were new drugs under the definition in 21 U.S.C. § 321(p)[60] would be difficult.[61] Furthermore, the FDA claimed that to deny immediate marketing would give unfair competitive advantage to manufacturers of me-too drugs marketed prior to DESI notice. They would be able to stay on the market while all other competitors would have to refrain while awaiting approval of an ANDA.[62]

The court rejected the FDA's arguments and held that the FDA policy of permitting new drugs to be marketed without an NDA contravened "clear statutory requirements of preclearance," was "not within the intendment of 1962 new drug amendments," and violated the FDA's own regulations.[63] This ruling resulted in the FDA reversing its policy and instituting many actions to enjoin manufacturers from marketing me-too drugs.[64]

The initial case to explore the question of whether a generic drug product is a new drug product, thereby requiring an NDA or an ANDA, was *United States v. Articles of Drug (Lannett Co.).*[65] The government brought an action to condemn and destroy certain drug products manufactured by Lannett because they were misbranded.[66] Instead of directly attacking Lannett's drugs by claiming they were "new drugs," and thereby having the difficult burden of affirmatively proving that 21 U.S.C. § 321(p) would apply, the government reasoned that the drugs, being prescription drugs, were misbranded for they failed to meet the requirement that the labeling be approved by an NDA.[67] Thus, by using the misbranding section which requires a

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[58] 425 F. Supp. at 891.

[59] *Id.* at 893.

[60] For definition of new drug, see notes 29 & 46 *supra.*

[61] 425 F. Supp. at 892-93; 40 Fed. Reg. 26,142, 26,145 (1975).

[62] 425 F. Supp. at 893.

[63] *Id.* at 894.

[64] *See* notes 62-63 *supra* & 65-124 *infra* and accompanying text.

[65] 585 F.2d 575 (3d Cir. 1978).

[66] *Id.* at 576.

[67] *Id.* at 579. A drug's label must bear "adequate directions for use," 21 U.S.C. § 352(f)(1) (1976), which are defined as "directions under which the layman can use a drug safely and for

lesser burden of proof than the new drug section, the government hoped to attain the same result, that an NDA would be required.[68]

Lannett's drugs had received marketing clearance under the 1938 Act and by 1962 were widely used by the medical profession. However, pursuant to the efficacy requirement in the 1962 Act, Lannett had received DESI notices requesting that ANDA's be filed with evidence of effectiveness of its drug products. Lannett filed ANDA's but continued to market its products. As this was in conflict with the *Hoffman-LaRoche* decision, whereby a manufacturer must cease marketing until its ANDA is approved, the government brought the condemnation suit.[69]

While the government asserted that Lannett's drugs were new, it further argued that Lannett was precluded from now challenging the FDA's new drug status claim since Lannett had failed to challenge the FDA's earlier DESI notices that the drugs were new. The district court agreed, but the Court of Appeals for the Third Circuit reversed, stating that Lannett could not be denied an opportunity to challenge the FDA's new drug determination since Lannett had not previously been in a position to do so.[70] Although the court of appeals limited the reversal to this procedural issue, in what has been subsequently construed as highly controversial dictum,[71] the court addressed the issue of whether or not Lannett's drug products were in fact "new."[72]

The court's dictum noted that a new drug is any drug that is not generally recognized by experts as safe and effective. The FDA conceded that the generic drug ingredients of Lannett's drugs were recognized as safe and effective; however, urging possible bioavailability, bioequivalence and quality control problems, the government contended that each specific drug product must be evaluated on the basis of its individual safety and efficacy.[73] Lannett countered that since its drug products were already admitted by the FDA to be generically the same as FDA approved drugs, the statutory requirements for an old drug were satisfied, thus rendering bioavailability, bioequivalence

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the purposes for which it is intended." 21 C.F.R. § 201.5 (1980). The government contended that "prescription drugs, by their very nature could not be used to inform the layman." 585 F.2d at 579. Thus, unless Lannett's drugs were "exempt from the 'adequate directions' requirements," *id.*, through proof that their drugs had approved NDA's or were generally recognized as safe and effective, 21 C.F.R. § 201.100(c)(2) (1980), they would be misbranded. 585 F.2d at 579.

[68] 585 F.2d at 576, 579. For discussion of the *Lannett* decision, see Benfield, *supra* note 14 at 217-24.

[69] 585 F.2d at 577-79.

[70] *Id.* at 580-81.

[71] *See* notes 81-138 *infra* and accompanying text.

[72] 585 F.2d at 582-84.

[73] *Id.* at 582.

and quality controls irrelevant in the determination of newness.[74] The court of appeals agreed with Lannett. Referring to the FDA's own regulations on new drugs, the court commented on the lack of any "reference to anything like quality control or a specific product's capabilities,"[75] and noted how the regulations portray newness as a "function of the novelty of a particular formulation, including a novel composition, combination, dosage or administration."[76] Through case law,[77] the court found additional support that generic versions of FDA approved drugs, whether identical to, or the combination of recognized ingredients not forming a new drug, and regardless of differing manufacturing methods, should be treated the same for purposes of determining new drug status. After applying the requisite regulations, case law and the concession that Lannett's drugs were generically identical to approved drug products, the court concluded that Lannett's products could not logically be considered new drug products.[78]

The *Lannett* dictum is subject to both narrow and broad interpretations. The broad construction suggests that a drug product is not new if its generic (active) ingredients are the same as those of an FDA approved drug.[79] A narrower reading portrays a drug product as old only if its ingredients, both active and inactive, are exactly identical to those of an approved drug.[80]

The broad interpretation was applied and rejected in *Pharmadyne Laboratories, Inc. v. Kennedy*.[81] In *Pharmadyne*, the manufacturer of two me-too drug products marketed without FDA approval sought a preliminary injunction restraining the FDA from litigating their new drug status in condemnation proceedings which the government had already initiated in several other district courts.[82] The government's theory was that the me-too drugs were new drugs being marketed illegally without ANDA or NDA approval.[83] Pharmadyne replied that under *Lannett*, me-too drugs were not new drugs; and therefore, pre-market clearance was unnecessary and the

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[74] *Id.*

[75] *Id.* at 583.

[76] *Id.* For regulations see note 121 *infra*.

[77] Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); United States v. An Article of Drug . . . "Mykocert," 345 F. Supp. 571 (N.D. Ill. 1972). For further discussion of case law, see notes 126-31 *infra* and accompanying text.

[78] 585 F.2d at 582-84.

[79] United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699, slip op. at 10 (D.N.J. Jan. 20, 1981).

[80] *Id.* at 10 n.4.

[81] 466 F. Supp. 100, 101-06 (D.N.J. 1979), *aff'd on other grounds*, 596 F.2d 568 (3d Cir. 1979).

[82] *Id.* at 100-01, 101 n.2.

[83] *Id.* at 106-07.

FDA should be preliminarily enjoined from litigating the new or old drug status of its products in the condemnation action.[84]

In rejecting this broad interpretation which would have found me-too drugs marketable without preclearance, Judge H. Curtis Meanor accused the *Lannett* court of "compartmentaliz[ing] the statute."[85] In examining the new drug definition contained in 21 U.S.C. § 321(p) separately, the *Lannett* dictum was plausible; however, Judge Meanor noted that the section must be read in conjunction with 21 U.S.C. § 355.[86] Section 355 defines an NDA as containing a "full list of the articles used as components of such drug" and a "full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug."[87] Judge Meanor reasoned that components of a drug include inactive ingredients as well as active ones. Common inactive ingredients are: binders that hold a drug in tablet form; coating that allows the tablet to be swallowed; and capsules that encase the drug. These inactive ingredients may directly effect a drug's bioavailability and thereby the drug's efficacy.[88] A binder, coating or capsule that allows the drug to dissolve too quickly or too slowly can result in an overdose or an ineffective dose.[89] With these dangers in mind, Judge Meanor persuasively argued that if Congress in section 355 was concerned with the inactive ingredients and manufacturing methods in new drugs, it would also be concerned about the production of me-too drugs. Thus, reading the two sections together, it is clear that Congress intended bioavailability, bioequivalence and quality controls to be considered in the newness determination of me-too drugs.[90]

On appeal, the Court of Appeals for the Third Circuit[91] affirmed *Pharmadyne* on different grounds, thus side-stepping the conflict with its *Lannett* dictum. The court noted that the facts differed: in *Pharmadyne* the active and inactive ingredients were suspected of not being the same, whereas in *Lannett* the ingredients were identical.[92] This comment supports the narrow interpretation that if a drug product's ingredients are identical to those of an approved drug, no NDA or ANDA is needed. The government's argument as to bioavailability, bioequivalence and manufacturing differences, however, remains.

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[84] *Id.*
[85] *Id.* at 103.
[86] *Id.*
[87] 21 U.S.C. §§ 355(b)(2), 355(b)(4) (1976).
[88] 466 F. Supp. at 103-04.
[89] *Id.* at 106.
[90] *Id.* at 104.
[91] Pharmadyne Laboratories, Inc. v. Kennedy, 596 F.2d 568 (3d Cir. 1979).
[92] *Id.* at 571 n.6.

While the *Lannett* and *Pharmadyne* decisions resulted in opposite views as to the question of what is a new drug, two middle-ground opinions have been rendered. In the case of *Premo Pharmaceutical Laboratories v. United States*,[93] the newness of Premo's me-too drug Insulase, used in the treatment of diabetes, was in dispute. The active ingredient in Insulase was the same as that in an FDA approved drug, but the inactive ingredients were different.[94] In accordance with the me-too drug pre-market clearance requirement, Premo filed an ANDA; the FDA, however, denied approval requesting additional evidence of bioequivalence between the me-too and the approved drug.[95] Premo chose to ignore the request and placed Insulase on the market.[96] The government moved to seize the drug on the grounds that, without FDA approval, it was being marketed illegally. Premo responded by suing for declaratory judgment that under 21 U.S.C. § 321(p)—Insulase was not a new drug requiring approval prior to marketing. Premo contended that the term "new drug" pertained only to the active ingredient of a drug product, and since the active ingredient in Insulase was recognized as safe and effective by the FDA, Insulase was not new.[97] The district court, however, in support of its finding that "new drug" refers to both active and inactive ingredients, reasoned that drugs are defined as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man;"[98] that "articles" should be interpreted to cover both ingredients; that case law supports the consideration of both ingredients;[99] and that the differences among inactive ingredients in similar drugs may render a drug unsafe or ineffective.[100]

In contrast, the government urged that a drug should be considered new if it were not generally recognized as safe and effective, if any of its ingredients differed from the approved product, or if the drug were not bioequivalent to the approved drug.[101] The court rejected the government's approach, noting that such a view would require approval for all drugs, thereby frustrating the Act's intent to

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[93] 475 F. Supp. 52 (S.D.N.Y. 1979), *rev'd*, 629 F.2d 795 (2d Cir. 1980).

[94] 475 F. Supp. at 53.

[95] 629 F.2d at 798-99.

[96] *Id.*

[97] 475 F. Supp. at 53-54.

[98] 21 U.S.C. § 321(g)(1)(B) (1976).

[99] United States v. X-Otag Plus Tablets, 441 F. Supp. 105, 111 (D. Colo. 1977); United States v. 1,048,000 Capsules, 347 F. Supp. 768, 773 (S.D. Tex. 1972); United States v. An Article of Drug . . . "Mykocert," 345 F. Supp. 571, 575-76 (N.D. Ill. 1972).

[100] 475 F. Supp. at 54-55.

[101] *Id.* at 55.

eliminate costly and time consuming approval procedures when unnecessary.[102]

Thus, in disapproving the arguments of both parties, the court fashioned its own standard, holding that:

> when the active ingredient in a questioned drug product is the same as the active ingredient in a drug product already on the market and generally recognized as safe and effective, and when the excipients in the two drug products are different, and when the excipients in the questioned product are generally recognized individually to be safe, the manufacturer of the questioned product is entitled to a declaration that its product is not a "new drug" within the meaning of 21 U.S.C. § 321(p), only if, the evidence has shown no reasonable possibility that differences between the excipients in the recognized and questioned products will make the questioned product less safe or effective than the recognized product.[103]

Aware that the final determination as to a drug's safety and effectiveness was granted by Congress to the FDA, the court nevertheless proceeded to apply its standard to the facts. Based on Premo's bioavailability studies and scientific and medical testimony, the unconvincing efforts by the FDA to rebut Premo's credible evidence, the fact that the product's active ingredients were the same as those in an already approved product, and the fact that the inactive ingredients were perfectly safe, the court concluded that Insulase was an old drug not requiring FDA approval prior to marketing.[104]

The second middle-ground case, *United States v. Generix Drug Corp.*,[105] was a preliminary injunction proceeding by the government to stop Generix from distributing unapproved generic drug products.[106] As in *Premo*, the government argued that both the active and the inactive ingredients must be considered when determining new drug status. Generix contended that only the active ingredient was relevant.[107] The district court, in rejecting both the *Lannett* and *Pharmadyne* opinions, found the rule in *Premo* to be correct, stating that "where the government demonstrates that there is some reasonable possibility that differences between the copied drug product and the generic drug product affect the safety and effectiveness of the generic drug product," it will be considered a new drug.[108] The court

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[102] *Id.*
[103] *Id.*
[104] *Id.* at 55-57.
[105] 498 F. Supp. 288 (S.D. Fla. 1980).
[106] *Id.* at 289.
[107] *Id.* at 291.
[108] *Id.* at 293.

determined that the government had established a reasonable possibility that the Generix drugs were unsafe and ineffective and that Generix had failed to refute the claim. Therefore, the Generix drugs were classified as new.[109]

In the *Premo* and *Generix* decisions the courts assumed they could make the decision as to whether or not a drug product was in fact safe and effective. In the government's appeal of *Premo* a month after the *Generix* decision, this premise was severely criticized and the district court opinion was reversed.[110] The Court of Appeals for the Second Circuit stressed that when a conflict arises as to whether or not a drug is generally recognized by experts to be safe and effective, the court's decision should be limited to that issue.[111] Congress' intent within the Act was that the highly technical and scientific questions could more appropriately be answered through the FDA's expertise than by the courts.[112] Limiting its inquiry to the extent that Premo's Insulase was generally recognized as safe and effective, the court of appeals found Insulase to be a new drug, noting that the drug had no publicly available safety and effectiveness studies, no general consensus by experts of its safety and effectiveness, and no evidence of its use for any substantial period of time.[113]

Since there was a difference between the inactive ingredients in Insulase and the approved drug it copied, the court of appeals did not have to consider whether a me-too drug, containing active and inactive ingredients identical to those of an approved drug, would still be a new drug subject to FDA clearance.[114] This issue, however, was

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[109] *Id.* at 294.

[110] 629 F.2d 795 (2d Cir. 1980). For case law applying the *Premo* decision, see United States v. Western Serum Co., Inc., 498 F. Supp. 863 (D. Ariz. 1980) (applied general recognition of safety and effectiveness test to animal drug); United States v. Articles of Drug . . . Hormonin, 498 F. Supp. 424 (D.N.J. 1980).

[111] 629 F.2d at 803. Qualifying for the generally recognized as safe and effective exemption would consist of "'in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by substantial support in scientific literature.'" *Id.* (quoting Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 652 (1973)).

[112] 629 F.2d at 803. The legislative history of the 1962 Amendment and its relevant Senate Committee Report further supports the fact that Congress intended all new drugs to be subject to FDA preclearance. Additionally, Congress intended that the exemption from new drug status for those drugs generally recognized as safe and effective, would mean the drug company could not substitute its opinion as to its drug's newness for that of the FDA. *Id.* at 802 & n.7.

[113] *Id.* at 804. The court of appeals rejected the district court's claim that subjecting me-too drugs to FDA approval would frustrate the Act's intent of reducing costly and time consuming approval procedures. The court noted that the expense and delay had already been minimized through the grandfather clauses and the filing of ANDA's for me-too products instead of full NDA's and that the intent of the Act was to subject all drugs which were not generally recognized as safe and effective to FDA preclearance. *Id.* at 804-05.

[114] *Id.* at 805 n.9.

addressed by district court Judge Frederick B. Lacey in *United States v. Premo Pharmaceutical Laboratories, Inc.*[115]

In that case the government, alleging that eight of Premo's me-too drugs were new, sued to enjoin Premo from marketing its drugs without first providing proof of their safety and effectiveness and obtaining FDA approval.[116] Premo contended that since the active ingredients, and in some products the inactive ingredients, were identical to FDA approved drugs, its drugs were not new.[117] The government countered that even if the active and inactive ingredients were the same, differences between the sources of the active ingredients and the manufacturing methods used could result in differences in safety and effectiveness between two manufacturers' products. Further, the government reasoned that since physicians and patients generally consider the generic and approved drug to be equivalent in safety and effectiveness and often substitute the generic drug for the approved drug because of its relative inexpensiveness, it was imperative that the two drugs be in fact equivalent in safety and effectiveness or bioequivalent.[118] In support of the government's claim, the court received extensive pharmacological testimony revealing that a drug's bioavailability can be effected by the "particle size and crystalline form of the active ingredient; the choice of inactive ingredients . . .; the facilities and controls used in the manufacture and processing of the drug; and the environmental conditions during manufacture and storage."[119]

Judge Lacey's opinion set forth a strong argument undercutting the two principal points relied on in the *Lannett* decision.[120] First, he disagreed with the *Lannett* court's interpretation that the FDA's own regulations did not support its view.[121] Reading 21 C.F.R. §§ 310.3(h)(1) and 310.3(h)(5) together, Judge Lacey noted that regardless of an inactive drug's ingredient being generally recognized for its

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[115] No. 80-699 (D.N.J. Jan. 20, 1981).

[116] *Id.* slip op. at 2. The government claimed Premo was in violation of 21 U.S.C. § 355(a), which states:

> No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an [NDA] filed pursuant to subsection (b) of this section is effective with respect to such drug.

Id.

[117] No. 80-699, slip op. at 2, 7.

[118] *Id.* at 3, 6.

[119] *Id.* at 7. For discussion of bioavailability testimony. see *id.* at 7-9. *See also* Findings of Fact, *id.* at 21-51.

[120] *Id.* at 14-15; Lannett, 584 F.2d at 583-84. For a discussion of *Lannett*, see notes 65-80 *supra* and accompanying text.

[121] No. 80-699, slip op. at 14-15. The relevant FDA regulations are as follows:

> (h) The newness of a drug may arise by reason (among other reasons) of:

safety and effectiveness for a particular use, if the ingredient were included in another product for a "new use," it would follow that a generic drug containing an inactive ingredient different from that in the approved drug it copied would be a new drug.[122] Also, based on section 310.3(h)(2), Judge Lacey stated that if the generic drug does not have both active and inactive ingredients identical to those of the approved drug, the resulting combination would be new, thus making the generic drug new.[123] Furthermore, assuming both the active and inactive ingredients were identical to those in the approved drug, section 310.3(h)(3) supports the Judge's position that possible differences in ingredient proportions could effect the drug's safety and effectiveness resulting in the generic drug being a new drug.[124] Thus, the FDA rules, urged by *Lannett* as "powerful evidence" against the FDA's position, can clearly be read in a reasonable and favorable light for the government.[125]

Secondly, Judge Lacey distinguished the two cases on which the *Lannett* court relied.[126] The *Lannett* court read *United States v. An Article of Drug . . . "Mykocert"*[127] as defining a new drug determination to concern only the active ingredient, but failed to acknowledge *Mykocert*'s overriding analysis that if experts disagreed as to a drug's safety and effectiveness, the drug would be considered new.[128] *Lannett*'s reliance on *Weinberger v. Hynson, Westcott & Dunning, Inc.*,[129] was also rejected using the analysis presented in *Pharma-*

(1) The newness for drug use of any substance which composes such drug, in whole or in part, whether it be an active substance or a menstruum, excipient, carrier, coating, or other component.

(2) The newness for drug use of a combination of two or more substances, none of which is a new drug.

(3) The newness for drug use of the proportion of a substance in a combination, even though such combination containing such substance in other proportion is not a new drug.

(4) The newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body.

(5) The newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug.

21 C.F.R. § 310.3 (h)(1)-(5) (1980).

[122] No. 80-699, slip op. at 15.

[123] *Id.*

[124] *Id.*

[125] *Id. See* Lannett, 585 F.2d at 583.

[126] No. 80-699, slip op. at 12-15 & 14 n.6a. *See* Lannett, 585 F.2d at 583-84.

[127] 345 F. Supp. 571 (N.D. Ill. 1972).

[128] No. 80-699, slip op. at 12, 15-16. *See* Lannett, 585 F.2d at 584.

[129] 412 U.S. 609 (1973).

dyne.[130] *Hynson* set forth the position that if an approved drug was found to be unsafe or ineffective, not only should the approved drug be removed from the market, but the generic copies should also be removed thereby treating approved drugs and their generic duplicates equally. The converse of the *Hynson* reasoning, as applied by *Lannett*, that after a drug is approved for marketing, all generic copies would also be marketable, is clearly not true.[131]

After a thorough discussion of *Pharmadyne* and *Premo*, Judge Lacey embraced *Pharmadyne*'s reasoning that 21 U.S.C. §§ 321 and 355 should be read together and *Premo*'s holding that the court's decision should be limited to the issue of general expert recognition of a drug's safety and effectiveness.[132] He further asserted that adherence to the *Lannett* dictum "would pose a substantial danger to [the] public health"[133] and if the *Lannett* court had had before it the "record developed before me here, it would not have uttered such *dictum*."[134]

Judge Lacey found Premo's eight me-too drugs to be new drugs by applying the rule that when "there [was] a substantial question as to the safety and efficacy" of a manufacturer's product, the question would be resolved by the FDA "unless there [was] general expert recognition of the safety and effectiveness of the products and they have been used to a material extent or for a material time."[135] As to the six of the eight me-too drugs which had different inactive ingredients than those of the approved drugs they copied, the voluminous, conflicting expert testimony concerning the safety and effectiveness of the me-too drugs created a genuine question, thereby precluding the drugs from qualifying for the exclusion as generally recognized.[136] With regard to the novel issue left unresolved by the Second Circuit's *Premo* decision of whether or not Premo's two me-too drugs, which had virtually identical ingredients as their approved counterparts, were new drugs, Judge Lacey found the above rule still applicable.[137] Since the evidence presented demonstrated a " 'genuine differ-

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[130] No. 80-699, slip op. at 12, 14 n.6a; Pharmadyne, 466 F. Supp. at 104 n.7. *See* Lannett, 585 F.2d at 583-84.

[131] No. 80-699, slip op. at 12, 14 n.6a.

[132] *Id.* at 13-14, 16-20. *See also* Premo, 629 F.2d at 803; Pharmadyne, 466 F. Supp. at 103-04. For a discussion of the *Premo* and *Pharmadyne* district court opinions, see notes 81-114 *supra* and accompanying text.

[133] No. 80-699, slip op. at 13.

[134] *Id.* at 21.

[135] *Id.* at 25-26.

[136] *Id.* at 21-24.

[137] *Id.* at 25.

ence of medical opinion among experts' " as to their safety and effectiveness, the two drugs must be considered new drugs.[138]

Notwithstanding the Court of Appeals for the Third Circuit's dictum in *Lannett*, the trend of future case law concerning statutory new drug interpretation should weigh heavily in favor of the Court of Appeals for the Second Circuit's *Premo* decision. The impact of applying the *Premo* rule, however, that to escape new drug classification the drug must be generally recognized by experts through publicly available data as safe and effective and must be used to a material extent over a substantial period of time, will result in few, if any, findings that a post-1962 drug is not a new drug.[139] First, the information required for general recognition is almost never publicly available since the inactive ingredients, the product's formula, and the manufacturing techniques are trade secrets protected from disclosure.[140] Thus, neither approved nor unapproved drugs could attain the general recognition standard without the manufacturer taking the unlikely action of publicly disclosing its trade secrets. Second, for a drug to satisfy the "used to a material extent over a substantial time" clause would necessitate the absurd action of the manufacturer ille-

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[138] *Id.* at 26. Apparently Premo and the FDA, instead of bringing further court actions, have agreed that Premo will drop all complaints against the FDA and will comply with ANDA procedures, and that in return the FDA will process nine of Premo's ANDA's within a nine month period. 43 F-D-C Reports, March 2, 1981, at 2.

[139] For an analysis of whether or not there exists such a thing as an "old drug," see Hyman, *Old Drug/New Drug: The Marketplace Influences the Law*, 35 FOOD DRUG COSM. L.J. 221 (1980).

[140] Applicable regulations are:

> (g) The following data and information in an NDA file are not available for public disclosure unless they have been previously disclosed to the public as defined in § 20.81 of this chapter or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in § 20.61 of this chapter:
>
> (1) Manufacturing methods or processes, including quality control procedures.
>
> (2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.
>
> (3) Quantitative or semiquantitative formulas.

21 C.F.R. § 314.14(g)(1981); and

> (e) After an approval letter has been sent to the applicant for a pending NDA, the following data and information in the NDA file are immediately available for public disclosure unless extraordinary circumstances are shown:
>
> . . . .
>
> (5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as defined in § 20.81 of this chapter.

Id. § 314(e)(5). *See* Defendant's Memorandum on Premo Pharmaceutical Laboratories, Inc. v. United States at 6 & n.4, United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699 (D.N.J. Jan. 20, 1981).

gally marketing the drug and hoping that the FDA would not bring a seizure action before the use and time requirements were satisfied.[141] Adding to these two points the district court holding in *Premo* that one manufacturer cannot produce an identical copy of another manufacturer's approved drug without there being some reasonable chance of a bioequivalence problem between the two drugs,[142] effectively eliminates any chance for a generic drug to be found to be an old drug.

Accepting the proposition that all drugs are subject to FDA approval, the length of time an NDA takes for approval becomes increasingly important both to the drug manufacturers and to the public. While the regulations allow the FDA 180 days to make a decision, the actual amount of time may be much longer due to FDA extensions requesting additional evidence of the product's safety and efficacy.[143] The FDA claims that in 1980 the median duration of time for NDA review of approved drugs was sixteen months, nine months less than the 1979 figure of twenty-five months.[144] However, compiling the data necessary for an NDA can take several years;[145] producing a drug from the laboratory to the marketplace can take approximately eight to ten years.[146] In the case of generic drugs, duplication of data already accumulated by the approved product creates unnecessary delay and expense. Thus, the government's attainment of total FDA review for all drugs has adversely affected its duty to expedite the approval of drugs.

The drug industry argues that the FDA's excessive regulation has curtailed drug innovation, increased development costs and denied the public rapid access to beneficial and inexpensive generic drugs.[147] The average cost for the full development of a drug is estimated at $70 million.[148] The generic drug company in preparing an NDA needlessly duplicates some of these expenses. Furthermore, industry officials reason that extensive pre-market NDA review results in unneces-

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[141] Defendants' Memorandum on Premo Pharmaceutical Laboratories, Inc. v. United States at 5 & n.2, United States v. Premo Pharmaceutical Laboratories, Inc., No. 80-699 (D.N.J. Jan. 21, 1981).

[142] *See* notes 137-38 *supra* and accompanying text.

[143] 21 U.S.C. § 355(c) (1976). *See* note 46 *supra*.

[144] 43 F-D-C Reports, April 20, 1981, at 6. Some New Drug Evaluation managers consider this median time to be the best obtainable under the current regulations. *Id.*

[145] S. PELTZMAN, REGULATIONS OF PHARMACEUTICAL INNOVATIONS: THE 1962 AMENDMENTS 18 (1974). *See also* Note, *New Drug Approval:* Lannett, *The Drug Lag, and the NDA System*, 11 RUT.-CAM. L.J. 231 (1980).

[146] 43 F-D-C Reports, April 13, 1981, at 12.

[147] Senate Select Committee on Small Business, 96th Cong., 1st Sess., COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY—DRUG TESTING 18 (Comm. Print 1979).

[148] 43 F-D-C Reports, April 13, 1981, at 12.

sary costs and delay since it is ultimately in the marketplace where the full impact of the drug is realized.[149] Critics of the FDA's overcautious and slow NDA procedures note that speedy approval is not encouraged, for there is no positive commendation, only immediate and stern condemnation for failing to prevent the approval of a dangerous drug.[150]

Recognizing the expensive and time consuming NDA process, the FDA permits the manufacturer of a generic drug of a pre-1962 approved drug to file an ANDA rather than a full NDA. The ANDA must only set forth the drug's good manufacturing practice and bioavailability data.[151] The FDA has also implemented a "paper NDA" for generic copies of post-1962 approved drugs which reduces cost and delay by eliminating the need for duplicative drug product testing if the manufacturer establishes through literature that its drug is safe and effective for a particular use.[152] Even with these procedures, the delay in NDA approvals is burdensome. Nevertheless, as the *Premo* cases indicate, it is in the public's best interest and is properly the paramount concern that no drug reach the market until it is proven safe and effective, and procedures to expedite drug approval must be secondary.

Rodger J. Wolf

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[149] Senate Select Committee on Small Business, 96th Cong., 1st Sess., COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY—DRUG TESTING 22 (Comm. Print 1979). In a 1973 study, economic analyst Sam Peltzman concluded that "'benefits foregone on effective new drugs exceed greatly the waste avoided on ineffective drugs.'" Peltzman, *An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments*, 81 J. POL. ECON. 1049 (1973).

[150] Senate Select Committee on Small Business, 96th Cong., 1st Sess., COMEPTITIVE PROBLEMS IN THE DRUG INDUSTRY—DRUG TESTING 20, 30 (Comm. Print 1979).

[151] 45 Fed. Reg. 82,052, 82,054 (1980); 40 Fed. Reg. 26,142, 26,147 (1975).

[152] 45 Fed. Reg. 82,052 (1980). Effective February 10, 1981, Health and Human Services Secretary Schweiker placed a temporary administrative stay on paper NDA's to allow time for his top staff to review the approval procedure. As of February 16, 1981, the stay was still in effect. 43 F-D-C Reports, February 16, 1981, at 3-4. On April 16, 1981, the "Secretary announced the resumption of [FDA] approval of 'paper NDA's.'" [1981] FOOD DRUG COS. L. REP. (CCH) ¶ 41,011, at 41,374 (April 27, 1981).