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PART IV

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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THERAPEUTICALLY EQUIVALENT DRUGS

Availability of List

[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 20]

[Docket No. 78N-0170]

THERAPEUTICALLY EQUIVALENT DRUGS

Availability of List

AGENCY: Food and Drug Administration.

ACTION: Proposal.

SUMMARY: The Food and Drug Administration (FDA) proposes to amend its public information regulations to make available a list of all approved drug products, together with therapeutic evaluations of listed products that are available from more than one manufacturer (multisource). This proposal offers the public an opportunity to comment on the proposed policy of making such a list available as well as the current content and form of the list itself.

DATES: Comments by April 12, 1979.

ADDRESSES: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Herbert Gerstenzang, Bureau of Drugs (HFD-32), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

FOR TECHNICAL INFORMATION ON THE LIST OF DRUG PRODUCTS CONTACT:

Gene G. Knapp, Bureau of Drugs (HFD-500), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2806.

FOR A COPY OF THE PROPOSED LIST ONLY CONTACT:

Margaret Lawrence, Consumer Inquiries Staff (HFJ-10), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3170.

NOTE.—Because the number of copies of the proposed list is limited, FDA asks that only those persons who contemplated commenting in response to this proposal request copies. The proposed list is subject to revision and is not intended for general distribution and use at this time.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration proposes to amend § 20.117 (21 CFR 20.117) of its public information regulations to include in the list of available computer printouts approved prescription drug products with proposed therapeutic equivalence evaluations. This list, which is being prepared in response to requests from State health agencies for assistance in administering their laws relating to generic substitution, is presented as a proposal so that interested persons may review and comment on all aspects of this proposed FDA activity, including the legal authority, rationale and criteria for the evaluation of approved multisource prescription drug products for therapeutic equivalence.

I. Policy Considerations in Proposing List

A. General Considerations

Three major considerations lead the agency to propose that FDA should make available a list of therapeutically equivalent drug products:

(1) Education of users of drug products, i.e., those who purchase, prescribe, or dispense drug products, as well as the patients for whose benefit the drug products are used.

(2) Cooperation with the States in carrying out their duties to protect and promote the health and welfare of their citizens.

(3) Facilitation of the President's program to control inflation in the American economy.

Several additional specific factors that also influenced the agency's decision to make this proposal are discussed in section I. B. of this preamble.

1. *Public education.* Decisions affecting the selection of prescription drug products to be used in the diagnosis, prevention, or treatment of disease in patients are made at many points in the health care delivery system.

Physicians, of course, exercise the primary control through their authority to prescribe drugs. They may prescribe by a generic name or by a brand name. The "generic" name is the established or common name of the active drug ingredient in a drug product (21 U.S.C. 352(e)(3)). The "brand name" is the privately owned trade name used by a manufacturer or distributor to identify its particular drug product and, if there are competing products containing the same active drug ingredient, to differentiate its product from those of the competitors.

Prescriptions are generally presented to pharmacists for filling. If the prescription uses only a generic name, the pharmacist is responsible for selecting the specific drug product to be dispensed. Over the last few years, physicians have shown an increasing tendency to prescribe by generic name. While 8.9 percent of all prescriptions in 1970 were written specifying only a generic name, by 1977 generic prescribing occurred 12.4 percent of the time, a rise of almost 40 percent.

If the prescription identifies a brand name, the pharmacist has, until recently, been required under most State pharmacy laws to dispense the precise product specified by the physician. Statutory restrictions against a pharmacist's dispensing a drug product other than the particular brand named in the prescription have been termed "antisubstitution laws." Between the early 1950's and 1972, virtually every State or jurisdiction had adopted an antisubstitution law or equivalent regulation. For a history of the spread of antisubstitution legislation, see Drug Product Selection, Bureau of Consumer Protection Staff Report to the Federal Trade Commission, pp. 141-151 (Dec. 1978) (hereafter called "FTC Staff Report").

Recently, restrictions on the authority of a pharmacist in filling prescriptions that identify drug products by brand name have been changed in many States. New statutes, often called "drug product selection laws" or "drug product substitution laws," have been adopted in approximately 40 States and the District of Columbia in the last decade; over half of these have been enacted since 1977. These laws generally authorize or direct the pharmacist to substitute a lower priced drug product if one is available that is therapeutically equivalent to the brand name product prescribed. Most the drug product selection laws also prohibit substitution if the physician clearly directs that the prescription be filled and dispensed as written. A history and analysis of current State drug product selection laws and an analysis of current State laws is set forth in FTC Staff Report, pp. 151-184.

Thus, because physicians may prescribe by generic name and appear to be doing so more frequently, and because State laws regarding the filling of prescriptions have changed, pharmacists now have a much greater responsibility for selecting the actual drug product that the patient will use than they formerly had.

Few pharmacies, however, are capable of stocking all brands of drug products containing a particular active drug ingredient. Consequently, at any one time, a pharmacist will be choosing the specific product to dispense from among a preselected group of drug products. This preselection of brands available for filling prescriptions may, of course, have been made by the dispensing pharmacist, if he or she were also responsible for purchasing the pharmacy's supplies. More commonly, especially in large pharmacy operations and chain drug stores,

purchasing is done through centralized or cooperative systems in which supervisory of other selected pharmacists choose which products to stock. Nonpharmacists, such as business or procurement officers, may also participate in the purchasing process. Clearly, the individuals who order drug products for stocking pharmacies have a significant role in drug product selection.

The system of drug dispensing may operate differently within hospitals and public health clinics. For example, many hospitals have worked with drug formulary systems under which only one brand of a drug product would be stocked, regardless of the number of brands marketed. Nevertheless, the same factors influencing drug product selection may be found.

All persons involved in drug product selection obviously need accurate, complete, and understandable information regarding prescription drug products. Because the health care delivery system contains so many decentralized decisionmaking points and so many decisionmakers, the information must also be widely available. FDA can contribute to assuring responsible prescription drug product selection decisions by disseminating necessary information about prescription drug products that the agency has evaluated for therapeutic equivalence, together with the basis for these evaluations.

The information contained in a list of therapeutically equivalent drug products will help to protect the public health. As just discussed, many persons in the health care delivery system need to know what therapeutically equivalent drug products are being marketed. The information is particularly needed by pharmacies, hospitals, State procurement agencies, and public health clinics, both in determining which products to purchase and in deciding which to dispense. Currently, in the absence of an offical list, pharmacists must make their own evaluations of therapeutic equivalence. Even with their professional training and experience, however, many pharmacists do not have the time, the resources, or the access to comprehensive scientific and regulatory data essential to making these evaluations. Consequently, risks exist that drug products that are not therapeutically equivalent may by mistake be substituted and dispensed, with possible adverse health consequences to patients. Although the number of situations in which therapeutically inequivalent drug products may create serious problems is quite small, the potential is sufficient to create a public health concern.

The Food and Drug Administration is the national agency charged with assuring the safety and effectiveness of the drug supply. It has also been designated as the unit responsible for assuring that the drug products purchased by Federal agencies meet all applicable quality standards. It is appropriate that FDA apply its expertise and experience in evaluating the safety, effectiveness, and quality control of drug products to minimize the public health problems that might arise in drug product selection by physicians, pharmacists, or drug procurement officers.

A list of therapeutically equivalent drug products is also needed to balance and correct materials disseminated widely in recent years alleging the therapeutic inequivalence of drug products. For example, in March 1976, *Private Practice*, the journal of the Congress of County Medical Societies, published a special supplement of materials that were used in the campaign against drug product substitution legislation in the State of Oklahoma. Opponents of similar legislation in other States were urged to consider the success of the Oklahoma campaign. These materials are reprinted in "Competitive Problems in the Drug Industry," Pt. 33: Hearings before the Subcommittee on Monopoly and Anticompetitive Activities of the Senate Select Committee on Small Business, 95th Cong., 1st Sess., pp. 16518-16528 (1977) (hereafter called "Drug Quality Hearings"). They included full-page newspaper advertisements and radio and television spots to be directed to the general public. Among the claims made were the following:

* * * chemically equivalent drugs may not have the same effect.

* * * * *

Generic drugs may cost a little less in dollars and cents, but they can exert a high price in health.

* * * * *

Those big drug companies didn't get big by making crummy medicine.

* * * * *

Despite the identical ingredients, the slight differences in fillers, coatings, acidity, and absorption rate in drugs can make them totally ineffective—or worse than that—potentially harmful and even fatal.

* * * * *

"Bioequivalence" or "therapeutic" equivalence means that the drug will produce the same effect in your body as the brand-named drug prescribed by your doctor. Most generic or chemically equivalent drugs do not, in fact, produce the same result because of differences in coating, fillers, quality controls, acidity and absorption rates.

* * * * *

The fact is, the government doesn't even require that all generic drugs be equal. They need only meet minimum standards to be on the market.

* * * * *

A diamond. A chunk of coal. Both pure carbon * * * chemically equal * * * but therapeutically different * * * and some difference! WOW!

A motion picture film with a similar message was sponsored by Warner/Chilcott Division of Warner-Lambert Co. called "The Consumer and Prescription Drugs." Narrated by television figure Frank Blair and featuring 11 physicians, this movie seeks to demonstrate that generic drug products are of lower quality, and possibly less safe and effective, than brand-named drug products. A flyer for the film prominently advises: "Available for your use with lay audiences!"

These materials have not conveyed an accurate or complete picture of the prescription drug marketplace. They imply that the minimum standards for drug quality are inadequate to assure such quality, that differences in chemically equivalent drug products generally produce differences in therapeutic effects, and that government regulation never assures therapeutic equivalence. Although illustrations can be offered to support each of these propositions, the generalizations are unfounded. The broad dissemination of these assertions to the general public, as well as to the health professionals, may lead to a decline of public confidence in the nation's drug supply. For this reason, an authoritative statement from the Federal agency charged with monitoring and assuring the safety, effectiveness, and quality of drugs is an appropriate contribution to public understanding.

2. *Cooperative federalism.* In our Federal system, the States bear the primary responsibility for protecting and promoting the health and welfare of their citizens. In doing so, the States and their subdivisions directly provide health care services through public hospitals, public health clinics, and special assistance to patients with unique medical needs. Additionally, State agencies engage in a variety of educational and regulatory activities pertaining to health care delivery in the private sector, including licensing professionals and establishing requirements for pharmacies, private hospitals and clinics, nursing and residential care homes, and other facilities in which health services are provided. Finally, States are charged with administering welfare programs that reimburse for medical expenses.

In these capacitites, the States are entitled to and should receive assistance from the Federal Government. This aid properly includes FDA advice

on therapeutically equivalent drug products.

As providers of health care services, States purchase and distribute prescription drug products. Like those of the Federal Government, State agencies are under great pressure to make the most efficient use of tax dollars in purchasing goods and services. The availability of drug products identified as therapeutically equivalent encourages effective competition, and permits each State to select suppliers on the basis of price and collateral services tailored to meet that State's needs. FDA now serves as the central agency for quality assurance in purchases of drug products by the U.S. Department of Defense, the Veterans Administration, and the U.S. Public Health Service. (See section III.B.4.(vi) below in this preamble.) State procurement agencies in eight States have now sought similar FDA assistance for their programs. In part to explore the feasibility of such assistance, in June 1978 the agency entered an agreement with the State of New York to provide a quality assurance service for that State's drug purchases. (See the FEDERAL REGISTER of July 14, 1978 (43 FR 30353).) Direct provision to all of the States of a list of FDA evaluations concerning therapeutically equivalent drug products offers another means of assisting the States in their drug purchasing activities, while the feasibility of providing additional quality assurance services to the States, e.g., evaluation of drug products not subject to new drug application requirements, is determined.

The States also can use an FDA list of therapeutically equivalent drug products in their relationship with the providers of private health care services. In response to recently enacted drug product selection laws, several States have undertaken preparation of formularies of drug products that may or may not be substituted under their respective statutes. See, e.g., "Safe, Effective and Therapeutically Equivalent Prescription Drugs," New York State Department of Health, Office of Public Health (Health Education Service, Albany, N.Y.) (April 1, 1978) (hereafter called "New York Drug List"). At least 19 of these States and the District of Columbia have approached FDA to aid in preparing these formularies. In response to such a request from the State of New York, FDA devoted significant resources to review and advise upon the New York Drug List. A similar evaluation was later made of a list submitted by the State of Illinois. Based upon these experiences, the agency concluded that continuing to provide assistance on a State-by-State basis would not be cost-effective, because of the number of requests and the varying definitions and criteria among the individual statutes for evaluating therapeutic equivalence. Instead, FDA decided that it should prepare a master list to provide a guidance and information that could be utilized by each State in meeting its own repsonsibilities under the particulars of its drug product selection law. The Commissioner sent a letter to appropriate State officials on May 31, 1978, informing them of FDA's plans to develop this list.

3. *Combatting inflation.* The President of the United States has repeatedly sought to bring the current inflation problem under control. On October 24, 1978, President Carter reaffirmend his commitment that the Administration will do everything in its power to ensure that its actions are consistent with the objectives of the anti-inflation program. These objectives include restraining the growth of government spending, encouraging more competition in our economy, urging voluntary action to slow wage and price increases to specified rates, and limiting government purchases to firms observing the pay and price standards (Predsidential Address to the Nation, 14 Pres. Doc. 1839; White House Fact Sheet on the President's Anti-Inflation Program, 14 Pres. Doc. 1845 (Oct. 24, 1978)).

An area of particular concern to the President is health costs. At a July 20, 1978 press conference, President Carter, in response to an inquiry regarding national health insurance, observed (14 Pres. Doc. 1325-1326):

> One of the very discouraging aspects of our present health care system is the enormous increase in costs that have burdened down the American people. The average increases in cost of health care per year has been more than twice as much as the overall inflation rate.

Federal, State, and private purchases of prescription drugs are significant. If lower cost, therapeutically equivalent drug products are available and are used more widely, immediate savings would accrue without a sacrifice in the quality of health care. As a result, the increase in health costs would be lessened, the growth in government expenditures for prescription drugs reduced, and the efforts to control inflation furthered.

It is true that prices for pharmaceuticals have not been rising as rapidly as prices of other components of the health care system, and that prescription drugs do not represent the largest factor in health expenditures. These facts do not mean, however, that cost savings in the prescription drug market would not be helpful to the economy, to the consumer, or to the taxpayer. They merely make clear that no single step will be adequate to restrain health costs. President Carter acknowledged this reality in his October 24 speech to the nation, and went on to say (14 Pres. Doc. 1840):

> If there's one thing I have learned beyond any doubt, it is that there is no single solution for inflation. What we have, instead, is a number of partial remedies. Some of them will help; other may not. But we have no choice but to use the best approaches we have and to maintain a constant search for additional steps which may be effective.

Lower cost, therapeutically equivalent drug products are in fact available. If these products were used more widely in place of higher priced products, fewer dollars would have to be spent by the government and by consumers in purchasing prescription drugs. Several studies to estimate the potential savings from substitution of lower or higher priced drug products have been made. The FTC Staff Report reviews eight studies done by others and one undertaken by the Federal Trade Commission (FTC Staff Report, pp. 196-219). Its conclusion is that "the potential for the realization of consumer savings is substantial" (id. at 219).

The President has announced his anti-inflation program and directed the excutive departments to act consistently with its objectives. Publication of a list of FDA evaluations of therapeutically equivalent drug products will advance this program by providing important information to drug product purchasers.

B. ADDITIONAL CONSIDERATIONS

In addition to the three major factors set forth above, several other considerations support the preparation and issuance of a list of drug products that FDA has evaluated on the basis of therapeutic equivalence.

1. *Cooperation with FTC.* The Department of Health, Education, and Welfare and the Federal Trade Commission have cooperated in the development of a "Model State Drug Product Selection Act." This draft legislation is being made available to the States to assist them in considering their own drug product selection legislation (FTC Staff Report, pp. 273-289). For purposes of drug product selection, the model act would require the establishment by an appropriate State health agency of a formulary that would list equivalent drug products, potentially including all drug products determined by FDA to be therapeutically equivalent. As one aspect of HEW's cooperation with FTC, FDA has been asked to prepare a list of such products to be provided to the State.

2. *Confusion over the legal status of certain drug products.* A recent court decision has created the potential for serious confusion over the legal status of certain drug products. Specifically, the United States Court of Appeals for

the Third Circuit suggested in dicta that it believed many drug products that FDA has classified as "new drugs" under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the "act") (21 U.S.C. 321(p)) and thus subject to premarketing clearance by FDA, may be incorrectly classified and thus not subject to FDA approval before marketing (*United States* v. *Articles of Drug, etc., The Lannett Co., Inc., claimant,* No. 77-2100, decided, Aug. 14, 1978, rehearing denied, Dec. 1, 1978 (hereafter called "Lannett")). Because the agency believes these dicta to be clearly wrong, FDA first sought, unsuccessfully, a rehearing by the Third Circuit and now intends to ask the Solicitor General to petition the Supreme Court to review the Lannett decision.

In the meantime, in reliance on the Lannett decision, some manufacturers are seeking to introduce drug products into the marketplace without FDA review or approval. (See, e.g., *Pharmadyne Laboratories, Inc.* v. *Kennedy,* Civ. No. 78-2792, (D.N.J., filed Nov. 17, 1978).) Other manufacturers with competing drug products are continuing to comply with FDA preclearance requirements, and FDA is continuing to enforce these requirements outside the jurisdiction of the Third Circuit.

Until the issues raised by the Lannett case are fully resolved, purchasers, prescribers, and dispensers of drug products may face considerable difficulty in determining which marketed products have been reviewed and approved by FDA. Section 301(l) of the act (21 U.S.C. 321(l)) prohibits a manufacturer from labeling or advertising that its product has an approved new drug application. Confirmation that an application has been approved is available from FDA under the Freedom of Information Act and implementing regulations (21 CFR 314.14). Unfortunately, this availability offers little benefit because of the volume of potential inquiries about a large number of products from a large number of individuals. A better solution lies in collecting the information in one list and distributing that list widely.

3. *"Man-in-the-plant" practice.* Under the so-called "man-in-the-plant" practice of some drug manufacturers, one drug firm, generally marketing a drug product under its own brand name, will contract with a second firm, who may independently market a competing product under either a brand or generic name, for the second to manufacture the first's drug product. Under the terms of the contract, the first firm will send one or more of its employees into the facility of the manufacturer to monitor operations. The designated employee, the so-called "man-in-the-plant," purportedly assures that the product meets the purchaser's standards. Because of this monitoring, the first firm claims to be the actual manufacturer of the drug product, and so represents itself on the labeling of the drug product. This practice reflects a judgment on the part of the brand name firms that engage in it that at least some generic firms—the ones with whom they contract—are capable of manufacturing drug products equal in quality to those made by the brand name firms themselves. FDA certainly has found no significant difference in quality between brand name and generic drugs made in the same plant, with or without the man-in-the-plant practice.

In November 1977, a Senate subcommittee chaired by Senator Gaylord Nelson held hearings regarding the man-in-the-plant practice (Drug Quality Hearings).

Additional hearings on the same topic were held in September 1978, before a House subcommittee chaired by Rep. John Moss (H. Rept. No. [unassigned at time of this publication], 95th Cong., 2d Sess. (1978); Hearings before the Subcommittee on Investigations and Oversight of the House Interstate and Foreign Commerce Committee, 95th Cong., 2d Sess. (1978)). Both congressional subcommittees found evidence that the price differentials were significant between the brand name firm's products and the product marketed by the second firm, even though both products were made in the same facility with the same equipment and essentially the same personnel. Moreover, the subcommittees heard testimony that in many instances the quality control standards did not differ between the products. The House subcommittee, in its report, found that the practice results in consumer deception. FDA has published a proposal in the FEDERAL REGISTER of October 3, 1978 (43 FR 45614) to prohibit information in drug product labeling that might mislead purchasers on the identity of the actual manufacturer of a drug product.

Even if this proposal is fully implemented, however, it will not provide complete information regarding the products that have been reviewed by FDA and found to comply with all applicable standards. More comprehensive information is necessary and a list of drug products, including FDA evaluations on their therapeutic equivalence, would fill this need.

4. *Voluntary compliance activities.* The agency has been directed by a Federal court not to follow a policy of permitting the marketing of drug products that FDA has determined to be a "new drugs" under the act without prior approval of new drug applications for that product (*Hoffmann-LaRoche* v. *Weinberger,* 425 F. Supp. 890 (D.D.C., 1975)). In response to this order, the agency issued a compliance policy guide establishing a priority sequence for identifying all violative new drug products and removing them from the market (FDA Compliance Policy Guide 7132c.08 (Oct. 6, 1976); notice of availability published in the FEDERAL REGISTER of September 23, 1976 (41 FR 41770)). The number of such products was known to be significant, and FDA at that time estimated that it would take at least 2 years to bring about full compliance. Given the magnitude of the problem, the limitations on FDA's resources, and the consequent length of the delay before compliance could be completely attained, FDA developed a strategy to deal on a priority basis with those drugs that most affected public health and safety, to provide equitable treatment among competing firms, and to have a maximum impact on violative products. One effect of this policy was to provide firms marketing lower priority drug products with an opportunity to comply voluntarily with the new drug application requirements of the law before FDA began enforcement proceedings.

At about this same time, FDA issued a list of drug products that (i) contained drugs with known or suspected problems of bioinequivalence and (ii) were subject to approved new drug applications. (See the FEDERAL REGISTER of Feb. 5, 1976 (41 FR 5339).) This list, which became known as the FDA "Blue Book" because of the color of its cover, soon became an important guide to public and private procurement officers in determining which products to purchase. As a result, a number of manufacturers promptly sought to obtain approval of new drug applications for their products in order to be added to the Blue Book list. In short, FDA found that the public availability of information about which products were covered by approved applications provided a valuable incentive toward voluntary compliance with the act.

In light of this experience, it appears likely that a broader list, containing all approved new drugs and not simply those with known or suspected bioequivalence problems, will further encourage voluntary compliance with the act. This purpose could, of course, be accomplished without providing FDA evaluations as to the therapeutic equivalence of approved products; however, for reasons discussed elsewhere in this section of the preamble, these evaluations will serve other useful purposes not necessarily related to voluntary compliance.

5. *Recommendation of the OTA Drug Bioequivalence Study Panel.* In 1974, the Office of Technology Assessment of the Congress created a panel to study issues relating to problems of

drug bioequivalence. The work and conclusions of this panel are discussed in great detail in section III.B.2. below in this preamble. It is appropriate to note here, however, that the last of the 11 recommendations of the panel, quoted in full below, proposed establishment of an official list of drug products evaluated for therapeutic equivalence. To date, no action has been taken on this recommendation. Completion of other FDA actions now makes it feasible for the agency to consider implementing this proposal.

C. LITIGATION REGARDING ISSUANCE OF LIST

The Pharmaceutical Manufacturers Association (hereafter called "PMA") has filed a lawsuit seeking to enjoin FDA from issuing a list of therapeutically equivalent drug products (*Pharmaceutical Mfr's Ass'n* v. *Kennedy*, No. T-78-2449, filed Dec. 7, 1978 (D. Md.)). That litigation provides no compelling reason to defer or delay this proposal. Because this notice constitutes only a proposal, because comments are requested on all factual, legal, and policy issues related to the proposal, and because both the decision to proceed with issuance of a list and the contents of the list with its proposed evaluations of therapeutic equivalence are subject to change in light of the comments received, publication of the proposal or public release of the proposed list does not affect the authority of the District Court in which the litigation is pending.

The objections of PMA to an FDA list of therapeutically equivalent drug products, as set forth in its complaint, need not be discussed point-by-point in this document. This preamble amply describes the reasons for issuing such a list, the legal, scientific, and regulatory bases on which such a list may be prepared and issued, and the details of the list that FDA proposes to issue. Opportunity to comment and raise specific objections, in light of the specific proposal in this notice, is being provided to the public, including PMA. The objections of PMA, both in its complaint and, if PMA chooses, as particularized by its comments on this proposal, will be considered by FDA in determining how to proceed in this matter.

II. LEGAL AUTHORITY AND LEGAL STATUS

A. LEGAL AUTHORITY TO ISSUE LIST

The Secretary of Health, Education, and Welfare is charged with several important duties in preparing and disseminating health information. Those duties that relate to the activities and responsibilities of FDA in regulating the safety and quality of the nation's foods, drugs, cosmetics, and other products have been delegated to the Commissioner of FDA.

Each of four separate statutory provisions relate directly to FDA authority for issuing a list of therapeutically equivalent drug products. A broad implied authority is also relevant.

1. *Public health information.* Section 310 of the Public Health Service Act (42 U.S.C. 242o) directs the Secretary to issue "information related to public health, in the form of publications or otherwise, for the use of the public" and to publish "other pertinent health information for the use of persons and institutions concerned with health services." Functions of the Secretary under section 310 that relate to functions of FDA have been delegated to the Commissioner (21 CFR 5.1(a)(2)).

The availability of drug products evaluated by FDA as therapeutically equivalent, as well as the identity of pharmaceutically equivalent drug products which are evaluated by FDA as not therapeutically equivalent, is important information related to the public health. Likewise, this type of information is quite pertinent for use by persons and institutions concerned with health services.

As discussed in section I.A.1. above in this preamble, a list of therapeutically equivalent drug products will serve the public health by notifying those persons responsible for decisions affecting drug product selection about those products that, in FDA's judgment, are or are not therapeutically equivalent and the reasons for these evaluations. The list will also serve to correct and balance other information being disseminated to the public that claims or implies that therapeutic equivalence among drug products cannot be either determined or assured.

Consequently, publication of an FDA list of therapeutically equivalent drug products is within the FDA functions described in section 310 of the Public Health Service Act.

2. *Advice to the States.* Section 311(a) of the Public Health Service Act (42 U.S.C. 243(a)) directs the Secretary to "advise the several States on matters relating to the preservation and improvement of the public health." Functions of the Secretary under section 311 which relate to functions of FDA have been delegated to the Commissioner (21 CFR 5.1(a)(2)).

The list of therapeutically equivalent drug products, as explained in section I.A.2. above in this preamble, will enable the States to carry out their duties to protect and promote the public health, both in providing health care services with efficiency and cost-effectiveness and in advising physicians and pharmacists on the requirements of State drug product selection laws.

For these reasons, distribution of an FDA list of therapeutically equivalent drug products is within the FDA duties described in section 311 of the Public Health Service Act.

3. *Information to the public.* Section 705(b) of the act (21 U.S.C. 375(b)) authorizes the Secretary to disseminate information regarding drugs "in situations involving, in the opinion of the Secretary, imminent danger to health, or gross deception of the consumer." The functions of the Secretary under the act have been delegated to the Commissioner (21 CFR 5.1(a)(1)).

The absence of a list of therapeutically equivalent drug products permits the continuation of a situation involving potential dangers to health as well as deception of consumers, as discussed in section I.A.1. above in this preamble.

The magnitude of the potential dangers or deception need not be estimated, however, because section 705(b) is not a limitation upon the authority of the Secretary or the Secretary's delegate. "The only purpose of this statute is to place within the express scope of the duties of the Secretary something that was one of his implied functions" (*Hoxsey Cancer Clinic* v. *Folsom*, 155 F. Supp. 376, 378 (D.D.C., 1957)). In that case, an injunction was sought against FDA's issuing a circular to post offices warning that the so-called Hoxsey cancer cure had been found worthless. The court held that "even in the absence of this statute there would be nothing to prevent the [Federal officials] from disseminating information to the public. * * * The [Federal officials] are performing a public duty when they are urging the use of certain treatments or warning against the use of certain treatment" (id.). A similar conclusion was reached in *United States* v. *An Article of Device* * * * *Diapulse Mfg. Corp., Claimant*, 262 F. Supp. 728 (D. Conn. 1967).

Because section 705(b) of the act merely amplifies implicit authority in the Secretary and the Commissioner, it is not necessary to determine whether the specific conditions for invoking the explicit authority under that section now exist. Potential health risks and consumer deception do exist and will continue to exist in the absence of information and evaluations by FDA of the therapeutic equivalence of drug products. Thus, distribution of this information is a proper FDA responsibility.

4. *Voluntary compliance activities.* Section 306 of the act (21 U.S.C. 336) authorizes FDA to use written notices in lieu of formal enforcement actions when the public interest will be adequately served by such notices. To the extent that a list of approved new drug products will encourage voluntary compliance by manufacturers of

new drug products that have not been approved, as discussed in section I.B.5. above in this preamble, issuance of such a list is within the authority delegated to the Commissioner under that section (21 CFR 5.1(a)(1)).

B. LEGAL STATUS OF LIST

The proposed FDA list of approved drug products, with evaluations on their therapeutic equivalence, would contain only public information and advice. This list would not constitute an order or a rule; it would neither determine nor adjudicate the legal rights of any drug manufacturer or distributor; it would impose no requirement or restriction upon any person; it would not interpret or apply the act in a manner that creates any obligation on any person; it would make no recommendation as to which products persons should purchase, prescribe, or dispense, or conversely, which products should be avoided.

To the extent that the list identifies drug products approved for marketing under sections 505 and 507 of the act (21 U.S.C. 355 and 357), it would merely set forth information to which the public is entitled under the Freedom of Information Act. (See 21 CFR 20.117; 314.14; and 431.71). Omission of a drug product from the list would not necessarily mean that the drug product is in violation of section 505 or 507 of the act, or that it is not safe or effective, or that it may not be therapeutically equivalent to other drug products. Decisions on whether specific drug products are subject to the requirements of either of those sections, or whether specific drug products have fulfilled those requirements, are made in clearly defined proceedings unrelated to the release of information on approval decisions. (See e.g., 21 CFR 314.100 and *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973).)

To the extent that the list sets forth FDA's evaluations of the therapeutic equivalence of drug products that have been approved, it would contain FDA's advice to the public and to the States regarding an important public health matter. These evaluations would not constitute determinations that any products are in violation of the act or that any products are preferable to others. They are based on the application of certain criteria, described below, to information contained in FDA files to make these nonregulatory evaluations.

The agency desires that the list be as well-informed as possible because of the public interest in and importance of the information it could contain. Issuance of the list would be significant activity by FDA, and the agency believes that it would profit from public participation during its development. Therefore, this notice is being published to solicit comments and suggestions on all aspects of the list, including the legal authority, rationale, and criteria for the evaluation of therapeutic equivalence. Because the list is not a rule, as defined in the Administrative Procedure Act (5 U.S.C. 551(4)), adherence to the rulemaking procedures of that statute (5 U.S.C. 553) is not required. Nevertheless, these procedures provide a useful model for the agency to present a proposal and request public comments on it.

If FDA decides to publish with a list such as proposed in this preamble, it is desirable that the public have a point of reference reflecting the availability of that list. To this end, the agency proposes to add a new paragraph to its regulations describing the FDA records and information that are and are not available to the public (21 CFR Part 20). Specifically, a new paragraph would be added to § 20.117 (21 CFR 20.117), which discusses the availability of various computer printouts of new drug information. The text of this proposed paragraph is set forth at the end of this document.

III. "THERAPEUTIC EQUIVALENCE": CONCEPT AND RATIONALE

The term "therapeutically equivalent drug products" simply means that two such drug products can be expected, in the judgment of FDA, to have equivalent therapeutic effect and equivalent potential for adverse effects when used under the conditions set forth in their labeling. Drug products that are therapeutically equivalent may still vary in certain respects: color, shape, taste, or packaging, for example. As a result, patients may not perceive them as identical or equally acceptable. For this reason, it cannot be stated that such drug products are substitutable or interchangeable in all cases. The judgment is not FDA's as to whether different drug products are substitutable or interchangeable for use by a particular patient; rather, it rests with practitioners who, in prescribing and dispensing drug products, can take into consideration the unique characteristics, needs, or problems of individual patients. It is the agency's position, however, that if one therapeutically equivalent drug product" is substituted for another under State law, with due professional regard for the individual patient, there is no substantial reason to believe that the patient will receive a drug product that is different in terms of the therapeutic effect intended.

Drug products may be evaluated as therapeutically equivalent if—

(1) They are pharmaceutical equivalents in that they contain identical amounts of the same active drug ingredient in the same dosage form, and they meet identical compendial or other applicable standards of identity, strength, quality, and purity;

(2) They are bioequivalent in that either they present no known or potential bioinequivalence problem or, if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard (bioequivalence refers to the comparative rates and extents of absorption of drug products into the human body; the assurance of bioequivalence of drug products is discussed in section III.B.2. of this preamble);

(3) They are adequately labeled; and

(4) They are manufactured in compliance with current good manufacturing practice.

On the basis of these factors, drug products can be said to be therapeutically equivalent. Moreover, if one of these products has been shown to be safe for its intended uses and has also been shown to be effective for those uses through adequate and well-controlled clinical trials, there is no scientific or medical justification for requiring clinical trials to establish the safety and effectiveness of the second product, without reasonable grounds for believing that the two products will not be of equivalent safety and effectiveness. It is neither feasible nor in the interest of the public health nor a productive use of the nation's scarce research resources to require costly duplication of these tests. A regulatory system that requires such duplicative testing is wasteful, anticompetitive, scientifically unsound, and ethically dubious.

In order to understand the basis on which FDA concludes that certain drug products are therapeutically equivalent, it is necessary first to define a number of terms and then to examine the assumptions and experience underlying the factors used in determining therapeutic equivalence.

A. THE CONCEPT OF "THERAPEUTIC EQUIVALENCE"

The starting point for understanding therapeutic equivalence is the term "therapeutic agent" or, as it is usually called, "therapeutic moiety." This term refers to the substance in a drug product that actually achieves the intended effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease or in affecting the structure or function of the human body. (See 21 U.S.C. 321(g)(1).) Although different substances may produce the same ultimate therapeutic effect, they are not necessarily identical therapeutic agents. For example, various narcotics produce analgesia, but do so through different, although related, therapeutic moieties. On the other hand the same therapeutic moiety may appear in slightly different chemical forms,

e.g., as different salts or esters of the same molecule. To distinguish these separate forms, the term "active drug ingredient" is used; each salt or ester of a therapeutic agent is a unique active drug ingredient. For example, tetracycline hydrochloride and tetracycline phosphate complex are distinct active drug ingredients containing the same therapeutic moiety.

The form in which a patient uses an active drug ingredient is s "drug product." This term has been defined in 21 CFR 320.1(b) to mean "a finished dosage form, e.g., tablet, capsule, or solution, that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients."

The first consideration in evaluating therapeutic equivalence among drug products is whether they are "pharmaceutical equivalents." This term is defined in 21 CFR 320.1(c) as follows:

"Pharmaceutical equivalents" means drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

Pharmaceutical equivalents may differ in characteristics such as color, taste, shape, packaging, stability and expiration time, and (within certain limits) labeling. Frequently, variations in these characteristics are described as "pharmaceutical elegance," a term that refers to aspects of s drug product relating to its physical attractiveness, cost, convenience to patients, or acceptance by patients, rather than referring to its safety or efficacy.

Drug products that contain different active drug ingredients but the same therapeutic moiety, or products that are different dosage forms of the same active ingredient, are called "pharmaceutical alternatives." To distinguish these products from pharmaceutical equivalents, the following definition is used in 21 CFR 320.1(d):

"Pharmaceutical alternatives" means drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

For present purposes of evaluating therapeutic equivalence, FDA proposes not to consider two drug products to be therapeutically equivalent unless they are pharmaceutically equivalent. Thus, drug products would not be evaluated as therapeutically equivalent even though they may contain (1) the same therapeutic moiety, but as different salts or esters, and thus as different active drug ingredients, or (2) the same active ingredients, but (i) in addition, contain other, different active ingredients, or (ii) are in different dosage forms (e.g., tablet v. solution), or (iii) do not meet identical compendial or other applicable standards. (Compliance with such standards is discussed in detail in section III.B.1. of this preamble.)

The second factor in evaluating whether two products are therapeutically equivalent is whether they are "bioequivalent drug products." To understand this consideration, two further definitions are needed:

"Bioavailability," as defined in 21 CFR 320.1(a), means "the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action." The site of drug action is the place in or upon the human body where the therapeutic moiety acts to achieve its intended effect.

The term "bioequivalent drug products" is also defined in 21 CFR 320.1, in paragraph (e), to mean:

Pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

The Food and Drug Administration presumes that pharmaceutically equivalent drug products are also bioequivalent unless there exists scientific evidence to the contrary. The basis for this presumption, and the issues surrounding bioequivalence among drug products, are discussed at length in section III.B.2. below in this preamble. As a consequence of this presumption, only where scientific evidence demonstrates a known or potential problem of bioinequivalence does the agency require each manufacturer to establish that its product is bioequivalent to a reference product, which generally is the pharmaceutically equivalent product marketed by the holder of the original new drug application. In such a situation, individual products are presumed not to be bioequivalent until proven otherwise by adequate scientific studies.

Under the definition quoted above, two drug products that are not pharmaceutically equivalent may still be bioequivalent. Such drug products would not, however, be designated as "therapeutically equivalent" for purposes of the proposed list. As stated above in section I of this preamble, a primary purpose of this list is to provide State agencies and officials with information relating to drug products that may be selected for dispensing under applicable State law. Under most State drug product selection statutes, pharmaceutical alternatives are excluded from the scope of substitution, i.e., pharmacists are not required or authorized to substitute with a pharmaceutical alternative. Thus, there is no need at this time to consider the circumstances under which pharmaceutical alternatives may be therapeutically equivalent.

Two other factors relate to therapeutic equivalence. Prescription drug products must be accompanied by labeling that provides information regarding proper use of the drug. The labeling must be adequate for licensed practitioners to prescribe, dispense, or administer the drug safely and for the purposes for which it is intended (21 U.S.C 352, 355, and 357; 21 CFR 201.100). In addition, the label of every drug product is required to identify the contents accurately and in detail (id.). Thus, the third consideration of therapeutic equivalence is whether the drug products are adequately labeled for the practioner and pharmacist.

The fourth and final factor in evaluating whether drug products are therapeutically equivalent is whether they are manufactured in accordance with current good manufacturing practice. Under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)), a drug product is deemed adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that" the drug product meets the requirements of the law. Current good practice is determined by FDA on the basis of an ongoing review of industry operations.

In summary, FDA proposes to evaluate as "therapeutically equivalent" those drug products that meet the following general criteria:

(1) They are pharmaceutical equivalents in that—

(a) They contain identical amounts of the same active drug ingredient in the same dosage form; and

(b) They meet compendial or other applicable standards of identity, strength, quality, and purity.

(2) They are bioequivalent in that—

(a) They do not present a known or potential bioinequivalence problem; or

(b) If they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard.

(3) They are adequately labeled.

(4) They are manufactured in compliance with current good manufacturing practice.

Specific criteria proposed to be used by FDA in evaluating therapeutic equivalence, based on the foregoing four factors, are set forth in section IV of this preamble. Before discussing these specific tests, however, it is appropriate to examine the scientific, regulatory, and practical foundations underlying the four general criteria.

B. THE SCIENTIFIC AND REGULATORY FOUNDATIONS FOR EVALUATION OF DRUG PRODUCTS AS "THERAPEUTIC EQUIVALENTS"

The scientific ad regulatory foundations for the evaluation of the therapeutic equivalency of drug products involve the following three major elements:

(1) Pharmaceutical equivalence.

(2) Bioequivalence.

(3) Controls to assure consistency of quality in, and pharmaceutical and bioequivalency among, individual batches produced by all manufacturers.

1. *Pharmaceutical equivalence.* The definition of "pharmaceutical equivalent" set forth above contains two key tests. First, the drug products must contain identical amounts of an identical active drug ingredient in identical dosage forms. This test is quite restrictive, for it excludes drug products that provide the same ultimate therapeutic effect from the identical therapeutic moiety, although through a different active drug ingredient (e.g., a different salt or ester), or through a different dosage form (e.g., tablet v. suppository), or with a different quantity of active drug ingredient. These excluded drug products are treated as pharmecutical alternatives and are not included in the category of therapeutically equivalent drug products.

The second test for pharmaceutical equivalence is that each product meet the identical compendial (or other applicable) standards of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. Under section 501(b) of the act, any drug recognized in an official compendium is required to meet the standards of strength, quality, and purity set forth in that compendium (21 U.S.C. 351(b)). The term "official compendium is defined in section 201(j) of the act to mean the United States Pharmacopeia (USP), the National Formulary (NF) or the Homeopathic Pharmacopeia (21 U.S.C. 321(j)). Section 507(b) of the act authorizes the Secretary to issue regulations prescribing similar standards for antibiotics (21 U.S.C. 357(b)). In cases where compendial standards do not exist, section 505 of the act authorizes FDA to require analogous standards to be included in a new drug application as part of assuring that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the drug (21 U.S.C. 355). (See also 21 CFR 314.1(c)(2) Form FD-356H, Item 8.)

Compendial, antibiotic, and similar new drug application standards prescribe a number of specifications, and corresponding tests or methods of assay, regarding the identity of the active drug ingredient and its strength or potency and purity, and the finished drug product and its strength or potency, purity, and sometimes packaging. Standards may establish limits upon or requirements for, e.g., sterility, pyrogenicity, pH, heavy metals, and package design.

The purpose of these standards is to provide manufacturers with workable means to assure that drug products achieve a level of quality sufficient for their safe and effective use. To the extent that compendial and antibiotic standards recognize a difference between adequate and the most stringent possible specifications, they do so in an attempt to balance the costs and burdens of meeting the requirements with the need for standards that adequately protect the health and safety of the patient using the drug product.

In recent years, some concern has been expressed as to the adequacy of existing compendial standards. For example, a study conducted for Congress by the Office of Technology Assessment on "Drug Bioequivalence" (July 15, 1974) (hereafter called "OTA Report") concluded in part that "[p]resent compendial standards * * * do not assure quality and uniform bioavailability of drug products" (id., p. 2). The PMA made a detailed attack on the quality of the compendia during HEW's proceedings to promulgate regulations relating to Federal reimbursement for prescription drugs (the "Maximum Allowable Cost" or "MAC" regulations) and in litigation challenging those regulations (*American Medical Ass'n et al. (Pharmaceutical Mfr's Ass'n, Intervenors)* v. *Mathews*, 429 F. Suppl 1179 (1977)). These criticisms have not gone unanswered. The United States Pharmacopeial Convention, Inc., which now publishes USP and NF, and the American Pharmaceutical Association, which published NF in 1974, have argued in congressional hearings before the Senate Health Subcommittee that the focus of the OTA Report is substantially narrower than the overall adequacy of compendial standards, in that it did not relate to all aspects of drug product quality, but solely to those aspects affecting bioequivalency. It was further urged that "[c]ompendial standards, although not perfect, do effectively minimize the possiblity that unsatisfactory products will be permitted on the market" (statement of Dr. Edward Feldmann, American Pharmaceutical Association, in Hearings on the Examination of the Office of Technology Assessment Report of the Drug Bioequivalence Study Panel before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare, 93d Cong., 2d Sess. 184 (1974) ("OTA Report Hearings")). Related hearings were held before the Senate Subcommittee on Monopoly in 1974. (See Hearings, Pt. 24, before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 93d Cong., 2d Sess. 1974) ("Monopoly Committee Hearings").)

In reference to the MAC regulations, the Department stated (OTA Report Hearigs, pp. 127-128):

> We cannot agree, however, that identifying those interchangeable drug products for which evidence of bioequivalence is not essential requires extensive new [compendial] standards. The task involved in developing such standards must be placed in perspective. Drug products which meet standards based on the best available technology are highly desirable. Applying appropriate tests to raw materials, precompression stages and to the finished drug product universally may also be important. But, if efforts to develop such standards and tests are expended precipitously on all marketed drugs, important and limited medical and investigational resources would be misspent to the exclusion of more urgent tasks.
>
> For drug products which are found not to require evidence of bioequivalency, the fact that these products have met present compendial standards as demonstrated by possession of an approved New Drug Application or Abbreviated New Drug Application is sufficient to support the assumption of interchangeability. We believe that this approach is reasonable, practical, and consistent with the spirit of the [OTA] Panel's evaluation. We further believe that this approach involves no hazard to the patient. It is and will continue to be desirable to improve the standards under which drugs are manufactured so that the possibility of bioinequivalence is reduced still further. The Panel's suggestions of ways to achieve this goal are appreciated and, in the main, enthusiastically supported by FDA.

The Food and Drug Administration adheres to these conclusions. Preparation of a list of therapeutically equivalent drug products can proceed without awaiting a comprehensive review and upgrading of all relevant compendial standards. The OTA Report is

correct in concluding that existing standards by themselves may not guarantee bioequivalence. But these standards do provide a basis for evaluating drug products as pharmaceutically equivalent, and in some cases provide dissolution rate standards that reduce the potential for bioinequivalence problems. In case where bioinequivalence problems are suspected or identified, bioequivalence standards may be imposed in addition to compendial specifications. Thus, it is safe to conclude that when supplemented by other appropriate tests and requirements, such as bioavailability testing and new drug application requirements, compendial and antibiotic applicable standards do provide a reasonable assurance of therapeutic equivalence.

Since 1974, when the OTA Report was issued, significant improvements have been made in the compendia. Responsibility for the NF has been transferred from the American Pharmaceutical Association to the United States Pharmacopeial Convention, Inc., so that USP and NF, and their improvement, are now fully coordinated. The compendia have also adopted important new requirements, including dissolution rate standards for many drug products (USP XIX, p. xv).

Furthermore, FDA has proposed that specifications for drug ingredients and drug products submitted by manufacturers in new drug applications or similar premarketing approval applications be available for public disclosure, unless the specifications serve no regulatory or compliance purpose and are exempt as trade secrets. (See the FEDERAL REGISTER of July 15, 1977 (42 FR 36485).) If adopted, this action will permit the official compendia to maintain current standards applicable to the drug products of all manufacturers.

In the past, individual manufacturers have claimed that they use standards exceeding the requirements of the compendia and that consequently their products are of higher quality than competing brands. Many of these firms refuse, however, to make public the standards they use; a number submitted comments opposing the FDA proposal to disclose specifications contained in submissions to the agency, on the ground that these specifications constitute "trade secrets." The argument runs roughly as follows: (1) Company A claims that it uses higher standards than the compendia require; (2) Company A further claims that these higher standards lead to better products; (3) the public prefers to buy better products; (4) to the extent that the public believes Company A's claims, the public (through physicians and pharmacists) will prefer to buy Company A's products; (5) to the extent that the public buys Company A's products because of a belief that they reflect a quality difference, Company A's standards provide a competitive advantage; (6) because the standards provide a competitive advantage, they constitute "trade secrets" that are prohibited from disclosure under section 301(j) of the act (21 U.S.C. 351(j)) and section 1905 of Title 18 of the U.S. Code (18 U.S.C. 1905). The success of this argument, of course, depends upon whether Company A's standards are in fact "higher" or merely different, and if truly "higher," whether the standards have any significance with regard to the safety or effectiveness of the product.

It is impossible for the public to evaluate Company A's claim that it uses higher standards because Company A insists that they are "trade secrets" and therefore cannot be seen by the public. FDA, which can and does look at these standards in reviewing new drug applications, ascertains that they are adequate to assure the quality of the product; if not, the application is not approved. The agency has observed firms adopting specifications beyond those needed to reasonably assure drug product quality in order to provide some pharmaceutical elegance. Although these standards are different, they do not necessarily make a "better" product.

Except for identified problems of bioinequivalence, FDA is not aware that any therapeutically significant differences currently exist among "pharmaceutically equivalent drug products" which result from differences between public compendial (or antibiotic) standards and "higher" internal standards of manufacturers.

If such therapeutic differences did exist, however, protection of the public health would require that the compendial standards be changed as quickly as possible. Means for avoiding significant problems in the safety or effectiveness of a drug product should not be viewed as a "competitive advantage," nor should the new drug approval process be viewed as a mechanism for perpetuating differences between compendial and private standards critical to assuring drug quality. Compendial standards should remain current with technological evolution and good industry practice.

To this end, it is in the public interest for manufacturers to make their standards available to the compendial officials, rather than to encourage a system of double standards in order to gain a "competitive advantage." As was stated in the FEDERAL REGISTER of July 15, 1977 (42 FR 36486):

> The public availability of drug specifications will help to assure that all manufacturers of the same drug product meet the same standards of identity, quality, purity and, where applicable, dissolution rate or other in vitro tests intended to assure bioequivalence. Furthermore, consumers and physicians will be able to select a particular brand of a drug product with confidence, knowing that the standards it is required to meet are comparable to those of other versions of the same drug product. Disclosure will permit the official compendia to maintain current standards applicable to the drug products of all manufacturers. Consistent compendial specifications and methods will contribute to improving the enforcement programs of Federal, State, and local regulatory agencies whose function is to assure full compliance with legal requirements for drug products.

It can be argued that a drug product may be called "better" without providing a therapeutically significant advantage, on the grounds that it offers other factors of benefit to the patient, such as greater acceptability (e.g., because of taste, size, color, or shape), longer storage life, or more convenient packaging. These attributes of pharmaceutical elegance do not relate to the essential safety and effectiveness of the drug product. Each carries with it a certain economic cost, which consumers may or may not be willing to pay in order to obtain the advantage. It must be recognized, however, that cost of medication may be as significant a factor to patients as taste, storage life, or packaging. Thus, to the extent that internal manufacturing standards result in a more elegant product, without providing greater safety or effectiveness, they do not justify any therapeutic distinctions among drug products and are not relevant to the evaluation of the therapeutic equivalence of those drug products.

For these reasons, it is appropriate to conclude that current compendial and antibiotic standards and similar standards in new drug applications provide a reasonable basis for evaluating whether two or more drug products are pharmaceutically equivalent and thus may be therapeutically equivalent. Although specifications in new drug applications may differ in some cases, all are adequate—and none are clearly superior—in assuring the quality of the drug products covered in those applications.

2. *Bioequivalence.* Bioequivalence involves the comparison of two drug products on the basis of the rate and extent to which their active drug ingredient is absorbed and becomes available at the site of drug action. Two drug products are generally said to be bioinequivalent if, under similar experimental conditions, the rate or extent of absorption of one differs significantly from that of the other.

Problems of bioinequivalence have undoubtedly existed since the development of drugs. Awareness of these problems, however, is a relatively recent phenomenon, arising in the last

decade. Before that time, variations in patient-response among different brands of drug products were generally attributed to patient variation rather than to drug nonuniformity. As the science of biopharmaceutics evolved, attention was focused on the clinical effects of differences in the bioavailability of drug products made by different firms, or in different batches of a drug product made by a single firm.

The bioavailability of a drug product, it is now known, can be affected by a number of biological and pharmaceutical factors. For example, for an orally administered drug, bioavailability is dependent upon factors such as the area in the gastrointestinal tract from which the drug is absorbed, the dissolution and stability of the drug in the gastrointestinal tract, the rate at which the drug is absorbed from the gastrointestinal tract, and the rate of metabolism of the drug in the intestinal wall and liver. In turn, these biological factors are influenced by the specific pharmaceutical characteristics of the product, including the physical structure and particle size or surface area of the active drug ingredient, the quantity and characteristics of inactive ingredients, the coating of a tablet or capsule, and the compression applied to produce a tablet. Variations in any of these factors, either from batch to batch of one manufacturer or from the product of one manufacturer to that of another, can produce variations in bioavailability or, in other words, bioinequivalence. If a patient using one product is given a different product, including a product from a different batch by the same manufacturer a bioinequivalence problem may result. Most commonly, bioinequivalence problems are discovered only by in vivo testing of blood levels. Therapeutic failures are uncommon and, when they occur, generally result in reduced effectiveness. Less frequently, absorption is significantly in excess of a previously used product, and thus bioinequivalence may produce toxicity.

In its first regulatory response to this problem, FDA began systematically in 1970 to require evidence of "biological availability" in support of abbreviated new drug applications (hereafter called "ANDA's") for many drug products subject to a Drug Efficacy Study Implementation (DESI) notice rating them as "effective" and requiring an ANDA as a condition to marketing. (Sec 21 CFR 314.1(f)(3).) Several problems resulted from these DESI notices. As firms inquired of the agency as to the availability of protocols for meeting this requirement, it became apparent that the state of the art was still inadequate for many drugs. Moreover, later FDA review found that a number of active ingredients and dosage forms covered by the DESI "biological availability" requirements did not pose any bioequivalence problems. It followed that such requirements were not scientifically warranted.

As a result of these developments, the agency advised firms that the bioavailability requirements spelled out in certain DESI notices were deferred. These actions were taken on an ad hoc basis, while many new DESI notices continued to impose bioavailability requirements. As a result, FDA reconsidered its policies with a view toward promulgating a comprehensive set of regulations in this area.

It was at this point that FDA and many in the pharmaceutical industry disagreed on the extent of the bioinequivalence problem. Indeed, the major controversy surrounding FDA's subsequent regulatory activities (and related issues of drug substitution and the MAC program) is whether bioinequivalence is relatively widespread or rare. The degree to which the problem is common to all drugs suggests the degree to which therapeutic equivalence cannot be determined without scientific studies on each specific drug product, and, indeed, each specific batch of each drug product. Some manufacturers and the PMA argue to this day the bioinequivalence is so prevalent that proof of bioequivalence should be required for every prescription drug product. See, e.g., proposed amendments to the Drug Regulation Reform Act of 1978 by PMA, in Senate Committee on Human Resources, 95th Cong. 2d Sess., section-by-section analysis of amendments submitted to S. 2755, pp. 41-42 (Comm. Print 1978).

Quite apart from the merits of these proposals, their economic implications would be quite favorable to firms already on the market, because the cost for a new manufacturer to enter the market would be greatly increased, and the time at which entry could occur would be significantly delayed. Thus, if accepted, the PMA proposals would have substantial anticompetitive effects. Such costs to the public from scientific studies and from a loss of competition require substantial justification in terms of protecting the public health.

Because of the fervor, persistence, and implications of the controversy over whether proof of bioequivalence should be required for every prescription drug product, a detailed history and discussion are appropriate.

On January 5, 1973, FDA published a notice of proposed rulemaking in the FEDERAL REGISTER (38 FR 885) to establish bioavailability requirements for prescription drugs. The preamble to that proposal stated (id. at 886):

It is not possible to specify at the present time the frequency with which lack of equivalence in bioavailability of chemically equivalent formulations may occur. However, the parameters associated with defining the bioavailability of a drug have been identified and the factors for assessing a drug's bioavailability in most instances are known or can be determined.

It is the responsibility of the manufacturer to assure by acceptable scientific evidence that each dosage form of each drug product is formulated so as to meet appropriate standards, is safe, and has the effectiveness claimed in its labeling. For some drugs a necessary part of this assurance is evidence that the active drug in a drug product is biologically available to a uniform and acceptable degree.

Suitable methodology for accurately measuring the bioavailability of a drug in humans is not currently available for many drug products. Practical limitations on the number of investigators and clinical research facilities available for such work also precludes the possibility of testing in the near future every formulation of every drug currently on the market. There is no reason to believe that a rigid across-the-board requirement for bioavailability testing of every marketed drug product would, on a benefit/risk ratio basis, improve the quality of drug products commensurate with the expenditure of human and technical resources. Thus, it is necessary to set priorities in the categories of drugs selected for bioavailability testing, with primary attention directed toward those in which a defect in bioavailability would be most detrimental to patient care.

In view of the above, the FDA will publish, from time to time, lists of drugs for which bioavailability data will be required on the basis of medical importance and/or indications that problems of bioavailability have been suggested or suspected.

To develop the lists of drugs referred to, FDA initiated an exhaustive search of published literature and agency files concerning any problems of bioinequivalence among multiple source drugs. This work necessitated examining scientific literature on the subject in order to determine which references adequately documented and supported the existence of actual drug bioinequivalence problems. FDA also sought to establish scientific criteria for determining in advance where a bioinequivalence problem was most likely to arise.

In addition, FDA reviewed drug application files to identify evidence of any actual bioinequivalence problems. The resulting information established in 1973 that in 6 of the 13 cases in which a bioinequivalence problem was identified, it was found that it was the reference product, rather than the new manufacturer's product, that was substantially less bioavailable. (Currently about one-third of 29 documented bioinequivalence problems involve the first-marketed product.) In other words, the pioneer's product was not delivering the quantity of active ingredient once believed to be available; the original clinical trials and de-

velopment of the initial manufacturing standards turned out not to have guaranteed the full potential bioavailability in the product. Therefore, in order to eliminate the product-to-product bioinequivalence, it would be necessary to upgrade the bioavailability of the pioneer. As a result of this conclusion, and the agency's experience of bioinequivalence among batches of individual brands of digoxin, the concern for bioinequivalence problems had to extend beyond multiple source drugs to include single source drugs as well.

After the January 5, 1973 proposal, there were numerous reports, symposia, and publications by academic institutions, industry, professional groups such as the Academy of Pharmaceutical Sciences, and organizations such as the National Academy of Sciences and the World Health Organization dealing with the subject of drug bioavailability. FDA actively participated in this dialog and sponsored some of the public meetings dealing with the subject of drug bioavailability. From these discussions new understandings of bioinequivalence problems have evolved, along with new procedures for their solutions. No final action was taken, however, on the January 1973 proposal.

Beginning on April 12, 1974, a Drug Bioequivalence Study Panel, formed by the Congress of the United States, Office of Technology Assessment (OTA), began to examine the relationships between the chemical and therapeutic equivalence of drug products and to assess the capability of current technology to determine—without therapeutic trials in human subjects—whether drug products with the same physical and chemical composition produce comparable therapeutic effects. FDA shared with the Panel its experience in preparing the lists of drugs with bioavailability problems, and the definitions, concepts, and solutions that had evolved since the 1973 proposal. On July 15, 1974, the OTA Report was released. Among the conclusions and recommendations contained in the report were the following:

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2. Variations in the bioavailability of drug products have been recognized as responsible for a few therapeutic failures. It is probable that other therapeutic failures (or toxicity) of a similar origin have escaped recognition.

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4. It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical should be identified. Selection of these classes should be based on clinical importance, ratio of therapeutic importance to toxic concentration in blood, and certain pharmaceutical characteristics.

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11. A system should be organized as rapidly as possible to generate an official list of interchangeable drug products. In the development of the list, distinctions should be made between two classes of drugs and drug products.

a. Those for which evidence of bioequivalence is not considered essential and that could be added to the list as soon as standards of pharmaceutical equivalence have been established and satisfied.

b. Those for which evidence of bioequivalence is critical. Such products should be listed after they have been shown to be bioequivalent or have satisfied standards of pharmaceutical equivalence that have been shown to insure bioequivalence.

In response to the evolution of ideas on bioavailability and bioequivalence after the January 1973 proposal, in the FEDERAL REGISTER of June 20, 1975, that proposal was withdrawn (40 FR 26142) and two separate notices of proposed rulemaking were issued, one dealing with bioavailability testing requirements (40 FR 26157), and the other, with establishing bioequivalence testing requirements for certain drug products (40 FR 26164). In the latter notice, it was stated (id. at 26165):

The Commissioner recognizes that a few bioequivalence problems have been noted in the past and others may become apparent in the future. However, he believes that relatively few of the currently marketed drug products meeting current in vitro standards and current good manufacturing practices will be found to have medically significant bioequivalence problems. For this reason, he does not believe that it is necessary or in the public interest to undertake the task of developing new in vitro bioequivalence standards for all drug products. The procedures being proposed by the Commissioner are intended to identify bioequivalence problems involving currently marketed drug products and to develop adequate in vitro bioequivalence standards for these drug products.

The Commissioner is of the opinion that it is neither necessary nor feasible to require in vivo bioavailability testing of all drug products which were evaluated as effective under the drug efficacy study. For many such drug products, such testing would involve human risk and would be a waste of human resources with little benefit to the public health. Furthermore, the Commissioner is of the opinion that, for many drug products, the use of a current in vitro test comparing the drug product to a reference material may be adequate to assure the quality and uniformity of drug products which are intended to be used interchangeably as well as all batches of the same drug product.

In the continuing controversy over whether proof of bioequivalence is necessary for all drug products, the Commissioner remains convinced that only a small fraction of all drugs present bioequivalence problems, and that, among those drugs that are currently marketed by more than one supplier, the problem drugs have now mostly been identified. For the remainder, bioequivalence can be pharmaceutical equivalence.

The agency has taken steps to eliminate the problems posed by those drugs that present bioinequivalence problems. Throughout the period 1970 through 1977, even without formal regulations on bioavailability and bioequivalence requirements, FDA continued to require bioavailability data in ANDA's for many generic drug products, even though in some cases compliance was deferred pending development of appropriate methodology. As a condition for obtaining FDA approval, The agency required newly submitted ANDA's for those drugs having known or potential bioinequivalence problems to contain evidence demonstrating that the drug product proposed for approval was bioequivalent to a reference product. Generally, the reference product was the pharmaceutically equivalent drug product that was subject to an approval full NDA. In conjunction with the June 20, 1975 FEDERAL REGISTER notices cited above, the agency limited these requirements to a specific list of drugs covered by DESI notices (40 FR 26142). The standards used in compiling this list were described in that notice, and more fully discussed in the FEDERAL REGISTER of January 7, 1977, in which the list was affirmed (42 FR 1624, 1626):

* * * The proposed [biocquivalence] regulations under § 320.3(b) [published on June 20, 1975 (40 FR 26164); codified as § 320.52 on January 7, 1977 (42 FR 1624)] listed factors that the Commissioner would consider in determining whether there is a bioequivalence problem that requires the establishment of a bioequivalence requirement. Using these criteria, the Commissioner made a tentative finding that the drug products listed in the preamble had a known or potential bioequivalence problem. The purpose of the list was to generage public understanding of how FDA intends to apply the factors set forth in proposed § 320.3(b) to identify drug products for which a bioequivalence requirement should be established. Although an attempt was made to identify each drug product with a known or potential bioequivalence problem, the Commissioner recognizes that the list may omit some drug products with a known or potential bioequivalence problem. Likewise, the Commissioner emphasizes that a drug product's inclusion on the list does not necesarily imply that FDA has positive evidence of bioinequivalence among the various brands of the drug product.

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In compiling the list, FDA took a conservative approach. Therefore, a drug product was included on the list if, in FDA's opinion, there was any suspicion that the drug product had a known or potential bioequivalence

problem or was a member of a class of drug products for which there was suspicion that at least on member of the class had a known or potential biocquivalence problem. The Commissioner is of the opinion that, as evidence of biocquivalence is closely exmined, few of the drug products listed will be determined to have well-documented, medically significant bioequivalence problems. A "medically significant bioequivalence problem" is one that would result in therapeutic failure or a hazard to a patient if different brands of the same drug product or different batches of the same brand are not bioequivalent. The Commissioner believes that a determination of bioequivalence is most critical in a drug product that has a narrow therapeutic-toxicity dosage range and requires careful patient titration and monitoring for safe and effective use.

* * * * *

The purpose of the list was to alert persons marketing a drug product on the list that, on the basis of an in-house review of data available to FDA, the Commissioner is concerned that the product has a bioequivalence problem and he will likely propose to establish a bioequivalence requirement for the drug product. At the time the Commissioner proposes a bioequivalence requirement, he will document the data to support the requirement. These persons, therefore, can rely on this advance information if they wish to conduct bioequivalence studies in anticipation of the establishment of the requirement by rulemaking.

The January 1977 notice went on to explain the regulatory requirements that were being applied for products containing drugs on the list pending the establishment of bioequivalence requirements (id.):

The Commissioner advises that FDA will continue to require the submission of bioavailability data in a full or abbreviated NDA for any of these products and for identical, related, or similar drug products. This policy is being codified in § 320.22(c) (21 CFR 320.22 (c)) * * *. The FDA intends to propose in the near future * * * the establishment of a bioequivalence requirement for all of these drug products, which upon examination, are determined to have well-documented, medically significant bioequivalence problems. If a bioequivalence requirement is finally established for a drug product after completion of these procedures, the applicant will be required to submit data in the full or abbreviated NDA to demonstrate that the product meets the bioequivalence requirement.

The Commissioner also advises that FDA's current policy is that, until a bioequivalence requirement is established for a drug product, manufacturers submitting a full or abbreviated NDA for a drug product already identified by FDA as having a known or potential bioequivalence problem will be required to meet the same requirements as previous manufacturers. Thus if previous manufacturers have been required to conduct in vivo studies, new manufacturers will be required to conduct in vivo studies even though there is evidence that a bioequivalence requirement could be established on the basis of an in vitro test. This assures that opportunity for public comment will be provided before an in vitro test is substituted for an existing in vivo test to demonstrate bioequivalence, and that competing firms are treated fairly and equally by the agency. The Commissioner advises that, pursuant to the agency's policy of minimizing human studies, FDA will give priority to the establishment of bioequivalence requirements to those products for which an in vitro test is available.

To summarize, since the early identification of bioequivalence problems, FDA has sought to assure the bioequivalence of pharmaceutically equivalent drug products. The agency undertook two parallel activities: (1) the development of requirements for bioavail- ability testing and for demonstrating bioequivalence (now codified in 21 CFR Part 320), and (2) in anticipation of such requirements, a review of the evidence of bioavailability and bioequivalence in ANDA's for those pharmaceutically equivalent drug products for which evidence of a bioinequivalence problem exists. Although the first activity has taken considerable time and effort to put into place, the second activity has functioned well for the last 8 years and has provided considerable bioequivalence data and information contained in ANDA submissions. For these products there is a reliable basis for determining the bioequivalence of specific pharmaceutically equivalent drug products.

3. *Controlling batch-to-batch consistency.* Bioequivalence is only one test of equivalent safety and effectiveness among different drug products that are pharmaceutical equivalents. Other factors that may affect safety and effectiveness of such drug products include both compliance of the manufacturing process with current good manufacturing practice and adequacy of drug product labeling. These factors, as well as conformity with compendial or other standards of identity, strength, quality, and purity, are regulated through mechanisms other than the bioequivalence requirements. These other mechanisms provide a further basis for concluding that pharmaceutically equivalent and bioequivalent products may be considered therapeutically equivalent. The mechanisms, described in the following paragraphs, are as follows: (a) the new drug approval and antibiotic certification processes, (b) the batch certification procedures, (c) the good manufacturing practice regulations, and (d) FDA's monitoring of the marketplace.

(a) The new drug approval and antibiotic certification processes: Section 505 of the act requires that each "new drug," as defined in section 201(p) of the act, be subject to an approved new drug application before being introduced into interstate commerce (21 U.S.C. 355, 321(p)). Agency regulations describe two types of application: a full new drug application (NDA) and an abbreviated new drug application (ANDA) (21 CFR 314.1). In general, the ANDA is currently permitted only for drug products subject to a DESI notice either rating the active drug ingredient as effective (see FEDERAL REGISTER of September 1, 1978 (43 FR 39126)) or requiring further studies to evaluate effectiveness (see FEDERAL REGISTER of February 17, 1978 (43 FR 7044)); the active drug ingredients in these drug products were all first marketed prior to 1962. Both types of application require submission of information on inactive ingredients, labeling, and manufacturing practices (21 CFR 314.1).

Under section 507 of the act, once an "antibiotic drug," as defined in that section, has been approved for safety and effectiveness, regulations providing for certification of batches of products containing the drug are issued (21 U.S.C. 357). These regulations require that persons seeking to market an antibiotic drug product through submission of a request for certification provide FDA with information on inactive ingredients, labeling, and manufacturing practices similar to that required in new drug applications (21 CFR 431.1, 431.17, 431.50).

The process of reviewing and approving new drug applications and antibiotic certification forms enables FDA, in addition to determining pharmaceutical equivalence and bioequivalence of the drug products, to review the inactive ingredients in the drug products, to assure the inactive ingredients in the drug products, to assure the adequacy of labeling, and to evaluate any proposed specific manufacturing controls to assure appropriate quality and batch-to-batch consistency. Only when all these elements meet regulatory requirements may an application be approved or an antibiotic drug product be eligible for certification. As discussed in subsection (b) below in this preamble, each batch of an antibiotic drug product also must be submitted for FDA testing and certification before being marketed. Once an application or certification form is approved, moreover, changes may not be made in any of the critical factors, including inactive ingredients, labeling, and manufacturing controls, without prior notice to, and generally prior approval of, FDA (21 CFR 314.8; 431.16). Changes are accomplished through supplemental applications and amended antibiotic applications. Thus, the new drug approval process and the antibiotic certification process are important parts of FDA's program for determining before marketing commences—and thereafter maintaining—the therapeutic equivalence of drug products subject to sections 505 and 507 of the act.

Conversely, the absence of any such process for drugs that are claimed to

be neither "new drugs" nor "antibiotic drugs" substantially vitiates FDA's present ability to evaluate the therapeutic equivalence of such drugs. Unlike antibiotic drugs and new drugs, these other drug products may be placed on the market at any time without prior notice to FDA; under section 510 of the act, the manufacturer is required only to notify the agency of the availability of the product in the first June or December following marketing (21 U.S.C. 360). Even when this notice is submitted, the manufacturer is required to provide only limited information: qualitative and quantitative identification of the active ingredients and a copy of the labeling of the drug product (21 CFR 207.25(b)(4) and (6)). The agency does not receive a qualitative or quantitative identification of inactive ingredients, evidence regarding bioavailability, or manufacturing controls, unless they are voluntarily supplied. Moreover, even if the manufacturer freely provides the information, it may change the formulation, the labeling, and the manufacturing process at any time without prior notice to FDA.

For such drugs, FDA can obtain information similar to that required in a new drug application only by conducting an on-site inspection of the manufacturer's records under section 704 of the act (21 U.S.C. 374). These records would probably not be organized in the format of an NDA or ANDA. Clearly, this procedure is quite costly, given the freedom of firms to enter the market and to modify their products. The procedure may also not be adequate for FDA to assure the safety, effectiveness, quality, or therapeutic effectiveness of a drug product at any given point; many batches of a product may already have been distributed before FDA could conduct an inspection, and the product could be substantially modified after an inspection without notice to the agency. Thus, FDA cannot accept, for example, the argument made by counsel for the National Association of Pharmaceutical Manufacturers that bioequivalence can be adequately monitored without premarketing review of drug products. (See statement of Milton Bass quoted in 40 *FDC Reports* (the "Pink Sheet"), No. 50, p. 22 (Dec. 11, 1978).)

With regard to drugs subject to the new drug approval process, it has been argued that the ANDA approval process is less demanding than the NDA approval process, and that therefore product quality is less reliable among drug products covered by an approved ANDA. (See, e.g., statement of C. Joseph Statler in Drug Quality Hearings, pp. 16529-16538, and pp. 15782; PMA's complaint in the Drug List Litigation, para. 12.) The argument appears to be more abstract than empirical. Because most members of PMA hold at least one approved ANDA is it to be inferred that these manufacturers apply different quality control standards internally for their ANDA products than for their NDA products, or that ANDA's are adequate for preclearing PMA member's generic drug products but not others? Despite these defects in reasoning, the argument and its underlying assumptions should be examined closely.

The criticisms of ANDA's appear to fall into three areas: (1) ANDA's do not contain adequate evidence of safety and effectiveness to justify approval of the drug product; (2) ANDA's do not contain evidence of bioavailability of the drug product or its bioequivalence with pharmaceutically equivalent drug products; (3) ANDA's do not contain, or contain substantially less, infomation regarding the manufacturing processes and controls for, and the packaging of, the drug product.

In FDA's opinion, none of these objections is valid.

First, regarding the absence of full safety and efficacy data, the abbreviated NDA is authorized in lieu of a full NDA only after a decision has been made through the DESI review process that further information is not necessary regarding the safety and effectiveness of the active drug ingredient in a specified indication for use (21 CFR 314.1(a)(1)). The full rationale for this policy has been discussed at length in several FEDERAL REGISTER notices; see, for example, notice of proposed rulemaking on acceptability of ANDA's, September 1, 1978 (43 FR 39126); and notices of opportunity for hearing published in the FEDERAL REGISTER of April 29, 1977 (42 FR 21847), June 10, 1977 (42 FR 30002), August 9, 1977 (42 FR 40248), and September 16, 1977 (42 FR 46592). If one drug product has been shown to meet the criteria for therapeutic equivalence with another drug product, and either has been shown by clinical trials to be safe and effective for its intended uses, there can be no justification for routinely requiring clinical trials to demonstrate the safety and effectiveness of the other drug product. In the absence of a reasonable scientific basis for believing that the two drug products may not be equivalent in safety and efficacy, duplicative clinical testing is unacceptable on ethical, social, economic, and scientific grounds.

The second criticism, that ANDA's do not assue bioavailability or bioequivalence, is dealt with at length in section III.B.2. of this preamble. In brief: (i) Only a small percentage of drugs for which ANDA's are permitted have known or potential bioinequivalence problems. For the others, bioavailability studies are neither necessary nor desirable. (ii) Since June 1975, the agency has identified publicly all of those multiple source drugs which it believes may warrant proof of bioequivalence. The drugs without bioinequivalence problems have not been required, in the ANDA approval process, to have their bioavailability or bioequivalence established, and they should not be so required until evidence becomes available raising a real risk that a bioinequivalence problem exists. The criteria for identifying such a risk have been carefully described in FDA regulations after a full public proceeding (21 CFR 320.52). (iii) For those drugs identified as presenting problems of bioinequivalence, and for which methodology exists, the agency has required evidence of bioequivalence to an approved pharmaceutically equivalent drug product, generally one that is subject to a full NDA. In sum, for many drug products it would be unnecessary and wasteful to require proof of bioequivalence in order to obtain approval of an ANDA; for the lesser number of drug products that are known to present potential or real bioequivalence problems, the ANDA process can and in fact generally does provide sufficient assurance that approved products are bioequivalent; for any drug product known to present a bioequivalence problem that has not been satisfactorily resolved by the ANDA process, FDA will not evaluate the drug as therapeutically equivalent.

The third criticism, that ANDA's require less information regarding drug product contents, manufacturing, and packaging, is in error. It is true that current FDA regulations do state that an ANDA need contain summaries or outlines of the formulation, manufacturing, and packaging information required in a full NDA (21 CFR 314.1(f)(1)). These regulations do not reflect current agency practice which, beginning in 1972, has required ANDA applicants to submit full information analogous to the information required to be submitted in full NDA's. These requirements were imposed under 21 CFR 314.1(f)(5) and have been complied with in most ANDA's approved in recent years. In the FEDERAL REGISTER of June 20, 1975 (40 FR 26156), the Commissioner proposed to conform the ANDA regulations with agency practice and to eliminate any differences between NDA and ANDA requirements in reference to product composition, manufacturing methods, facilities and controls, and packaging. In a notice published in the FEDERAL REGISTER of September 1, 1978 (43 FR 39126), the agency recently affirmed its intention to act upon this proposal in the near future. In conclusion, FDA believes that new drug approval process, including the ANDA review proc-

ess, and the process for reviewing antibiotic drug certification requests, constitute important and effective mechanisms for determining whether drug products are therapeutically equivalent and for controlling batch-to-batch consistency of approved drug products in order to maintain assurance of therapeutic equivalence.

(b) The batch certification process: Under section 507 of the act, each batch of an antibiotic drug product, unless exempted by the agency, is subject to testing by FDA and must be certified by the agency as meeting applicable standards before it may be marketed (21 U.S.C. 357). This requirement is in addition to the submission and approval of components, labeling, and manufacturing processes required under 21 CFR 431.1 and 431.17, described in this section of this preamble, and has served to increase confidence that antibiotic drug products are of consistent quality batch. Over the last 5 years, from January 1974 through October 1978, approximately 20,000 batches have been submitted annually to FDA. The rejection rate has averaged less than one-half of 1 percent of the batches submitted. The existence and success of this pogram provides a further basis for concluding that certified antibiotic drug products that meet the criteria for therapeutic equivalence may reasonably be considered to provide the same therapeutic effects.

The agency has also employed the batch certification process to solve an important bioinequivalence problem. In 1974, because of the potential of serious risks to patients, FDA acted to require ANDA's for all digoxin products in order to assure their bioequivalence. Studies had demonstrated clinically significant differences in the bioavailability of different batches of digoxin by single manufacturers as well as in different batches by different manufacturers. (See the FEDERAL REGISTER of January 22, 1974 (39 FR 2471); now codified in 21 CFR 310.500.) The firm that first marketed digoxin in the United States objected and, in the face of a prolonged legal challenge, compliance with the ANDA requirements was postponed indefinitely. (See the FEDERAL REGISTER of March 8, 1974 (39 FR 9184).) Pending resolution of the legal issues raised by this firm, FDA instituted a program by which manufacturers would submit batches to FDA for dissolution rate testing before releasing them to the market. As a result of this special program, a serious health problem related to bioinequivalence was rapidly and effectively brought under control and batch-to-batch consistency within and among manufacturers was assured. An analogous effort is now being conducted with regard to two other drugs, digitoxin and prednisone in tablet form. Upon completion, the agency will be able to evaluate the therapeutic equivalence of tableted prednisone drug products; digitoxin, however, is not subject to approval under section 505 of the act and therefore will not be evaluated for therapeutic equivalence.

The authority to adopt similar programs for other drug products, should serious bioinequivalence problems arise, is confirmed in 21 CFR 320.55. The availability of this proven mechanism to address future problems further justifies the belief that the batch approval process reasonably assures the batch-to-batch consistency of drug product quality. Such assurance supports the conclusion that drug products that are pharmaceutically equivalent and bioequivalent are also generally therapeutically equivalent.

(c) Good manufacturing practice regulations: Section 501(a)(2)(B) of the act requires that drug products be made in conformity with current good manufacturing practice ("CGMP") in the industry (21 U.S.C. 351(a)(2)(B)). To implement this provision, the agency has long had regulations that set forth objectives, or standards of performance, to be achieved by individual firms in their facilities, equipment, personnel, production methods, quality control procedures, and related aspects of manufacturing (21 CFR Parts 210 and 211). The objectives reflect the results attained by those manufacturing practices that FDA has found to be "current" and "good" in the industry. The current good manufacturing practice (CGMP) regulations are not generally designed to prescribe specific manufacturing processes; such an approach would be difficult to implement, because of the wide variety of drug products, and would unduly interfere with technological evolution. Moreover, at least for new drugs, the new drug approval process provides a superior mechanism for addressing unique problems in manufacturing specific drug products.

The CGMP regulations are more appropriate for problems common to the manufacture of all drug products or of all drug products of a particular class, e.g., large volume parenteral drug products, medical gases, or radioactive pharmaceuticals. Central among these problems, of course, are the general practices and procedures necessary to assure batch-to-batch consistency in drug quality. CGMP regulations specifically focus on matters such as responsibilities for quality control operations, building and equipment design and maintenance, control of ingredients and in-process materials, production and process controls, packaging and labeling controls, expiration dating, warehousing and distribution procedures, laboratory controls, and testing and releasing products for distribution.

The CGMP regulations, adopted in 1963 and revised in 1971, will be completely superseded on March 28, 1979, by regulations published in the FEDERAL REGISTER of September 29, 1978 (43 FR 45014). These new regulations are the product of a lengthy and comprehensive review of industry practices as reflected in agency records such as NDA's, ANDA's, and establishment inspection reports, a proposal published in the FEDERAL REGISTER of February 13, 1976 (41 FR 6878), and extensive comments from the industry. Many older requirements were updated and clarified; important new quality assurance measures were added; and the legal status of CGMP regulations was strengthened. Consequently, it is now the position of the agency, as stated in the new 21 CFR 210.1:

> (a) The [CGMP] regulations * * * contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.
>
> (b) The failure to comply with any [CGMP] regulation * * * in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

The agency evaluates compliance with CGMP regulations during factory inspections under section 704 of the act (21 U.S.C. 374). In the event of noncompliance, the agency notifies the firm of the alleged violation through a Notice of Adverse Finding or a Regulatory Letter. (See 21 CFR Part 7, Subpart B, published in the FEDERAL REGISTER of June 23, 1978 (43 FR 27498).) If corrective action is not taken, or the violation is such that formal enforcement action should not be delayed, FDA may begin proceedings to seize the violative products or to enjoin future violations. Criminal penalties may also be sought, and new drug applications can be withdrawn. FDA has been successful in enforcing the standards contained in the previous CGMP regulations. (See, e.g., *United States* v. *An Article of Drug * * * White Quadrisect*, 484 F.2d (7th Cir., 1973).)

Because of this success, because of the substantive improvements in the new CGMP regulations, these regulations should provide another important assurance of batch-to-batch consistency in drug product quality. Again, this assurance, when applied to drug products otherwise known to be pharmaceutically equivalent and bioe-

quivalent, makes it reasonable to believe that they will provide the same therapeutic effect.

(d) FDA's monitoring of the marketplace: In implementing its quality assurance activities, the FDA relies on a variety of its facilities and resources, including the National Center for Drug Analysis in St. Lous, the National Center for Antibiotic Analysis in Washington, and 20 district laboratories. More than 200 trained drug investigators are stationed in the 20 FDA district offices. Each year these investigators conduct inspections of over 6,000 establishments in which human drugs are manufactured; they also provide a critical capacity for fast and effective followup to reports to problems with drugs. The National Center for Drug Analysis is now capable of performing approximately 100,000 analyses annually on marketed drug products. The National Center for Antibiotic Analysis performs batch certification and postcertification testing on batches of antiobiotics and insulin; approximately 20,000 batches are submitted to FDA each year for certification, release, or check testing. The Bureau of Drugs, headquartered in Rockville, Maryland, provides direction and coordination of FDA's drug quality activities. The Bureau employs over 1,100 doctors, pharmacists, chemists, compliance officers, and other professional and support personnel.

The agency carries out a number of programs to evaluate marketed drug products, to gather information regarding defective products, and to assure compliance with CGMP regulations, NDA and ANDA commitments, and compendial or other applicable standards. Any products that are found through any of these programs to be out of compliance with applicable standards are promptly subjected to followup regulatory action. These programs include the following:

(i) *Factory inspections.* FDA inspects every establishment in which drug products are manufactured at least once every 24 months. As noted, over 6,000 drug inspections occur each year. Most drug firms appearing on the proposed list are inspected several times during that period. In addition, the agency will not approve an NDA or ANDA for a drug product unless the manufacturer has been inspected and has been found to be in compliance with CGMP regulations within the preceding 12 months.

(ii) *The Quality Assurance Program for Selected Marketed Drugs.* Each year categories of drugs are selected by the Bureau of Drugs on the basis of therapeutic importance, amount of usage, past quality problems, or other parameters, for testing by FDA laboratories. Under this program, district offices are directed to collect samples, which are then analyzed by various FDA laboratories for the appropriate specifications. About 1,500 batches are analyzed annually under this program.

(iii) *The Drug Product Problem Reporting Program.* This surveillance system is conducted jointly by FDA and USP officials. Under this program, pharmacists and other health professionals report to the USP any unusual observations regarding drug products they pruchase or dispense. Officials of USP, in turn, send copies of these reports to FDA, where review and followup are instituted. In addition, each manufacturer is supplied with a copy of any report involving one of its products. Under this program, over 5,000 reports are submitted annually.

(iv) *The Antibiotic Post-Certification Sampling Program.* FDA district offices are directed to collect samples of antibiotics that have previously been certified by the agency. To assure that marketed antibiotics meet specifications for the length of expiration dating, samples are collected from the oldest batches available. Samples are then analyzed by FDA's National Center for Antibiotic Analysis.

(v) *The District-Initiated Sampling Program.* Finished drug products that are not covered under any of the above programs may be monitored for acceptability under the FDA District-Initiated Sampling Program. Each FDA district office selects particular products to sample and test for appropriate specifications. Selections are made on the basis of factory inspections within the district, consumer complaints, previous experience with particular products or manufacturing facilities, or other factors of relevance to the field enforcement efforts.

(vi) *The Government-Wide Quality Assurance Program.* The agency is responsible for assuring the quality for drugs purchased by the Department of Defense, the Veterans Administration, and the Health Services Administration. This program provides that before any government contracts for drug purchases are issued, FDA must determine that the supplier is in compliance with regulatory requirements applicable to the drug to be purchased. After a contract is let, FDA inspects to evaluate whether the supplier has operated in conforming with CGMP regulations. In certain instances, specific products are analyzed by FDA laboratories to determine that these products do, in fact, meet appropriate quality criteria. Delivery of the finished drugs will not be accepted by the purchasing government agency without a final FDA review and evaluation of the supplier. In the 3½ years since this program began, FDA has made approximately 45,000 quality determinations related to Federal drug procurement. In response to requests from 8 States for similar quality assurance assistance from FDA, the agency has recently begun a pilot program at the request of the State of New York to examine the feasibility of providing similar services to State procurement programs.

(vii) *MAC program.* The Maximum Allowable Cost (MAC) regulations of the Department of Health, Education, and Welfare authorize the establishment of a limit on the amount the Federal government will pay under the Medicare and Medicaid statues in reimbursing for the cost of multiple source prescription drug products (45 CFR Part 19). Such limits are imposed on a drug-by-drug basis through defined procedures by the Pharmaceutical Reimbursement Board. Under these regulations, FDA is charged with the responsibility for reviewing drugs that are candidates for MAC Limits to assure that there are no bioequivalence issues or regulatory actions pending that should prevent the establishment of a MAC limit (45 CFR 19.5(b)). These documented reviews are carefully conducted by FDA under established procedures. As part of the review, results from bioequivalence and quality surveys are examined, inspection profiles of approved manufactures are reviewed, the Drug Product Problem Reporting System is queried, product specifications are compared and other quality assurance indices are reviewed. A written, documented response, which becomes part of the public administrative record, is then forwarded to the Pharmaceutical Reimbursement Board, the body that establishes the MAC limits.

(viii) *Biopharmaceutics Research Program.* The agency has sponsored a number of studies to determine whether a bioinequivalence problem exists among multiple source drug products and to develop methodology and standards for measuring and assuring bioequivalence. To date, 24 drugs have been evaluated for bioequivalence through FDA funded clinical studies; the majority of these studies were carried out by FDA contractors who have published their findings.

(ix) *Manufactures' reports of problems involving their own drug products.* FDA regulations require manufacturers of new drugs and antibiotic drugs to report promptly to the agency any information concerning manufacturing mixups or failures or unexpected adverse reactions or therapeutic failures in patients (21 CFR 310.300, 431.60). All manufacturers are required to notify FDA or firm-initiated removals from the market of drug products that the firm believes violate the act; with nonviolative products, firms are advised to consult with FDA (21 CFR 7.46, published in the FEDERAL REGISTER of June 16, 1978 (43 FR

26202)). The agency conducts a follow-up investigation on these reports, as appropriate, to determine the cause of the problem and the need for any FDA-initiated activity to correct the problem or prevent its recurrence.

(x) Manufacturers' reports of problems involving competitors' drug products. Although not required to do so, many manufacturers conduct tests on their competitors' products. FDA is frequently notified by these firms that, in their judgment, one or more competing products fail to meet compendial standards, or are bioinequivalent, or otherwise are in violation of the act or present a public health problem. Here, too, the agency conducts appropriate followup investigations that may lead to regulatory actions against the violative product or a change in applicable standards to protect the public health.

The agency concludes that these diverse programs, with different scopes and purposes but somewhat overlapping perspectives on the prescription drug market, provide assurance that manufacturers and drug products deviating from established requirements will be detected with reasonable promptness. Once a problem is detected, FDA can take a variety of regulatory enforcement activities to remove any violative products from the market and to prevent further distribution of violative drug products. The enforcement tools available to FDA include seizure of violative products (21 U.S.C. 334), injunctions against further violations (21 U.S.C. 332), criminal prosecution of those responsible for violative products (21 U.S.C. 333), and requests for voluntary recalls of violative products (21 CFR Part 7, Subpart C, published in the FEDERAL REGISTER of June 16, 1978 (43 FR 26202)).

All of the FDA's monitoring activities described above furnish additional grounds for concluding that drug products found to be pharmaceutically equivalent and bioequivalent will remain so and thus may be evaluated as therapeutically equivalent.

C. THE PRACTICAL FOUNDATION FOR EVALUATION OF DRUG PRODUCTS AS "THERAPEUTIC EQUIVALENTS"

Notwithstanding the scientific priciples and regulatory controls discussed above, concern has been expressed that, on the level of daily experience, FDA is unable to assure the consistent quality of "generic" drug products, so that therapeutic equivalence is not and can never be a practical reality. The PMA and some others have argued that products made by a certain segment of the pharmaceutical industry, defined variously as PMA members, "large" manufacturers, or "research-intensive" firms, are consistently of a higher quality than products made by the rest of the industry. (See, e.g., statement of Mr. C. Joseph Stetler, President, PMA, in "Drug Quality Hearings," 16529-38, and Pauls and Kloer, "FDA Enforcement Activities Within the Pharmaceutical Industry: Analysis of Relative Incentive" (hereafter called "Lilly Study").) Consequently, the argument implies, if a patient receives a competing drug product in place of that made by the PMA member (or large company or research-intensive firm), the patient has a much greater probability of using a substandard product that may be ineffective or even unsafe.

The question must then be asked: When a patient hands a pharmacist a prescription written for a brand name product, and the pharmacist selects a substitute product evaluated by FDA as being therapeutically equivalent to fill the prescription, how likely is it that the substitute product will be of the same quality as the brand name product prescribed by the patient's physician?

The answer given by FDA to this question is that it is overwhelmingly likely that the substituted product will be equal in quality to the prescribed product. Indeed, it is so likely that the products will be equal in quality, that the possibility that they will not be equal can properly be disregarded for practical purposes. There are several reasons for this conclusion.

First, as a result of the laws and programs previously discussed in this preamble and of the general competence of firms in the pharmaceutical industry, the overall quality of approved drug products sold in the United States is very high. FDA's monitoring of the marketplace and its antibiotic certification program disclose an excellent record of drug products that meet all applicable standards. Compared with the volume of drugs manufactured every year, the frequency of recalls and other regulatory actions is quite small. This general conclusion extends to all segments of the pharmaceutical industry engaged in the manufacture of drug products that are the subject of approved applications. Only these products are proposed to be included in the FDA list. By any measure of compliance with quality requirements, the level of industry performance is exceptionally good.

Second, the vast majority of generic drug products that are sold in the United States are manufactured by the very same group of companies that manufacture brand name products. Taking, for example, the members of PMA as one accepted definition of brand-name manufacturers, it appears that these firms account for about 95 percent of the sales of all approved multiple source drug products proposed to be evaluated as therapeutically equavalent. These drug products include the "pioneer" brand drug products, generic drug products marketed under a brand name (so-called "branded generics"), and generic drug products marketed without a brand name. Even if one examines the sales of drug products marketed solely under a generic name, PMA members supply an estimated 80 percent of the approved, therapeutically equivalent drug products. (Under 21 U.S.C. 374(a) FDA is precluded from obtaining sales and financial data from drug firms; the foregoing estimates were derived from published market survey data of wholesale drug purchases of prescription drug products, other than biologicals, by retail drug stores and hospital pharmacies in 1977.) Obviously, when one drug product evaluated by FDA as therapeutically equivalent is substituted for another, it is quite probable that the substituted product will also have been manufactured by a PMA member. No one takes the position that, when a product made by one PMA firm is substituted for a competing product made by another PMA firm, the substituted product is likely to be lower in quality. On the contrary, as far as FDA knows, there is unanimous agreement within PMA that these substituted products will not be inferior, whether labeled by brand name or generic.

Third, the remaining generic products that have been evaluated as therapeutically equivalent—those manufactured by firms that do not also manufacture brand name products—are overwhelmingly likely to be equal in quality to the brand name products. FDA's experience in regulating these products and their manufacturers discloses little meaningful difference in the ability of these firms to meet all applicable standards, nor in their actually doing so.

On June 1, 1978, a study sponsored by Eli Lilly and Co., was released purporting to show that FDA's experience is quite different with respect to firms other than brand name manufacturers. Specifically, the Lilly Study identifies 23 "research-intensive" pharmaceutical firms and compares records of FDA regulatory and monitoring actions on products made by these firms with those involving products of all other drug manufacturers. The authors conclude that products of the "research-intensive" firms "are recalled much less often and * * * have far fewer seizures, injunctions, and prosecutions and fewer drug product problem reports than 'other' companies" (Lilly Study, p. 3).

The Lilly Study has numerous methodological defects. It divides the pharmaceutical industry into two separate categories: "research-intensive" firms

and "other" firms. The authors do not state that criteria by which this distinction was made. When analyzing the study, FDA asked Paul deHaan, an internationally recognized expert on the pharmaceutical industry, to make a similar division, and his list of research-intensive and other firms differs significantly from Lilly's. The agency also divided the universe of drug manufacturers into other pairs: PMA members v. nonmembers firms listed by IMS America as the top 50 drug manufacturers v. all others, firms with sales over $100 million annually v. those with smaller total sales, firms with sales over $10 million annually v. those with less, and those with annual sales exceeding $1 million v. Those with less. Utilizing these divisions, FDA has analyzed recall data for prescription drug products. The agency's conclusion is that no reliable conclusions can be drawn on the relative competence of pairs of drug manufacturers by using the type of analysis Lilly proposed. The FDA analysis of recall data is now being completed and will be made available in the near future. Notice of its availability will be published in the FEDERAL REGISTER, and comments on the Lilly Study and the FDA analysis may be submitted to the agency in conjunction with comments on this proposal.

In analyzing the recall data used in the Lilly Study, FDA discovered that Lilly had included recalls that had nothing to do with drug quality and even recalls that did not involve drug products. The Lilly Study also included recalls of products that would not be evaluated by FDA as therapeutic equivalents. This last error, in particular, renders the Lilly Study irrelevant to the issue of the quality of drug products that might be substituted for brand name products. Lilly included all prescription drug products in its universe for study. FDA would consider only those FDA-approved prescription drug products that are evaluated as therapeutically equivalent.

Within this universe, FDA has no reason to believe that any meaningful quality differences exist among drug products.

To illustrate this, one can look at the data on recalls of prescription drug products in 1977. Of the 94 recalls involving product defects likely to have adverse health consequences, 74 involved drug products that did not have approved new drug applications and therefore would even be eligible for evaluation as therapeutic equivalents. Of the remaining 20, a total of 16 were recalls of products that FDA proposes not to evaluate as therapeutically equivalent. Thus, only 4 recalls in 1977 related to products that FDA would list as being therapeutic equivalents.

Clearly the policies proposed for evaluating drugs as therapeutically equivalent will effectively screen out the vast majority of products that have been subject to recall in recent years. The recall data, when properly analyzed according to the policies proposed for the evaluation of therapeutic equivalence, support the view that the general level of quality of products on the proposed list is very high. Similar results would probably be obtained if one analyzed the products listed as therapeutic equivalents using other measures of compliance with regulatory requirements. There is little meaningful difference in drug product quality between large and small manufacturers, or between brand and generic labels, for products evaluated as therapeutic equivalents.

In summary, arguments that serious differences exist in the quality of competing drug products ignore the very high level of quality for all drug products, rely principally on a methodologically unsound study, and are quite misplaced when applied to drug products that meet FDA's proposed criteria for evaluating therapeutic equivalence. In the absence of reliable data to the contrary, and based on FDA's broad experience in regulating drugs, it is sound and appropriate for FDA and the public to rely on the requirements of law, compendial standards, the drug approval process, and FDA's monitoring, compliance, and enforcement programs to conclude that, for practical purposes, therapeutically equivalent drug products included in the list will be of equal quality.

It should be emphasized, however, that no member of the public is required to rely on these regulatory controls or to accept this conclusion. FDA's evaluations of therapeutic equivalence are not binding on any State, any physician, any pharmacist, or any patient. The list is intended to facilitate substitution and assure that drug product selection decisions are well-informed. FDA's proposed list does not mandate substitution, nor does it require that, when substitution occurs, any particular product is to be dispensed.

Under all State substitution laws now in effect, pharmacists retain the authority and responsibility for the exercise of professional judgment in determining which drug products to keep in stock for purposes of dispensing and in determining which product to use in filling a particular prescription. If a pharmacist believes that a particular product is not of adequate quality, he or she need not stock that product and need not use it for substitution.

A patient who is not willing to rely on the list as an assurance of quality can rely on the professional judgment of his or her physician and pharmacist. Under most drug product selection statutes, a physician can direct that the particular drug product prescribed by the physician be dispensed to the patient. Also, most States require that a pharmacist inform a patient that a substitution may be made. Thus, patients are able to consult with both physician and pharmacist as to the wisdom of substitution in a particular case.

The patient has yet one more protection as well. Under all State substitution laws now in effect, the patient retains the right to insist that certain generic products not be used for substitution or that the prescription be filled with some particular substitute product. If, for example, a patient believes that only five firms make high quality products, the patient can insist that the substitute product be one made by one of those firms. The patient may pay a premium price for that product, because therapeutically equivalent products may differ widely in price, but would simply be exercising a right recognized by law. In some States, however, a patient may only receive his or her chosen substitute if it meets the standards considered equivalent and is less expensive than the prescribed product.

IV. SPECIFIC CRITERIA PROPOSED TO BE USED IN PREPARATION OF LIST

The agency proposes to issue a list that identifies drug products that have been affirmatively approved by FDA for marketing in the United States and evaluates those products on that list that are available from more than one source of supply as to their therapeutic equivalence.

A. IDENTIFICATION OF DRUG PRODUCTS

1. *Approved new drugs and antibiotic drugs.* FDA proposes that the list include all drug products that have been affirmatively approved by FDA under sections 505 and 507 of the act, with certain exceptions.

(a) Exclusions of certain approved products: The agency proposes to exclude from the list two groups of drug products that are subject to approvals under sections 505 and 507 of the act.

(i) *Over-the-counter drug products.* The proposed list does not include drug products that may be sold over-the-counter (OTC) without a prescription, in accordance with section 503(b)(1) of the act (21 U.S.C. 353(b)(1)). Only a small percentage of these drug products are being marketed with approved new drug applications. All OTC drug products are currently being reviewed for safety and effectiveness (21 CFR Part 330). Until that review is completed, the identification of safe and effective OTC drugs is not feasible. Furthermore, the con-

siderations underlying this proposal, as explained in section I.A. of this preamble. apply almost entirely to prescription drug products. Consequently, the agency proposes to exclude OTC drugs approved under section 505 of the act from the list.

(ii) *Prescription drug products not yet determined to be effective.* The DESI review is not yet completed for certain drug products marketed under new drug applications that became effective between 1938 and 1962. Under section 107(c) of the Drug Amendments of 1962 (21 U.S.C.A. 321 note), these applications are "deemed approved" pending a determination on the effectiveness of the drug. Under section 507(h) of the act, regulations were issued permitting certification of antibiotic drugs pending a determination of their effectiveness. The DESI review represents FDA's efforts to apply the efficacy provisions of the act to these drug products.

If substantial evidence of the drug's efficacy is not submitted to the agency in the DESI review, FDA must proceed to withdraw approval of the new drug application. This review program is not yet finished, with the result that there remain on the market "deemed approved" drug products, the effectiveness of which is still in doubt. Inclusion of these products on the FDA list, however, might mislead users into believing that their effectiveness had been established.

In addition, in order to conserve agency resources and concentrate on more serious health priorities, FDA has neither required nor permitted approval of new drug applications for the marketing of drug products that are identical, similar, or related to the drug product covered by a "deemed approved" application until a final decision on effectiveness is made (FDA Compliance Policy Guide 7132c.08). Recently, in a notice published in the FEDERAL REGISTER of February 17, 1978 (43 FR 7044), this policy was changed for certain DESI drugs that are subject to further testing requirements, but implementation is only starting. Consequently, listing of the "deemed approved" products, without permitting others to obtain such an approval, would be unfair and discriminatory.

The agency proposes therefore to exclude from the list at this time all prescription drug products, whether or not subject to a "deemed approved" new drug application, for which a final DESI determination of effectiveness has not been made. "Deemed approved" applications will be included in an appendix to the list for information purposes only.

(b) Listing of unmarketed approved products: The inclusion of a drug product on this FDA list does not necessarily mean that it is being marketed at the present time. The list reflects the products that have been approved for marketing under sections 505 and 507 of the act. A manufacturer may, however, withdraw any of its products from active marketing at any time, while still maintaining an active application in FDA files. The agency, in cooperation with manufacturers, seeks to terminate approvals for products that are not intended to be remarketed in the future. FDA files are, therefore, not generally out of date, and the agency believes that most of the products in this list are marketed at the present time. Nevertheless, some products included in the list may not actually be available for purchase in the United States.

(c) Identification of other distributors or brand names for approved products: The proposed FDA list would identify only the holder of the approved application in FDA files. Frequently, approved products are manufactured for, or purchased and repackaged or relabeled by, distributors who in turn market these products under other labels. These labels may or may not identify the actual manufacturer of the drug product. Because these distributors often shift their sources of supply in the commercial marketplace, there is no feasible way at this time for the FDA to maintain an up-to-date and complete list either linking every approved manufacturer with the distributors currently handling its product or linking each distributor with its current suppliers. Purchasers and dispensers wishing to know the manufacturing source of a particular batch offered by a distributor must rely upon the distributor to disclose such information, either in the labeling or otherwise. Disclosure of the actual manufacturer is not required by the act (21 U.S.C. 352(b)(1)). Absent voluntary labeling or disclosure, there is no ready and convenient way for a purchaser or dispenser to verify that the distributor's product was manufactured under an approved new drug application.

(d) Listing of approved products subject to regulatory actions: From time to time approved products may be found to be in violation of one or more requirements of the act. In such circumstances, the agency will commence appropriate enforcement action to remove the violative product from the market, e.g., by voluntary recall or seizure. If the problem leading to the violation is continuing, so that there exists a risk of future noncomplying products entering the market, FDA will undertake steps to eliminate that risk, e.g., by court injunction, withdrawal of the approval of the new drug application, or revocation of the antibiotic certification. Where the violation is corrected by removal of the particular batch of the product from the market, no need exists to exclude the product from this list; the approval continues and other batches are not tainted. Where additional preventive action is indicated, the agency will utilize appropriate legal procedures to keep the product off the market; exclusion from this list prior to completion of those procedures might be considered improper or an infringement of the application holder's legal rights. Consequently, it is proposed that no such product be excluded from the list until completion of FDA proceedings to withdraw approval of the product under section 505 or 507, as applicable. Retention of a violative product on the list will not have any adverse health consequences because other legal tools are available to the agency to prevent actual marketing of violative products.

2. *Drug products not subject to approved new drug applications or antibiotic certifications.* A number of drug products are currently being marketed under claims of exemption from the applicability of sections 505 and 507 of the act. By far the greatest proportion of these drug products rely upon claims of marketing prior to 1938 and consequent exclusion from the definition of "new drug" in section 201(p)(1) of the act (21 U.S.C. 321(p)(1)). Because these drugs have been distributed in one form or another for many years, patent protection has expired and often several firms are now competing in the market.

For the reasons discussed in section III.C.1. above, the agency proposes to exclude from the list any drug product that has not been reviewed and approved through the new drug or antibiotic approval process. This exclusion does not necessarily mean that any such drug would not meet the current legal standards for a new drug, or is in violation of the law, or is unsafe or ineffective. Rather, the exclusion is based on the premise that FDA has not had the authority or opportunity to evaluate and assure the safety, effectiveness, and quality of the drug product.

B. EVALUATION OF THERAPEUTIC EQUIVALENCE

1. *Scope of evaluations.* The agency proposes to limit its evaluations of therapeutic equivalence to those drug products that are included in the list of products approved under sections 505 and 507 of the act. For the reasons discussed in section III.C.1. above, FDA lacks sufficient information at this time to assess the therapeutic equivalence of drug products not regulated under new drug applications or antibiotic certifications. The agency is not asserting that these products may not be therapeutically equivalent;

their equivalence simply cannot be evaluated or assured. The agency has no current plans to review unapproved drug products for therapeutic equivalence; however, such evaluations may become feasible in the future for at least certain classes of these drug products. At such time, inclusion of these drug products and their therapeutic evaluations in the list will be considered.

FDA also proposes to make no therapeutic equivalence evaluations of approved drug products that are available from only one manufacturer. Obviously only when two or more products are available in the market does the question of therapeutic equivalence arise.

2. *Evaluation of pharmaceutical equivalence.* It is proposed that two drug products will not be evaluated as being therapeutic equivalents unless they are pharmaceutical equivalents, as defined in 21 CFR 320.1(c).

This criterion would be applied as described in the following examples.

(a) Different salts or esters: Different salts and esters of the same therapeutic moiety are regarded as not pharmaceutically equivalent. Therefore, drug products containing different salts or esters will be presumed to be therapeutically inequivalent. Data could be developed adequate to demonstrate the therapeutic equivalence of different salts or esters on a product-by-product basis. But in practice, there are insufficient cases in which such equivalence has been demonstrated to warrant evaluating the therapeutic equivalence of pharmaceutical alternatives. There are no known instances in the proposed list where different salts are evaluated as therapeutically equivalent.

On the other hand, anhydrous and hydrated entities are not considered to be different salts or esters. Thus, as in the case of ampicillin, these two forms will be treated as pharmaceutical equivalents.

(b) Variations in amount of active drug ingredient: Different products may be labeled as containing slightly different quantities of the same active drug ingredient. In practice, the quantity of active ingredient in individual drug products will vary from the amount shown on the label; as long as these variations are within applicable compendial or antibiotic standards, the products are viewed as being in compliance with the act. Similar variations between different brands of drug products should be similarly tolerated. Therefore, two drug products labeled as having different amounts of the same active drug ingredients will be considered as pharmaceutically equivalent, if the difference between declared potencies does not exceed 1 percent.

(c) Products requiring reconstitution, dilution, or other manipulation before dispensing: A drug product may require dissolution, reconstitution, dilution, or other manipulation before dispensing. Pharmaceutical equivalence will be evaluated on the basis of the properties of the drug product before such manipulation. The agency recognizes that the process of manipulation may introduce differences in the drug products. For example, pharmaceutically equivalent powders to be reconstituted for administration as oral or injectable liquids may vary in their expiration time or storage conditions after reconstitution. An FDA evaluation that such products are pharmaceutically equivalent is applicable only when those products are reconstituted, stored, and used under the conditions specified in the labeling of each product.

Although drug products that are solids for reconstitution, diluted solutions, or concentrated solutions contain different concentrations of active ingredients, and thus are not considered to be pharmaceutical equivalents, this evaluation is not intended to prevent the exercise of accepted professional practice to render pharmaceutically different concentrations into pharmacuetical equivalents. For example, concentrated solutions may be diluted to lower strengths by using proper procedures designed to maintain the quality of the product.

(d) Variations in package size: Where package size variations have therapeutic implications, drug products packaged in different sizes are not considered to be pharmaceutical equivalents. For example, many oral contraceptives are supplied in 21- and 28-tablet packets, the 28-tablet packets containing 7 placebo tablets. These two packaging configurations are not regarded as pharmaceutically equivalent and thus not therapeutically equivalent.

(e) Deficiencies in compendial or other applicable standards: As discussed in section III.B.1. above, the agency believes that existing compendial standards are generally adequate to provide a reasonable assurance of therapeutic equivalence. Nevertheless, from time to time specific standards may be found by FDA to be deficient and, until they are corrected or supplemented, they may not permit an FDA evaluation of either pharmaceutical or therapeutic equivalence. When these situations arise, it is proposed that drug products subject to the standard in question not be considered to be pharmaceutically equivalent.

(f) Solutions and powders for aerosol-nebulizer drug delivery systems: Uncertainty about the therapeutic equivalence of aerosolized products arises primarily because of differences in their drug delivery systems. If powders or solutions for aerosolization are marketed without restriction to a specific delivery system, they generally present no therapeutic equivalence issues and may be treated as pharmaceutical equivalents. Those products, however, that are marketed so that they are only compatible with, or are only a component of, a specific delivery system may present significant differences, e.g., in the dose of drug or particle size delivered by different products. The agency proposes that the drug products for use in specific delivery systems not be regarded as pharmaceutically equivalents.

(g) Injectable oil solutions: The absorption of drugs in injectable oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Therefore, FDA proposes that it consider injectable oil solutions to be pharmaceutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.

(h) Aqueous injectable (parenteral) solutions: All injectable products are listed under the general category "Injectable; Injection" but specific routes of administration are not shown. Some multisource products that are pharmaceutical equivalents are labeled by their different manufacturers for different routes of administration. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route of administration stated in the labeling.

The agency proposes that, unless otherwise noted, injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection, all be considered to be pharmaceutically equivalent if they are designed to produce the same concentration for injection and are equivalently labeled.

(i) Large volume parenteral drug products: Certain commonly used large volume intravenous products are not included in this list, e.g., dextrose 5 percent with water, dextrose 10 percent with water, and sodium chloride injection. Virtually all of these drugs came on the market in glass containers before 1938 and have not been required to obtain an approved new drug application as a condition of marketing. When packaged in plastic containers, however, these same drugs are considered to be new drugs requiring approved new drug applications for marketing (21 CFR 310.509, published in the FEDERAL REGISTER of December 15, 1978 (43 FR 58557)). The proposed

list thus includes only those approved solutions in plastic containers.

All large volume parenteral products are manufactured under similar standards regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence. Nevertheless, in keeping with the policy of evaluating only approved drug products, large volume parenterals packaged in glass containers are not included on the proposed list.

(j) Drug products for nonsystemic use: There are a variety of drug products available for topical, ophthalmic, otic, rectal, and vaginal administration that are not intended to produce their therapeutic effect by means of systemic absorption. Dosage forms of these drug products can include solutions, creams, ointments, gels, lotions, pastes, sprays, and suppositories. Different nonsystemic dosage forms are not pharmaceutically equivalent, even though they may contain the same active ingredient. Therefore, FDA proposes that they not be considered therapeutically equivalent. On the other hand, products in the same nonsystemic dosage form will be evaluated as therapeutically equivalent if they are pharmaceutically equivalent.

3. *Evaluation of bioequivalence.* The agency proposes that, in evaluating the bioequivalence of drug products, FDA presume that pharmaceutically equivalent drug products are also bioequivalent, unless there is a scientific reason to believe that an actual or potential problem of bioinequivalence exists with respect to the drug products. When a bioinequivalence problem is identified, however, a drug product will be presumed not to be bioequivalent until a new drug application is approved. The application must contain adequate scientific evidence demonstrating the bioequivalence of the product to an appropriate reference product or reference standard.

The following examples show how this criterion will be applied in particular situations.

(a) Active drug ingredients or dosage forms with documented bioinequivalence problems: FDA has identified those new drugs originally marketed between 1938 and 1962 that are now known or suspected to present bioinequivalence problems (21 CFR 320.22). In compiling this list, the agency took a conservative approach, so that as evidence of bioequivalence is closely examined, a number of the drugs on this list will probably be found not to present a real problem. (See the FEDERAL REGISTER of January 7, 1977 (42 FR 1624).) The criteria that will be used in determining the existence of a bioinequivalence problem are set forth in 21 CFR 320.52. Until the determinations are made, however, bioequivalence, rather than bioequivalence, is presumed. In addition, for any drug product for which a bioequivalence requirement is established under 21 CFR Part 320, Subprt C, bioinequivalence will of course be presumed. No drug product containing an active drug ingredient on the list in 21 CFR 320.22 in the dosage form specified, and no drug product for which a bioequivalence requirement is established, will be considered as bioequivalent unless the manufacturer of the drug product has submitted studies acceptable to FDA fulfilling the bioequivalence requirements.

(b) Active drug ingredient or dosage forms with suspected bioinequivalence problems: FDA's bioequivalence regulations contain criteria and procedures for determining the existence of a bioequivalence problem among drug products other than those identified in the 1977 list (21 CFR Part 320, Subpart C). It is proposed that for any drug ingredient or dosage form that, in FDA's opinion, meets these criteria, bioinequivalence will be presumed. This presumption is solely for purposes of evaluation of therapeutic equivalence and therefore may be made before the commencement of proceedings under the bioequivalence regulations.

(c) Controlled release dosage forms: Controlled release tablets, capsules, and injectables are subject to bioavailability and bioequivalence differences, primarily because different firms developing controlled release products for the same active ingredient rarely employ the same approach to formulating their controlled release products. The agency proposes that different controlled release dosage forms containing the same active ingredient in equal strength not be evaluated as bioequivalent unless equivalence between individual products has been specifically demonstrated through appropriate bioequivalence studies.

(d) Enteric coated oral dosage forms: Drug products in enteric coated dosage forms containing the same active ingredients are subject to significant differences in absorption. Such products cannot necessarily be considered as pharmaceutically equivalent because they do not necessarily meet similar standards, and few manufacturers of enteric coated products have studied the pharmacokinetics of their products. FDA proposes that different enteric coated products containing the same active ingredients not be considered as bioequivalent unless appropriate bioequivalence studies are satisfactorily performed.

(e) Injectable suspensions: Injectable suspensions containing an active ingredient suspended in an aqueous or oleagenous vehicle are subject to bioinequivalence problems because differences in particle size, polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and the rate of absorption. FDA proposes that it not consider pharmaceutical equivalents of these products as being bioequivalent without adequate evidence of bioequivalence being presented to the agency.

(f) Suppositories for systemic use: The absorption of active ingredients from suppositories that are intended to have a systemic effect, as distinct from suppositories administered for local effect, can vary significantly from product to product. Therefore, the agency proposes to consider pharmaceutically equivalent systemic suppositories as bioequivalent only if positive evidence of bioequivalence is presented to FDA.

4. *Evaluation of other factors.* FDA proposes that the drug products that are pharmaceutically equivalent, are bioequivalent, and are approved under sections 505 or 507 of the act be evaluated as therapeutically equivalent, unless special circumstances prevent such an evaluation. The definition of "therapeutic equivalence" refers to two factors in addition to pharmaceutical equivalence and bioequivalence; these two are related to labeling and manufacturing practices. In the opinion of the agency, approval of a new drug application or antibiotic certification for a drug product is a sufficient basis for assuring that the drug product has been reviewed for unsafe inactive ingredients and contaminants; that its labeling is adequate and complies with legal requirements; and that no deficiencies are known to exist in the manufacturing controls applied to the drug product at the time of approval. Therefore, it is unnecessary to conduct a specific review of product formulations, labeling, and current manufacturing practices in evaluating therapeutic equivalence.

(a) Inactive ingredients: FDA regulates and reviews inactive ingredients through a variety of mechanisms. The GRAS (generally recognized as safe) review of food ingredients, described in the FEDERAL REGISTER of July 26, 1973 (38 FR 20044), includes most of the common inactive ingredients, including flavors. Color additives are already regulated under section 706 of the act (21 U.S.C. 376) and the implementing regulations in 21 CFR Parts 70 through 82. Further, the agency has, through approval of new drug applications and antibiotic certifications, specifically reviewed and approved most inactive ingredients currently in

use in regard to their safety. In addition, FDA has in the past identified, and may from time to time in the future identify, specific ingredients that may not be used in packaging or in drug products because of safety concerns (e.g., the vinylchloride document published in the FEDERAL REGISTER of April 22, 1974 (30 FR 14238), and the chloroform document published in the FEDERAL REGISTER of June 29, 1976 (41 FR 26842)).

These regulatory procedures, in conjunction with review of new applications for drug products, have proven adequate to prevent problems of therapeutic inequivalence among drug products from developing because of inactive engredients in the drug products. Consequently, it is proposed that FDA evaluate as being therapeutically equivalent approved drug products that meet the standards for pharmaceutical equivalence and bio-equivalence, unless a specific problem affecting the safety or effectiveness of a drug product is known to result from a specific inactive ingredient used in that drug product.

(b) Labeling: FDA has established standards for the format and content of all drug product labeling, e.g., 21 CFR 201.56. From time to time specific requirements are also established for specific drug products. (See 21 CFR Part 201, Subpart G, and Part 310, Subpart E.) Generally, however, labeling is reviewed and approved during the new drug application and antibiotic certification process.

Occasionally there may be variation among pharmaceutically equivalent products in the labeling instructions for admininstering the dose. For example, one antibiotic drug product may contain labeling that requires giving the dose on an empty stomach, while another's labeling permits the drug to be given without regard to food intake, based upon in vivo studies of the latter product that establishes that blood levels of the drug are not affected by the presence of food. An FDA evaluation of therapeutic equivalence of pharmaceutically equivalent drug products in such a case is applicable only when each product is taken in accordance with its particular labeling directions.

(c) Manufacturing controls and drug quality: Even after a drug product has been approved, problems may arise in the manufacturing process that casue one or more batches of the product to be out of compliance with applicable standards and requirements. Where regulatory action, such as a recall or seizure, serves to remove a violative batch or batches from the market, the evaluation of the therapeutic equivalence of the approved product need not be changed. Thus, the remaining stocks and future batches of the product which are available for purchase are untainted.

(d) Insufficient data: In isolated situations, the agency lacks sufficient data to evaluate whether specific drug products, or drug products containing a specific active drug ingredient, are therapeutically equivalent under the criteria set forth above. The agency proposes that in these situations drug products be presumed to be inequivalent until adequate information becomes available to make a full evaluation of therapeutic equivalence.

V. PROCEDURES FOR PREPARING AND DISTRIBUTING THE LIST

A. THE PROPOSED REGULATION

The agency proposes to add a new provision to its public information regulations reflecting the proposed policy of making available a list of all approved drug products, together with evaluations of therapeutic equivalence. Adoption of this regulation would affirm the tentative decision to proceed with the proposed policy. The proposed regulation under 21 CFR 20.117(a)(3) offers the public an opportunity to comment on all aspects of this proposal. FDA invites these comments and will carefully consider all of them before finally deciding whether the agency should publish a final list of approved drug products with evaluations on therapeutic equivalence.

B. THE PROPOSED LIST

Concurrent with this proposal, the agency is also making available a proposed list. This document is being sent to State health officials, and is on display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857. Additional copies of the draft will be printed and available after January 22, 1979, from Margaret Lawrence, Consumer Inquiries Staff (HFJ-10), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, (301-443-3170).

Because copies are limited in number, the agency asks that only persons contemplating submitting documents in response to this notice request a copy of the proposed list. This version is tentative and is subject to change in light of the comments received; it is not intended for general distribution and use at this time.

The proposed list contains a preface, the actual drug product list, and four additional aids to using the list. In the preface, a statement of the background and status of the list is provided, together with explanations of the criteria used in developing the list and the evaluations of thereapeutic equivalence. These materials essentially summarize this notice to help users of the list. The preface also contains an explanation of the codes used in the list to describe the therapeutic evaluations made by FDA of the listed multiple source drug products. Finally, there is an explanation of special situations not adequately described by the therapeutic codes and a guide to reading the list.

The proposed list itself sets forth, to the best of FDA's knowledge, all drug products with approved new drug applications, under section 505 of the act, or approved antibiotic certification forms, under section 507 of the act. In preparing this list, FDA initially drew from its computerized files of approved NDA's, and antibiotic Form 5's. In order to minimize the potential for error, a complete list of approved NDA's, ANDA's, and antibiotic Form 5's, as of April 1978, was published as an interim document in May, and sent to appropriate State officials and agencies, including health officers, boards of pharmacy, and drug procurement agents, for review and comment. By notice published in the FEDERAL REGISTER of June 30, 1978 (43 FR 28557), this interim list was also made publicly available, with a request for additions, deletions, or corrections. In addition, on two separate occasions, FDA sent to each application holder data worksheets listing its products that FDA had identified as being approved; corrections were solicited; the agency received a 100 percent response with considerable updating information, indicating a serious and careful review by the firms. Information received in response to these requests has been incorporated in the proposed list. Information regarding approved antibiotic Form 6's (the antibiotic certification analogous to the ANDA) has also now been included. Errors may still remain, however, and additional corrections are solicited by this proposal.

The proposed therapeutic equivalence evaluations have not previously been circulated. They reflect FDA's application of the specific criteria proposed in section IV above to the approved multisource drug products on the list. The evaluations are presented in the form of code letters that explain the basis for the evaluation made. An explanation of the code is in the preface.

After the list, four additional items are provided to assist the reader: an index of drug products by trade or brand name, an index by name of the holder of the approval, an abbreviation list for the drug firms listed, and an appendix regarding drug products still being evaluated for effectiveness in the DESI review.

The agency invites comments and suggestions on the proposed list. Because the list is to be a working tool,

FDA wants its style and format to be most helpful to users.

C. PUBLISHING AND DISTRIBUTING THE LIST

FDA is presently planning to have copies of the list, when finally issued, printed and sold through the U.S. Government Printing Office, Washington, DC 20402. The agency invites suggestions on other methods of publication and distribution.

D. UPDATING THE LIST

FDA proposes that after the initial list is issued, it will be revised on a quarterly basis during the first year. These revisions would include the addition or deletion of approved drug products as well as any changes in evaluations of therapeutic equivalence during the preceding 90 days. After the first year, the frequency of revisions would be reevaluated. The agency solicits comments on this plan and how these revisions might best be disseminated.

The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 201 et seq., 52 Stat. 1040 et seq. as amended (21 U.S.C. 321 et seq.)), the Public Health Service Act (sec. 1 et seq., 58 Stat. 682 et seq. as amended (42 U.S.C. 201 et seq.)), and the Freedom of Information Act (Pub. L. 90-23, 81 Stat. 54-56 as amended by 88 Stat. 1561-1565 (5 U.S.C. 552)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that § 20.117 of Part 20 of Title 21 of the Code of Federal Regulations be amended by adding a new paragraph (a)(3) to read as follows:

§ 20.117 New drug information.

(a) * * *

(3) A listing of all new drug applications, abbreviated new drug applications, antibiotic Form 5's, or antibiotic Form 6's, which were approved since 1938 and which are still approved covering prescription drug products, except prescription drug products covered by applications deemed approved under the Drug Amendments of 1962 and not yet determined to be effective in the Drug Efficacy Study Implementation program, showing the name of the active ingredient, the type of dosage form, the trade name of the product, the application or certificate holder, and the strength or potency of the product. This listing shall also include, for each active ingredient in a particular dosage form for which there is more than one approved application or certificate, an evaluation of the therapeutic equivalence of the drug products covered by such applications or certificates.

* * * * *

Interested persons may, on or before April 12, 1979, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

This proposal to make available to the public a list of approved drug products, including FDA's evaluation of the therapeutic equivalence of multisource drug products on that list, does not fall under the purview of Executive Order 12044 which governs the process for developing significant regulations. Consequently, a regulatory Analysis is not required. The availability of this information may affect the purchasing, prescribing, and dispensing of prescription drug products. It is currently expected that this activity will promote competition, reduce prescription durg prices, and thus benefit the consumer. FDA intends to examine the economic impact associated with this activity more closely and solicits comments and supporting data that may be relevant to this examination.

Dated: January 8, 1979.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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