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An Overview on the Orange Book in Regulatory Affairs

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ABSTRACT

The Orange Book database published by the U.S. Drug and Food Administration (FDA) was analyzed for the frequency of occurrence of different counterions used for the manufacturing of pharmaceutical salts. The data obtained from the present analysis of the Orange Book are compared to reviews of the Cambridge Structural Database (CSD) and of the Martindale "The Extra Pharmacopoeia". As well as showing overall distributions of counterion usage, results are broken down into 5-year growth to identify trends in counterion selection. Chloride ions continue to be the most frequently utilized anionic counterions for the manufacturing of salts as active pharmaceutical ingredients (APIs), while sodium ions are most widely used for the formation of salts starting from acidic molecules. A strong trend toward a wider variety of counterions over the past decade is determined. This trend can be explained by a stronger need to improve the physical-chemical properties of research and development compounds.

This review explain in brief regarding Orange book it's ,History and Purpose of FDAs Orange Book, Safety and effectiveness, Drug Lists in Approved Drug Products, Therapeutic equivalence, Bioavailability and Bioequivalence, Waxman-Hatch history, The Orange-Book-Standard and other European cases,,Exclusivity, Availability of the Orange Book .

INTRODUCTION

A common question most pharmacists in the United States have been presented with at some time in their career is ''Why does this drug cost so much?'' Faced with increasing costs of healthcare, consumers seek alternative ways to decrease their overall healthcare expenditure. Some measures consumers have taken include such things as buying medicines from foreign countries, or through the Internet, alternative therapies such as herbal remedies, and increased use of generic drug products. Variations of the above question posed to pharmacists may include questions about the availability of a generic drug. Regulatory issues facing the US Food and Drug Administration (FDA) concerning this question need to be viewed from the innovator and generic sides of the industry with particular attention ultimately given to US consumers. The interests of the innovator or ''pioneer'' drug firms that bear the research and development costs must be considered as well as the interests of the generic drug industry that can increase competition and lower the cost of the drug. Most importantly, the needs of the American consumer must be addressed. Additionally, rising healthcare costs are a concern to federal and state governments as these governments share in the burden of paying for the high cost of drugs. Achieving a balance in this industry is paramount to this country's overall quality, availability, and affordability of drug products and healthcare. (1)

1. History and Purpose of FDAs Orange Book

The Orange Book was proposed in January 1979 and the first edition was finalized in October 1980. The orange-colored cover of the book, Halloween, and the month of October (which was when the book was first published) is related to the orange Book nickname that

''Approved Drug Products with Therapeutic Equivalence Evaluations'' was later given. After repealing brand name antisubstitution laws by individual states, the need for the agency to compile a list of marketed drugs approved for safety and efficacy became obvious as the agency received many requests for assistance in developing drug formularies. The FDA commissioner notified state health officials of the agency's intent to prepare such a list. The Orange Book publication that resulted is a source of public drug information and is used to advise state and federal health

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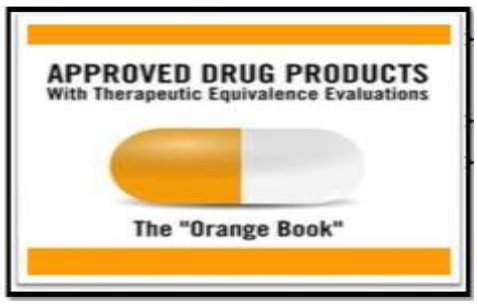
agencies, as well as physicians, pharmacists, and health care professionals.
scribed below comes together to form the basis of the Orange Book. (1)



Orange Book

In 1906, The Pure Food and Drug Act was signed by President Theodore Roosevelt. This act established the regulation of foods and drugs in the United States and signaled the birth of the US Food and Drug Administration. Before 1906, the food and drug industries were
not regulated industries in this country.

The next major legislation relative to the Orange Book was borne out of a disaster. National attention was given to the elixir of sulfanilamide in 1937. The following year, Congress passed the Federal Food, Drug, and Cosmetic Act of 1938. This new law required new drugs to be demonstrated as safe before marketing in the United States. Drug products that were already on the market at this time stayed on the market. They have now known as ‘‘grandfather’’ drugs.
Lastly, the 1984 Drug Price Competition and Patent Term Restoration Act, commonly called as the Waxman-Hatch Amendments, sought a balance between the pioneer and generic drug industries. The passage of this act expedited the availability of less costly generic drugs, while at the exact time providing incentives for innovative new medicines to be developed. (2)

2. **Safety and effectiveness**

- Today, there exist two categories of drug products that are marketed in the US but have not gone through the current new drug approval process.
- As mentioned above, these drugs are ‘‘grandfather’’ drugs and less than effective ‘‘DESI’’ 3 drugs. Grandfather drugs were on the market in the US before 1938.
- These drugs are on the market in the absence of safety and efficacy data having been reviewed by the agency; regulatory action is deferred on these products.
- Less than-effective DESI drugs are drugs that were marketed in the US before 1962 and although have been determined safe, their effectiveness has not been established.
- Grandfather and less-than-effective DESI drugs are not listed in the Orange Book.
- The agency considers products to be therapeutically equivalent even though the products may differ in minor aspects such as color, preservatives, inactive ingredients, and labeling. The basic theory behind the 1984 law is that bioequivalent drugs are therapeutically equivalent and therefore interchangeable. (3,4)

3. Drug Lists in Approved Drug Products

The Orange Book includes products for which new drug applications (NDAs) or abbreviated new drug applications (AND.As) have been approved by the FDA under the provisions of section 303 of the Federal Food. Drag and Cosmetic. Act (FD&C Act) and. It should be noted that the act when passed in 1938, required only those drags to be safe; however, 1962 amendments to the FD&C Act require that drugs must also be effective to receive approval.

Before the enactment of a new law in 1984, generic versions of drugs approved and marketed before 1962 could be processed by an ANDA, and duplicates of products that were approved for marketing on or after October 10, 1962, could be handled by an administrative process known as the "Paper NDA" (literature supported NDA). In September 1984, the Drug Price

Competition and Patent Term Restoration Act (1984 Amendments to the FD & C Act, also known as the Waxman-Hatch Act) became effective. The 1984 Amendments extended eligibility for ANDA processing to drugs marketed after 1962 and also codified the Paper NDA process. The ANDA process does not require the sponsor of a product to repeat clinical research on active ingredients already found to be safe and effective, making the marketing of generic versions of products approved after 1962 economically feasible. Since the 1984 Amendments went into effect, generic versions have been introduced for several hundred drugs previously available only as brand name (innovator or pioneer) products. (4)

Drug products that have been discontinued from marketing or that have had their approvals withdrawn for reasons other than safety or efficacy

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concerns are also listed. Other lists in the Orange Book are the Orphan Drug Product List, Drug Products That Must Demonstrate In vivo Bioavailability Only if Product Fails to Achieve Adequate Dissolution, Biopharmaceutic Guidance Availability, and ANDA Suitability Petitions. (2)

4. Therapeutic equivalence

The US Food and Drug Administration (FDA) considers drug products to be therapeutically equivalent if they meet certain criteria. The drug products must be pharmaceutically equivalent. This means that they contain the same amount of active drug in the same dosage form and be given by the same route of administration. At the same time, the drugs must meet the conspectus standards for purity, strength, identity, and quality that are outlined for the drug in the United States Pharmacopeia. (5)

In the Orange Book, the concept of therapeutic equivalence applies only to products containing the same active ingredients. FDA classifies as therapeutically equivalent to those products that meet the following criteria:

1. They are approved as both safe and effective.
2. They are pharmaceutical equivalents, in that they (a) contain identical amounts of the same active 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 FDA's Good Manufacturing Practice regulations. (6)

5. Bioavailability and Bioequivalence

1) Bioavailability: -

Bioavailability is defined as the rate and extent to which a drug enters the systemic circulation unchanged following administration by any route. The formulation of the dosage form and route of administration affect a drug's bioavailability and may influence the intensity and duration of the pharmacological effect.

bioavailability is more commonly defined as "the rate and extent that the active drug is absorbed from a dosage form and becomes available in the systemic circulation." (7,8)

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2)Bioequivalence: -

A drug product is a finished dosage form (e.g., tablet, capsule, paste, injectable preparation) that contains the active drug ingredient (therapeutic moiety) generally, but not necessarily, in association with inert ingredients. (8)

Bioequivalence refers to the comparison made between a generic formulation of a drug, or a product in which a change has been made in one **or** more of the ingredients or the manufacturing process, and a reference (standard) dosage form of the drug. (7,9)

6.Waxman-Hatch history

The 1984 Drug Price Competition and Patent Term Restoration Act (1984 amendments) was enacted on September 24, 1984. This act gave the agency clear statutory authority for FDA approval of pre- and post-1962 generic drugs. It also provided for reduced costs of health care with the use of generic drugs and the elimination of duplicative clinical trials. This act includes measures to ensure the continued development of new drugs through patent extension and exclusivity granted to certain new drug applications (NDAs). (10)

The act that was passed was comprised of two parts

- Title I was part of the act providing for increased eligibility of drug products to be approved through ANDAs (abbreviated new drug applications) or generic applications. Increased availability of generic drugs would lead to reduced costs of healthcare. Title I also provided for exclusive marketing rights and patent protection for innovator new drug applications and prohibits generic approval until the expiration of the patents listed in the Orange Book or expiration of the exclusive marketing rights.
- Title II of the 1984 Amendments was designed to promote the development of new drugs and provided for up to five years of patent extension to compensate for patent time lost due to the drug review process. (11,12)

7. **The Orange-Book-Standard and other European cases**

An early but interesting European case showing the fundamental difficulties of gaining

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access to essential patents under a de facto standard is the German Federal Supreme Court Orange-Book-Standard case from 2009.In the Orange-Book-Standard case, which concerned the CD-R and CD-RW technologies, the question was whether a patentee could get injunctive relief following a patent infringement suit when the infringer had tried to receive a license on commercial grounds but the patentee had refused. Interestingly, the Court started by maintaining that licensing an essential patent under a standard is a market in itself and the proprietor is that market's sole supplier, and is thus a monopolist. The German Federal Supreme Court concluded that a defendant may successfully plead that the patentee is abusing its dominant position in the market if the patentee refuses to conclude a patent license agreement with the defendant on non-discriminatory and non-restrictive terms and conditions. (13)

There have been cases, for example, the new Motorola and the Samsung cases from 2014, where the EU Commission has had the opportunity to apply the Orange-Book-Standard doctrine, and where it has distanced itself from the German case law development, indicating that the Orange-Book-Standard case was too SEP-holder friendly. (14,15)

8. Exclusivity

Exactly what then is exclusivity? How is it related to patents and why does it exist if a drug can be patented? Exclusivity is a period of exclusive marketing rights granted to a new drug application (NDA) or supplemental NDA by the FDA upon approval of an application if certain statutory provisions are met. This period of exclusive marketing rights is granted to NDAs only, except the 180-day patent challenge exclusivity granted to ANDA (generic) applications. Marketing exclusivity serves to delay the submission or final approval of generic applications.

Several types of marketing exclusivity may be granted to an application upon approval. Each type of exclusivity has Specific requirements and results in various lengths of time for which the applicant is granted exclusive marketing rights. (16,17)

Three main types of exclusivities are:

1) orphan
2) Waxman-Hatch
3) pediatric.

Non-new chemical entity exclusivity or ‘‘other’’ Waxman-Hatch exclusivity is awarded for a new or innovative change to an existing application or to an NDA that is not a ‘‘new chemical’’ NDA.

The last type of Waxman-Hatch exclusivity to be discussed is unique in that it is exclusivity granted to generic applications only. This exclusivity is a patent challenge or 180-day exclusivity. 10 This exclusivity protects the first approved generic application from competition from subsequent generic applications 11 for a period of 180 days from either the first commercial marketing or a final court decision, whichever comes first. The gain of this type of exclusivity for a generic application gives the first generic on the market a jump-start on market share for the generic use of the drug. (18)

Pediatric exclusivity is a newer form of exclusivity awarded to innovative drug applications used for children. In November 1997, the FDA Modernization Act was passed. This act included provisions to award drug sponsors with periods of exclusivity for conducting

This exclusivity has the potential to translate into revenue for the drug sponsor while at the same time increasing the knowledge base on how to use certain drugs in the pediatric population and an improvement in public health as a result. (19,20)

9. Availability of the Orange Book

The printed version of the Orange Book is available by subscription from the US Government Printing Office. It is also available at no cost on the Internet at the website of the Centre for Drug Evaluation and Research. (21,22)

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