

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 79P-0484]

Response to Petition Seeking Withdrawal of the Policy Described in the Agency's "Paper" NDA Memorandum of July 31, 1978

AGENCY: Food and Drug Administration.
ACTION: Notice.

SUMMARY: The Commissioner of Food and Drugs has considered a petition (Docket No. 79P-0484) that the agency policy described in a staff memorandum of July 31, 1978, on "NDA's for Duplicate Drug Products of Post-1962 Drugs" be withdrawn and implemented, if at all, only after it is published in the Federal Register as a proposal subject to notice-and-comment rulemaking. This notice announces that the Commissioner has determined that the policy stated in the memorandum does not require rulemaking procedures, that the policy is a lawful exercise of FDA's statutory authority, and that the public health and safety would be best served by continued implementation of the policy, popularly known as the "paper NDA" policy. Therefore, the current stay on implementation of the policy, granted by the Commissioner during the period of consideration of the petition, will extend only to and including December 22, 1980.

EFFECTIVE DATES: Denial of Procedure Requested in Paper NDA Petition: December 12, 1980; resumption of implementation of Paper NDA Policy: December 23, 1980.

ADDRESSES: Communications concerning this notices should be identified with the docket number appearing in the heading of this notice and addressed to the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Carol A. Kimbrough, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

SUPPLEMENTARY INFORMATION:

I. Introduction

On July 31, 1978, the Associate Director for New Drug Evaluation of FDA's Bureau of Drugs sent a memorandum to the directors of the bureau divisions responsible for new drug application (NDA) review. (The memorandum is attached as exhibit 1 to the petition which is on file, as

discussed below, at the Dockets Management Branch (HFA-305), Food and Drug Administration.) The memorandum was entitled "NDAs for duplicate drug products of post-1962 drugs," (hereafter referred to as the July 31 staff memorandum). It advised in pertinent part as follows:

A drug marketed for the first time after 1962 under an approved new drug application may be marketed by a second firm only after the second firm has received the approval of a full new drug application for that product. Current agency policy does not permit NDAs for this purpose. Present interpretation of the law is that no data in an NDA can be utilized to support another NDA without express permission of the original NDA holder. Thus, in the case of duplicate NDAs for already approved post-1962 drugs, the agency will accept published reports as the main supporting documentation for safety and effectiveness. The agency will not interpret the "full reports of investigations" phrase in the law [21 U.S.C. 355(b)(1)] as requiring either case reports or an exhaustive review of all published reports on the drug. Depending upon the quality of the published data, selected pre-clinical and perhaps additional clinical studies may be required of the new sponsor prior to NDA approval. (Statutory reference added.)

Because the July 31 staff memorandum referred to the use of literature reports as the main supporting documentation of a drug's safety and efficacy, such a submission became known as a "Paper NDA." While the agency has relied on and continues to rely on the information in the scientific literature in the NDA review process, the paper NDA is contrasted with a new drug application which, while it may contain reports from the published literature, also contains reports of investigations for which raw data (such as laboratory reports, or physician evaluation forms) are included or are available. The latter application usually is submitted when a sponsor has conducted clinical investigations of a new chemical entity, new formulation, or new indications, while paper NDA's have been submitted whenever adequate reports exist in the scientific literature.

The significance of the paper NDA policy as applied to duplicate products of post-1962 drugs arises from its capacity to eliminate the need for duplicative drug product testing. When it is well established in the literature that a drug is safe and effective for a particular use, the agency believes that there is no valid scientific reason to require more tests in animals and humans to show that the same drug is safe and effective for the same use. Such tests are ethically questionable because they may expose human subjects to risk

without medical justification, and they are wasteful of limited resources.

The paper NDA policy is also significant due to its potential effects on prescription drug competition. As a practical matter, the requirement for the submission of raw data to substantiate studies may serve as an entry barrier to potential competitors because raw data usually are available only to the person conducting the studies, e.g., the originator of a new drug. If the sponsor-originator of an approved new drug application can maintain sole access to the raw data underlying studies of safety and efficacy, the only way (absent a paper NDA policy) in which any other sponsor could attempt to secure an approved application for marketing the same drug would be to conduct additional (and duplicative) studies of the drug. In the lawsuit, discussed below, that preceded this petition, the petitioners admitted that they object to the paper NDA policy:

*** because a competing manufacturer winning approval of a duplicate product without having borne the expense of clinical investigation and the "raw data" required of the pioneer applicant will have a less costly product, the marketing of which would place the pioneer applicant at a competitive disadvantage.

Hoffman-La Roche, Inc. v. Harris, 484 F. Supp. 58, 62 (D.D.C. 1979).

The agency believes that the paper NDA policy will help to reduce prescription drug costs through increased competition that can result from the marketing of generic drug products. The policy is, therefore, consistent with departmental and agency initiatives to reduce health care costs. For example, in January 1979 the Department of Health and Human Services (then the Department of Health, Education, and Welfare) and the Federal Trade Commission released a Model State Law to assist the States in developing new or more effective legislation governing generic drug product selection. FDA has published a list of approved prescription drug products with therapeutic equivalence evaluations. (See 45 FR 72583; October 31, 1980.) The List has the potential for assisting the States in reducing prescription drug costs as they provide health care services that include the purchase or reimbursement of drug products and for assisting the States in reducing drug product costs to private citizens who purchase such products from pharmacists operating under State laws that authorize generic drug product selection. FDA believes that the paper NDA policy will help to eliminate unnecessary testing, conserve scientific resources, and encourage competition.

II. The Petition

On January 10, 1980, two drug manufacturers, Hoffman-La Roche, Inc., and American Hospital Supply Corp., and the Pharmaceutical Manufacturers Association (PMA) jointly petitioned that the paper NDA policy, as described in the staff memorandum of July 31, 1978, be implemented, if at all, only after publication in the Federal Register as a proposal subject to notice and opportunity for comment as required, petitioners contend, by the Administrative Procedure Act, 5 U.S.C. 553, and the agency's procedural regulations, 21 CFR 10.40. (The petition, the exhibits submitted with the petition, additional exhibits referred to herein, and correspondence concerning the petition received from the public have been filed with the Dockets Management Branch, Food and Drug Administration, and may be seen from 9 a.m. to 4 p.m., Monday through Friday. The petitioners also seek a ruling that the policy stated in the memorandum cannot be promulgated without congressional authorization.

The petition followed a lawsuit brought against the agency by Hoffman-La Roche (later joined in a consolidated suit by American Hospital Supply Corp. and the PMA) in which the plaintiffs sought to have the court prevent the FDA from approving any application by a competing drug manufacturer for approval to market a generic version of a drug previously approved by the agency subsequent to 1962, unless the competing applicant filed reports of clinical tests to support the drug's safety and efficacy, and the raw data were supplied to or made available for the agency. Three parties intervened in the law suit in support of the policy stated in the July 31 staff memorandum: National Association of Pharmaceutical Manufacturers; American Federation of Independent Pharmaceutical Manufacturers, and IMS Limited (the company that has obtained the first approval of a literature supported NDA for a generic version of a post-1962 drug).

The court dismissed the complaint on the ground that the plaintiffs had failed to invoke or exhaust their remedy under the Administrative Procedure Act, 5 U.S.C. 553(e), in that they could and should have petitioned the Commissioner, using the administrative procedure provided in 21 CFR 10.25, before seeking judicial intervention. *Hoffman-La Roche, Inc. v. Harris*, 484 F. Supp. 58 (D.D.C. 1979) notice of appeal filed, (D.C. Cir., February 19, 1980).

III. The Requirement of the Federal Food, Drug, and Cosmetic Act for "Full Reports" of Investigations Showing Safety and Effectiveness

The Federal Food, Drug, and Cosmetic Act (the act), as passed by Congress in 1938, established a system of premarket clearance for drugs under which proponents of a drug were required to submit to FDA a new drug application containing, among other things, data showing the drug's safety. (See section 201(p)(1) and 505(a) of the act as enacted; 52 Stat. 1041 and 52 Stat. 1052.) In 1962, Congress amended the act to require a showing of effectiveness as well as safety before an NDA could be approved. (See 21 U.S.C. 355 (b) and (e).)

The contents of an application are prescribed in 21 U.S.C. 355(b) and, in pertinent part, are required to include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" (21 U.S.C. 355(b)(1) (emphasis added).) As a matter of historical fact, most NDA's have been and continue to be submitted for compounds about which extensive public information is not yet available. For such applications, the "full reports" requirement of 21 U.S.C. 355(b)(1) generally will operate to require the availability for inspection of the data underlying the reports of investigations of the safety and efficacy of the drug. As a consequence, manufacturers must generate the needed evidence of safety and effectiveness by conducting or sponsoring their own investigations. Raw data which provide the basis for the submitted reports are required to be available, and the regulations, as applied to such applications, require that such data be maintained for inspection should the FDA decide that an inspection is desirable or needed (21 CFR 314.1(c)(2)12.c.).

The accessibility of raw data is usually regarded as a necessary safeguard for reports of investigations of a new compound. In most cases information about such a new compound is limited; reports in the literature, if any, are scanty and preliminary. Consequently, FDA decisions to approve NDA's for such new compounds must be based upon reports submitted by the company. Considering the magnitude of the financial commitment to necessary studies, there is motive as well as opportunity to submit false or misleading reports favorable to the drug if raw data are not available for inspection. In addition, there is understandably a sincere hope by the companies and their investigators that a

drug will be a valuable new therapy. The operation of bias that may lead interested persons to minimize adverse data and overemphasize favorable results cannot be discounted. The knowledge that the data may be checked inhibits a tendency to give effect to unconscious bias and provides an important external check on the veracity and quality of the reports that are based on such data. It is therefore the FDA's usual practice to examine pertinent raw data reports of original research sponsored by drug companies on their new compounds. (See the statement providing background information prepared by Marion J. Finkel, M.D., Associate Director for New Drug Evaluation, Bureau of Drugs, paragraph 18, filed with the FDA Dockets Management Branch as Exhibit A (hereafter referred to as "Finkel statement").

The applicable regulations also reflect the fact that most NDA's are submitted for new compounds. For example, the regulations require the submission of reports on preclinical studies (i.e., laboratory and animal studies) performed by or for new drug applicants; 21 CFR 314.1(c)(2)10.b. states:

b. Detailed reports or preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained should be clearly set forth. *Such information should include . . . a statement of where the investigations were conducted and where the underlying data are available for inspection.* (Emphasis added.)

Similar requirements apply to clinical investigations to show the safety and effectiveness of the drug. In pertinent part, 21 CFR 314.1(c)(2)12.c. describes the information to be submitted as follows:

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. *These reports should include adequate information concerning each subject treated with the drug or employed as a control . . . together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection.* Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects . . . (Emphasis added.)

However, the new drug regulations also anticipate that NDA's may be submitted for compounds that are not entirely new discoveries. Thus, 21 CFR 314.1(c)(2)10.d. requires the submission of:

* * * a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety and effectiveness of the drug. (Emphasis added.)

Similarly, 21 CFR 314.1(c)(2)12.3. requires the submission of:

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing * * *, or reports in the scientific literature, involving the drug that is the subject of the application and related drugs * * *. (Emphasis added.)

While FDA usually examines pertinent raw data underlying reports of original research sponsored by drug companies on their new compounds, only in a very rare instance would all raw data be submitted to or reviewed by FDA. Complex studies in large patient populations produce tens of thousands of pieces of raw data in the form of laboratory reports, patient diaries, physical examination reports, drug dispensing records, and numerous other records. The agency does not request manufacturers to submit all raw data in their NDA filings, but requires that such data and records be maintained available for inspection. (See Finkel statement, paragraph 18.)

IV. FDA's Reliance on Published Literature To Satisfy the "Full Reports" Requirement of the Act

In contrast to FDA's requirement for the availability of raw data for studies on new compounds, FDA has for decades relied on published reports—for which raw data are not usually available—of adequate and well-controlled clinical investigations from the scientific literature. FDA has relied on such reports as "substantial evidence" of a drug product's safety and effectiveness and as "full reports" of such investigations, as required by 21 U.S.C. 355(b) and 21 CFR 314.1(c)(2)12.c. (See Finkel statement, paragraphs 20-27.) This policy reflects the agency's recognition of the reliability of a group of independently published reports of adequate and well-controlled studies, all of which reach consistent conclusions about the safety and effectiveness of a drug. (See Finkel statement, paragraph 17.) The reports are often subject to peer review prior to publication, and all published reports are potentially subject to widespread critical review after publication. Other researchers may initiate studies to confirm reported findings. Through this process, which rarely involves the scrutiny of raw data by a researcher's peers, reported

scientific observations are challenged, retested, and confirmed or rejected. Thus, the verification of published reports of research is not accomplished through the examination of raw data but rather through public exposure of the results of retesting by others engaged in similar research. (See statement of Mortimer B. Lipsett, M.D., filed with the FDA Dockets Management Branch as Exhibit B, paragraphs 14-16, 18, 20-21 (hereafter "Lipsett statement").) The validity of this verification process is also demonstrated by the requirement of some countries that studies must have been accepted for publication in an approved scientific journal before they may be considered in support of a new drug application. (See, e.g., *Pharmaceutical Administration in Japan*, 2d ed. p. 19 (1980), filed with the FDA Dockets Management Branch as Exhibit C.)

As discussed below, FDA's reliance on published reports to satisfy the "full reports" requirement of 21 U.S.C. 355(b) is illustrated by FDA's practice of relying on such reports in the review of pre-1962 drugs for effectiveness, the approval of new indicatives and labeling changes for marketed drugs, the approval of some pioneer NDA's and the approval of duplicate drug products of post-1962 drugs.

A. Abbreviated New Drug Applications for Generic Formulations of DESI Drugs

After Congress amended the act in 1962 to require that new drugs be shown to be effective as well as safe, FDA was faced with the task of reviewing over 4,000 drug formulations and 20,000 products to determine whether they were effective for the indications in their labeling. Because FDA lacked the resources needed to accomplish this task on its own, it obtained the assistance of the National Academy of Sciences/National Research Council (NAS/NRC). The NAS/NRC reviewed, among other things, the publicly available studies on each of these drugs; under the guidelines established by the NAS/NRC, the effectiveness review specifically considered published reports in the literature. (See *Pharmaceutical Manufacturers Assn. v. Finch*, 307 F. Supp. 858, 864 (D. Del. 1970).) The NAS/NRC advised FDA of its conclusions, which, for the most part, the agency adopted as part of its Drug Efficacy Study Implementation (DESI) program.

In the course of the DESI review the agency modified its new drug application requirements for generic formulations of drugs that were reviewed by the NAS/NRC and were found to be effective. Under the

modified requirements, NDA's for generic versions of these pre-1962 drugs may be abbreviated when the efficacy criteria have been satisfied through the DESI review. Such abbreviated new drug applications (ANDA's) are not required to contain any safety and effectiveness data other than the bioavailability studies, when specifically required by FDA. (See 21 CFR 314.1(f); Finkel statement, paragraph 27.)

The rationale underlying ANDA's for generic versions of pre-1962 drugs that were found to be effective in the DESI review is that basic preclinical and clinical testing of every product of the same drug is unwarranted. When it is well established that a drug is safe and effective for a particular use, there is no reason to conduct more tests in animals and humans to show that the same active drug compound contained in another manufacturer's product is safe and effective for the same use. It is common knowledge in the prescription drug industry that a widely prescribed nonpatented drug may be marketed by many different firms. Thus, a requirement for duplicative testing could require that many firms conduct repetitive, scientifically unnecessary and ethically questionable human drug experiments. Once the safety and effectiveness of the drug for a particular use is established, the important question is not whether a second manufacturer can establish *de novo* the safety and effectiveness of the drug, but whether that manufacturer can produce a finished drug product that will be as safe and effective as the first approved ("pioneer") drug product. FDA requires that all the information and data to answer this question be contained in the ANDA. The applicant's facilities, processes, methods, equipment and controls used to manufacture the product are described in the ANDA. The manufacturer and its suppliers are subject to FDA inspection to determine whether they have maintained and can continue to maintain the standards necessary to ensure product purity and quality. (See Finkel statement, paragraph 12(b)-(d).)

For some products, no further information is needed. Once it is determined that all ingredients to be used meet pharmaceutical specifications and that the inactive ingredients are compatible with the active ingredient, it may in some cases be concluded that the product is the equivalent of the pioneer drug. In other cases, it is necessary to require the applicant to conduct bioavailability studies in which the proposed generic is compared to the

pioneer drug. If the studies show bioequivalence, the two products are regarded as of comparable safety and effectiveness. (See Finkel statement, paragraph 24.)

Apart from FDA's ability to rely upon bioequivalence as a ground for approving a product as safe and effective, additional preclinical and clinical studies of ANDA products are unwarranted for other reasons. Scientific resources now available to test promising new compounds and to explore new uses for marketed drugs would be diverted to conducting studies on drugs that have already been fully tested. Unnecessary human testing also presents ethical problems when ill patients are subjected to rigors of closely controlled clinical trials.

As Dr. Finkel reports in her statement, paragraph 27, since 1969 FDA has evaluated 2,165 pre-1962 products formulations as effective. Manufacturers have submitted 4,708 ANDA's covering generic versions of these formulations. PMA member companies filed 1,035 ANDA's; 715 of these applications have been approved. In none of these applications have the companies been required to perform duplicative clinical testing. For each applicant to have been required to conduct individual clinical tests in support of each of these applications would have been wasteful of scientific resources.

B. Approval of Pioneer New Drug Applications and New Uses and Labeling Changes for Marketed Drugs

In addition to DESI drugs, FDA has in some cases based its approval of pioneer NDA's on published reports supplemented by studies done by the manufacturers. In these instances, the agency determined that studies could be verified as acceptable on a basis that did not include the submission of raw data to the extent ordinarily required under 21 U.S.C. 355(b). For example, the petitioner Hoffmann-La Roche received approval in 1974 for an NDA for sodium nitroprusside largely, though not entirely, on the strength of published reports. The company did limited preclinical studies to provide information on issues not addressed in the published literature and a small clinical trial to confirm that its formulation containing sodium nitroprusside produced clinical effects consistent with those from other formulations discussed in the literature. The published reports in the literature were critical to the approval of the NDA. (See Finkel statement, paragraph 21.) Another example of the approval of a pioneer NDA is Abbott Laboratories' sodium valproate, approved largely on

the basis of clinical studies reported in the literature. As the Finkel statement explains in paragraph 21, the studies performed by the sponsor and reported to FDA with "raw data" would have been inadequate in themselves to permit approval.

Dr. Finkel's statement, paragraph 21(a)-(g), describes a number of other examples of NDA approvals based largely on reports from the published literature:

1. The approval of a combination of propranolol and hydrochlorothiazide (Inderide, Ayerst) was based wholly on data in the literature as well as the long history in the marketplace of the combined use of the two agents.
2. The approval of the NDA for bretylium tosylate (Bretylol, Arnar-Stone) was based on four studies, two of which were reports from the literature for which case reports were not filed.
3. The approval of methyltyrosine (Demser, Merck) was based almost entirely on several reports in the literature. In this instance FDA agreed in advance of the NDA filing in 1975 that the literature reports were considered an acceptable basis for the submission of the NDA at that time under those particular circumstances.
4. The approval of two NDA's for potassium iodide (Thyro-block, Carter-Wallace) for use as a thyroid-blocking agent in nuclear emergencies was based upon published literature cited by the FDA in the Federal Register of December 15, 1978 (43 FR 58798). The literature reports were regarded as providing substantial evidence of safety and effectiveness of the drug for the proposed indications.
5. The approval of two NDA's for somatropin (Ascclacrin, Calbio Pharmaceuticals and Crescormon, Kabi Group) for pituitary dwarfism was based almost exclusively on reports from the published literature.
6. The NDA for xylose (Xylo-pfan, Pfanstiehl), a drug for use as a diagnostic test for intestinal absorption, was approved exclusively on the basis of published literature.
7. The approvals of 33 NDA's for radioactive drugs listed at 21 CFR 310.503 were each based upon published reports supporting the safety and effectiveness of the drugs. As Dr. Finkel's statement points out at paragraph 21(g), a number of these approvals were granted to member companies of the PMA.

The petitioners attempt to dismiss these approvals as a "mere handful of isolated and inappropriate cases gathered together in a post hoc rationalization" of the July 31 staff memorandum (Pet. 42 n. 14). However,

they are not presented to "rationalize" FDA's reliance on published reports in the approval of NDA's. Rather, these examples show that FDA has relied on published reports as the main supporting data, and in some instances as the entire support, for demonstrating a drug's safety and effectiveness for NDA approval.

In addition to the pioneer NDA's described above, FDA has for decades permitted the conditions of approval for drugs marketed under NDA's to be revised on the basis of reports in the literature; new warnings, side effects information, contraindications and dosage directions have been added on the basis of such reports. (See Finkel statement, paragraph 20.) When independent investigators have published reports of studies on marketed drugs that prove the safety and effectiveness of new drug uses, FDA has accepted such reports as the basis for approving addition of those uses to the drug's labeling. In her statement, Dr. Finkel includes three examples in which NDA supplements for new uses were approved between 1971 and 1973 on the basis of reports in the published literature. *Id.* These approvals, together with the requirements of the NDA regulations and other instances in which FDA has relied on published reports, reflect the scope of the agency's long-standing policy of reliance on published reports for demonstrating a drug's safety and effectiveness in the approval of NDA's.

C. New Drug Applications for Generic Formulations of Post-1962 Drugs

For generic formulations of post-1962 drugs, the ANDA concept, as applicable to pre-1962 drugs evaluated in the DESI program, has not yet been made available, and the lawful marketing of such drugs therefore requires the approval of full NDA's. However, the agency has recognized that there are a number of post-1962 drugs for which the number and quality of literature reports are such that the safety and effectiveness of the generic versions of such drugs may be established on the basis of the published reports. In response to inquiries concerning the feasibility of literature-supported NDA's for such generic products, the FDA has advised prospective new drug applicants that literature reports could be relied upon to the extent that they were reliable and described adequate and well-controlled investigations of the drug. Even when not specifically asked about literature reports, FDA has advised firms that use of published (and unpublished) reports was acceptable. (See Finkel statement, paragraph 31;

exhibits 17 and 18 attached to the petition.)

As Dr. Finkel's statement explains at paragraph 36, the increasing frequency of inquiries from firms wishing to market generic versions of post-1962 drugs led to her preparation of the July 31 staff memorandum as a means of guiding her staff in replying consistently to inquiries about the policy reviewed in the memorandum and its application to post-1962 generic drug products. The memorandum was not prepared because it addressed a new policy, but because questions could arise in applying the policy. The memorandum acknowledges that data in the pioneer NDA cannot now be used to support an NDA for a generic version of the pioneer product, but advises that published reports can be used as the "main supporting documentation for safety and effectiveness," and, if inadequate, "selected preclinical and perhaps additional clinical studies may be required of the new sponsor prior to NDA approval." In addition, Attachments A and B to the July 31 staff memorandum specify that the literature-supported NDA is required to comply fully with applicable FDA regulations such as those requiring full manufacturing and controls information.

Although data and reports in the pioneer NDA are not now used as support for the duplicative product's NDA, FDA does refer to the pioneer NDA to determine whether the results reported in the published literature are consistent with what is known about the active drug compound common to both products. If the results in a published report deviated significantly from data in the NDA, that study may or may not be considered "adequate." Thus, the data in the file for the pioneer NDA could be used to deny approval of the subsequent product, but not to support such approval. As Dr. Finkel has noted in her statement, FDA scientists have an obligation to use all information available to them in evaluating NDA's. Although the information from the pioneer NDA is not used to provide critical information missing from the published literature, it cannot be ignored in the evaluation of published reports of clinical studies. (See Finkel statement, paragraph 30.)

In accord with the policy stated in the July 31 staff memorandum, FDA on January 9, 1979, approved a paper NDA submitted by IMS Ltd. for Furosemide injection—the first post-1962 generic drug product approved on the basis of a so-called paper NDA submission. The agency's analysis of the published literature supporting the IMS NDA

approval is set out in the Summary Basis of Approval, which is attached to the Finkel statement. In addition to the IMS NDA, the agency has received at least 45 literature-supported NDA's for duplicate drug products of post-1962 drugs. Several were filed by member companies of the PMA. (See Finkel statement paragraph 32.) Pending the stay that has been in effect while the petition was under review, no additional approvals have been issued.

IV. Commissioner's Response to Petitioners' Arguments

The petition requests that the agency implement the guidance set forth in the July 31 staff memorandum, if it is implemented at all, only after it is published in the Federal Register as a proposal subject to notice and opportunity for comment as required, petitioners contend, by FDA regulations (21 CFR 10.40) and the Administrative Procedure Act (5 U.S.C. 553). Petitioners contend that the July 31 staff memorandum reflects a significant departure from prior agency policy and that notice and comment is particularly important because the memorandum raises public policy issues that could adversely affect research and development of new drug compounds by discouraging pioneer drug research and by discouraging the publication of the results of studies on new drugs.

The purpose of a notice-and-comment rulemaking procedure is to give interested persons, particularly those who would be subject to a rule, an opportunity to participate in the rulemaking by submitting to an agency comments on the potential new rule published in the Federal Register in proposed form. In its decision in *Hoffmann-La Roche v. Harris*, 484 F. Supp. 58, 64-65 (D.D.C. 1979), the lawsuit that preceded this petition, the court noted that the record before it reflected some consideration within the FDA staff about the advisability and legal necessity of notice and comment procedure with respect to the July 31 staff memorandum. But the court pointed out that the staff consideration "never culminated in any focused decision by the FDA Commissioner as to whether the matter should be submitted to the rule-making process." On the basis of my consideration of the petition and the record accompanying this response, I have concluded that the guidance contained in the July 31 staff memorandum is not a "new rule," but instead reflects longstanding practice and interpretation that is well known to the petitioners and to the drug industry generally and that it does not require

rulemaking procedures for application to generic formulations of post-1962 drugs.

A. *Petitioners' Contention That the Staff Memorandum Establishes A Significant New Rule*

The petitioners contend that the July 31 staff memorandum (Pet. Ex. 1) constitutes a radical departure from past FDA policy that substantially modified the requirements for submission of NDA's because for the first time FDA stated its willingness to accept published reports rather than require original research. Petitioners contend (Pet. 4) that it was understood by the industry that a manufacturer of a generic version of a post-1962 drug could obtain full NDA approval only by performing or contracting for the performance of its own clinical testing. I have found that these contentions are not factually accurate.

1. *FDA's reliance on published reports.* FDA's willingness to accept published reports in the literature in place of original research in satisfaction of the "full reports" requirement for NDA's is well established as evidenced by the approval of NDA's dated from 1971. (See Finkel statement, paragraphs 20-21.) This interpretation of the statute and regulations as applied to particular NDA's, including NDA's for generic versions of post-1962 drugs for which one or more NDA's have been approved, is not a new rule; rather, it is the application of an already established interpretation. The July 31 staff memorandum was intended to provide guidance to the various division directors in the Bureau of Drugs in response to the increasing frequency of the submission of NDA's for generic versions of post-1962 drugs. (See Finkel statement, paragraphs 28-37.) It was no more than a continuation of FDA's policy in many other contexts to accept published reports in lieu of original research. *Id.* paragraphs 20-26.

A number of examples illustrate that the agency considered the policy applicable to generic versions of post-1962 drugs before the July 31 staff memorandum was circulated. In response to an October 1975 inquiry, the agency advised in a letter dated January 13, 1976 (Pet. Ex. 18) that to obtain approval of a generic version of a post-1962 drug for which an NDA had been approved the requirements of an NDA set forth in 21 CFR 314.1(c)(2) must be met, and, in appropriate cases, the Bureau of Drugs has accepted references to published or otherwise public records in lieu of newly generated data. The letter therefore indicated the agency's willingness to accept published reports in the context of NDA's submitted for

generic versions of post-1962 drug products. In addition, the application for the only approved paper NDA, furosemide injection, was submitted on April 21, 1977, more than a year before the July 31 (1978) staff memorandum was circulated. (See Finkel statement, paragraph 15.)

Moreover, FDA's practice of accepting detailed reports from the literature was known to the industry. The practice was discussed in the Federal Register of April 29, 1977 (45 FR 21847) in connection with a proposal to refuse approval of certain NDA's on the ground that they contained inadequate evidence of drug safety and effectiveness. The applicants had contended that the safety and effectiveness of the active ingredients in their products were so well established that ANDA's, in which basic safety and effectiveness data need not be included, should be accepted. The FDA rejected this argument (among other reasons, because the agency has not made a finding that an ANDA would be sufficient for the products) and explained:

Fourth, the fact that FDA does not waive any of the requirements of an NDA for a particular product does not necessarily mean that an applicant must conduct its own preclinical and clinical studies regarding safety or effectiveness. *The applicant may be able to include in its applications published articles and other publicly available data and information that provide an adequate basis for the agency's making the evaluation and approvability decision required under section 505. An NDA can be approved on such a submission.* 42 FR at 21852. (Emphasis added.)

On September 8, 1977, then PMA President C. Joseph Stetler wrote to Dr. J. Richard Crout, Director of the Bureau of Drugs, concerning "differing regulatory treatment of manufacturers of new drugs." (See letter filed with FDA Dockets Management Branch as Exhibit D.)

In his letter, Mr. Stetler argued that the statute "requires that reported investigations be undertaken by or on behalf of the sponsor of the application." *Id.*, p. 2. He explained his position as follows:

* * * In addition to indicating a failure by FDA to enforce the clear demand of the new drug provisions of the Act, the process described could result in unequal and arbitrary burdens for some applicants which are not imposed on others. Thus, the first NDA applicant must conduct adequate and will controlled preclinical and clinical studies which satisfy statutory requirements. A later application would be permitted to rely on published studies and still receive a full NDA (although there is no discussion as to the time span or the quality and quantity of the published data). Clearly these are unequal

obstacles to NDA Approval, yet each successful applicant would receive the traditional full NDA. *Id.*, p. 2.

Notwithstanding the initial statements in his letter, Mr. Stetler concluded:

The industry and the scientific community have agreed for some time that complete and exact duplication of data should not be required of a second manufacturer with respect to a product that has been on the market for some time. It is agreed that such a rigid requirement would be unnecessary and a wasteful duplication of scientific resources. The objective of ensuring that there are no important differences between the original product and subsequent similar products and that the intent of the Act is satisfied, could be met by developing data which is significantly less than that required for an NDA but more than FDA now frequently requires.

Therefore, PMA agrees with the Agency's objective of eliminating unnecessary animal and human experimentation and avoiding unnecessary duplication of scientific resources. However, companies which market new drugs *should be required* to document, according to the demands of the Act the company's ability to produce safe and effective drug products of acceptable quality. *Id.*, p. 4 (Emphasis in original).

In his response, Dr. Crout noted that there had been a number of NDA approvals "with published literature serving as the sole or major evidence to support approval." (See letter filed with FDA's Dockets Management Branch as Exhibit E., p. 2.) After citing some examples, he wrote:

* * * Because many PMA members have received approvals of "full" NDA's on the basis of published reports, and because of PMA's professed opposition to unnecessary scientific research, it is somewhat surprising that PMA objects to reliance on scientific literature for approval of a drug product for marketing. *Id.*

Dr. Crout concluded:

* * * Section 505 requires that (1) reports of studies on safety and efficacy be submitted (§ 505(b)(1)) and (2) these investigations (i) include "adequate tests by all methods reasonably applicable to show whether or not such drug is safe" (§ 505(d)(1)), (ii) provide sufficient "information to determine whether such drug is safe" (§ 505(d)(4)), and (iii) provide "substantial evidence that the drug will have the effect it purports or is represented to have" (§ 505(d)(5)). *The statute neither suggests that the applicant must conduct any of these investigations nor excludes consideration of studies presented in the published literature.*

If you have any documentation to support PMA's contrary view of the law, we would be quite interested in reviewing it. *Until such time, FDA will adhere to its past and present policy of considering for approval, and in appropriate cases approving, NDA's for drugs, the safety and effectiveness of which is demonstrated by published scientific literature.* *Id.*, p. 4. (Emphasis added.)

2. Petitioners' arguments based on statements of FDA officials and congressional testimony. The petitioners have collected statements of FDA officials and congressional testimony that they contend support their contention that the July 31 staff memorandum reflected a significant change in regulatory policy. These appear in such documents as internal FDA memoranda, Federal Register documents, and the Congressional Record. I have reviewed the statements cited by the petitioners with consideration for their context and the time that they were made and have concluded, as explained in detail below, that the statements, individually and collectively, do not support the propositions for which they are cited.

Petitioners refer to a memorandum describing an April 24, 1979, conference between FDA officials and IMS, the first manufacturer to obtain a paper NDA approval (Pet. Ex. 2, p. 3). The memorandum states in pertinent part:

Dr. Crout [Director, Bureau of Drugs] and Dr. Temple [Director, Division of Cardio-Renal Drug Products] explained that the furosemide approval took unusually long because it involved a *significant new step for the agency. It was our first approval of a post-62 drug entirely on the basis of reports in the literature (a 'paper NDA').* Because of its precedential implications, that decision required participation by more people in the agency. Dr. Crout pointed out that the agency exposed itself to controversy, and, possibly, litigation with IMS' competitors by granting that approval. (Emphasis supplied.)

The underlying statements are accurate, but do not establish that a significant regulatory change occurred when the July 31 staff memorandum was issued. The IMS furosemide approval was a new step, not a reflection of a new policy. The step was an approval of a generic version of a post-1962 pioneer drug, not as in the past, an approval of the pioneer drug itself, and the approval was "entirely" on the basis of published reports. It was "significant" because, in view of the known concern among some members of the industry regarding their competitive advantages, the approval was likely to be closely scrutinized, perhaps challenged in litigation.

The petitioners also refer to a memorandum of Dr. Robert Temple, Director, Division of Cardio-Renal Drug Products, analyzing a pending paper NDA for dopamine hydrochloride (Pet. 10; Pet. Ex. 3, at 1-2). The memorandum, as quoted by petitioners, states:

It would be possible to conclude that the literature never can provide substantial evidence of effectiveness because it is never sufficiently detailed. As Dr. Dunham notes: "in their published form, by editorial and

journalistic necessity [studies fail] to contain details of materials and methods and original data whereby the study might be independently validated * * *. Dr. Dunham felt policy decisions were needed before the Division could make this choice. Since the memo was written, however, such a policy statement has been developed. Dr. Marion Finkel's memor of July 31, 1978 makes it clear that FDA will approve me-too drugs on the basis of well-controlled studies in the literature. (Emphasis supplied in part by petitioners.)

The statements emphasized, however, do not establish that the July 31 memorandum represents a new policy that requires notice and comment procedure to implement. The observation attributed to Dr. Dunham that a published report does not include sufficient detail to permit its independent validation on the basis of the raw data associated with the study reported is correct. As discussed above, however, validation of published scientific reports is customarily accomplished in ways other than through the examination of the raw data underlying the reported study. The statement attributed to Dr. Dunham that policy decisions were needed reflects a need for administrative guidance that the July 31 staff memorandum was intended to satisfy. Dr. Temple's reference to the July 31 staff memorandum as a "policy statement" does not mean that the memorandum states "new" policy. It simply refers to the July 31 staff memorandum as a policy statement, which it is in a general sense, although it is one that reflects the longstanding policy to rely on published reports of studies in the NDA approval process to the extent that the published reports are adequate. Thus, though the statement (July 31 staff memorandum) may have been new, the policy was not new.

Turning to the act and its implementing regulations (Pet. 12-13), the petitioners point out that an NDA covers a particular product and is personal to the manufacturer that files it, citing *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 664 (1973). The agency, of course, agrees. Petitioners also argue that the FDA has consistently recognized that the information contained in a manufacturer's NDA file is trade secret data that may not be publicly disclosed or used to support a NDA of another applicant without the express permission of the original NDA holder. That issue is not relevant here, for paper NDA's are based on published literature. Petitioners first contend that statutory and regulatory requirements have had the practical effect of requiring manufacturers wishing to market

generic versions of post-1962 drugs to conduct their own tests of safety and efficacy. They also contend that, prior to the July 31 staff memorandum, it was understood by both the agency and the industry that such testing was required. The agency does not agree with either contention.

The language of the Federal Register statement (39 FR 44634; December 24, 1974) relied on by petitioners contradicts their contention (Pet. 18-19). There, the agency stated, in response to a request that safety and effectiveness reports and data in NDAs be released upon approval of the applications, that the reports and data were protected from disclosure and that an abrogation of that protection required congressional action. At the same time, FDA noted that if the reports were available to the public they could be used to support approval of a competitor's NDA for a generic drug:

If a manufacturer's safety and effectiveness data are to be released upon request, thus permitting [generic versions] drugs to be marketed immediately, it is entirely possible that the incentive for private pharmaceutical research will be adversely affected. 39 FR 44634.

The statement accurately reflects the state of existing law. Reports in NDA's can be used by anyone to obtain NDA approval of an identical product once those reports are in the public domain. The fact the person using the reports has not conducted the studies and does not have the raw data does not diminish their value as a basis to obtain marketing approval for a competitive product. The value of published reports of well-controlled studies is likewise not diminished merely because the company relying on the reports did not conduct the studies or does not have the raw data. (See Lipsett statement, paragraphs 22-26.)

The petitioners similarly contend (Pet. 14-22) that their position that the July 31 staff memorandum reflects a new policy is supported by the record of FDA's consideration of possible modifications in requirements for NDA's for duplicate drug products. An examination of the records cited by petitioners belies their contention. For example, petitioners argue (Pet. 14-15) that the possibility that paper NDA's might be permitted was recognized as a change in regulatory policy, quoting a statement of the Director of the Bureau of Drugs that:

I think we must recognize that the principles stated are a departure from past policies, or at least seem to depart from our stated past policies which have emphasized a need for raw data in support of clinical trials and full animal toxicology as part of a full NDA. In short, we have had 'full NDA's' and

ANDA's but we have really not had anything in between, at least as a matter of policy. (Pet. Ex. 4, 1) (Emphasis in original.)

The petitioners also assert that the memorandum (Pet. Ex. 4) from which the quoted statement was taken establishes that it was the Bureau Director's position that "regulations" would be necessary to implement a paper NDA policy for post-1962 generic drugs. However, an examination of the entire memorandum shows the context in which the quoted statements appear and makes it quite clear that the Bureau Director was not advocating notice-and-comment rulemaking; in the fact, his recommendation goes no further than the consideration of the publication of a statement of policy to explain the requirements for NDA approval generally.

In reviewing other similar statements quoted by the petitioners, I find that they do not support the petitioners' contention (Pet. 17) that there was a "consistent view within the agency * * * that any change in the requirements for NDA's was a matter for rule-making." Agency memoranda do reflect ongoing consideration of a variety of possible procedures for the agency's approval for marketing of post-1962 generic drugs, for example, the institution of a monograph system or an ANDA system. But I do not regard these memoranda as advocating that rulemaking was necessary or desirable for the agency merely to permit the already existing paper NDA policy to be applied to post-1962 generic drug products as it had been applied to pioneer NDA's. Some confusion may be traced to staff recommendations concerning the desirability of publicizing the potential applicability of the paper NDA policy to post-1962 generic drug products. Of course, publicizing and rulemaking are not at all synonymous. In any event, even if an individual opinion that rulemaking was required had been advanced within the agency, it would have occurred at a preliminary stage in the decisionmaking process, and it has now been superseded by my analysis and decision contained in this notice.

The statements quoted by the petitioners from Federal Register documents also fail to establish that rulemaking is required. For example, petitioners refer (Pet. 18) to a Federal Register document (39 FR 44634; December 24, 1974), which included a response to a comment that the information in one manufacturer's NDA file should be available to other manufacturers, thereby relieving them of the responsibility for conducting or

relying on their own studies. However, the agency's response, as quoted at page 18 of the petition, related solely to the "release of such information." The response is, therefore, irrelevant to the paper NDA policy which does not involve the disclosure of information, but relies on data that have been disclosed through publication in the scientific literature.

Petitioners also refer (Pet. 19) to a statement published in the Federal Register which advised that a generic company must do its own safety and effectiveness testing to market an approved drug. That statement is accurate when reports of investigations on the pioneer products are not available to a potential follow-on manufacturer, and the published literature about the drug is insufficient to satisfy the paper NDA policy. As pointed out above, the generic applicant cannot now, without the NDA holder's permission, reference the data in the pioneer manufacturer's NDA. While it is true that legislation has been proposed that would, as the petitioners point out (Pet. 20-22), modify the "full reports" requirement of section 505 of the act (21 U.S.C. 355), that is irrelevant to the issues raised by the petition, because NDA's supported by adequate reports of studies from the published literature satisfy the "full reports" requirement.

Petitioners quote the testimony of Senators Schweiker and Kennedy in support of their contention that published reports do not meet the "full reports" requirement of section 505 of the act (Pet. 21). In context, however, Senator Schweiker's remarks did not suggest that published literature reports are inappropriate under the present statute. The Senator's full remarks show that he was referring to a provision in a pending bill that would authorize manufacturers of generic drugs to obtain NDA approval without filing any reports whatsoever dealing with safety or efficacy:

As a matter of legislative history, I would like to return to the duplicate testing question for a minute. The bill sets up an abbreviated application procedure, after seven years, for subsequent manufacturers of approved drugs I think it is very clear that the committee bill intends that this section be used as the primary procedure under which FDA is authorized to waive the requirements of section 505(b)(1) that drug sponsors submit full reports (or comprehensive summaries) or original full safety and effectiveness tests in support of their products, as opposed, for example, to published literature reports. I ask Senator Kennedy if that is his understanding of the bill. Mr Kennedy: Yes, Mr. President, it is my understanding. (Emphasis added.) 125 Cong. Rec. S13469 (Daily ed. Sept. 28, 1979).

According to our understanding of the quoted remarks, the legislation, if enacted, would be intended to dispense with the present and obviously acknowledged system of literature-supported NDA's for generic drugs.

Thus, Senator Schweiker was acknowledging the current practice of relying on published reports and did not question its lawfulness. In any event, the legislative history of pending legislation does not provide any authoritative guidance in interpreting the provisions of the current law. *National Confectioners Assn. v. Califano*, 569 F.2d 690, 693 (D.C. Cir. 1978).

In further support of their contention that the July 31 staff memorandum establishes a significant new rule, the petitioners suggest (Pet. 22-23) that the circulation of the memorandum lacked the concurrence of other Bureau of Drugs officials. However, the agency documents relied on by the petitioners establish that the Director of the Bureau of Drugs concurred in the circulation of the July 31 staff memorandum to staff personnel (Pet. Ex. 10, at 1). The suggestion of Bureau officials, referred to by the petitioners (Pet. 23), that the instructions contained in the July 31 staff memorandum be published, was not inconsistent with the distribution of that memorandum intramurally to staff personnel (see Pet. Ex. 10, at 1-2; Ex. 12; Ex. 11, at 2). Thus, the internal circulation of the July 31 staff memorandum was not contrary to the comments of other Bureau officials, as the petitioners contend (Pet. 23). The circulation of the July 31 staff memorandum did not, as the petitioners contend (Pet. 24), eliminate the "requirements" of 21 CFR Part 314 for detailed patient information and the availability of raw data, because there is not an absolute requirement that such information be available for each NDA. (See discussion in section C *infra*.)

I have concluded that the construction of the regulations governing NDA's implicit in the July 31 staff memorandum is not contradicted by statements of agency officials cited by the petitioners (Pet. 25-26). Petitioners refer to an August 1975 agency memorandum (Pet. Ex. 15, at 2) discussing the requirements for NDA's for post-1962 drugs that included the statement that "literature, if relied upon, must be verifiable through hard data in the same way as any other study." However, that statement, in context, does not support the petitioners' position. The statement recognizes that literature must be verifiable and refers to "hard data" as the basis for such verification. But the statement does not analyze the issue in

detail nor purport to support the proposition advanced by the petitioners that the agency's reliance on published reports requires the availability of every piece of paper that may be regarded as "raw data." Likewise, references to statements from a January 1976 letter (Pet. Ex. 17, at 2) and a February, 1976 letter (Pet. Ex. 18, at 3) also fail to present a detailed analysis of the verifiability of reports in the published literature. The statements of former Commissioner Kennedy cited by the petitioners (Pet. 25 n. 12) are not germane to the question whether FDA properly may rely on reports from the literature in the NDA approval process. As is apparent from their context, those statements relate to the question whether summaries of data, as required by pending legislation, would be adequate for the evaluation of NDA's for new compounds. (See Pet. Ex. 16.) The statements do not relate to NDA's for generic versions of approved drugs.

If the statements relied on by the petitioners are understood to mean that the agency cannot rely on published reports in the new drug evaluation process without the submission of the raw data underlying the reports, the statements did not reflect the agency's longstanding practice at the time the statements were made. In addition, as explained above, the statements referred to by the petitioners, if understood from the point of view advocated by the petitioners, are not consistent with the requirements of the regulations governing drug investigations and the contents of NDA's. Accordingly, I have concluded that the statements do not support the petitioners' conclusion (Pet. 26) that the Bureau recognized that the data underlying published reports would almost never be available and decided simply to dispense with that requirement. In point of fact, there was, and is, no "requirement" for the availability of the data underlying published reports relied on by the agency in the NDA approval process and there was, therefore, no such "requirement" to be dispensed with. (See Finkel statement, paragraph 18.)

3. *Rulemaking requirements of the Administrative Procedure Act.* The petitioners contend (Pet. 6) that the paper NDA policy could not properly be implemented without notice-and-comment rulemaking required by section 4 of the Administrative Procedure Act, 5 U.S.C. 553, and by FDA's own procedural regulations, 21 CFR 10.40. In support of this contention, the petitioners cite instances in which the agency has followed that procedure (Pet.

38-39). However, those examples are irrelevant here because, as explained above, the paper NDA policy is not, as petitioners argue, a "new" policy. Since the paper NDA policy does not represent either new policy or a "change" in policy, I have concluded that the petitioners have failed to establish that notice-and-comment rulemaking is required as a matter of law (Pet. 30-46).

The Administrative Procedure Act does require, as petitioners point out (Pet. 40), notice-and-comment procedure for rulemaking, 5 U.S.C. 553. However, 5 U.S.C. 553(b)(A) specifically exempts from notice-and-comment rulemaking "interpretative rules, general statements of policy, or rules of agency organization, procedure, or practice." In deciding the case that led to this petition, the court observed that the July 31 staff "memorandum more nearly resembles a general policy [statement] than the rules at issue in other cases," citing, *Guardian Federal Savings and Loan Assn. v. Federal Savings and Loan Insurance Corp.*, 589 F. 2d 658, 669 (D.C. Cir. 1978), *Hoffmann-La Roche, Inc. v. Harris*, supra, 484 F. Supp. at 64. In *Guardian*, the court explained that:

The term "general statements of policy," has been explicated in the Attorney General's Manual as embracing "statements issued by an agency to advise the public prospectively of the manner in which the agency proposes to exercise a discretionary power." * * * a critical test of whether a rule is a general statement of policy is its practical effect in a subsequent administrative proceeding: "A general statement of policy * * * does not establish a 'binding norm.' It is not finally determinative of the issues or rights to which it is addressed." *Pacific Gas and Electric Co. v. FPC*, 508 F. 2d 33, 38 (D.C. Cir. 1974). (Footnote omitted).

Decisions in subsequent cases have reaffirmed the continuing validity of the principles stated in *Guardian* and *Pacific Gas*. (See *Batterton v. Marshall*, No. 78-1414 (D.C. Cir. August 28, 1980); *Chamber of Commerce of the United States v. OSHA*, No. 78-2221, slip. op. at 8 n.4 (D.C. Cir. July 10, 1980); *Regular Common Carrier Conf. v. United States*, 627 F.2d 248 (D.C. Cir. 1980); *American Bus Assn. v. United States*, 627 F.2d 525 (D.C. Cir. 1980).) These decisions identify two attributes of an agency action that are determinative of its character as a statement of policy: (1) It acts prospectively in that it merely announces the agency's future intention; and (2) it preserves the agency's administrative discretion.

Under the policy explained by the July 31 staff memorandum the agency retains the full range of discretion available to it

under section 505 of the act. The policy is also consistent with the regulations governing NDA's, 21 CFR 314.1, and it retains the full range of discretion available to the agency under those regulations. The July 31 staff memorandum does not bind the agency to rely on the report of any particular study—whether the report is published or unpublished—without the availability of the underlying raw data. The discretionary determination whether access to the raw data for any particular report is required will be made by the agency upon its review of the reports submitted in support of an NDA. The July 31 staff memorandum does not bind the agency to approve any literature supported NDA; it simply advises that published reports will be accepted in the sense that they may be relied on to provide the safety and effectiveness data to support an NDA. However, the July 31 staff memorandum recognizes that the quality of the published data may require that an applicant conduct additional preclinical and clinical studies prior to NDA approval. Moreover, the July 31 staff memorandum specifies that published reports submitted in support of an NDA, like any other report, are required to meet other applicable criteria, in that the:

* * * published literature [must provide] substantial evidence of effectiveness and appropriate evidence of safety for the claimed indication(s) * * *. Published reports from scientific journals should encompass papers in which adequate and well-controlled studies are described in detail. Abstracts, reviews, and anecdotal reports are not useful. * * * The compilation of published reports (preclinical and clinical) should be the major papers in the literature relating to the drug and should be "balanced" and include those demonstrating negative as well as positive findings. Each submitted paper (or unpublished report) of a clinical trial offered in support of effectiveness should be accompanied by a summary describing the protocol, the results and how the study meets 21 CFR Sec. 314.111(a)(6)(ii), i.e., the essentials of a controlled clinical investigation. (Pet. Ex. 1, p. 3).

Far from limiting the exercise of discretion, the July 31 staff memorandum identifies several determinations that require the exercise of discretion. For example, the "quality of the published data" must be evaluated; and the reports of studies must be reviewed to determine whether they are "adequate and well-controlled," whether they include the "major papers in the literature" and whether they are "balanced." To paraphrase the language of the court in *Batterton v. Marshall*, supra, slip. op. at 28, the July 31 staff memorandum "at issue is [not] a formula, and leaves

* * * [wide] discretion to weigh or alter the contributing elements." (Emphasis in original.)

Similarly, the July 31 staff memorandum merely represented the agency's future intention concerning a course it expects to follow in the NDA review process. The July 31 staff memorandum does nothing more than provide guidance on the criteria to be applied in reviewing literature-supported NDA's. The application of those criteria is still required to be determined on a case-by-case basis with respect to each NDA. The July 31 staff memorandum does not itself bind the agency to approve any particular NDA, whether or not it is supported by published or unpublished reports of studies. Compare the July 31 staff memorandum with the "statement of policy" reviewed in *Regular Common Carrier Conf. v. United States*, supra. As the court observed in *Hoffmann-La Roche, Inc. v. Harris*, supra at 64, the July 31 staff memorandum:

* * * is not by its terms determinative of any particular application. It appears to retain to FDA broad discretion to approve or to reject any particular application unsupported by "raw data."

The agency also was not required by its own regulation, 21 CFR 10.40(d), to follow notice-and-comment procedure. That regulation, which requires that the agency follow notice-and-comment procedure in adopting interpretive rules, became effective on February 24, 1977 (42 FR 4680-4719), and it obviously is not binding on interpretations made prior to that date; only the APA provisions are applicable. Because the agency's reliance on published reports in the new drug evaluation process involves a policy that was adopted long before the effective date of 21 CFR 10.40(d), as evidenced by the agency's past practice, the regulation is inapplicable to the July 31 staff memorandum even if it were held to be an interpretative rule.

B. Petitioner's Contention That Policy Considerations Require Notice and Comment Procedure

The petitioners contend (Pet. 26A) that public policy considerations compel the agency to engage in notice-and-comment procedure to implement the instructions to staff contained in the July 31 staff memorandum. However, the premise underlying this contention is the petitioners' position that the agency is "changing" the requirements for establishing the safety and efficacy of new drugs. As discussed above the July 31 staff memorandum did not "change" new drug approval requirements.

Nonetheless, I have considered the policy considerations advanced by the petitioners, and the statements of individuals filed in support, to determine whether, as a matter of sound administration, the paper NDA policy should be implemented through notice-and-comment procedure, and I have concluded that notice-and-comment procedure is not justified.

In their effort to establish that policy considerations require notice-and-comment procedure, the petitioners attempt to identify potentially serious effects on the prescription drug industry that will be produced by the "paper NDA" policy. The petitioners charge that the research and development of new drug products would be seriously jeopardized by the policy. The statements of individuals submitted in support of the allegation, when carefully analyzed, do not substantiate that broad contention. For example, many of the statements filed by the petitioners focus primarily on research concerning unpatented compounds or compounds under patents with relatively short expiration dates rather than research concerning new drugs generally. However, the petitioners do not maintain that such drugs would be the subject of more extensive research, even if the agency did not rely on published reports for any purpose in the course of the NDA approval process. The absence of any such contention is understandable, because the only certain barrier to market entry by competitors is patent protection.

Although the agency and the Department of Health and Human Services have recognized the importance of research incentives in the development of legislation for the regulation of new drugs, the petitioners' discussion of that issue in relation to pending legislation does not accurately describe the agency's position. (Pet. 34-38). The Drug Regulation Reform Act as passed by the Senate in 1979 would provide for the disclosure of certain data supporting an NDA as part of a procedure for public participation in the drug approval process coupled with a period of exclusive entitlement by the innovator to rely on the data supporting the approval. The new legislation also would authorize an abbreviated approval procedure that would enable subsequent manufacturers to rely on the data submitted by the innovator. (See S. 1075, 96th Cong. 1st Sess., passed Senate September 26, 1979, sec. 125.) Absent patent protection, however, there would be no barrier to earlier marketing by a subsequent manufacturer who independently developed adequate data

and obtained NDA approval for the product prior to the end of the 7-year period. (See 125 Cong. Rec. S13465 (Daily ed. Sep. 26, 1979).) Accordingly, the quoted views of agency and department officials concerning pending new legislation are not relevant to consideration of the paper NDA policy.

The petitioners also contend that notice-and-comment procedure is needed to determine whether the paper NDA policy will affect new drug research by creating a disincentive on the part of drug companies to permit the publication of reports of research they sponsor. I have concluded that notice-and-comment procedure is not needed. First, it is well known that there already exist disincentives for the sponsors of research to permit publication, where the sponsors hope to prolong a monopoly beyond the period provided by the patent law. Even if a published report of scientific research were not sufficiently detailed to provide adequate data to support the approval of a competitor's product, enough information could still be provided to enable a competitor to conduct the investigations needed for approval at a substantial saving in cost. Thus, it is common knowledge that drug manufacturers frequently submit reports of investigations in support of drug approvals that they do not allow to be published in the medical literature.

Although petitioners focus on the potential disincentive to the publication of research that they contend the paper NDA policy will create, they entirely ignore the powerful incentives for the publication of research that are well-known to the scientific community. Scientific journals are the primary method for achieving widespread communication of developments in the field of drug research. Publication can generate further analysis and research on a product which may beneficially advance a firm's knowledge of a product, and perhaps even more significantly, it may be a vital stimulant to new or increased sales of a product. Most research scientists regard publication in scientific journals in their field as a vital component of their research function, and they highly value its role in the peer review process, in defining and developing new research methodologies, and in identifying new areas for research. (See Finkel statement, paragraph 18.) The ability of a drug firm to secure the research capability of highly skilled scientists would in many instances be compromised if it attempted to impose undue burdens upon publication. Moreover, for approved products that

are already on the market and that may be of general interest in the scientific community, a firm would have no way of restricting publication of others' studies of its product undertaken subsequent to its entry into the marketplace. Thus, the publication of research on drug products, where such research has not been sponsored by a drug manufacturer, would not be affected by any potential disincentive for publication that might be created by the paper NDA policy. (See Finkel statement, paragraphs 38-39).

In evaluating this issue, I have carefully considered the statements filed by the petitioners. I share the concern expressed in those statements that incentives for new drug research and the publication of results of scientific investigations should not be diminished. But the statements do not present an analysis to support a prediction that such effects are likely to occur; the statements, essentially, express a concern that such potential effects may be associated with the implementation of the paper NDA policy. In light of FDA's prior reliance on published reports and the lack of any perceived adverse effect on the new drug evaluation process caused by such reliance, I have concluded that the mere possibility that some effect might occur is insufficient to require notice-and-comment procedure prior to the implementation of the paper NDA policy. As Dr. Finkel's statement establishes, reliance upon reports of controlled trials reported in the literature was the operative basis for the Drug Efficacy Study Implementation Program initiated in 1969. (See Finkel statement, paragraph 26.) On the basis of conclusions adopted by FDA, effectiveness determinations were announced, and FDA approved generic versions of the formulations under regulations providing for ANDA's. As pointed out above, such applications do not require the submission of any safety and effectiveness data with the exception of bioavailability data, when specifically required by FDA. In reliance upon these determinations that were based largely on the literature, member companies of the Pharmaceutical Manufacturers Association have filed 1,121 ANDA's; 659 of these applications have been approved.

For none of these applications were the companies required to perform duplicative clinical testing. Moreover, the PMA firms did not then nor do they now complain that the ANDA process for pre-1962 drugs, even though it rests on reports from the published literature, diminished their research incentives or

discouraged the publication of the results of scientific investigations.

C. Petitioners' Contention that the July 31 Staff Memorandum can be Implemented only Through Congressional Authorization

The petitioners contend (Pet. 46-49) that the paper NDA policy is unlawful and that it cannot be adopted without congressional amendment of the act. In support of this contention, the petitioners argue that reports of investigations published in the medical literature do not satisfy the requirement of section 505(b)(1) of the act for the submission of "full reports of investigations," because the published reports are not accompanied by the underlying data. I have concluded, however, that the "full reports" provision of the act does not require the availability of the raw data underlying clinical investigations except where the agency determines in its discretion in the course of the new drug evaluation process that the review of such data is needed to ensure a valid scientific determination with respect to the reports of investigations submitted in support of a particular NDA.

As pointed out above, section 505 of the act requires the filing of "full reports" and authorizes a refusal to approve an NDA if the "reports" do not show safety and effectiveness. Since the term "reports" is not defined by the act, it should be understood to have its usual meaning as a description of an event or an investigation and not the data it describes. (See, *Websters' Third International Dictionary*, p. 1925 (1961 ed.)) However, the petitioners are companies that do experimental drug research on new compounds. Their NDA's often contain reports on original research, which ordinarily cannot be verified and accepted without resort to the study data. (See Finkel statement, paragraph 18.) Such research is conducted under the exemption provision of 21 U.S.C. 355(i), which allows shipments of experimental drugs for human testing. Testing is permitted according to regulations that "may, within the discretion of the Secretary," require:

The establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b). 21 U.S.C. 355(i)(3). (Emphasis supplied.)

The regulations that govern experimental drug testing require that investigators maintain the raw data generated by the studies and make them available for inspection should the FDA decide to review them (21 CFR 312.1(a)(12)6.a.). FDA cannot require the submission of reports of raw data directly from the investigators to the agency; the reports required to be made of the investigations must be submitted to the manufacturers for inclusion in their NDA's (21 U.S.C. 355(i); 21 CFR 312.1(a)(12)6.d.).

Similarly, the regulations governing the contents of NDA's to be submitted to FDA require that "reports" are to be submitted but do not require raw data as part of the applications. (See Finkel statement, paragraph 18.) All that the applicant "should" do with respect to raw data is provide "a statement of where the underlying data are available for inspection" (21 CFR 314.1(c)(2) 10 and 12). The regulations addressing preclinical and clinical reports are divided into separate sections. Reports from the literature are required for both preclinical and clinical investigations; for such reports, NDA sponsors are not required to specify the location of raw data. For clinical reports "sponsored by the applicant or received or otherwise obtained," the regulations call for a description of the location of raw data (21 CFR 314.1(c)(2)12.c.). Although 21 CFR 314.1(c)(2)10 does not describe the source of the preclinical reports for which raw data locations must be provided, it is apparent from the parallel organization of the sections discussing preclinical and clinical reports that the identification of the location of preclinical data is made in connection with studies that were conducted by the manufacturer or its hired investigators.

Under 21 CFR 314.1(c)(2)12.c., reports are required to include "adequate information concerning each subject treated" and other factors necessary to evaluate properly the execution of the study. This information is required to be in the report. The adequacy of the report is central. The regulation also states that "ordinarily" the reports will not be considered adequate unless they are supplied by at least two independent investigators who maintain case histories and other data. It is, of course, clear that what is "ordinarily required" is not necessarily required in every case. When published reports on a drug are acceptable as a basis for drug evaluation regardless of the availability of raw data, FDA is not precluded from considering them. This is the view that FDA has taken when considering literature-supported NDAs'. (See Pet. Ex.

19, pp. 2-3). This construction of the regulations is plainly consistent with the regulations' terms.

The agency's construction of its statutory authority and implementing regulations accords with the Supreme Court's recognition that reports of adequate and well-controlled investigations available in the public literature may serve as a basis upon which experts can recognize a drug as safe and effective for use. In a series of cases FDA proposed to withdraw approvals for FDA's on the ground that the drugs were not shown to be effective. The manufacturers argued, among other things, that the drugs were generally recognized as safe and effective by experts and, therefore, not new drugs under 21 U.S.C. 321(p)(1) for which approved FDA's were required. The Court held that "hurdle of 'general recognition' of effectiveness requires at least 'substantial evidence' of effectiveness for approval of an NDA." *Weinberger v. Hynson, Wescott and Dunning, Inc.*, 412 U.S. 609, 630 (1973). The determination whether there is substantial evidence of effectiveness requires a body of publicly available information, including reports of adequate and well-controlled clinical investigations:

* * * Whether a particular drug is a "new drug," depends in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by substantial support in scientific literature. (Emphasis added.)

Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 653 (1973). See *Premo Pharmaceutical Corp. v. United States*, No. 79-6227 (2d Cir. July 29, 1980). Surely, if the existence of reports of well-controlled trials in the literature could be considered adequate to exempt a drug wholly from the applicability of the NDA provisions, reports in the literature should be considered adequate also to satisfy the NDA provisions.

I believe it is apparent, and the petitioners cannot seriously dispute, that the act and regulations do not require that duplicative and ethically questionable drug experiments be carried out in humans if the existence of publicly available reports supplies the kind of evidence that would be generated by original tests. The manufacturers' tenacity in defending the confidentiality of their reports on original investigations and their recognition that the public disclosure of the reports will aid potential competitors in securing NDA approvals is telling. The value of published reports in establishing drug effectiveness and

petitioners' reliance on such reports in their own NDA's shows clearly that they are adequate to support NDA approvals.

In accord with my conclusions that there are neither legal requirements nor policy reasons for granting petitioners' request, I am ordering that implementation of the instructions stated in the July 31 staff memorandum be resumed on December 23, 1980.

The agency is, of course, willing to consider at any time additional points of view on this and other aspects of the paper NDA policy discussed in this notice. Those wishing to express such views should identify their correspondence with the Docket No. 79P-0484 and send them to the Dockets Management Branch at the address specified at the beginning of this notice.

Dated: December 5, 1980.

Jere E. Goyan,

Commissioner of Food and Drugs.

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