

**What's Inside...**

PRN's Q & A: The FDA Orange Book..... 1

PRN's Q & A (continued)..... 2

PRN's Q & A (continued)..... 3

Editorial..... 4

Pharmacy Fun (answers only)..... 4

## PRN's Q & A on: **THE FDA ORANGE BOOK**

This month's issue represents the first in an ongoing series of special editions of PRN, each of which will focus on one particular aspect of pharmacy practice. These special editions will be produced periodically, and will be presented in a question and answer format. The questions are numbered to allow for easy cross-reference, rather than to assign a specific order of importance. For our inaugural effort, we have chosen to discuss the FDA Orange Book, among the most important reference tools available to the pharmacist. New York is one of 30 states which mandate the use of the Orange Book in choosing drugs for generic substitution. As such, it is essential that pharmacists practicing in New York State have a thorough understanding of the Orange Book and the leading role it plays in ensuring the safety and effectiveness of the drug products dispensed in their pharmacies. To that end, we present this special edition of PRN on the FDA Orange Book.

### 1. What is the FDA Orange Book?

Its official title is *Approved Drug Products with Therapeutic Equivalence Evaluations*. Commonly known as the Orange Book due to the orange cover of the original print version, it is the Food and Drug Administration's list of all drugs approved in the United States as safe and effective. In addition to listing all approved drugs, the Orange Book is also the authoritative source of information on the therapeutic equivalence of drug products.

#### History

In the middle of the past century, many states enacted laws banning the substitution of drugs in an attempt to prevent the spread of inferior or counterfeit products. By the 1970s, however, economic pressures had led to the repeal of these anti-substitution laws, and states, beginning with New York, began looking to the Federal government for guidance in creating formularies to regulate substitution. In response to such requests, the FDA announced its intention to create a list of approved drugs and therapeutic equivalence determinations. The first edition appeared in October, 1980. A new edition is published each year and cumulative supplements are made available on a monthly basis. The current (2008) Orange Book is the 28<sup>th</sup> Edition.

#### Contents

The Orange Book consists of five main sections: an introduction, a "how to use" section, the drug product lists, appendices, and a patent and exclusivity information addendum. For community pharmacists, the most relevant section is that of the drug product lists, in particular the prescription drug product list. Here you will find all approved drug products and their respective therapeutic equivalence (TE) codes, which guide the practitioner in the proper substitution of pharmacologic agents (see Question 3 for an explanation of the TE codes).

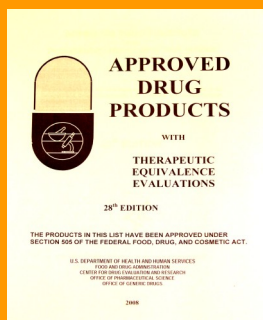
#### Access

In the past, many pharmacists had access to the Orange Book through the annual publication of Volume III of the USP Drug Information series (USP DI). Unfortunately, as of 2007, publication of the USP DI has been discontinued.

Thanks to the internet, however, the Orange book and its monthly supplements are now easily accessed, free of charge, at:

[www.fda.gov/cder/ob](http://www.fda.gov/cder/ob)

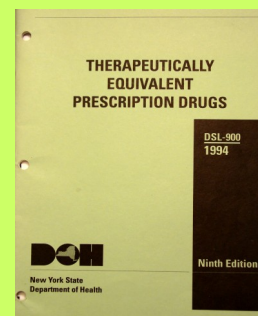
At this site the latest edition may be searched, using either brand or generic name, or the entire volume may be downloaded in PDF format by clicking on "Publications." The cumulative monthly supplements are also available in PDF format.



The Orange Book (2008)

### 2. What was New York State's Green Book?

When New York State adopted its Generic Substitution Law in 1977, one of the provisions called for the Commissioner of Health to establish and publish a list of therapeutically equivalent drug products. Thus was born, in March, 1978, the Green Book, its name based on the color of the cover. While basically a replica of the Orange Book, the Green Book had some additional and advantageous features. For example, it listed drugs for which "authorized generics" were available, information which the Orange book does not contain (see Question 4 for a discussion of this continuing problem). In March, 1997, the Department of Health announced that it was discontinuing publication of the Green Book. Since that date, the Orange Book has taken its place as the official list of therapeutically equivalent drug products in New York State.



The Green Book (1994)

# PRN's Q & A on: THE FDA ORANGE BOOK

## 3. What do the Therapeutic Equivalency (TE) Codes in the Orange Book signify?

Before discussing the specific meaning of each of the Orange Book TE codes, a few definitions are in order:

**Pharmaceutical Equivalents** are drug products which contain the same active ingredients in the same strength and dosage form delivered by the same route of administration.

**Bioequivalent Drug Products** are those which have shown comparable bioavailability when studied under similar conditions (e.g., the rate and extent of absorption of a test drug does not significantly differ from that of the reference drug).

**Therapeutic Equivalents** are *Pharmaceutical Equivalents* that are *Bioequivalent*. Only drug products which are *Therapeutic Equivalents* (i.e., "A"-rated) may be legally substituted for FDA approved drugs in Orange Book states such as New York.

TE codes are divided into two categories, A-rated and B-rated.

**A-rated Drugs** are those which the FDA considers to be **therapeutically equivalent** and, therefore, substitutable where permitted by the prescriber. They are further divided as follows:

**AA:** ingredients and dosage forms presenting neither actual or potential bioequivalence problems (e.g., oral solutions). Some dosage forms are assigned specific codes based on criteria used to demonstrate bioequivalence: **AN** for aerosolized drugs, **AO** for injectable oil solutions, **AP** for injectable aqueous solutions, and **AT** for topical products.

**AB:** actual or potential bioequivalence problems have been resolved through adequate *in vivo* and/or *in vitro* testing.

**B-rated Drugs** are those which the FDA considers **NOT** to be therapeutically equivalent due to actual or potential bioequivalence problems which have not been resolved. B-rated drugs are not legally substitutable in Orange Book states such as New York.

## 4. Some of the drugs that I dispense as generics for FDA approved brand-name drugs do not appear anywhere in the Orange Book. Are these substitutions legal?

This question raises the controversial issue of so-called **authorized generics**. The normal process for bringing generic drugs to market involves a generic manufacturer submitting an application, called an Abbreviated New Drug Application (ANDA), to the FDA demonstrating a product's bioequivalence to the innovator's brand-name drug. Under the Hatch-Waxman Act (1984), the first generic to market is granted a 180-day exclusivity period. Generic manufacturers believe this exclusivity is effectively nullified by the practice of brand-name manufacturers marketing authorized generics shortly before patent expiration. Authorized generics are actually original brand-name drugs re-labeled as generics through a variety of arrangements between innovator companies and their subsidiaries, licensees, or contract manufacturers

This practice also creates an issue for pharmacists because the Orange Book **does not list authorized generics**. The stated reason for this practice is that the FDA does not consider these products generics. Since they are manufactured under the original, approved New Drug Application (NDA) submitted for the brand-name drug, the FDA considers authorized generics to be identical to the brand.<sup>1</sup> All authorized generics are substitutable for the brand when the prescription does not prohibit substitution. Indeed, a reasonable argument could be made that authorized generics may even be dispensed on prescriptions marked "dispense as written" (DAW) by the prescriber, at a cost savings to the patient, since they are, in fact, identical drugs. Below are three examples of authorized generics, marketed under differing corporate arrangements, *none of which appear in the Orange Book*.

**1. Licensing Agreement:** This is often the most transparent arrangement, and therefore the least difficult for the pharmacist to recognize. In figure 1, the label on generic Fosamax, distributed by Watson, clearly states "Manufactured by Merck & Co," the NDA holder for Fosamax brand. Even though the Orange Book lists only Barr and Teva products as AB-rated generics, the Watson distributed product may also be dispensed since it is an authorized generic.

**2. Generic Subsidiary:** In this situation, a generic is marketed by a company which is a subsidiary of the brand-name manufacturer. Figure 2 shows the label for Greenstone's Azithromycin, generic for Pfizer's Zithromax. There is no indication of a parent company on the label, and this product is *not* listed in the Orange Book. Due to this lack of transparency, it is left for the pharmacist to ascertain the fact that Greenstone is a wholly-owned subsidiary of Pfizer, and that this product is an authorized generic.

**3. Contract Manufacturing:** In what may be the most confounding alignment, in terms of understanding the source of a product and its actual TE code, some companies have contracted out the manufacture of their approved drugs to other firms, known as contract manufacturers. In the context of the myriad corporate mergers and acquisitions in the pharmaceutical industry, such arrangements can lead to confusion and uncertainty as to the provenance of a drug product. The history of the anti-diabetic drug DiaBeta (glyburide) serves as a good example. In 1984, the FDA approved two versions of a new sulfonylurea, glyburide; one was Upjohn's Micronase, the other Hoechst's DiaBeta. Micronase was named the reference listed drug (RLD) against which all future generics would be compared for bioequivalence, while Micronase and DiaBeta were never rated equivalent to each other. In an early example of an authorized generic, Hoechst agreed to produce, under its NDA, glyburide to be labeled and sold by its majority-owned subsidiary, Copley.<sup>2</sup> This product was, therefore, substitutable for DiaBeta but *not for Micronase*. Subsequently,

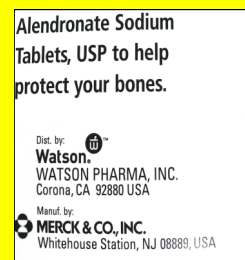


Figure 1



Figure 2

(continued on page 3)

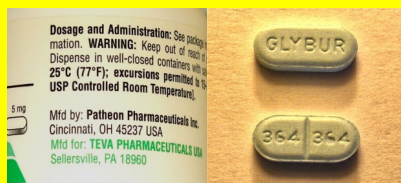
# PRN's Q & A on: THE FDA ORANGE BOOK

## Question 4 (continued from page 2)

in 1999, Copley was purchased by Teva and Hoechst merged with Rhone-Poulenc to form Aventis, which became Sanofi-Aventis in 2004. Meanwhile, in 2002, Aventis sold the Cincinnati plant where it manufactured glyburide to the contract manufacturer Patheon, Inc. As part of that sale, Patheon was contracted to continue manufacturing glyburide, under the original NDA, to supply both Diabeta to Sanofi-Aventis and the authorized generic to Teva.<sup>3</sup> Adding to the confusion, Teva also markets a glyburide, made by Novopharm, which is AB-rated to Micronase and appears in the Orange Book. Unfortunately, the labels on these products shed no light on their complex pedigree, leaving the pharmacist in the position of having to become something of a detective in order to dispense the correct product for a particular prescription (see figures 3, 4, and 5). We at PRN feel there is a simple and inexpensive remedy to this problem, and are preparing to petition the FDA to adopt a policy change to effect that remedy (see our Editorial on page 4).



**Figure 3**  
**DiaBeta by Sanofi-Aventis**  
**Made by Patheon**  
**Rated BX**



**Figure 4**  
**Glyburide by Teva**  
**Made by Patheon**  
**Not in Orange Book**  
**(Authorized Generic for DiaBeta)**



**Figure 5**  
**Glyburide by Teva**  
**Made by Novopharm**  
**Rated AB to Micronase**

## 5. Why are some TE codes followed by a number, such as AB1, AB2, AB3, etc.?

In some cases there are two or more drug products, containing the same ingredient, with the same strength and dosage form, which are not bioequivalent to each other. In such instances, there will be more than one reference listed drug (RLD), and any generic seeking approval must prove bioequivalence to one particular RLD. In order to avoid confusion, the FDA assigns numbers to TE codes to differentiate which RLD a generic is equivalent to. Therefore, a generic rated AB1 can be substituted for a brand rated AB1, but *can not* be substituted for a brand rated AB2. A commonly prescribed oral contraceptive, **Norethindrone 0.35 mg**, is a case in point:

Product	TE Code	RLD or Generic
Nor-QD	AB1	RLD
Camila	AB1	Generic
Micronor	AB2	RLD
Errin	AB2	Generic

Other drugs with multiple TE codes include **Diltiazem capsules**, **Nifedipine tablets**, and **Nitroglycerin Transdermal Patches**. The most complicated case involves **Levothyroxine tablets**, where many products have proved equivalence to more than one RLD (see below):

- Levothroid** is rated **AB4**
- Synthroid** is rated **AB1 and AB2**
- Levoxyl** is rated **AB1 and AB3**
- Levo-T** is rated **AB2 and AB3**
- Unithroid** is rated **AB1, AB2, and AB3**
- Mylan's Levothyroxine** is rated **AB1, AB2, AB3, and AB4**

## 6. What are 505(b)(2) drugs?

There are three pathways for FDA drug approval. New drugs go through the 505(b)(1) process of submitting a New Drug Application (NDA) proving safety and effectiveness. Generics use the 505(j) pathway, which requires only proof of bioequivalence to an existing product via an abbreviated NDA (ANDA). The third option, 505(b)(2), allows for approval of a drug which contains the same active ingredient as an existing approved drug, but which differs significantly in some way, such as dosage form, route of administration, salt formulation, strength, indication, etc. Some examples of drugs approved under section 505(b)(2) include:<sup>4</sup>

<b>Altoprev</b>	<b>Fortical</b>
<b>Avinza</b>	<b>Luxiq Foam</b>
<b>Canasa</b>	<b>Vandazole</b>

The FDA does NOT consider 505(b)(2) drugs to be bioequivalent to other products. **505(b)(2) drugs are not generics and can not be substituted for drugs with the same or similar ingredients.**

## 7. Why does my pharmacy software sometimes substitute with non-AB-Rated drugs?

Unfortunately, some pharmacy software programs link brand and generic drugs based on active ingredient only, regardless of FDA rating. Pharmacists practicing in Orange Book states must be particularly careful to verify drug product selections in order to avoid illegal substitution. Popular programs, such as First DataBank, also use their own "Z" codes to rate products which are not rated by the FDA. Pharmacists should understand how these codes are assigned:

- ZA** - approved products under different labels (e.g., repacks)
- ZB** - products not appearing in the Orange Book (e.g. prenatal vitamins)
- ZC** - single source products which appear in the Orange Book, but are not rated (e.g., brand products with no generics available)

P.R.N. (ISSN # 1941-9481)

is published monthly by:

PRN Publishing LLC

68-37 Yellowstone Boulevard  
Suite C-22

Forest Hills, New York 11375

Phone & Fax (718) 263-4632

Founder and Editor:

**James Murphy, RPh**

Associate Editor:

**Margaret Irving, PharmD**

Contributors:

**Loriann Irving, PharmD**

**Lilian Bejarano, RPh**

©2008 by PRN Publishing LLC

All rights reserved. No part of this publication may be reproduced without the express written permission of the publisher.

The information contained in P.R.N. is for educational purposes only. Always use professional judgment in clinical practice.

We welcome your input. Please forward any comments, suggestions, or questions to us at:

[askprn@prnnewsletter.com](mailto:askprn@prnnewsletter.com)

Visit us on the web at:

[www.prnnewsletter.com](http://www.prnnewsletter.com)

## SUBSCRIPTION INFORMATION

Subscriptions are available:

One year (12 issues).....\$48.00

Make check or money order payable to:

**PRN Publishing**  
68-37 Yellowstone Boulevard  
Suite C-22  
Forest Hills, New York 11375

## EDITORIAL: *FDA Urged to Change Label Requirements*

Pharmacists are in a unique position among healthcare professionals; they alone are charged with the responsibility of choosing the appropriate drug product with which to fill a practitioner's prescription. As the drug experts, it is rightfully their duty to perform this task, and they have been well served in executing this duty by the existence of the FDA Orange Book. Without the appearance of this resource in 1980, it would have rapidly become impossible for the community pharmacist to keep track of the expanding generic drug market, and impossible to ensure that only therapeutic equivalents would be dispensed to their patients.

In recent years, however, due, in part, to the acceleration in the pace of corporate mergers and acquisitions, it has become more difficult for the pharmacist to determine the status of the prescription drug products on his or her shelf. The source of this problem is the disconnect between the label on the manufacturer's or distributor's bottle and the information available in the Orange Book. As stated in the introduction to the 28th edition of *Approved Drugs with Therapeutic Equivalence Evaluations* (2008):

"Distributors or repackagers of products on the List [the Orange Book] are not identified. Because distributors and repackagers 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 product approval with the distributor or repackager handling the product."

We agree completely with the FDA that it would be impractical to try to keep up with the frequent changes in the structure and alignment of the pharmaceutical industry. In fact, such an attempt would quickly render obsolete each new edition of the List. Fortunately, there is a much simpler solution to the problem, one which requires no changes in the Orange Book itself. There is one fact, a single 5-digit number, which is associated with each and every approved drug in the United States, a number which does not change, regardless of how many times the product's repackager, distributor, or manufacturer may change. That number is the New Drug Application number, or NDA, under which the product was granted the right to be marketed as safe and effective. This number appears next to every product listed in the Orange Book. Like an automobile's VIN number, an NDA tells us all about how, and under what conditions, a drug was produced; unlike a VIN number, the NDA is not required to appear anywhere on the product.

The solution to the problem of correct identification of drug products and their equivalence status is to require manufacturers and/or distributors of prescription drugs to include the product's NDA number on the label of each bottle. This small change in the Federal label law would benefit all the stakeholders. First and foremost, it protects the patient from illegal substitution, whether intentional, or, as is most often the case, unintentional. Secondly, it relieves the pharmacist from the undue burden of acting as investigative reporter just to ensure the appropriate drug product is selected. And finally, it benefits the drug maker in that it guarantees that its NDA, which the company may have spent millions to secure, is firmly attached to its product in whatever form it is distributed.

PRN is currently preparing a Citizen's Petition to the FDA calling for this change in the regulations regarding what must appear on the label of a manufacturer's or distributor's bottle. We will keep our readers informed on the progress of our petition.

**We welcome your opinion on this topic, or any other issues involving the practice of pharmacy today. Please write us at: [askprn@prnnewsletter.com](mailto:askprn@prnnewsletter.com)**

### Answers to last month's **PHARMACY FUN**:

1. *Purple foxglove*: Digoxin
2. *French lilac*: Metformin
3. *Rauwolfia serpentina*: Reserpine
4. *Deadly nightshade*: Atropine
5. *Chincona ledgeriana*: Quinine
6. *Papaver somniferum*: Morphine
7. *Ephedra sinica*: Ephedrine
8. *Autumn crocus*: Colchicine

### References:

1. *Approved Drug Products and Therapeutic Equivalence Evaluations*. 28th Edition. FDA; 2008: vii.
2. SEC filing. Copley Pharmaceutical Inc 10-Q EX-10. Available at [www.secinfo.com/dPaHc.85.b.htm](http://www.secinfo.com/dPaHc.85.b.htm). Accessed April 18, 2008.
3. Patheon's strategic platform launched in U.S. October 16, 2002. Available at [www.advancesinlifescience.com/news\\_29.htm](http://www.advancesinlifescience.com/news_29.htm)
4. Lauren S. Schlesselman. Understanding the 505(b)(2) approval process. *Drug Store News*. 2006. Available at [www.cedrugstorenews.com](http://www.cedrugstorenews.com).

**Credits:** Photographs by James Murphy