**THE ORANGE BOOK CONCEPTS AND SIGINIFICANCE**

# Definition

* It is the publication of “Approved Drug Products with Therapeutic Equivalence Evaluations” by the Food and Drug Administration.
* It is prepared by The Orange Book Staff, Center for Drug Evaluation and Research.
* It identified drug products on the basis of safety and effectiveness by the Food and Drug Administration under the Federal Food, Drug, and Cosmetics Act.
* Drugs marketed only on the basis of safety or pre-1938 drugs.
* The list is independent of any current regulatory action against a drug product.
* 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of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons.
* The FDA does not recommend substituting drugs that have not been determined to be bioequivalent.
* Drugs that are not listed as bioequivalent should not be substituted for each other.

|  |  |
| --- | --- |
| YEAR | ACTION |
| May 31, 1978 | The Commissioner of the Food and Drug Administration 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. |
| January, 1979 | The list was distributed (included only currently marketed prescription drug products approved by FDA through NDAs and ANDAs under the provisions of section  505 of the Act) |
| October 31, 1980 | The final rule (includes FDA’s response to the public comments on the proposal) was published in the Federal Register (45 FR 72582).  The list incorporated appropriate corrections and additions. |

# Objectives

* To allow review of patterns of access and usage
* To allow discovery of use of unusual privileges
* To allow discovery of repeated attempts to bypass protections
* To serve as a deterrent by its existence
* To supply an additional form of user assurance

# Contents of “THE ORANGE BOOK”

|  |  |
| --- | --- |
| **1.** | **INTRODUCTION** |
| 1.1 | Content and Exclusion |
| 1.2 | Therapeutic Equivalence-Related Terms |
| 1.3 | Statistical Criteria for Bioequivalence |
| 1.4 | Reference Listed Drug |
| 1.5 | General Policies and Legal Status |
| 1.6 | Practitioner/User Responsibilities |
| 1.7 | Therapeutic Equivalence Evaluations Codes |
| 1.8 | Description of Special Situations |
| 1.9 | Therapeutic Equivalence Code Change for a Drug  Entity |
| 1.10 | Change of the Therapeutic Equivalence Evaluation for  a Single Product |
| 1.11 | Discontinued Section |
| 1.12 | Changes to the Orange Book |
| 1.13 | Availability of the Edition |
| **2.** | **HOW TO USE THE DRUG PRODUCTS LISTS** |
| 2.1 | Key Sections for Using the Drug Product Lists |
| 2.2 | Drug Product Illustration |
| 2.3 | Therapeutic Equivalence Evaluations Illustration |
| **DRUG PRODUCT LISTS** | |
|  | Prescription Drug Product List |
|  | OTC Drug Product List |
|  | Drug Products with Approval under Section 505 of the Act Administered by the Center for Biologics  Evaluation and Research List |
|  | Discontinued Drug Product List |
|  | Orphan Products Designations and Approvals List |
|  | Drug Products Which Must Demonstrate in vivo Bioavailability Only if Product Fails to Achieve  Adequate Dissolution |
| **APPENDICES** | |
| A. | Product Name Index A-1 |
| B. | Product Name Index Listed by |
| C. | Uniform Terms |
| **PATENT AND EXCLUSIVITY INFORMATION ADDENDUM** | |
| A. | Patent and Exclusivity Lists |
| B. | Patent and Exclusivity Terms |

1. **INTRODUCTION**

# Content and Exclusion

* + - Approved OTC drug products for those which are not marketed
    - Approved prescription drug with therapeutic equivalence evaluations
    - Drug products with Biologics Evaluation and Research
    - List of approved products that have been discontinued from marketing

# Therapeutic Equivalence-Related Terms

* Pharmaceutical equivalents
  + Contain the same active ingredient(s),
  + Have the same dosage form and route of administration, and
  + Identical in strength or concentration
  + May differ in shape, release mechanisms, and packaging
* Pharmaceutical alternatives
  + Contain the same therapeutic moiety but might differ in ,
    - Salts, esters, or complexes form of the same moiety,
    - Different dosage forms,
    - Different strengths
* Therapeutic equivalents
  + Therapeutic equivalents are expected to have the same clinical effect and safety profile.
  + Drug products are considered therapeutic equivalents if they are all of the following
    - Pharmaceutical equivalents
    - Bioequivalent
    - Approved as safe and effective
    - Adequately labeled
    - Manufactured in compliance with current Good Manufacturing Practice regulations
* Bioequivalence and Bioavailability
  + Drug products are considered bioequivalent if they are pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to subjects at the same molar dose under similar experimental conditions
  + Bioequivalence use to determine Therapeutic Equivalents

# Statistical Criteria for Bioequivalence

* In short Bioequivalence refers to equivalent release of the same drug substance from two or more drug products.
* The standard bioequivalence (PK) study is conducted in 24-36 adults using a two-treatment crossover study design.
* Alternately, a four-period, replicate design crossover study can also be used.
* The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure.
* Two situations are tested with this statistical methodology
* Pharmacokinetic parameters determine are AUC and Cmax.
* Two criteria includes,

1. Whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable. (A limit of test-product average/reference-product average of 80%)
2. Whether a brand-name product when substituted for a generic product is significantly less bioavailable. (A limit of reference-product average/test-product average 125%)

* A difference of greater than 20% for each of the above tests was determined to be significant
* The confidence interval for both pharmacokinetic parameters, AUC and Cmax, must be entirely within the 80% to 125% boundaries cited above.

# Reference Listed Drug

* A reference listed drug means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.
* The aim of FDA is to avoid possible significant variations among generic drugs and their brand name counterpart.
* The reference listed drug is identified by the symbol "+" in the Prescription and Over-the-Counter (OTC) Drug Product Lists.
* List is available for oral dosage forms, injectables, ophthalmics, otics, and topical products.

# General Policies and Legal Status

* The List contains public information and advice.
* It is not compulsory the drug products which may be purchased, prescribed, dispensed, or substituted for one another, nor does it, should be avoided.
* Exclusion of a drug product from the List does not necessarily mean that the drug product is not safe or effective, or that such a product is not therapeutically equivalent to other drug products.
* Rather, FDA has not evaluated the safety, effectiveness, and quality of the drug product.

# Practitioner/User Responsibilities

* Professional care and judgment should be exercised in using the list.
* Practitioner should be aware of the multi-source and single-source drug products.

1. Multisource Drug Product means those pharmaceutical equivalents available from more than one manufacturer. For such products, a therapeutic equivalence (TE) code is included and, in addition, product information is highlighted in bold face and underlined.
2. Single-Source Drug Product means only one approved product is available for particular active ingredient, dosage form, route of administration, and strength. For such product no therapeutic equivalence code is included.

* Products on the List are identified by the names of the holders of approved applications (applicants) who may not necessarily be the manufacturer of the product:
* Applicants like Manufacture, Contract Manufacturer, Repackager, Distributor or Marketer.

# Therapeutic Equivalence Evaluations Codes

* The coding system for therapeutic equivalence evaluations
* First letter: therapeutically equivalent to other pharmaceutically equivalent products
* Second letter: provide additional information on the basis of FDA's evaluations

# Description of Special Situations

*Example*

|  |  |
| --- | --- |
| Drugs | Description of Special Situations |
| Amino-acid and Protein Hydrolysate injections | These products differ in the amount and kinds of amino-acids they contain, and therefore, are not considered pharmaceutical equivalents. For this reasons, these products are not considered therapeutically equivalent. |

# Therapeutic Equivalence Code Change for a Drug Entity

* Such changes occur in response to a petition or on its own initiative.
* Changes will generally occur when new scientific information affects the therapeutic equivalence of an entire category of drug products in the List.

# 1.11 Discontinued Section

* When the product have been discontinued from marketing,
* Are for military use,
* Or have had their approvals withdrawn for other than safety or efficacy reasons
* Drug Products for exportation

# Key Sections for Using the Drug Product Lists

* + - This contains illustrations, along with Drug Product Lists, indices, and lists of abbreviations and terms which facilitate their use.

1. Illustration: Depicts the format found in the Prescription Drug Product List.
2. Drug Product Lists: The Prescription and OTC drug product lists, arranged alphabetically by active ingredient (s), contains product identification information (active ingredients, dosage forms, routes of administration, product names, application holders, strengths) for single and multiple ingredient drug products. Also shown are the application number and drug product number.
3. Product Name Index.
4. Product Name Index Listed by Applicant.
5. Uniform terms.

# Drug Product Illustration

* ACTIVE INGREDIENT
* DOSAGE FORM : ROUTE OF ADMINISTRATION
* TRADE OR GENERIC NAME
* APPLICANT
* AVAILABLE STRENGTH OF PRODUCT
* APPLICANT NUMBER & PRODUCT NUMBER
* PRODUCT NUMBER IS FOR FDA INTERNAL COMPUTER DATA USE ONLY

# Therapeutic Equivalence Evaluations Illustration

* + - Drug Product reviewed
    - It includes only full approval products and not tentative approval products
    - Drug Product of Repackager/Distributor is considered to be therapeutically equivalent to the Application Holder’s product
    - The new approvals and required changes in data are included in each subsequent edition. Even monthly cummulative supplements are published
      * **THE GREEN BOOK & THE BLUE BOOK**

|  |  |
| --- | --- |
| **THE GREEN BOOK** | **THE BLUE BOOK** |
| * It is a list of all animal drug products approved for safety and effectiveness. * It consist of eight sections which are as follow,   Section 1 - NADA Number, Trade Names and Sponsors arranged by Tradename, NADA Number  Section 2 - Active Ingredients Section 3 - Patent Information Section 4 - Exclusivity Periods  Section 5 - Products Subject to Notice of Hearing Section 6 - Voluntary Withdrawals  Section 7 - Suitability Petition Actions Section 8 - 2006 Monthly Updates | * The FDA publication Requirement of Laws and Regulations Enforced by the U.S. Food and Drug Administration * It has been discontinued as of October 2002. * In its place there is a Wealth of Compliance Information on the FDA Website. |

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/325069043 THE ORANGE BOOK **Presentation** · May 2018 DOI: 10.13140/RG.2.2.13564.64647