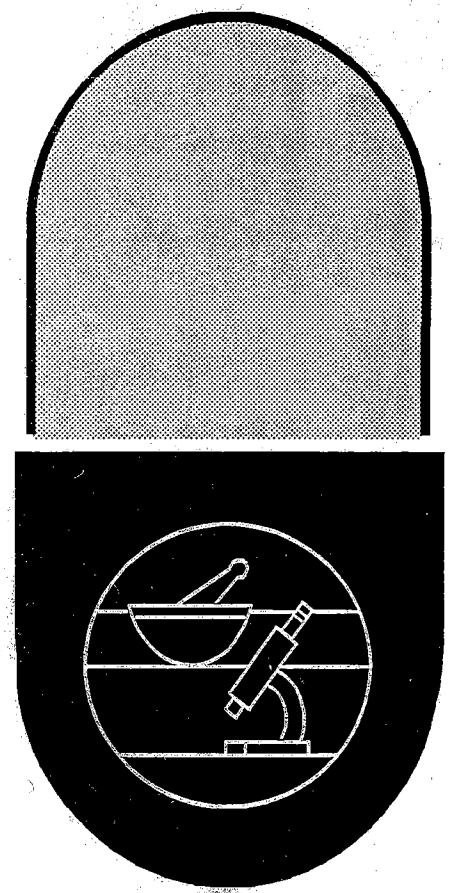
APPROVED DRUG PRODUCTS
With Therapeutic Equivalence Evaluations

The "Orange Book"

FDA data supplied by DrugPatentWatch.com

FDA data supplied by DrugPatentWatch.com



APPROVED DRUG PRODUCTS

WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

12TH EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTIONS 505 AND 507 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF MANAGEMENT

1992

FDA data supplied by DrugPatentWatch.com

APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under sections 505 and 507 of the Federal Food, Drug, and Cosmetic Act. This volume and accompanying first supplement are current through January 31, 1992.

12TH EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF MANAGEMENT

1992

FDA data supplied by DrugPatentWatch.com

FDA data supplied by DrugPatentWatch.com

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
APPROVED DRUG PRODUCTS
with
Therapeutic Equivalence Evaluations

CONTENTS

FDA data supplied by DrugPatentWatch.com

FDA data supplied by DrugPatentWatch.com

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
APPROVED DRUG PRODUCTS
with
Therapeutic Equivalence Evaluations

PREFACE TO TWELFTH EDITION

The *Approved Drug Products with Therapeutic Equivalence Evaluations* publication (the List) identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the Act). Unapproved drugs on the market (covered by the ongoing Drug Efficacy Study Implementation (DESI) review or products not subject to enforcement action as unapproved drugs) are not included in this publication. The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products on the List is independent of any current regulatory action through administrative or judicial means against a drug product. In addition, the List contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers and pharmacists to promote public education in the area of drug product selection and to foster containment of health costs. Therapeutic equivalence evaluations in this publication are not official FDA actions affecting the legal status of products under the Act.

Background of the Publication. To contain drug costs, virtually every state has adopted laws and/or regulations that encourage the substitution of drug products. These state laws generally require either that substitution be limited to drugs on a specific list (the positive formulary approach) or that it be permitted for all drugs except those prohibited by a particular list (the negative formulary approach). Because of the number of requests in the late 1970s for FDA assistance in preparing both positive and negative formularies, it became apparent that FDA could not serve the needs of each state on an individual basis. The Agency also recognized that providing a single list based on common criteria would be preferable to evaluating drug products on the basis of differing definitions and criteria in various state laws. As a result, on May 31, 1978, the Commissioner of Food and Drugs sent a letter to officials of each state stating FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.

The List was distributed as a proposal in January 1979. It included only currently marketed prescription drug products approved by FDA through new drug applications (NDAs) or abbreviated new drug applications (ANDAs) under the provisions of Section 505 or 507 of the Act.

The therapeutic equivalence evaluations in the List reflect FDA's application of specific criteria to the approved multisource prescription drug products on the List. These evaluations are presented in the form of code letters that indicate the basis for the evaluation made. An explanation of the code appears in the *Introduction*.

A complete discussion of the background and basis of FDA's therapeutic equivalence evaluation policy was published in the *Federal Register* on January 12, 1979 (44 FR 2932). The final rule, which includes FDA's responses to the public comments on the proposal, was published in the *Federal Register* on October 31, 1980 (45 FR 72582). The first publication, October 1980, of the final version of the List incorporated appropriate corrections and additions. Each subsequent edition has included the new approvals and made appropriate changes in data.

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act (1984 Amendments). The 1984 Amendments require that FDA, among other things, make publicly available a list of approved drug products with monthly supplements. The *Approved Drug Products with Therapeutic Equivalence Evaluations* publication and its monthly Cumulative Supplements satisfy this requirement. The *Addendum* to this publication identifies drugs that qualify under the 1984 Amendments for periods of exclusivity (during which ANDAs or applications described in

FDA data supplied by DrugPatentWatch.com

Section 505(b)(2) of the Act for those drugs may not be submitted for a specified period of time and if allowed to be submitted would be tentatively approved with a delayed effective date) and provides patent information concerning the listed drugs. The *Addendum* also provides additional information that may be helpful to those submitting a new drug application to the Agency.

The Agency intends to use this publication to further its objective of obtaining input and comment on the publication itself and related Agency procedures. Therefore, if you have comments on how the publication can be improved, please send them to the Director, Division of Drug Information Resources, Office of Management, Center for Drug and Evaluation and Research, HFD-80, 5600 Fishers Lane, Rockville, MD 20857. Comments received are publicly available to the extent allowable under the Freedom of Information regulations.

FDA data supplied by DrugPatentWatch.com

1. INTRODUCTION

1.1 Content and Exclusion

The List is composed of four parts: (1) approved prescription drug products with therapeutic equivalence evaluations; (2) approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs because they are not covered under the existing OTC monographs; (3) drug products with approval under Section 505 of the Act administered by the Division of Blood and Blood Products, Center for Biologics Evaluation and Research; and (4) products that have never been marketed, have been discontinued from marketing or have had their approvals withdrawn for other than safety or efficacy reasons. This publication also includes indices of prescription and OTC drug products by trade or established name (if no trade name exists) and by applicant name (holder of the approved application). All established names for active ingredients conform to official compendial names, or *United States Adopted Names* (USAN) as prescribed in 21 CFR 299.4(e). The latter list includes applicants' names as abbreviated in this publication; in addition, a list of uniform terms is provided. An *Addendum* contains drug patent and exclusivity information for the Prescription and OTC Drug Product Lists, and for the Drug Products with Approval under Section 505 of the Act Administered by the Division of Blood and Blood Products List.

Prior to the 6th Edition, the publication had excluded OTC drug products and drug products with approval under Section 505 of the Act administered by the Division of Blood and Blood Products, because the main purpose of the publication was to provide information to states regarding FDA's recommendation as to which generic prescription drug products were acceptable candidates for drug product selection. The 1984 Amendments require the Agency to publish an up-to-date list of all marketed drug products, OTC as well as prescription, that have been approved for safety and efficacy and for which new drug applications are required. In general, OTC drug products may be marketed as old drugs not requiring approved NDAs if they meet existing OTC drug monographs. The products included in the OTC Drug Product List are limited to those for which approved applications are currently required as a condition of marketing. Under the 1984 Amendments, some drug products are given tentative approvals with delayed effective dates. Prior to the effective date, the Agency will not represent the drug products with tentative approval in the List. When the tentative approval becomes a full approval through a subsequent letter to the applicant holder, the Agency will list the drug product and the final, effective approval date in the appropriate approved drug product list.

Distributors of the products on the List are not identified. Because distributors are not required to notify FDA when they shift their sources of supply from one approved manufacturer to another, it is not possible to maintain complete information linking the product approval with the distributor or repackager handling the products.

1.2 Therapeutic Equivalence-Related Terms

Pharmaceutical Equivalents. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form and are identical in strength or concentration, and route of administration (e.g., chlordiazepoxide hydrochloride, 5mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

Pharmaceutical Alternatives. Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules). Data are generally not available for FDA to make the determination of tablet to capsule bioequivalence. Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.

Therapeutic Equivalents. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect

FDA data supplied by DrugPatentWatch.com

when administered to patients under the conditions specified in the labeling.

FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. *The concept of therapeutic equivalence, as used to develop the List, applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., propoxyphene hydrochloride vs. pentazocine hydrochloride for the treatment of pain).* A single source drug product in the List repackaged and/or distributed by other than the applicant holder is considered to be therapeutically equivalent to the single source drug product.

FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, packaging, excipients (including colors, flavors, preservatives), expiration time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information). When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect as the prescribed product.

Bioavailability. This term describes the rate and extent to which the active drug ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action.

Bioequivalent Drug Products. This term describes pharmaceutically equivalent products that display comparable bioavailability when studied under similar experimental conditions. Section 505 (j)(7)(B) of the Act describes conditions under which a test and reference (listed) drug shall be considered bioequivalent:

> the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
>
> the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. Where these above methods are not applicable (e.g., for topically applied products intended for local rather than systemic effect), other *in vivo* tests of bioequivalence may be appropriate.

Bioequivalence may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data or in other situations through comparative clinical trials or pharmacodynamic studies.

1.3 Statistical Criteria for Bioequivalence

Under the Drug Price Competition and Patent Term Restoration Act of 1984, manufacturers seeking approval to market a generic drug must submit data demonstrating that the drug product is bioequivalent to the pioneer (innovator) drug product. A major premise underlying the 1984 law is that bioequivalent products are therapeutically equivalent and, therefore, interchangeable.

The standard bioequivalence study is conducted in a crossover fashion in a small number of volunteers, usually with 12 to 24 healthy normal male adults. Single doses of the test and reference drugs are administered and blood or plasma levels of the drug are measured over time. Characteristics of these concentration-time curves, such as the area under the curve