Generic Drug Substitution: Role and Function

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FOREWORD

This report has been prepared in response to Senate Concurrent Resolution No. 242, S.D. 1, which requested the Legislative Reference Bureau to conduct a study on the use of generic drug products in Hawaii.

The Bureau does not have and has never claimed to have any expertise with respect to the technical, scientific, medical, and economic issues in this area. This study attempts to explain the principles of generic drug substitution, describe the potential problems associated with generic drug substitution, estimate the economic benefits of generic drug use in Hawaii, and identify those policy decisions that can be made by the Legislature in a rational manner.

The Bureau extends its sincere appreciation to: Donald Hare, Special Assistant to the Director of the Office of Generic Drugs, U.S. Food and Drug Administration; Edward Heon, Senior Information Coordinator for the Hawaii Medical Service Association; Alison Keith of Pfizer, Inc. (formerly Alison Masson of the Federal Trade Commission); Rebecca Kendro, Assistant Executive Director of the Hawaii Medical Association; Melvin Kumasaka, Chairperson of the State Drug Product Selection Board, Chief Pharmacist for Longs Drug Stores in Hawaii, and vice-President of the Hawaii Pharmaceutical Association; Jay Molishever, Director of Public Affairs for the Generic Pharmaceutical Industry Association; Anne Neff, Project Director for Market Measures, Inc.; Peter Sybinsky, Deputy Director of Health Resources, Department of Health; Omel Turk, Pharmacy Consultant for the Department of Human Services; Rosalind Wagner, Executive Director of the Epilepsy Foundation of Hawaii; Chandra Yamane, Administrative Coordinator for the Hawaii Dental Service; Roy Yamauchi, Manager of Pharmacy Benefits for the Hawaii Medical Service Association; and all the pharmacists who participated in the Bureau's survey of prescription drug prices. Without the generous assistance and cooperation of these individuals and countless others, the preparation of this report would have been much more difficult than it already was, if not totally impossible.

Samuel B. K. Chang
Director

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TABLE OF CONTENTS

Tables

Appendices

Glossary

In addition to providing the reader with an easily accessible guide to the many technical and legal terms used in this study, this glossary provides some uniformity to the plethora of terms and definitions that have been used by different authors (including government agencies) at different times to describe similar aspects of the same subject matter--drug legislation in the United States. The Bureau notes that achieving absolute uniformity with respect to the terminology used in this study would have been impractical and, in some cases, impossible.

"Academy" - the American Academy of Family Physicians.

Active drug ingredient - the chemical form of a therapeutic moiety.

Adjunctive monitoring - monitoring of a patient that is in addition to or in excess of monitoring that would normally be required had generic drug substitution not occurred.

Allergy (chemical) - an adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one.

Anticonvulsant or antiepileptic drug - a drug used to control the onset of seizures.

AUC - area under the plasma (blood, serum) drug concentration-time curve, representing the extent of drug absorption from a dosage form.

Bioavailability - 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.

Bioequivalence requirement - a requirement imposed by the Food and Drug Administration for in vitro or in vivo testing, or both, of specified drug products which must be satisfied as a condition of marketing.

Bioequivalent drug products - 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.

"Board" - the State's Drug Product Selection Board, which is presently attached to the Department of Health for administrative purposes.

Brand-name drug - the innovator's product, the one whose brand name has become a synonym for the drug itself.

Branded generic drug - a duplicate product sold with a trade name.

C_{max} - the maximum serum concentration achieved.

Cause of action - the fact or facts which give a person a right to judicial relief. The legal effect of an occurrence in terms of redress to a party to the occurrence. A situation or state of facts which would entitle a party to sustain action and give him a right to seek a judicial remedy in his behalf.

Compendial standards - standards that 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.

Current Good Manufacturing Practice regulations - regulations that 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.

DESI - the Drug Efficacy Study Implementation Review.

Dispenser - a person authorized to dispense drugs in the State.

Dissolution - the act or process of dissolving, refers to the absorption of a solid in and by a liquid.

Drug - an active drug ingredient or a drug product, or both.

Drug product - 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.

Drug product selection - the dispensing of a generic drug product or a brand-name drug product that was prescribed according to its therapeutic moiety or active drug ingredient.

Epilepsies - chronic seizure disorders characterized by a tendency for recurrent seizures.

Excipient - any substance added to a medicine to permit it to be formed into the proper shape and consistency; the vehicle for the drug.

Generic drug - a duplicate product, whether sold with a trade name or not.

Generic drug substitution - the act of dispensing a therapeutically equivalent generic drug product for the brand-name drug product prescribed.

In vitro - made to occur in a laboratory vessel or other controlled experimental environment rather than within a living organism or natural setting. In vitro literally means "in glass".

In vivo - made to occur within a living organism or natural setting. In vivo literally means in something alive.

Multiple-source drug product - a drug product for which there is more than one supplier.

Official compendium - the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them.

"Orange Book" - the publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (U.S., Department of Health and Human Services, Food and Drug Administration).

Pharmaceutical alternatives - 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 or dissolution rates, or both.

Pharmaceutical equivalents - 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 or dissolution rates, or both.

Pharmaceutical substitution - drug substitution involving pharmaceutical alternatives.

Pharmacodynamics - the study of drugs and their actions on living organisms.

Pharmacokinetics - the metabolism and action of drugs with particular emphasis on the time required for absorption, duration of action, distribution in the body, and method of excretion.

Plasma (blood) - a medium for the circulation of corpuscles and platelets, nutritive substances, and waste products, that consists of serum and protein substances in solution.

"Pre-1938" drugs - drug products marketed prior to the federal Food, Drug, and Cosmetic Act of 1938, or drug products generally recognized as safe and effective.

Prescriber - a person licensed by the State to prescribe drug products.

Risk - the probability that a substance will produce harm under specified conditions. Sometimes mistakenly used to mean the possibility that a substance will produce harm under specified conditions.

Serum (blood) - the clear liquid portion of blood without its fibrin and corpuscles. (Fibrin is a protein that, together with white blood corpuscles, red blood corpuscles, and platelets, form coagulums or clots.)

State drug formulary of equivalent drug products - the Hawaii Drug Formulary of Equivalent Drug Products (Section 11-33-3, Hawaii Administrative Rules, (Department of Health, Drug Product Selection Board)).

T_{max} - the measurement of time, after administration of the drug, at which the maximum serum concentration of a product is achieved.

Therapeutic moiety - 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.

Therapeutic ratio - the relationship between the dose of a drug product required to produce a toxic effect (in this case death) and the dose required to produce a desired therapeutic response. Therapeutic ratio is generally expressed as the quotient of the dose required to produce death in 50 percent of a population (LD_{50}) and the dose required to produce a desired therapeutic response in 50 percent of a population (ED_{50}), and commonly referred to as the "therapeutic index" of a drug product.

Therapeutic substitution - drug substitution involving different therapeutic moieties.

Therapeutically equivalent drug products - pharmaceutical equivalents that can be expected to have the same clinical effect when administered to patients under the conditions specified in the labeling. The FDA classifies as therapeutically equivalent drug products those drug products that meet the following general criteria:

(1) The drug products are approved as safe and effective, or approved under section 505(j) of the Food, Drug, and Cosmetic Act (21 USCA 355(j));

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

(3) The drug products are bioequivalent drug products in that they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard or, if they do present a known or potential bioequivalence problem, they are shown to meet an appropriate bioequivalence standard demonstrating comparable rate and extent of absorption;

(4) The drug products are adequately labeled; and

(5) The drug products are manufactured in compliance with Current Good Manufacturing Practice regulations.

Titration - the process of adjusting, through trial and error, the dosage of a drug product to obtain a desired therapeutic effect. The optimal dosage of a drug product is one that minimizes patient risks (from either subtherapeutic or toxic dosages of a drug product) while maximizing the benefits of that treatment regimen.

"White Paper" - the American Academy of Family Physicians' "White Paper on Generic Drugs".

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"White Paper" - the American Academy of Family Physicians' "White Paper on Generic Drugs".

CHAPTER 1

Introduction

> ...There is just no method that enables scientific theories to be proven true or even probably true. ...[T]here is no method that enables scientific theories to be conclusively disproved either.[1]

Senate Concurrent Resolution No. 242, S.D. 1, which is included in this report as Appendix A, requests the Legislative Reference Bureau (Bureau) to:[2]

(1) Study the economic benefits that Hawaii's consumers have derived from the use of generic drug products;

(2) Study the risk and dangers of generic drug products for certain patients or conditions;

(3) Recommend whether generic drug substitution for brand-name anticonvulsant drug products prescribed for persons with epilepsies should be permitted only with the authorization of both the physician and the patient;

(4) Recommend whether generic drug substitution for brand-name drug products prescribed for persons with allergic sensitivities should be permitted only with the authorization of both the physician and the patient; and

(5) Recommend legislation and policies that allow for the assessment of fines and the removal of pharmaceutical companies from the Hawaii Drug Formulary of Equivalent Drug Products,[3] where approval from the FDA has been obtained improperly, until the safety and effectiveness of their generic drug products can be proven.

To understand the nature of the Legislature's request and the scope of this study, it is important to understand the subtle difference between a generic drug product and a brand-name drug product. According to Bill Rados, editor of FDA Consumer:[4]

> It's a common misconception that brand-name drugs are produced only by large, well-known firms while generics are made by small, unknown companies. A small drug company can put a brand name on its product just as a large company can market a drug under the generic name. And many large drug firms distribute, under their brand names, products that have been manufactured, packaged and labeled by firms that make generic drugs. Some manufacturers may make a drug and sell it under both a trade name and its generic name. In other instances, large firms may make a generic version of a drug product but put their own brand name on it, even though it is not the original version of the product. These "branded generics" usually sell at a price somewhere between the original brand-name drug and "true" generic drug products. To avoid confusion, FDA [the U.S. Food and Drug Administration] prefers to reserve the term "brand-name drug" for the innovator's product, the one whose brand name has become a synonym for the drug itself (for example, Valium, Darvon, Dyazide) and to call all other duplicate

products generic drugs, whether they are sold with a trade name or not.

Like the FDA, the Bureau uses in this report the term "brand-name drug" for the product that has become a synonym for the drug itself, and calls all other duplicate products generic drugs, whether they are sold with a trade name (i.e., a brand or proprietary name) or not. The Bureau notes, however, that even this simple naming convention begins to break down when the pricing of drug products becomes the primary issue.

The next important term that must be defined is "generic drug substitution". For the purpose of this study, the term "generic drug substitution" means "the act of dispensing a therapeutically equivalent generic drug product for the brand-name drug product prescribed". Setting aside the term "therapeutically equivalent" for the moment, generic drug substitution involves the substitution of a generic drug product for the brand-name drug product prescribed.

Generic drug substitution is distinguishable from "drug product selection", which involves the dispensing of a generic drug product or a brand-name drug product that was prescribed according to its therapeutic moiety or active drug ingredient. Setting aside the terms "therapeutic moiety" and "active drug ingredient" for the moment, drug product selection involves the dispensing of a generic drug product or a brand-name drug product that has been prescribed without regard to a brand name or specific manufacturer. Generic drug substitution and drug product selection are possible only with "drug products" (i.e., finished dosage forms) since neither a therapeutic moiety nor an active drug ingredient exists in a marketable form insofar as the general public is concerned.

Although part VI of chapter 328, Hawaii Revised Statutes, is entitled "Drug Product Selection," this is a misnomer in that a pharmacist must select the generic drug product or brand-name drug product to be dispensed if the prescriber has not done so. In reality, part VI of chapter 328, Hawaii Revised Statutes, regulates generic drug substitution and not drug product selection.

Generic drug substitution and drug product selection are also distinguishable from one another in that the former involves only "therapeutically equivalent" drug products while the latter is not similarly constrained. Because the concept of "therapeutic equivalence" is built upon other concepts, definitions, and laws, it is not possible to accurately define the term "therapeutically equivalent drug products" without making reference to these concepts, definitions, and laws. Chapter 2 of this study, entitled "What is Generic Drug Substitution?", explains these concepts, definitions, and laws, and defines the term "therapeutically equivalent drug products".

Chapter 3 reviews the State's laws that regulate generic drug substitution. Chapter 4 reviews the evolution of drug regulation in the United States, with special emphasis on the events leading up to the passage of the federal Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), and the publication of the FDA "Orange Book". Chapter 5 explores the so-called "generic drug scandal" and the findings of the special testing, inspection, and review programs initiated by the FDA in the aftermath of the scandal. Chapter 6 reviews the decision of the State's Drug Product Selection Board not to remove four anticonvulsant drugs from the State's drug formulary of equivalent drug products, the FDA's October 1989 report on generic anticonvulsant drugs, and the January 1988 report of the FDA's Bioequivalence Task Force. Chapter 7 reviews the American Academy of Family Physicians' "White Paper on Generic Drugs" which, together with the generic drug scandal and the ongoing controversy over the substitution of four brand-name anticonvulsant drugs in

Hawaii, served to heighten the Legislature's awareness of the potential risks associated with generic drug substitution. Chapter 8 discusses the relationship between epilepsies, allergies, and the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products.

Chapter 9 discusses the policy issues raised in Chapters 2 through 8 and the policy questions that confront the Legislature. Chapter 10 discusses the Bureau's attempt to quantify the economic benefits that Hawaii's consumers have derived from the use of generic drug products. Finally, Chapter 11 summarizes the findings and recommendations of the Bureau.

The Bureau notes that it does not possess the specialized skills, knowledge, and capability to make a technical, scientific determination as to whether:

(1) Generic drug substitution for brand-name anticonvulsant drug products prescribed for persons with epilepsies should be permitted only with the authorization of both the physician and the patient; and

(2) Generic drug substitution for brand-name drug products prescribed for persons with allergic sensitivities should be permitted only with the authorization of both the physician and the patient.

The Bureau also notes that it has neither the technical expertise nor the access to the data needed to quantify cost-savings attributable to the use of generic drug products. Funds were not available to hire independent pharmaceutical marketing firms that have the necessary skills, knowledge, and capability to conduct this kind of inquiry. Finally, the enforcement and administration of the State's generic drug substitution law are also beyond the scope of this study.

ENDNOTES

1. A. F. Chalmers, What is this thing called Science? An assessment of the nature and status of science and its methods, 2nd ed. (St. Lucia, Queensland, Australia: University of Queensland Press, 1982), p. xvi.

2. Senate Concurrent Resolution No. 242, S.D. 1, Fifteenth Legislature, State of Hawaii, 1990.

3. Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board)

4. Bill Rados, "Generic Drugs: Cutting Cost, Not Corners", FDA Consumer, U.S., Department of Health and Human Services, Food and Drug Administration, HHS Publication No. (FDA) 86-3156 (Washington, D.C.: U.S. Government Printing Office, 1987)(reprinted from the October 1985 edition of FDA Consumer), p. 1.

CHAPTER 2

What is Generic Drug Substitution?

Introduction

For the purpose of this study, the term "generic drug substitution" means "the act of dispensing a therapeutically equivalent generic drug product for the brand-name drug product prescribed".[1] However, like the tip of an iceberg, this definition only hints at the complex scientific, medical, and ethical issues that underlie it. To understand these issues and effectively weigh the conflicting opinions regarding generic drug substitution, it is necessary to develop a working knowledge of the terminology used by the parties in this debate.

This chapter discusses the differences between "therapeutic moieties", "active drug ingredients", and "drug products", which in turn form the bases for discussing the differences between "pharmaceutical equivalents" and "pharmaceutical alternatives".[2] Continuing with the definition of pharmaceutical equivalents, the chapter then defines "bioequivalent drug products" using criteria that form the basis for the concept of "bioavailability". Using the concept of bioequivalence, the chapter explains the procedures, conditions, and criteria for establishing a "bioequivalence requirement" for a specific drug product, which must be satisfied as a condition of marketing. This chapter also explains the labeling requirements for prescription drug products and the Current Good Manufacturing Practice regulations applicable to all active drug ingredients and drug products. Using the Current Good Manufacturing Practice regulations, the concept of "adulteration" is explained.

Using the definitions, concepts, and criteria discussed above, this chapter also explains the general criteria used by the FDA to classify drug products as "therapeutically equivalent drug products". The chapter concludes by explaining the differences between "generic drug substitution", "pharmaceutical substitution", "therapeutic substitution", and "drug product selection".

Therapeutic Moieties, Active Drug Ingredients, and Drug Products

The starting point for understanding generic drug substitution is the term "therapeutic moiety". The 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"[3] (e.g., tetracycline, a broad-spectrum antibiotic). Although different substances may produce the same therapeutic effect, the substances are not necessarily identical therapeutic moieties (e.g., tetracycline hydrochloride and chlortetracycline hydrochloride are both broad-spectrum antibiotics but different therapeutic moieties). The same therapeutic moiety may appear in different chemical forms, such as different salts or esters of the same molecule. The term "active drug ingredient" is used to distinguish these different chemical forms. Each chemical form of a therapeutic moiety is a unique active drug ingredient (e.g., tetracycline hydrochloride and tetracycline phosphate complex are different active drug ingredients but the same therapeutic moiety).[4]

The form in which a patient uses an active drug ingredient is referred to as a "drug product" (e.g., tetracycline hydrochloride, 250mg, oral capsule).[5] The term "drug product" means "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".[6]

Pharmaceutical Equivalents and Pharmaceutical Alternatives

At the center of the generic drug substitution controversy is the term "therapeutically equivalent drug products". Functionally speaking, therapeutically equivalent drug products are "pharmaceutical equivalents that can be expected to have the same clinical effect when administered to patients under the conditions specified in the labeling".[7] Although the term "therapeutically equivalent drug products" also 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",[8] the FDA will not evaluate as therapeutically equivalent drug products two drug products that are not pharmaceutical equivalents.[9]

Consequently, the first consideration in evaluating whether two drug products are therapeutically equivalent drug products is whether the two drug products are "pharmaceutical equivalents".[10] The term "pharmaceutical equivalents" means "drug products that contain identical amounts of the identical active drug ingredient, i.e., the same sat [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".[11]

More simply stated, two drug products are considered pharmaceutical equivalents if the drug products contain the same active drug ingredient (e.g., tetracycline hydrochloride) or ingredients and are identical in strength or concentration (e.g., 250mg), dosage form (e.g., capsules), and route of administration (e.g., oral). Pharmaceutical equivalents are formulated to contain the same amount of active drug ingredient in the same dosage form and to meet the same or compendial[12] or other applicable standards[13] (i.e., strength, quality, purity, and identity), but may differ in characteristics such as shape, scoring, configuration, packaging, excipients (including colors, flavors, and preservatives), expiration time and, within certain limits, labeling.[14]

Variations in characteristics such as color, taste, shape, packaging, stability, expiration time and, within certain limits, labeling, are described by the FDA as "pharmaceutical elegance" if the variations relate to a drug product's physical attractiveness, cost, convenience to patients, or acceptance by patients, rather than the drug product's safety or efficacy.[15] Drug products that contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety (e.g., tetracycline hydrochloride versus tetracycline phosphate complex) or are different dosage forms (e.g., tablet versus capsule) or strengths (e.g., 500mg versus 250mg) are "pharmaceutical alternatives".[16] Different dosage forms and strengths within a product line by a single manufacturer are pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active drug ingredient.[17]

Bioequivalent Drug Products and Bioavailability

The second consideration in evaluating whether two drug products are therapeutically equivalent is whether the drug products are "bioequivalent drug products".[18] The term "bioequivalent drug products" means:[19]

> ...[P]harmaceutical 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.

More concisely stated, bioequivalent drug products are pharmaceutical equivalents "that display comparable bioavailability when studied under similar experimental conditions".[20] The term "bioavailability" 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".[21]

Although two drug products that are not pharmaceutical equivalents may still be bioequivalent drug products, the FDA will not evaluate as therapeutically equivalent drug products two drug products that are not pharmaceutical equivalents.[22] As a matter of policy, the FDA presumes that pharmaceutical equivalents are also bioequivalent drug products unless there exists scientific evidence to the contrary. The FDA explained the consequences of this presumption in the following manner:[23]

> ...As a consequence of this presumption, only where scientific evidence demonstrates a known or potential problem of bioinequivalence does the agency [FDA] 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.

In addition, the FDA will not evaluate as therapeutically equivalent drug products those drug products with known or potential bioequivalence problems[24] that have not been resolved with adequate evidence supporting bioequivalence.[25]

Bioequivalence Requirement

Where there is well-documented evidence that specific pharmaceutical equivalents[26] intended to be used interchangeably for the same therapeutic effect:

(1) Are not bioequivalent drug products;

(2) May not be bioequivalent drug products based on the criteria set forth at 21 CFR 320.52; or

(3) May not be bioequivalent drug products because the pharmaceutical equivalents are members of a class of drug products that have close structural similarity and similar physicochemical or pharmacokinetic[27] properties to other

drug products in the same class that the Commissioner of Food and Drugs (hereinafter "the Commissioner") finds are not bioequivalent drug products;

the Commissioner, on the Commissioner's own initiative or in response to a petition by an interested person, may propose and promulgate a regulation to establish a bioequivalence requirement.[28] The term "bioequivalence requirement" means "a requirement imposed by the Food and Drug Administration for in vitro[29] and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing".[30]

The Commissioner is required to consider the following factors, when supported by well-documented evidence, to identify specific pharmaceutical equivalents[31] that are not or may not be bioequivalent drug products and to determine whether to propose or promulgate a regulation to establish a bioequivalence requirement for these drug products:[32]

(1) Evidence from well-controlled clinical trials or controlled observations in patients that the drug products do not give comparable therapeutic effects;

(2) Evidence from well-controlled bioequivalence studies that the drug products are not bioequivalent drug products;

(3) Evidence that the drug products exhibit a narrow therapeutic ratio[33] or have less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration[34] and patient monitoring;

(4) Competent medical determination that a lack of bioequivalence would have a serious adverse effect in the treatment or prevention of a serious disease or condition;

(5) Physicochemical evidence that the active drug ingredient has a low solubility in water or, if dissolution in the stomach is critical to absorption, the volume of gastric fluids required to dissolve the recommended dose far exceeds the volume of fluids present in the stomach; the dissolution rate of one or more drug products is slow or differs significantly from the dissolution rate of an appropriate reference material such as an identical drug product that is the subject of an approved full new drug application; the particle size or surface area, or both, of the active drug ingredient is critical in determining the active drug ingredient's bioavailability; certain physical structural characteristics of the active drug ingredient dissolve poorly and this poor dissolution may affect absorption; the drug products have a high ratio of excipients to active ingredients; and specific inactive ingredients either may be required for absorption of the active drug ingredient or therapeutic moiety or, alternatively, if present, may interfere with the absorption of the active drug ingredient or therapeutic moiety; and

(6) Pharmacokinetic evidence that the active drug ingredient, therapeutic moiety, or its precursor is absorbed in large part in a particular segment of the gastrointestinal tract or is absorbed from a localized site; the degree of absorption of the active drug ingredient, therapeutic moiety, or its precursor is poor even when the active drug ingredient, therapeutic moiety, or its precursor is administered in pure form; there is rapid metabolism of the therapeutic moiety in the intestinal wall or liver during the process of absorption so the

therapeutic effect or toxicity, or both, of the drug product is determined by the rate as well as the degree of absorption; the therapeutic moiety is rapidly metabolized or excreted so that rapid dissolution and absorption are required for effectiveness; the active drug ingredient or therapeutic moiety is unstable in specific portions of the gastrointestinal tract and requires special coatings or formulations to assure adequate absorption; and the drug product is subject to dose-dependent kinetics in or near the therapeutic range,[35] and the rate and extent of absorption are important to bioequivalence.

A bioequivalence requirement may involve one or more of the following, as specified by the FDA:[36]

(1) An in vivo test in humans;

(2) An in vivo test in animals other than humans that has been correlated with human in vivo data;

(3) An in vivo test in animals other than humans that has not been correlated with human in vivo data;

(4) An in vitro bioequivalence standard; i.e., an in vitro test that has been correlated with human in vivo bioavailability data; and

(5) A currently available in vitro test (usually a dissolution rate test) that has not been correlated with human in vivo bioavailability data.

In vivo testing in humans is ordinarily required if there is well-documented evidence that pharmaceutical equivalents[37] intended to be used interchangeably for the same therapeutic effect meet one of the following conditions:[38]

(1) The drug products do not give comparable therapeutic effects;

(2) The drug products are not bioequivalent drug products; or

(3) The drug products exhibit a narrow therapeutic ratio or there is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentration in the blood, and safe and effective use of the drug product requires careful dosage titration and patient monitoring.

The following in vivo approaches, listed in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability of a drug product:[39]

(1) In vivo testing in humans in which the concentration of the active drug ingredient or therapeutic moiety or its metabolite or metabolites, in whole blood, plasma,[40] serum, or other appropriate biological fluid is measured as a function of time, or in which the urinary excretion of the therapeutic moiety, or its metabolite or metabolites, is measured as a function of time;

(2) In vivo testing in humans in which an appropriate acute pharmacological effect of the active drug ingredient or therapeutic moiety, or metabolite or metabolites, is measured as a function of time if the effect can be measured with sufficient accuracy, sensitivity, and reproducibility;

(3) Well-controlled clinical trials in humans that establish the safety and effectiveness of the drug product; and

(4) Any other in vivo approach approved by the FDA.

Labeling

The third consideration in evaluating whether two drug products are therapeutically equivalent drug products is whether the two drug products are adequately labeled for the practitioner and pharmacist.[41] According to the FDA:[42]

> ...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 [the drug] is intended. [citation deleted] In addition, the label of every drug product is required to identify the contents accurately and in detail [citation deleted].

Current Good Manufacturing Practice

The fourth consideration in evaluating whether two drug products are therapeutically equivalent durg products is whether the two drug products are manufactured in accordance with "Current Good Manufacturing Practice" regulations.[43] Current Good Manufacturing Practice 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."[44]

The Current Good Manufacturing Practice regulations are not generally designed to prescribe specific manufacturing processes because of the wide variety of drug products and the possibility of interfering with technological evolution. Rather, the regulations are designed to address problems common to the manufacture of all drug products or of all drug products of a particular class. Unique problems encountered in the manufacturing of specific drug products are addressed through the new drug approval process and the abbreviated new drug approval process, rather than the Current Good Manufacturing Practice regulations.[45]

An active drug ingredient or drug product is deemed "adulterated" and subject to regulatory action 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 active drug ingredient or drug product meets the requirements of the Federal Food, Drug, and Cosmetic Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.[46] Current good manufacturing practice is determined by the FDA on the basis of an ongoing review of operations within the drug manufacturing industry.[47]

Therapeutically Equivalent Drug Products

Drug products considered to be therapeutically equivalent drug products "are pharmaceutical equivalents that can be expected to have the same clinical effect when administered to patients under the conditions specified in the labeling".[48] The FDA classifies as therapeutically equivalent drug products those drug products that meet the following general criteria:[49]

(1) The drug products are approved as safe and effective, or approved under section 505(j) of the Food, Drug, and Cosmetic Act (21 USCA 355(j));

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

(3) The drug products are bioequivalent drug products in that they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard or, if they do present a known or potential bioequivalence problem, they are shown to meet an appropriate bioequivalence standard demonstrating comparable rate and extent of absorption;

(4) The drug products are adequately labeled; and

(5) The drug products are manufactured in compliance with Current Good Manufacturing Practice regulations.

Pharmaceutical and Therapeutic Substitution, and Drug Product Selection

Generic drug substitution is distinguishable from "pharmaceutical substitution", which involves the substitution of pharmaceutical alternatives, and "therapeutic substitution", which involves the substitution of different therapeutic moieties. Generic drug substitution, pharmaceutical substitution, and therapeutic substitution are distinguishable from "drug product selection", which involves the dispensing of drug products that were prescribed according to their therapeutic moiety or active drug ingredient.

Summary

No two drug products are exactly alike; minute differences exist within and between batches of drug products manufactured by the same company, so there is no basis in fact for expecting drug products manufactured by different companies to be exactly alike. The controversy over generic drug substitution is whether or not these differences, which can include variations in individual manufacturing tolerances and the use of different inactive ingredients, are "clinically significant", i.e., whether or not these differences will result in potentially adverse therapeutic outcomes.

The possibility that these differences will result in potentially adverse therapeutic outcomes can never be totally dismissed--not even for single-source brand-name drug products. Consequently, the practical question is not whether it is possible that these

differences will result in potentially adverse therapeutic outcomes, but rather, how probable and what constitutes an "acceptable risk".[50]

ENDNOTES

1. Generic drug substitution is not possible with single-source drug products, i.e., drug products for which no therapeutically equivalent drug products are available at a specified point in time. Generic drug substitution does not include the dispensing of drug products that were prescribed according to their therapeutic moiety (e.g., tetracycline) or active drug ingredient (e.g., tetracycline hydrochloride), as opposed to drug products that were prescribed according to their proprietary name (e.g., Sumycin) or the name of the drug product's manufacturer (e.g., Squibb). Theodore Goldberg and others, eds., Generic Drug Laws: A Decade of Trial--A Prescription for Progress. U.S., Department of Health and Human Services, National Center for Health Services Research and Health Care Technology Assessment, NCHSR Report No. 86-30, (Virginia: National Technical Information Service, 1986) pp. 2-3 and 541-544.

2. Failure to fully appreciate these differences can result in invalid reports of generic drug product failure. For example, examination of a published case report alleging generic procainamide failure revealed an invalid comparison between the brand-name drug product, which was a sustained-release product, and its generic equivalent, which was an immediate-release product. Sustained-released drug products and immediate-release drug products are considered by the FDA to be pharmaceutical alternatives, not pharmaceutical equivalents. Carl Peck, Director, Center for Drug Evaluation and Research, U.S., Department of Health and Human Services, Food and Drug Administration, "Text of talk to the Reference Committee of the American Academy of Family Physicians on the subject of the Academy's 1989 position paper on generic drugs", (Maryland: September 16, 1989), p. 3.

3. 44 FR 2937, Jan. 12, 1979.

4. 44 FR 2937-2938.

5. 44 FR 2938.

6. 21 CFR 320.1(b).

7. U.S., Department of Health and Human Services, Food and Drug Administration, Approved Drug Products with Therapeutic Equivalence Evaluations, 10th ed., (Washington, D.C.: U.S. Government Printing Office, 1990) (hereinafter cited as "Orange Book"), p. 1-1.

8. 44 FR 2937.

9. 44 FR 2938.

10. 44 FR 2938.

11. 21 CFR 320.1(c).

12. The term "official compendium" means "the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them". 21 USCA 321(j).

    Compendial 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". 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". 44 FR 2939.

13. The federal Food, Drug, and Cosmetic Act requires a drug recognized in an official compendium to meet the standards of strength, quality, and purity set forth in that

compendium. Where compendial standards do not exist, the Food, Drug, and Cosmetic Act authorizes the 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 USCA 351(b).

14. U.S., Department of Health and Human Services, "Orange Book", supra note 7.

15. 44 FR 2938.

16. The term "pharmaceutical alternatives" means:

> ...[D]rug 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.

21 CFR 320.1(d).

17. U.S., Department of Health and Human Services, "Orange Book", supra note 7.

18. 44 FR 2938.

19. 21 CFR 320.1(e).

20. U.S., Department of Health and Human Services, "Orange Book", supra note 7.

21. 21 CFR 320.1(a).

The bioavailability of a drug product can be affected by a number of biological and pharmaceutical factors. 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". These biological factors are influenced, in turn, "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". 44 FR 2941.

22. The FDA has stated that it will not evaluate the therapeutic equivalence of pharmaceutical alternatives since the primary purpose of performing these evaluations is "to provide State agencies and officials with information relating to drug products that may be selected for dispensing under applicable State law". According to the FDA:

> ...Under most State drug product selection [generic drug substitution] 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.

44 FR 2938.

23. 44 FR 2938.

According to the FDA:

> ...[F]or those active ingredients for which no bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed for some dosage forms (e.g., solutions) or satisfied for solid oral dosage forms by a showing that an acceptable in vitro standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications....
>
> * * *
>
> ...[F]or those DESI drug products containing active ingredients that have been identified by FDA as having actual or potential bioequivalence problems [citations deleted], and for post-1962 drug products, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through in vivo studies the bioequivalence of the product to a selected standard product.

U.S., Department of Health and Human Services, "Orange Book", supra note 7. See Chapter 5, The Drug Amendments of 1962.

24. 45 FR 72593, Oct. 31, 1980.

25. 21 CFR 320.58

26. Although the procedures for establishing or amending a bioequivalence requirement are also applicable to pharmaceutical alternatives, the FDA's policy regarding the evaluation of pharmaceutical alternatives as therapeutically equivalent drug products makes the establishment of such a bioequivalence requirement for pharmaceutical alternatives unlikely. 21 CFR 320.51(a).

27. The term "pharmacokinetics" refers to the metabolism and action of drugs with particular emphasis on the time required for absorption, duration of action, distribution in the body, and method of excretion. A closely related term, "pharmacodynamics", refers to the study of drugs and their actions on living organisms. Clayton Thomas ed., Taber's Cyclopedic Medical Dictionary, 14th ed. (Pennsylvania: F.A. Davis Company, 1981), p. 1085.

28. 21 CFR 320.51.

29. The term "in vitro" means "made to occur in a laboratory vessel or other controlled experimental environment rather than within a living organism or natural setting". In vitro literally means "in glass". The term, "in vivo", means "made to occur within a living organism or natural setting". In vivo literally means "in (something) alive". Stuart Flexner, ed., The Random House Dictionary of the English Language, Unabridged 2nd ed.; (New York: Random House, Inc., 1987), p. 1004.

30. 21 CFR 320.1(f).

31. Although the criteria and evidence for establishing a bioequivalence requirement are also applicable to pharmaceutical alternatives, the FDA's policy regarding the evaluation of pharmaceutical alternatives as therapeutically equivalent drug products makes the establishment of such a bioequivalence requirement for pharmaceutical alternatives unlikely. 21 CFR 320.52.

32. 21 CFR 320.52.

33. The term "therapeutic ratio" refers to the relationship between the dose of a drug product required to produce a toxic effect (in this case death) and the dose required to produce a desired therapeutic response. Therapeutic ratio is generally expressed as the quotient of the dose required to produce death in 50 percent of a population (LD_{50}) and the dose required to produce a desired therapeutic response in 50 percent of a population (ED_{50}), and

commonly referred to as the "therapeutic index" of a drug product. Curtis Klaassen and John Doull, "Evaluation of Safety: Toxicologic Evaluation", in John Doull and others eds. Casarett and Doull's Toxicology: The Basic Science of Poisons, (New York: Macmillan Publishing Co., Inc., 1980), p. 22.

34. Titration refers to the process of adjusting, through trial and error, the dosage of a drug product to obtain a desired therapeutic effect. The optimal dosage of a drug product is one that minimizes patient risks (from either subtherapeutic or toxic dosages of a drug product) while maximizing the benefits of that treatment regimen.

35. Phenytoin reportedly exhibits dose-dependent elimination (kinetics) in the therapeutic range. Steven Mayer and others, "Introduction; The Dynamics of Drug Absorption, Distribution, and Elimination" in Alfred Goodman Gilman and others, eds., The Pharmacological Basis of Therapeutics, 6th ed. (New York: MacMillan Publishing Co., Inc., 1980), p. 25.

36. 21 CFR 320.53(a).

37. Although these bioequivalence requirements are also applicable to pharmaceutical alternatives, the FDA's policy regarding the evaluation of pharmaceutical alternatives as therapeutically equivalent drug products makes the establishment of bioequivalence requirements for pharmaceutical alternatives unlikely. 21 CFR 320.53(b).

38. 21 CFR 320.53(b).

39. 21 CFR 320.24(c).

40. "Plasma" (blood) is a medium for the circulation of corpuscles and platelets, nutritive substances, and waste products that consists of serum and protein substances in solution. "Serum" (blood) is the clear liquid portion of blood without its fibrin and corpuscles. "Fibrin" is a protein that, together with white blood corpuscles, red blood corpuscles, and platelets, form coagulums or clots. Thomas, Taber's Cyclopedic Medical Dictionary, supra note 27, pp. 1111, 1301, and 536.

41. 44 FR 2938.

42. 44 FR 2938.

43. 44 FR 2938.

44. 44 FR 2945.

45. 44 FR 2945.

46. 44 FR 2938.

47. 44 FR 2938.

48. U.S., Department of Health and Human Services, "Orange Book", supra note 7.

49. U.S., Department of Health and Human Services, "Orange Book", supra note 7.

50. The term "risk" means "the probability that a substance will produce harm under specified conditions". Klaassen and Doull, supra note 33, p. 12.

As pointed out by Morton Corn:

> Inherent in consideration of risk is the acceptance of the statistical basis for assigning risk to any hazard. As Alvin Weinberg has noted, there is a category of problems with which society deals that he designates as "trans-science." These problems do not have objective proof or certainty and such proof or certainty is unattainable [citation deleted]. The public perception of

what constitutes an acceptable risk can be viewed as an exercise in "trans-science" problem solving.

Morton Corn, "Regulatory Toxicology" in John Doull and others, eds., supra note 33, p. 713.

Continuing this discussion, M. Alice Ottoboni stated:

> The term "trans-science" was proposed by Alvin M. Weinberg to describe wisdom that cannot be achieved through scientific methodology. In his discussion of the relation between scientific knowledge and societal decisions [cross reference deleted], he notes, "Many of the issues which arise in the course of the interaction between science or technology and society...hang on the answers to questions which can be asked of science and yet which cannot be answered by science. I propose the term trans-scientific for these questions since, though they are, epistemologically speaking, questions of fact and can be stated in the language of science, they are unanswerable by science; they transcend science.
>
> Dr. Weinberg cites three causes for the inability of science to answer trans-scientific questions: (1) "science is inadequate simply because to get answers would be impractically expensive"; (2) "science is inadequate because the subject-matter is too variable to allow rationalisation according to the strict scientific canons established within the natural sciences"; and (3) "science is inadequate simply because the issues themselves involve moral and esthetic judgments: they deal not with what is true but rather with what is valuable." The great majority of trans-scientific questions asked of toxicology can be placed in the first category, which for our purposes, will also include questions which science does not yet have sufficient knowledge or techniques to answer."

M. Alice Ottoboni, The Dose Makes the Poison (California: Vincente Books, 1984), p. 95.

CHAPTER 3

Generic Drug Substitution in Hawaii

Generic drug substitution in Hawaii is governed by part I (Hawaii Food, Drug, and Cosmetic Act) and part VI (drug product selection) of chapter 328 (food, drugs, and cosmetics), Hawaii Revised Statutes. In the interest of accuracy, this chapter describes the State's drug product selection (i.e., generic drug substitution) law using the terms embodied in chapter 328, Hawaii Revised Statutes.

Drug Product Selection

State law[1] requires a dispenser[2] or the dispenser's authorized agent[3] to:

(1) Offer a consumer substitutable and lower cost equivalent drug products[4] from the State's drug formulary of equivalent drug products;

(2) Inform a consumer of the retail price difference between the brand name drug product and the substitutable drug product; and

(3) Inform a consumer on the consumer's right to refuse substitution.

A dispenser is required to substitute a prescribed drug product with an equivalent drug product if:

(1) The consumer consents;

(2) The prescriber[5] does not prohibit substitution; and

(3) The price of the substitute equivalent drug product is less than the price of the prescribed drug product.[6]

A dispenser is prohibited from substituting an equivalent drug product for a prescribed drug product if the consumer refuses substitution.[7] A dispenser is also prohibited from substituting an equivalent drug product for a prescribed drug product if the prescriber, and only the prescriber, handwrites "do not substitute" on the written prescription. A dispenser is similarly prohibited from substituting an equivalent drug product for a prescribed drug product if a prescription is ordered orally and the prescriber or an authorized employee of the prescriber orally orders "do not substitute".[8]

In refilling prior written prescriptions, a dispenser is prohibited from substituting an equivalent drug product for a prescribed drug product if the (subsequent) oral prescription is a refill of a prior written prescription that did not permit the selection of an equivalent drug product. A dispenser is allowed to substitute an equivalent drug product for a prescribed drug product if the prior written prescription permitted the selection of an equivalent drug product. A dispenser is prohibited, however, from substituting an equivalent drug product for a prescribed drug product if a refill of a (prior) prescription is ordered orally and the prescriber or an authorized employee of the prescriber orally orders "do not substitute".[9]

State law prohibits the designation of "do not substitute" and a physician's signature from being preprinted or stamped on a prescription.[10] State law also prohibits a dispenser from substituting an equivalent drug product for a prescribed drug product unless the price of the equivalent drug product is less than the price of the prescribed drug product.[11]

Violations of the State's drug product selection law are classified as misdemeanors. The county prosecutors and the Attorney General may bring actions to enjoin violations of the State's drug product selection law upon complaints of aggrieved persons or upon their own motion in the name of the State.[12]

Prescription Label

State law[13] requires that dispensers indicate, on the label affixed to the immediate container in which the drug product is sold or dispensed, the name and strength of the drug product and the name or commonly accepted abbreviation of the principal labeler,[14] and the statement "Substituted for (Brand name of the drug product prescribed)" unless the prescriber specifically states otherwise. A dispenser is also required to record, on the prescription form, the brand name or the name or commonly accepted abbreviation of the principal labeler of the drug product dispensed.

Prescription Record

State law[15] requires a dispenser to maintain a record of any substitution of a generically equivalent drug product for a prescribed brand name product.

Drug Product Selection Board

The State's drug product selection board is composed of:

(1) One representative from the Department of Health;

(2) One representative from either the University of Hawaii School of Medicine or the University of Hawaii School of Public Health;

(3) Two physicians;

(4) Two pharmacists; and

(5) The Director of Health or the Director's designated representative.[16]

All members of the Drug Product Selection Board (hereinafter "the Board"), excluding the Director of Health, are appointed by the Governor with the advice and consent of the Senate. The Board appoints a chairperson from among the Board's six duly appointed members.[17] The Board is placed, for administrative purposes only, within the Department of Health.[18] Members of the Board serve without compensation, but are reimbursed for expenses, including travel expenses, incurred in the performance of their duties.[19]

Drug Formulary

State law[20] requires the Board to adopt rules, pursuant to chapter 91, Hawaii Revised Statutes (the Hawaii Administrative Procedure Act), for the establishment and maintenance of a state drug formulary of equivalent drug products, and to effectuate the purposes of the State's drug product selection law. The Board is allowed, without regard to chapter 91, to establish in the formulary those equivalent drug products that the Commissioner of Food and Drugs, United States Food and Drug Administration, has approved as safe and effective and has determined to be therapeutically equivalent. The formulary is required to list all drug products that the Commissioner of Food and Drugs has approved as safe and effective and has determined to be therapeutically equivalent. The formulary is allowed to list additional drug products that are determined by the Board to meet requirements adequate to assure product quality and therapeutic equivalence. The formulary is also allowed to delete approved drug products upon a finding that product quality or therapeutic equivalency or bioequivalency,[21] as appropriate, is not adequately assured.

State law[22] allows the formulary to be changed, added to, or deleted from as the Board deems appropriate. A person who requests that a change be made or that a generic name or brand name drug product be included or added to or deleted from the formulary has the burden of proof to show cause why the change, inclusion, addition, or deletion should be made.

The Board is required to provide for the revision or supplementation of the formulary as necessary, but not less than annually.[23]

State law[24] requires the Department of Health to provide for the distribution of the formulary, revisions, and supplements to all dispensers and prescribers licensed and practicing in the State and to other appropriate individuals. The Department of Health is allowed to establish fees to be charged to persons who receive the formulary, revisions, and supplements. The amounts of the fees charged for the formulary, revisions, and supplements are required to be approximately the same as the costs of producing and distributing the formulary, revisions, and supplements.

State law also requires the Department of Health to provide for public education regarding the provisions of the State's drug product selection law and to monitor the effects of the same.[25]

Posting Requirements

State law[26] requires pharmacies to prominently display, in clear and unobstructed public view, a sign in block letters that reads: "HAWAII LAW REQUIRES THAT LESS EXPENSIVE GENERICALLY EQUIVALENT DRUG PRODUCTS BE OFFERED TO THE CONSUMER. CONSULT YOUR PHYSICIAN AND PHARMACIST CONCERNING THE AVAILABILITY OF THE LEAST EXPENSIVE DRUG PRODUCT FOR YOUR USE". State law also requires that the letters be at least one inch in height.

Dispenser Liability

Dispensers who select an equivalent drug product pursuant to the State's drug product selection law assume no greater liability for selecting a dispensed equivalent drug product than would be incurred in filling a prescription for a drug product prescribed by the drug product's established name.[27]

Record of Prescriptions

State law[28] requires licensed physicians, druggists, and apothecaries, who compound, sell, or deliver prescriptions containing a poisonous drug, or substance deleterious to human life, to be used as medicine, to enter upon the physician's, druggist's, or apothecary's books the prescription written out in full, with:

(1) The date of the prescription; and

(2) The physician's, druggist's, or apothecary's own name; or

(3) The name of the physician who prescribed the poisonous drug or deleterious substance, and the name of the person to whom the poisonous drug or deleterious substance was delivered.

State law[29] prohibits the compounding, sale, and delivery of a prescription containing a poisonous drug or deleterious substance unless the name of the person compounding, selling, or delivering the poisonous drug or deleterious substance, or the name of the physician prescribing the poisonous drug or deleterious substance is appended to the prescription. State law also requires that prescriptions for medicines containing a poisonous drug or deleterious substance be preserved for a period of not less than five years. The books and prescriptions of licensed physicians, druggists, and apothecaries who compound, sell, or deliver prescriptions containing a poisonous drug or deleterious substance are subject at all times to the inspection of the Director of Health or the Director's agent.

Out-of-State Prescriptions

State law[30] allows an original prescription written by an out-of-state practitioner within the confines of the practitioner's license and in accordance with Hawaii statutory law and regulation, excluding narcotics and habit-forming drugs, to be filled once and only if filled within 90 days of the date of the original prescription. A pharmacist filling an out-of-state prescription is required to demand proper identification from the person whose name appears on the prescription prior to filling the prescription. A pharmacist who fills an out-of-state prescription is responsible in case the prescription is not written in the form prescribed by State law and regulation. A pharmacist is required to properly identify the prescriptions as "Out-of-State Filled" together with the date of filling and the local address of the person whose name appears on the prescription. Filled out-of-state prescriptions are required to be kept in a special file for two years.

Exemptions

Out-of-state prescriptions filled pursuant to section 328-101, Hawaii Revised Statutes (out-of-state prescriptions), are exempt from the State's drug product selection law.[31]

Prohibited Acts

Except as provided in part VI of chapter 328, Hawaii Revised Statutes, state law prohibits the dispensing of a different drug or brand of drug in place of the drug or brand of drug ordered or prescribed without the expressed permission in each case of the person ordering or prescribing.[32]

ENDNOTES

1. Hawaii Rev. Stat., sec. 328-92(a).

2. The term, "dispenser" means "a person authorized to dispense drugs in the State". Hawaii Rev. Stat., sec. 328-91.

3. The term, "agent" means "a person under the direct supervision of a dispenser, acting in the dispenser's presence". Hawaii Rev. Stat., sec. 328-91.

4. The term, "equivalent drug product" means "a drug product with the same established name, active ingredient strength, quantity, and dosage form as the drug product identified in the prescription, and listed as therapeutically equivalent in the current state drug formulary". Hawaii Rev. Stat., sec. 328-91.

   The term, "established name" has the meaning "given in section 502(e)(3) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 352(e)(3))". Hawaii Rev. Stat., sec. 328-91.

   The meaning given to "established name", with respect to a drug or ingredient thereof, means "(A) the applicable official name designated pursuant to section 358 [authority to designate official names] of this title, or (B), if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium, or (C) if neither clause (A) nor clause (B) of this subparagraph applies, then the common or usual name, if any, of such drug or of such ingredient: Provided further, That where clause (B) of this subparagraph applies to an article recognized in the United States Pharmacopeia and in the Homeopathic Pharmacopoeia under different official titles, the official title used in the United States Pharmacopeia shall apply unless it is labeled and offered for sale as a homeopathic drug, in which case the official title used in the Homeopathic Pharmacopoeia shall apply". 21 USCA 352(e)(3).

   Pursuant to 21 USCA §358(a), the Secretary of Health and Human Services, United States Department of Health and Human Services, is authorized to designate an official name for a drug if the Secretary determines that this action is necessary or desirable in the interest of usefulness and simplicity. An official name designated under section 358 for a drug is the only official name of that drug that can be used in any official compendium published after the name has been prescribed or for any other purpose of this chapter [chapter 9 -- Federal Food, Drug, and Cosmetic Act]. The Secretary is prohibited from establishing an official name that would infringe a valid trademark.

5. The term, "prescriber" means "a person licensed by the State to prescribe drug products". Hawaii Rev. Stat., sec. 328-91.

6. Hawaii Rev. Stat., sec. 328-92(a).

7. Hawaii Rev. Stat., sec. 328-92(a).

8. Hawaii Rev. Stat., sec. 328-92(b).

9. Hawaii Rev. Stat., sec. 328-92(b).

10. Hawaii Rev. Stat., sec. 328-92(b).

11. Hawaii Rev. Stat., sec. 328-92(c).

12. Hawaii Rev. Stat., sec. 328-92(d).

13. Hawaii Rev. Stat., sec. 328-93.

14. The term, "principal labeler" means "the manufacturer, packer, or distributor whose name is on the package which contains the finished drug and is distributed to the dispenser. If more than one name is on the package, the principal labeler shall be the manufacturer, packer, or distributor whose name is on the package and who had possession of the package immediately before the dispenser of the drug". Hawaii Rev. Stat., sec. 328-2.

15. Hawaii Rev. Stat., sec. 328-94.

16. Hawaii Rev. Stat., sec. 328-95(a).

17. Hawaii Rev. Stat., sec. 328-95(a).

18. Hawaii Rev. Stat., sec. 328-95(b).

19. Hawaii Rev. Stat., sec. 328-95(c).

20. Hawaii Rev. Stat., sec. 328-96(a).

21. The term, "bioequivalents" means "chemical equivalents which, when administered to the same individuals in the same dosage regimen, will result in comparable bioavailability, as defined by the Federal Food and Drug Administration". Hawaii Rev. Stat., sec. 328-91.

22. Hawaii Rev. Stat., sec. 328-96(b).

23. Hawaii Rev. Stat., sec. 328-96(c).

24. Hawaii Rev. Stat., sec. 328-96(d).

25. Hawaii Rev. Stat., sec. 328-96(e).

26. Hawaii Rev. Stat., sec. 328-97.

27. Hawaii Rev. Stat., sec. 328-98.

28. Hawaii Rev. Stat., sec. 328-100.

29. Hawaii Rev. Stat., sec. 328-100.

30. Hawaii Rev. Stat., sec. 328-101.

31. Hawaii Rev. Stat., sec. 328-99.

32. Hawaii Rev. Stat., sec. 328-6(15).

CHAPTER 4

In Bits and Pieces

> There's a common misconception that FDA is responsible for testing drugs before they're approved for sale. While the agency does a great deal of testing to check on the purity and potency of drugs, it's the drug sponsor--a pharmaceutical company, a research organization, a public or private agency, even an individual--that is required to initiate studies to assess drug safety and effectiveness. FDA's role is to examine the design and conduct of those studies, and, of course, the results, as part of the process of deciding whether a new drug can be approved for marketing.[1]

The Food and Drugs Act of 1906

Prior to the passage of the Food and Drugs Act of 1906, there was no effective regulation of drug products in the United States, and no assurance that drug products were in fact safe and effective for their intended use.[2]

The Food and Drugs Act of 1906 designated The Pharmacopeia of the United States of America and The National Formulary as the official standards of strength and purity for active drug ingredients and drug products, and empowered the federal government to enforce these standards.[3] The law required that active drug ingredients and drug products comply with the standards of strength and purity established by The Pharmacopeia of the United States of America and The National Formulary, but placed the burden of proof on the FDA to show that a drug product's labeling was false and fraudulent before it could be taken off the market.[4] It was not until the passage of the Federal Food, Drug, and Cosmetic Act that drug products were actually required to demonstrate their safety before being legally marketed.[5]

The Federal Food, Drug, and Cosmetic Act (1938)

Following the now classic "Elixir Sulfanilamide" tragedy in which 107 people died after ingesting a poisonous diethylene glycol[6] solution of sulfanilamide, the Congress of the United States passed legislation that required a manufacturer to prove the safety of a drug product before the drug product could be marketed.[7] The Federal Food, Drug, and Cosmetic Act also contained provisions to prevent the premature marketing of drug products containing new active drug ingredients[8] not properly tested for safety by requiring the manufacturer to submit a "new drug application" (NDA) to the government for a review of safety studies before the drug product could be marketed.[9]

The Drug Amendments of 1962

Following the thalidomide[10] incident in Western Europe, the Congress of the United States passed the Drug Amendments of 1962, sometimes referred to as the Kefauver-Harris Amendment. The Drug Amendments of 1962 required a manufacturer to prove, before marketing, that a drug product was both safe and effective for the drug product's intended use. This requirement was applied retroactively to 1938, when the Federal Food, Drug, and Cosmetic Act was enacted. Drug products marketed prior to 1938 were "grandfathered" in,

i.e., allowed to be sold after 1962, unless evidence to the contrary developed, because the drug products were generally recognized as safe and effective.[11]

To facilitate the task of evaluating all drug products introduced between 1938 and 1962, the FDA in 1966 contracted with the National Academy of Sciences and its research arm, the National Research Council, to review the effectiveness of drug products approved after 1938, i.e., drug products approved solely on the basis of safety. This program of studying the supporting data for therapeutic claims was called the Drug Efficacy Study Implementation (DESI) review. As a result of the DESI review, some therapeutic claims were withdrawn from the labeling of some drug products and some drug products were either withdrawn from the market or reformulated.[12]

During the DESI review, special attention soon became focused on over-the-counter drug products since 75 per cent of 512 over-the-counter drug products evaluated lacked substantial evidence[13] of effectiveness. Because of the overwhelming number of over-the-counter drug products--there were more than 300,000 on the market--the FDA revised the DESI review procedures for over-the-counter drug products. Rather than attempting to review all 300,000 over-the-counter drug products on the market, the FDA elected to evaluate the 700 or so active drug ingredients that made up these over-the-counter drug products. The 700 active drug ingredients were classified according to treatment category (e.g., antacids, laxatives, etc.) and evaluated by outside panels of advisors who determined whether the active drug ingredients could be generally recognized as safe and effective for self-use. The FDA's review of over-the-counter drug products for safety and effectiveness, which involves the review and publication of each panel's findings and the publication of final regulations to establish product-treatment category standards, is still ongoing. The FDA has published final regulations, or monographs, for 18 of the 81 product-treatment categories.[14]

The Drug Price Competition and Patent Term Restoration Act of 1984

> ...As more and more of these so-called "post-1962" drugs gained approval, it became apparent that a new public policy question would soon need attention: what would happen with the expiration of the patents for these new drugs?
>
> Many health policy experts advocated increased competition in the pharmaceutical marketplace by encouraging the availability of "generic" copies of brand name prescription drugs--that is, competing versions of brand-name drugs whose patents have expired. Increased competition, it was argued, would reduce the future costs of these "multi-source" drugs and help ease spiraling health care costs.[15]

The Drug Price Competition and Patent Term Restoration Act of 1984, sometimes referred to as the Waxman-Hatch Act, amended the Federal Food, Drug, and Cosmetic Act to give the FDA the statutory authority to approve, through an abbreviated new drug application (ANDA) process, generic copies of brand-name drug products approved after 1962. Although the FDA had begun, by the late 1960s, to review requests to manufacture generic copies of brand-name drug products initially approved for safety before 1962 and then reevaluated for effectiveness after the passage of the Drug Amendments of 1962, the FDA lacked explicit statutory authority to approve, through the ANDA process, generic copies of brand-name drug products approved after 1962.[16]

ANDAs contained information on drug product formulation, manufacturing, and quality, but were not required to include data demonstrating that the drug product was safe and effective for its intended use. An ANDA was authorized instead of a NDA only after a decision had been made through the DESI review process that further clinical studies demonstrating the safety and effectiveness of a drug product were not necessary.[17] During this period of time, the FDA also created the "Paper New Drug Application" process to allow manufacturers to use published studies to demonstrate the safety and effectiveness of generic copies of brand-name drug products first approved after 1962.[18]

The Drug Price Competition and Patent Term Restoration Act of 1984 required the FDA to make broader use of the ANDA procedure for generic copies of patented drug products. The abbreviated new drug application procedure[19] waived requirements for testing to demonstrate that the drug product was safe and effective and instead required that a generic drug product, among other things, be shown to be bioequivalent and to contain the same active drug ingredient as the original drug product, which had already undergone safety and efficacy testing. The FDA's existing practice until 1984 had been to allow ANDAs to be submitted only for generic copies of drug products that had received FDA marketing approval prior to 1962.[20]

The "Orange Book"

On December 19, 1973, the U.S. Department of Health, Education, and Welfare[21] announced the "promulgation of regulations to 'limit drug reimbursements under programs administered by the Department (Medicare and Medicaid) to the lowest cost at which the drug is generally available unless there is a demonstrated difference in therapeutic effect'". The announcement of the Maximum Allowable Cost (MAC) program culminated more than ten years of Congressional hearings, debates, and studies on the issue of generic drug substitution that were initiated by U.S. Senator Estes Kefauver in 1959. It was estimated that the MAC program would save the federal government $48,000,000 in 1974 and $32,000,000 in 1975, based on coverage of 32 multiple-source drug products.[22]

Although the U.S. Department of Health, Education, and Welfare attempted to address the pharmaceutical industry's objections to the MAC regulations by stating that the regulations would not impose a restrictive formulary and interfere with a physician's right to prescribe whatever medicines the physician felt were appropriate, and that the regulations would create rather than impede competition, pharmaceutical manufacturers, physicians, pharmacists, and special interest groups (most notably the American Association of Retired Persons) found themselves at odds on the issue of generic drug substitution.[23]

In 1974, U.S. Senator Edward Kennedy requested the Congressional Office of Technology Assessment to report on whether "'the technological capability was available to assure that drug products with the same physical and chemical composition will produce comparable therapeutic effects'".[24] The pertinent findings and recommendations of the Drug Bioequivalence Study Panel of the Congressional Office of Technology Assessment, released on July 12, 1974, were:[25]

(1) Current standards and regulatory practices do not insure bioequivalence for drug products.

(2) 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 to toxic concentration in blood, and certain pharmaceutical characteristics.

(3) Present compendial standards and guidelines for current good manufacturing practice do not insure quality and uniform bioavailability for drug products. Not only may the products of different manufacturers vary, but the product of a single manufacturer may vary from batch to batch or may change during storage.

(4) 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.

Not surprisingly, the report was supported by both opponents and proponents of generic drug substitution and did little to settle the controversy surrounding bioequivalence.[26]

On November 16, 1974, the U.S. Department of Health, Education, and Welfare's proposed MAC regulations were published in the Federal Register. The Pharmaceutical Manufacturers Association, a major opponent of the MAC program, argued that the FDA was unable to guarantee product quality and interchangeability, and that the U.S. Department of Health, Education, and Welfare's estimates of cost savings and projected long-term negative effects on drug research were inaccurate. Despite these and other objections to the proposed MAC regulations, the U.S. Department of Health, Education, and Welfare published the final MAC regulations on July 31, 1975. The MAC regulations went into effect in August 1976.[27]

On June 20, 1975, the FDA published proposed regulations on bioavailability and bioequivalence in the Federal Register. The FDA's proposed regulations "presented procedures for establishing requirements for bioequivalence, as well as a list of 193 drugs [active drug ingredients and drug products] that would be subjected to testing, or were of questionable quality". This list was reportedly developed, at least in part, "to meet the demands of the MAC program requiring FDA approval of drug substitutions".[28]

Prompted by a request from the State of New York in 1977 to review that state's list of "Safe, Effective, and Therapeutically Equivalent Prescription Drugs",[29] the submission of similar requests from other states and the District of Columbia, and the realization 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 for evaluating therapeutic equivalence, the FDA began the preparation of what would eventually become known as the "Orange Book" (i.e., the FDA publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations).[30]

On May 31, 1978, the Commissioner of Food and Drugs sent a letter to officials of each state indicating the FDA's intention to provide a list of all prescription drug products that were approved by the FDA for safety and effectiveness, along with therapeutic equivalence determinations for multiple-source drug products. The FDA's proposed list of approved drug products with therapeutic equivalence evaluations was distributed in January 1979. A discussion of the background and basis of the FDA's policy for evaluating the therapeutic equivalence of multiple-source drug products was published in the Federal Register on January 12, 1979.[31] The final rule, which included the FDA's responses to public comments on the proposal, was published in the Federal Register on October 31, 1980.[32] The first publication, October 1980, of the final version of the FDA's list of approved drug products with therapeutic equivalence evaluations incorporated appropriate corrections and additions to the list proposed in January 1979.[33]

ENDNOTES

1. Ken Flieger, "Testing in 'Real people'", in U.S., Department of Health and Human Services, Food and Drug Administration, ed. From Test Tube to Patient: New Drug Development in the United States, HHS Publication No. (FDA) 88-3168 (Maryland: January 1988), p. 13.

   The term, "drug" has been used at different times and by different authors to mean either an active drug ingredient or an active drug ingredient and an individual drug product. Much of the confusion stems from the fact that Congress never clearly indicated whether the term meant an active drug ingredient or an active drug ingredient and an individual drug product. Consequently, the courts have played a substantial role in defining the meaning of the term "drug". The FDA presently interprets the meaning of the term "drug" to include both an active drug ingredient and an individual drug product. Telephone interview with Donald Hare, Special Assistant to the Director, Office of Generic Drugs, U.S., Department of Health and Human Services, Food and Drug Administration, July 2, 1990.

2. U.S., Department of Health and Human Services, Food and Drug Administration, "An Interim Report on Generic Drugs" (Maryland: November 17, 1989) (hereinafter cited as "Interim Report"), p. 1.

3. Betty Bergersen, Pharmacology in Nursing 14th ed., (Missouri: The C.V. Mosby Company, 1979), p. 21.

4. Dixie Farley, "Benefit vs. Risk", in U.S., Department of Health and Human Services, ed., supra note 1, p. 30.

5. U.S., Department of Health and Human Services, "Interim Report", supra note 2.

6. Diethylene glycol is used as an antifreeze. Martha Windholz and others, eds., The Merck Index, 10th ed. (New Jersey: Merck & Co., Inc., 1983), p. 3111.

7. Farley, supra note 4.

8. The term, "new drug" did not include active drug ingredients subject to the Food and Drugs Act of 1906, i.e., active drug ingredients that were marketed before the Federal Food, Drug, and Cosmetic Act. 21 USCA 321(p)(1).

9. Bergersen, supra note 3.

10. Thalidomide, a drug used to control nausea during pregnancy, increased the risk of a deformity characterized by extremely short legs and arms, in the offspring of some human

mothers who used it. Elizabeth Whalen, Toxic Terror (Illinois: James Books, Inc., 1985), p. 43.

11. Farley, supra note 4.

12. Farley, supra note 4.

Bergersen, supra note 3, p. 23.

13. The term, "substantial evidence" was and still is defined to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof". 21 USCA 355(d).

Uncontrolled observations and testimonial-type endorsements were not accepted as scientific evidence. Bergersen, supra note 3, p. 23.

14. Farley, supra note 4.

The FDA's review of prescription drug products subject to the DESI review process was completed in 1984 in accordance with a court-mandated deadline. Hare, Telephone interview, supra note 1.

15. U.S., Department of Health and Human Services, "Interim Report", supra note 2, p. 2.

16. U.S., Department of Health and Human Services, "Interim Report", supra note 2, p. 2.

Donald Hare, Special Assistant to the Director, Office of Generic Drugs, U.S., Department of Health and Human Services, Food and Drug Administration, "The FDA and the Orange Book in Drug Selection" (Unpublished paper presented at the North Dakota State University College of Pharmacy, Pharmacy Seminar, Fargo, ND: October 7, 1988), p. 10.

17. 45 FR 72593, Oct. 31, 1980.

Although some drug products were approved through the ANDA process before the FDA implemented the bioequivalence requirements described at 21 CFR 320 and, therefore, dependent on empirical evidence to establish their bioequivalence, the FDA stated:

> ...[I]t would be unnecessary and wasteful to now require proof of bioequivalence of all these products when there has been no documented evidence of or potential for bioinequivalence. For those products that do present known or potential bioequivalence problems, FDA can require bioavailability data at any time....

45 FR 72593.

18. U.S., Department of Health and Human Services, "Interim Report", supra note 2, p. 1-2.

19. 21 USCA 355(j).

20. Congressional Quarterly, Inc., Congressional Quarterly Almanac, 98th Congress, 2nd Session, 1984, Vol. XL (Washington, D.C.: 1985), p. 451.

21. The U.S. Department of Health, Education, and Welfare was the predecessor of the U.S. Department of Health and Human Services.

22. Dan Ermann and Mike Millman, "The Role of the Federal Government in Generic Drug Substitution", in Theodore Goldberg and others, eds. Generic Drug Laws: A Decade of

Trial--A Prescription for Progress. U.S., Department of Health and Human Services, National Center for Health Services Research and Health Care Technology Assessment, NCHSR Report No. 86-30, (Virginia: National Technical Information Service, 1986), pp. 100 and 102.

23. Ermann and Millman, supra note 22, p. 102.

24. Ermann and Millman, supra note 22, p. 102.

25. Calvin Azama, Generic Drug Substitution: Feasibility for Hawaii, Legislative Reference Bureau, Report No. 1 (Honolulu: 1979), pp. 25-27.

26. Ermann and Millman, supra note 22, p. 102.

27. Ermann and Millman, supra note 22, p. 103.

28. Ermann and Millman, supra note 22, p. 103.

29. "In January 1978, the FDA gave its blessings to the New York list on the basis that 'pharmaceutically equivalent drug products can be considered therapeutically equivalent providing they are marketed under approved new drug applications, are manufactured under the same standards, meet identical or comparable standards and, in those instances where positive evidence of bioequivalence is necessary, are shown to be bioequivalent.'" Ermann and Millman, supra note 22, pp. 104-105.

30. Ermann and Millman, supra note 22, p. 104.

44 FR 2934, Jan. 12, 1979.

31. 44 FR 2932.

32. 45 FR 72582.

33. U.S., Department of Health and Human Services, Food and Drug Administration, Approved Drug Products with Therapeutic Equivalence Evaluations, 10th ed., (Washington, D.C.: U.S. Government Printing Office, 1990), p. v.

CHAPTER 5

When the Wheels Fall Off

> The generic-drug scandal broke in April, 1989, with news that U.S. Food and Drug Administration employees had accepted payoffs from generic-drug firms. Soon after, a second revelation grabbed headlines: A generic company had substituted a brand-name drug for its own in crucial tests for gaining drug approval. Then came reports that other firms had also cheated to obtain approvals.
>
> Not surprisingly, a nationwide Gallup Poll last fall reported that 77 percent of generic-drug users said their confidence in the drugs had been shaken by the scandal. Events since then, however, indicate that more damage was done to reputations than to the quality of the drugs themselves.[1]

Introduction

This chapter discusses the history of the so-called "generic drug scandal" and the findings of the special testing, inspection, and review programs initiated by the FDA in the aftermath of the scandal. The chapter does not discuss regulatory actions stemming from the scandal or the policy and management reforms that have taken place at the FDA since the scandal.

Illegal Gratuities

The first event in the generic drug scandal was the revelation that several FDA employees had accepted illegal gratuities from executives representing several generic drug companies. According to Consumers Union, publisher of Consumer Reports magazine:[2]

> The generic-drug scandal was actually exposed by a generic firm, Mylan Laboratories. Mylan executives suspected that some employees in the FDA's generic-drug division had accepted payoffs from competing firms in exchange for speedy drug approvals.
>
> Mylan hired a private investigator to follow a particular FDA employee. The investigator found evidence that payoffs had indeed occurred. They were paid to a few FDA generic-drug division chemists, who review applications and recommend their approval or denial.

Although the illegal gratuities were intended to speed-up the FDA's review of a company's drug products, the FDA reported finding no evidence that the companies involved actually received faster approval because of the gratuities and, perhaps more importantly, no evidence that the guilty employees approved applications that did not merit approval. The scandal caused by the acceptance of the illegal gratuities was summed up by Consumers Union, which stated: "So the payoffs, unconscionable as they were, apparently didn't endanger public health".[3]

Fraudulent Data

The second event in the generic drug scandal, which appeared to be unrelated to the acceptance of illegal gratuities,[4] was the discovery that several generic drug companies submitted fraudulent data as a part of their premarketing drug applications. According to Consumers Union:[5]

> The initial fraud involved Vitarine Pharmaceutical's generic version of Dyazide, a best-selling diuretic and blood-pressure drug marketed by SmithKline Beecham. While effective, Dyazide is notorious for being so poorly formulated that the amount of active ingredients it delivers is unpredictable. That makes the drug extremely difficult to copy. As a result, Dyazide faced no generic competition until 1987.
>
> Vitarine's ploy for gaining approval was crude but effective: An employee substituted Dyazide capsules for Vitarine capsules in the bioequivalence test. So the test compared Dyazide with Dyazide. Not surprisingly, Vitarine's supposed generic candidate passed the test. FDA investigators later found that one of the largest generic firms, Bolar Pharmaceutical, had cheated the same way to gain approval for its generic version of Macrodantin, an antibiotic used for urinary-tract infections.
>
> Five more firms--Chelsea Laboratories, American Therapeutics, Par Pharmaceutical, Quantum Pharmics, and Superpharm Corporation--were found to have rigged the drug-approval test in other ways. Most commonly, they altered records describing the size of the drug "batch" prepared for the bioequivalence test. They'd make up a small number of capsules especially for the test, but record the larger batch size required by the FDA.[6]

Despite the fact that approvals for at least 57 drug products were obtained fraudulently and subsequently removed from the market, the FDA has stated that it knows of no reports in which a fraudulently approved generic drug product caused a toxic reaction or was ineffective.[7]

As part of a wide-scale survey to "assess the potency, dissolution, content uniformity, and other relevant specifications that affect the safety and quality of generic drugs in the marketplace", the FDA collected and analyzed samples of the 30 most-prescribed generic drugs and their brand-name counterparts.[8] According to the FDA:[9]

> Of the nearly 2500 samples tested, only 27 (or 1.1%) were found not to conform to product quality specifications established by the United States Pharmacopeia or FDA. This sampling approach was used as a proxy for analysis of therapeutic effectiveness, given the time and resource limitations that prevented us from measuring bioequivalency of a significant number of drugs during the four-month interval subsequent to the July oversight hearing. Although no products were found to be unsafe, our laboratory findings to date have led to the recall of 12 different strengths of four drug products.[10]

Because the FDA's testing program for marketed drug products was designed to cover a large percentage of the most widely-used generic drugs, few if any, of the "top-30 selling" generic drugs could also be classified as narrow therapeutic range generic drugs.[11] In his statement to the U.S. House of Representatives' Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. Commissioner of Food and Drugs Frank Young stated:[12]

> Even before your September 26 letter to me regarding the reported deaths associated with carbamazepine [an anticonvulsant drug], I had raised concern about the adequacy of the standards for these drugs. All of us share the concern of representatives of the epilepsy community and this Subcommittee that these kinds of drugs need to be given special review in the same fashion as the "top-30" drugs. This is because of the potential for adverse reactions or therapeutic failure resulting from significant deviations in bioequivalence, which can affect the drug concentration in patients' blood.
>
> Therefore, we are undertaking an additional program of analyses designed to verify the quality of marketed versions of these drugs with narrow therapeutic ranges. Over 20 drugs are to be evaluated, each of which is available in generic form, including important drugs used to treat epilepsy, asthma, high blood pressure and heart problems. Like our earlier surveys, we are obtaining product samples from all brand-name and generic manufacturers.

On September 12, 1990, the FDA announced that based on tests of more than 400 drug samples, the agency had found that virtually all "narrow therapeutic range" generic and brand name drugs met applicable standards of purity and quality. According to the FDA, the agency "tested these samples of generic and branded versions of 24 kinds of drugs for which quality specifications are generally considered to be critical and found only one drug product made by two firms that showed minor deviations from acceptable limits". U.S. Secretary of Health and Human Services Louis Sullivan was quoted as saying "[t]hese results should be reassuring to consumers who use generic drugs...since the drugs that were examined are the kind that critics of generics are most likely to claim could cause problems".[13]

Current Good Manufacturing Practices

The third event in the generic drug scandal, which emerged as a result of the FDA's efforts to identify further fraudulent submissions through inspections of select firms, was the substandard level of Good Manufacturing Practice compliance on the part of several generic drug companies.[14] Using the Agency's best and most experienced inspectors, the FDA conducted "very unusual, in-depth inspections" at 20 of the largest generic drug companies.[15] According to Consumers Union:[16]

> ...While no other cases of fraud were uncovered, other problems were. More than half the firms were found to have violated production standards known as "current good manufacturing practices." The infractions were of the type routinely found in drug-plant inspections, such as errors in record-keeping, and none resulted in unsafe products. But there were more infractions than

usual. Ordinarily, inspectors find violations in only about 10 percent of the plants they inspect.

"The White Paper"

The fourth event in the generic drug scandal, which is discussed at length in Chapter 7, was the adoption of the American Academy of Family Physicians' "White Paper on Generic Drugs" and the passage of a resolution that expressed strong concerns about generic drugs.[17]

Commercial Testing Laboratories

On July 31, 1990, the FDA announced that:[18]

> As part of a continuing examination of the nation's generic drug industry, FDA recently conducted an investigation of 14 commercial testing laboratories that perform an estimated 95 percent of the bioequivalence studies done for manufacturers of generic drugs in support of their applications for approval. Recent disclosure of one of the FDA inspection reports, this one involving Biodecision Laboratories of Pittsburgh, resulted in news articles about the agency's findings....
>
> Biodecision, in recent years, has conducted about 150 bioequivalence studies per year and contracted with approximately 150 client firms, including some brand name drug makers. FDA completed an inspection of records for 13 bioequivalency tests done since 1972 in January.
>
> The agency found numerous instances where the firm's operations did not conform to accepted good manufacturing practices. In a summary of findings, FDA listed more than 15 kinds of problems in 11 studies. The problems were such things as selective reporting of test results (reporting some data while ignoring other information), use of unacceptable (non-U.S. Pharmacopeia) materials, improper storage of samples and materials, poor record keeping, lack of written standard operating procedures and inadequate training of personnel.
>
> * * *
>
> FDA is monitoring the firm's corrective actions and evaluating the findings to determine which products previously approved, and which products now under review pending approval, are affected by the flawed studies.
>
> Approvals of any products currently being evaluated will be held up until uncertainties in the studies on them are resolved. To date, no safety problems have been found involving a drug currently on the market.

Summary

Regulatory work can be expensive. With the power and authority to regulate an activity comes the responsibility for appropriating and allocating the necessary resources to enable government to effectively carry out its appointed duties. The public is usually not sympathetic to rhetoric about budgetary constraints and resource limitations during a crisis; it demands immediate answers to questions and solutions to problems regardless of the cost to other programs. This is the nature of crises.

Although the executive and legislative branches of government are equally responsible for ensuring that government carries out its appointed duties, much of this is forgotten during a crisis. As pointed out by Consumers Union:[19]

> During the Reagan years, the FDA staff was cut back. Excluding people working on newly instituted AIDS-related projects, staff levels fell from 7816 in 1980 to 6829 in 1989. At the same time, Congress passed more than 20 laws increasing the agency's responsibilities. Equally significant, the Reagan-era FDA de-emphasized law-enforcement, relying instead on voluntary industry cooperation.
>
> Between 1980 and 1988, the number of FDA field inspectors visiting companies to insure compliance declined from 972 to 836. Meanwhile, the 1984 drug law [the Drug Price Competition and Patent Term Restoration Act of 1984] led to a sharp increase in the number of new firms requiring inspection.

While the generic drug scandal has tarnished the FDA's image and raised questions about the agency's ability to effectively carry out its appointed duties,[20] the Bureau believes that the question to be asked here is: "Can the State do a better job of regulating the generic drug approval process than the FDA?" If the answer to this question is "yes", then the next question to be asked here is: "How much is the State willing to spend on a program to regulate the generic drug approval process?" If the answer to this question is that "no price tag can be placed on matters of public health and safety", then the final question to be asked is: "What existing or new programs is the State going to sacrifice in order to fund a program to regulate the generic drug approval process?"

The Bureau believes that any legislation which duplicates the FDA's generic drug approval process should only be enacted if there is a clear understanding of what is expected to be gained by such an endeavor. If the ultimate goal of this legislation is to deter fraud and deceit or to award reparations to persons who consume a drug product approved through fraud or deceit, then state regulation may not be the most effective means to this end.

ENDNOTES

1. "Generic Drugs: Still Safe?", Consumer Reports, Vol. 55, No. 5 (May 1990) (hereinafter cited as "Generic Drugs"), p. 310.

2. "Generic Drugs", Consumer Reports, supra note 1, p. 311.

3. "Generic Drugs", Consumer Reports, supra note 1, p. 311.

4. U.S., Department of Health and Human Services, Food and Drug Administration, "Statement by Carl C. Peck, M.D., Director, Center for Drug Evaluation and Research,

Before the Subcommittee on Housing and Consumer Interests, Select Committee on Aging, U.S. House of Representatives" (Maryland: March 1, 1990)(hereinafter cited as "Statement of Carl C. Peck, Director, Center for Drug Evaluation and Research"), p. 2.

5. "Generic Drugs", Consumer Reports, supra note 1, pp. 311-312.

6. According to Consumers Union:

> In another part of its investigation, the FDA went back and analyzed leftover tablets and capsules that had been submitted for bioequivalence testing by 20 of the largest generic firms. Generic firms generally contract out such testing, sending their samples to a private laboratory. Fortunately one of the laboratories used by the 20 firms had retained many unused samples.
>
> The FDA knew by then that one firm, Vitarine, had substituted the brand-name drug for its own when it submitted samples for testing. By analyzing the powder in leftover generic samples and their brand-name counterparts, the FDA could determine if that kind of fraud was extensive.
>
> The FDA has nearly finished analyzing more than 1500 samples the firms submitted. So far, the tests have uncovered only one case of product switching: Bolar's previously mentioned substitution of Macrodantin for its own product. Otherwise, according to an FDA interim report, "the results to date are reassuring".

"Generic Drugs", Consumer Reports, supra note 1, p. 313.

7. "Generic Drugs", Consumer Reports, supra note 1, p. 312.

8. U.S., Department of Health and Human Services, Food and Drug Administration, "Statement by Frank E. Young, M.D., Ph.D., Commissioner of Food and Drugs, Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives" (Maryland: November 17, 1989)(hereinafter cited as "Statement of Frank E. Young, Commissioner of Food and Drugs"), p. 5.

9. U.S., Department of Health and Human Services, "Statement by Frank E. Young, Commissioner of Food and Drugs", supra note 8, p. 2.

10. According to the FDA, the 1.1 percent rate of nonconformance observed in this survey was consistent with other FDA brand-name and generic drug sampling surveys conducted over the last five years. U.S., Department of Health and Human Services, "Statement by Frank E. Young, Commissioner of Food and Drugs", supra note 8, p. 5.

11. The "top-30 selling" generic drugs were: acetaminophen/codeine; allopurinol; amitriptyline hydrochloride; amoxicillin; ampicillin; cephalexin; diazepam; dipyridamole; doxycycline; erythromycin; erythromycin stearate; ferrous sulfate; furosemide; hydrochlorothiazide; hydrocortisone; ibuprofen; imipramine hydrochloride; lorazepam; meclizine hydrochloride; metronidazole; nitroglycerin; nystatin; penicillin v. potassium; phenobarbital; prednisone; propoxyphene napsylate/acetaminophen; tetracycline; thyroid; triamcinolone; and trimethoprim/sulfamethoxazole. U.S., Department of Health and Human Services, Food and Drug Administration, "An Interim Report on Generic Drugs" (Maryland: November 17, 1989), p. 19.

12. U.S., Department of Health and Human Services, "Statement by Frank E. Young, Commissioner of Food and Drugs", supra note 8, pp. 9-10.

13. U.S., Department of Health and Human Services, Food and Drug Administration, "FDA Announces Over 400 Samples of Generic and Brand Named Drugs Tested Meet Applicable Standards of Purity and Quality" (Press Release)(Maryland: September 12, 1990), 3 pp.

According to the FDA, the agency "collected samples of 429 batches of the 24 different drugs it considers to be [sic] narrow therapeutic range from 73 generic and brand name manufacturers". Whenever available, at least three different batches from each manufacturer of each of the 24 drugs were tested. All 24 drugs were tested for potency

and, where applicable, dissolution rate and content uniformity at 16 FDA laboratories in the United States. Not all dosage forms of the 24 drugs tested possessed a narrow therapeutic range.

The drug products that were examined are: aminophylline tablets (antiasthmatic); **carbamazepine tablets (anticonvulsant)**; clindamycin capsules (antibiotic); clonidine tablets (antihypertensive); disopyramide capsules (antiarrhythmic); dyphylline tablets (antiasthmatic); ethinyl estradiol tablets (contraceptive); guanethidine tablets (antihypertensive); isoetharine mesylate inhaler (antiasthmatic); isoproterenol inhaler (antiasthmatic); lithium carbonate capsules and tablets (antidepressant); metaproterenol tablets (antiasthmatic); minoxidil tablets (antihypertensive); oxtriphylline tablets (antiasthmatic); **phenytoin capsules and tablets (anticonvulsant)**; prazosin capsules (antihypertensive), **primidone tablets (anticonvulsant)**; procainamide hydrochloride capsules and tablets (antiarrhythmic); quinidine gluconate tablets (antiarrhythmic); quinidine sulfate capsules and tablets (antiarrhythmic); theophylline capsules and tablets (antiasthmatic); **valproic acid capsules (anticonvulsant)**; **valproate sodium syrup (anticonvulsant)**; and warfarin sodium tablets (anticoagulant).

Five batches of aminophylline tablets from two manufacturers were found to contain incorrect amounts of a necessary stabilizing ingredient and voluntarily recalled; samples from four other manufacturers were tested and found to be satisfactory.

14. U.S., Department of Health and Human Services, "Statement by Carl C. Peck, Director, Center for Drug Evaluation and Research", supra note 4, p. 3.

15. "Generic Drugs", Consumer Reports, supra note 1, p. 313.

16. "Generic Drugs", Consumer Reports, supra note 1, p. 313.

17. U.S., Department of Health and Human Services, "Statement by Carl C. Peck, Director, Center for Drug Evaluation and Research", supra note 4, p. 3.

18. U.S., Department of Health and Human Services, Food and Drug Administration, "Investigation of Biodecision Laboratories" (Corrected Version of Talk Paper Dated July 23, 1990)(Maryland: July 31, 1990), 2 pp.

19. "Generic Drugs", Consumers Report, supra note 1, p. 311.

20. According to the FDA, the recent discovery that several generic drug companies submitted fraudulent data as part of their premarketing drug applications (see Fraudulent Data, this chapter) was the first documented instance of such a fraud. Telephone interview with Donald Hare, Special Assistant to the Director, Office of Generic Drugs, U.S., Department of Health and Human Services, Food and Drug Administration, November 21, 1990.

CHAPTER 6

Yesterday's News

Introduction

This chapter begins by reviewing the activities of the State's Drug Product Selection Board just prior to the convening of the 1990 legislative session, specifically focusing on the Board's decision not to remove four anticonvulsant drugs from the Hawaii Drug Formulary of Equivalent Drug Products[1] following a meeting on this matter. This chapter then reviews the FDA's October 1989 report on generic anticonvulsant drugs, which addressed issues relating to the generic drug review process and seven commonly used anticonvulsant drugs, four of which were the subject of the State Drug Product Selection Board's hearing.

Finally, the chapter reviews sections of the January 1988 report of the FDA's Bioequivalence Task Force (on recommendations from the bioequivalence hearing conducted by the FDA, September 29 - October 1, 1986) that were immediately relevant to the American Academy of Family Physicians' "White Paper on Generic Drugs",[2] anticonvulsant drugs, and allergic reactions.

Drug Product Selection Board

During October 1989, the State's Drug Product Selection Board (hereinafter "the Board") accepted and reviewed testimony provided by various physicians and drug manufacturers regarding the substitution of anticonvulsant drugs. On November 17, 1989, the Board voted to continue to allow the substitution of generic counterparts for the anticonvulsant drugs Depakene, Dilantin, Mysoline, and Tegretol, under chapter 328, part VI, Hawaii Revised Statutes.[3]

Melvin Kumasaka, Chairperson of the Drug Product Selection Board, explained the Board's decision in the following manner:[4]

> Ultimately, the board's decision was based upon one key factor: that by statute, both a physician and/or patient is able to control the specific brand of medication she/he desires. Because it recognizes the potential problems of switching anti-convulsants from one brand to another, and because anti-convulsant drugs possess an extremely narrow therapeutic range, the board realizes that constant supervision and control of a patient's medication and its manufacturer are imperative. And it is especially with the public's health and safety in mind that the board renders such a decision. Our confidence in each physician's, as well as his patient's, ability to discern what is best for herself/himself, lend credence to continued substitution, and allows, as the law intends, for less costly alternatives.

Prior to the Board's November 17, 1989 decision to continue to allow the substitution of anticonvulsant drugs, the Board recommended the formation of an anticonvulsant subcommittee at its March 22, 1989 meeting. The Board's actions were prompted by the introduction of House Bill No. 1382 and Senate Bill No. 1243 during the 1989 legislative

session.[5] Both bills proposed to amend section 328-92, Hawaii Revised Statutes, by prohibiting a dispenser[6] from substituting a therapeutically equivalent generic drug product for the brand-name drug product prescribed, in the case of the anticonvulsant drugs.[7]

According to the minutes of the Board's meeting:[8]

> ...The DOH [Department of Health] submitted testimony opposing the bills saying essentially that determination of generic drug substitution is a function of the Drug Product Selection Board and that the bill [sic] is a bad precedent. The bills were drafted by the Epilepsy Society, who is very concerned that generic anti-convulsant drugs are substitutable and that they are not equivalent. They mentioned 5 drugs in their testimony that should not be substituted.

The anticonvulsant subcommittee, chaired by Nadine Bruce, Chairperson of the Drug Product Selection Board, met on July 10, 1989 and came to the following conclusions and recommendations:[9]

1. The drug substitution law has proven itself to be overall safe.

2. We need to avoid the peace-meal [sic] repeal of this law, which would happen if removals occur from the formulary drug by drug with every concern raised about bioequivalency.

3. The safeguard for substitution problems is the physician's right to state "Do not substitute." on his or her prescriptions.

4. There are drugs that should not be substituted because they are not bioequivalent, but it is the physician's responsibility to become educated concerning these drugs.

5. It is the responsibility of community groups to educate consumers (e.g., Epilepsy Society) and the medical community to educate physicians (e.g., HMA [the Hawaii Medical Association], specialty societies, hospital continuing medical education programs).

6. It is the responsibility of the Drug Product Selection Board to respond to community concerns and investigate any complaints concerning drug substitution.

The subcommittee concluded by recommending the following to the Drug Product Selection Board:[10]

> ...[Notify] interested parties, including drug companies, the Epilepsy Society, Hawaii Neurologists and Neurosurgeons, that the Board is interested in receiving written or verbal input from these groups and individuals concerning the problems perceived nationally or in the community with the substitution of anticonvulsant drugs. If it can be demonstrated to the Board that there is a serious

> problem with these drugs leading to potential harm in our patient population, then the Board should move to delete these drugs from the state formulary.

Report on Generic Anticonvulsants

In a November 7, 1989 letter to William Haddad, Chairman of the Generic Pharmaceutical Industry Association, Frank Young, Commissioner of Food and Drugs, stated:[11]

> ...[I]t is important to understand that, at present, there is no credible evidence that the use of Agency approved generic anticonvulsants results in an increased frequency of seizures. As you are undoubtedly aware, epilepsy is characterized by an unpredictable, intermittent pattern of seizures. Even patients who have been well controlled with adequate blood levels may, for unknown reasons, suddenly experience an increase in seizure frequency. If one considers, in addition, the well known phenomenon of poor patient compliance, as well as multiple other factors, it is not surprising that, periodically, the medication that patients are receiving may be perceived to have "failed." If this increase in frequency happens to have coincided with the introduction of a generic anticonvulsant, a causal relationship may be postulated, but such a relationship is simply one of many possible explanations. As I have said, a review of the cases we have seen has failed to reveal any scientifically valid evidence that a generic anticonvulsant failed to deliver appropriate amounts of active ingredient.

The letter from Young to Haddad included an October 1989 report prepared by the FDA's Center for Drug Evaluation and Research. Entitled, "Report on Generic Anticonvulsants",[12] this document addressed issues relating to the generic drug review process and seven commonly used anticonvulsant drugs. The drugs were carbamazepine (Tegretol), clonazepam, ethosuximide, phenobarbital, phenytoin (Dilantin), primidone (Mysoline), and valproic acid (Depakene).[13]

Bioequivalence Task Force

The January 1988 report of the Bioequivalence Task Force (hereinafter "the Task Force") is, arguably, the most exhaustive review of generic drug substitution conducted since the federal Drug Price Competition and Patent Term Restoration Act of 1984.[14]

To foster public participation in FDA's bioequivalence program and to elicit data on claimed problems with the program and with generic drugs generally, the FDA sponsored a three-day informal public hearing from September 29 to October 1, 1986 in Washington, D.C. The hearing, which attracted 50 speakers and over 800 participants, consisted of five sessions on topics related to the issue of bioequivalence of immediate-release,[15] solid oral dosage form drug products. Following the hearing, Frank Young, Commissioner of Food and Drugs, and John Norris, Deputy Commissioner of Food and Drugs, appointed a task force to analyze the issues raised at the hearing and the comments submitted to the public docket,

and to make recommendations for actions the FDA should take in response to those comments concerning the bioequivalence program.[16]

Although the Task Force issued 21 separate conclusions related to the design of bioequivalence studies, decisional criteria for bioequivalence, and FDA procedures and regulatory aspects of bioequivalence, only those conclusions immediately relevant to the Academy's "White Paper", anticonvulsant drugs, and allergic reactions are discussed here.[17]

Use of Normal Volunteers. In response to the question, "Does the use of normal volunteers adequately account for the potentially altered absorption capacity and metabolism of special populations?", the Task Force stated:[18]

> The important question is not whether patients are different from volunteers, but whether, and when, these differences could cause two products that seem bioequivalent in normals to be bioinequivalent in a clinical setting. A search of the literature to identify these factors in patients revealed very few relevant publications.
>
> The Task Force believes that it is preferable to subject healthy people, rather than patients, to the rigors of blood sampling and other discomforts of bioequivalence testing. Moreover, use of patients would invariably increase intersubject variability and possibly intrasubject variability as well. Thus far there have been few, if any documented examples of problems associated with the use of normals to predict bioequivalence, although there have been relatively few rigorous attempts to document problems. The Task Force believes that at this time it remains appropriate to determine bioequivalence based on testing in healthy volunteers. The Agency recognizes the possibility that some conditions could affect bioavailability and is prepared to modify its position regarding the use of normal subjects if such a situation is adequately documented for a given drug.

Dissolution Testing.[19] In response to the questions, "Can dissolution testing assure bioequivalence? Should it be employed as a substitute for in vivo study in humans? Does adequate information exist to justify a waiver of in vivo studies based on dissolution alone? Should drugs be approved based on dissolution only without a relationship of in vitro data to in vivo performance?", the Task Force stated:[20]

> The Task Force believes there is not yet evidence to show that any particular dissolution pattern alone will assure bioequivalence. Dissolution testing can be used for drugs where there is a known in vivo/in vitro relationship, and is used for pre-1962 drugs[21] not suspected of having, or not likely to have, a bioavailability problem [cross reference deleted]. For all other solid oral drugs, an in vivo bioequivalence study on the drug product is required to support at least one strength of the product.
>
> The Task Force believes that dissolution testing is important in assuring lot-to-lot uniformity, and in supporting minor alterations to drug products [citation deleted]. Also, it is FDA policy that

> if a product meets in vivo bioequivalence study requirements at one strength, and the formulations of additional strengths are proportional to the strength tested in the in vivo bioequivalence study, and the additional strengths meet dissolution requirements, then further in vivo bioequivalence studies are not required for the additional strengths unless there is evidence of safety or efficacy problems. This policy applies to generic and innovator products. The Task Force believes these policies are sound, but does not recommend expanding the use of in vitro testing beyond these limits.

In discussing the rationale for its conclusion, the Task Force noted the following:[22]

> Current requirements provide for the use of in vitro dissolution testing in place of in vivo data when older drugs (those first approved before 1962) do not pose an actual or potential bioequivalence problem as defined in the 1977 regulations [citation deleted], or when an in vivo/in vitro correlation has been shown. For example, the Agency has determined that an in vitro/in vivo correlation exists for prednisone. This decision was based on bioavailability studies conducted on a variety of prednisone products sponsored under FDA contract. These studies established an in vitro and in vivo correlation with a variety of in vitro apparatus and media.

Allergies and Toxicity to Excipients.[23] In response to the questions, "Do or should bioequivalence studies consider the effect of excipients on bioavailability of drug products? What is the likelihood of an excipient causing toxicity in a patient?", the Task Force stated:[24]

> The Task Force agrees that the rare incidence of allergies and toxicity to excipients may pose a problem for a few patients. Information on excipients for all drug products is currently being addressed by the Pharmaceutical Manufacturers Association (PMA) and the Proprietary Association (PA) with their voluntary labeling guidelines and this information will help enable patients to be alerted to an allergenic potential.[25] The effect of excipients on bioavailability is assessed by current bioequivalence studies.

Bioequivalence Criteria. In response to the questions, "Should the current equivalence criteria be changed? What do these differences mean clinically?", the Task Force stated:[26]

> The Task Force favors the use of a 90% confidence interval based on the two one-sided t-test approach as the best available method for evaluating bioequivalence. The Task Force concludes that some drugs or drug classes may require tighter limits than the generally applied ± 20% rule. These situations must be identified on the basis of clinical evidence demonstrating a need to tighten the generally applied standard. Such evidence could include, for example, a prospective clinical study demonstrating that the usual criteria for bioequivalence measurements are not stringent enough. The Task Force also concludes that the requirement that the entire

> 90% confidence interval lie within the limits of ± 20% effectively precludes true differences in means beyond those limits. The Task Force believes that there may be merit to the consultant's proposal for an additional criteria, because it would add significantly to the assurance of the bioequivalence of generic drugs, and would also preclude the unusual case of a real difference beyond ± 10%. However, the Task Force does not believe it is necessary to require an additional criteria beyond the current requirements.

In discussing the rationale for its conclusion, the Task Force noted the following:[27]

> There was consensus at the Hearing that differences of less than 20% in AUC and C_{max} between products in normal subjects are unlikely to be clinically significant in patients. Clinical studies of effectiveness have difficulty detecting differences in dose of even 50-100%. Few drugs are given on a mg per kg basis to account for weight differences and few drugs have their dosage adjusted in actual clinical practice for factors that may affect blood concentrations in individuals. Thus, the variability inherent in medical practice and biological variation may cause plasma levels to vary in individuals by much more than 20%.

The ± 20% Requirement. In response to the question, "Could the ± 20% requirement lead to differences in products of 40-50%?", the Task Force stated:[28]

> The Task Force notes that for post-1962 drugs approved over a two-year period under the Waxman-Hatch bill,[29] the mean bioavailability difference between the generic and innovator product is 3.5% [cross reference deleted]. Additionally, 80% of the values for drugs approved since 1984 were within ± 5.0% of the reference drug value. [cross reference deleted].

In discussing the rationale for its conclusion, the Task Force noted the following:[30]

> The notion that a 40% or 50% difference actually occurs between the mean values of two generic products is based on the erroneous impression that products with bioavailability ratios of 0.80 and 1.20 would be approved. With such differences in mean AUCs, the requirements involving confidence intervals would not be met.

Therapeutic Failures. In response to the questions, "Have there been therapeutic failures with approved generic products? Is the current adverse drug reaction monitoring program adequately detecting therapeutic failures? How useful is Form 1639 for reporting therapeutic failures?", the Task Force stated:[31]

> The Task Force concludes that FDA should enhance current procedures to better detect and evaluate reports of therapeutic failures that could be indicative of failure of a product. FDA should fully investigate possible inequivalence only when there is good evidence of a problem, and not on unsupported anecdotes. The medical community and the manufacturers should be encouraged to submit

reports of therapeutic inequivalence with as much detail as possible, including blood level data.

In discussing the rationale for its conclusion, the Task Force noted the following:[32]

> Two physicians related personal experiences with generic drug products that they believed were therapeutically inequivalent [citations and cross references deleted]. Of these cases, the Task Force has been unable to obtain further documentation. Had adequate documentation been provided to the Agency by Drs. O'Connor or Stoffer, these problems would have been investigated through a bioequivalence study. To date, there has been no instances in which clinical inequivalence has been documented and verified for approved products.
>
> * * *
>
> Therapeutic failures are a relatively common component of most drug treatment, even when the drug is not changed. Blood pressures can rise on previously effective therapy; heart failure can worsen on a stable digoxin/diuretic regimen; seizures can break through, for example, phenytoin. A report of a single instance of failure is, therefore, almost impossible to interpret unless there is a deliberate attempt to study it further with blood level data or an on-off-on-off procedure. Estimated rates of failure would also be extremely difficult to derive from ADR [adverse drug reaction] data.
>
> In general, we believe that if a product fails, it will led [sic] to more than one report, so we are not primarily concerned with one idiosyncratic report. However, in order to spot as early as possible any widespread problems such as problems with an entire lot, the agency will in some cases, look at single, isolated, well documented cases. Additionally, the Agency recognizes that important knowledge may be gained from the study [sic] an isolated case.

The Significance of One Generic Failure. In response to the question, "What would be the significance of one documented generic failure?", the Task Force stated:[33]

> The Task Force concludes that there is no reason to doubt the fundamental principle that drug products delivering comparable blood levels of a therapeutic moiety in bioequivalence tests in normals will generally yield comparable therapeutic results. There are known differences among patients, such as gut transit time or gastric pH that could, combined with differences between products, such as pH dependency of dissolution, theoretically yield differences in performance of products in certain patients. Whether this hypothesis actually is manifested clinically in any significant way has not been shown. A distinction must be drawn between a single case of a patient who does not respond to a drug product and evidence that a drug product is not performing.

> Virtually all products are, from time to time, the subject of isolated reports of therapeutic failures. The Agency looks particularly for patterns of such reports or cases which may indicate a generalized problem with a drug product or a batch of the product. The documentation of a single instance of clinical inequivalence does not, in the Task Force's view, undermine the much wider experience that shows bioequivalence testing to be an excellent predictor of clinical performance. A product failure, on the other hand, would necessitate that the Agency investigate thoroughly and take steps to deal with the particular case and others that might arise from similar circumstances.

Summary

The therapeutic equivalence and substitutability of the generic counterparts for Depakene, Dilantin, Mysoline, and Tegretol have been independently addressed and reaffirmed by the State's Drug Product Selection Board and the FDA. Consequently, any recommendation to prohibit generic drug substitution for Depakene, Dilantin, Mysoline, or Tegretol without the authorization of both the physician and the patient would have to dispute these findings to be considered scientifically valid. The Bureau has no technical expertise in matters concerning the therapeutic equivalence and substitutability of multiple-source drug products and is therefore in no position to evaluate the correctness of the evaluations made by the Board and the FDA.

The Bureau believes that decisions regarding the therapeutic equivalence and substitutability of multiple-source drug products should be made by the Board and the FDA since they possess the requisite expertise needed to make these decisions in a consistent and orderly manner. Likewise, decisions regarding the acceptability of the risks posed by generic drug substitution should be made by the Board since generic drug substitution cannot be considered absolutely "risk free". The Bureau believes, however, that the Legislature--and not the Board--should retain the authority to decide by which criteria the risks of generic drug substitution should be judged "acceptable" or "unacceptable", i.e., should generic drug substitution be permitted if "constant supervision and control of a patient's medication and its manufacturer are imperative"?[34]

ENDNOTES

1. Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

2. American Academy of Family Physicians, "White Paper on Generic Drugs" (Missouri: 1989), 10 pp.

3. Letter from Melvin Kumasaka, Chairperson of the Drug Product Selection Board to various individuals informing them of the Board's decision to continue to allow the substitution of anticonvulsant drugs, November 30, 1989, p. 1.

4. Kumasaka, Letter, supra note 3.

5. Hawaii, Department of Health, "Drug Product Selection Board Meeting, Minutes of Meeting" (March 22, 1989) (hereinafter cited as "Minutes of Meeting"), p. 3.

6. The term, "dispenser" means "a person authorized to dispense drugs in the State". The Bureau notes that the terms "dispenser" and "prescriber" are not mutually exclusive since it is possible for a person who is authorized to prescribe drugs to also dispense them. The term "prescriber" means "a person licensed by the State to prescribe drug products". Section 328-91, Hawaii Rev. Stat.

7. House Bill No. 1382, Fifteenth Legislature, 1989, State of Hawaii.

   Senate Bill No. 1243, Fifteenth Legislature, 1989, State of Hawaii.

8. Department of Health, "Minutes of Meeting", supra note 5.

9. Hawaii, Department of Health, Drug Product Selection Board, "Anticonvulsant Subcommittee Report for the Drug Product Selection Board" (undated) (hereinafter cited as "Subcommittee Report"), 1 p.

   The minutes of the Board's July 24, 1989 meeting indicate that the conclusions and recommendations of the subcommittee were presented to the Board, but that a written report was not submitted at this meeting. The minutes of subsequent meetings do not mention the subcommittee's report, so it is uncertain as to when the written report was actually submitted to the Board.

10. Department of Health, "Subcommittee Report", supra note 9.

11. Letter from Frank Young, Commissioner of Food and Drugs, U.S., Department of Health and Human Services, Food and Drug Administration, to William Haddad, Chairman of the Generic Pharmaceutical Industry Association, regarding drug product substitution of anticonvulsants, November 7, 1989, p. 1.

12. U.S., Department of Health and Human Services, Food and Drug Administration, "Report on Generic Anticonvulsants" (Maryland: October 1989), 6 pp.

13. Tegretol, Dilantin, Mysoline, and Depakene were the four anticonvulsant drugs reviewed in November 1989 by the Drug Product Selection Board.

14. P.L. 98-417.

15. Extended-release or controlled-released products are considered pharmaceutical alternatives when compared with immediate- or standard-release formulations of the same active ingredient and, therefore, to be bioinequivalent drug products. U.S., Department of Health and Human Services, Food and Drug Administration, Approved Drug Products with Therapeutic Equivalence Evaluations, 10th ed. (Washington, D.C.: U.S. Government Printing Office, 1990), p. 1-1.

   Furthermore, different controlled-release dosage forms containing the same active ingredients in equal strengths are not evaluated as bioequivalent unless equivalence between individual products has been demonstrated through appropriate bioequivalence studies. 45 FR 72600, Oct. 31, 1980; 21 CFR 320.22(c)(1); 21 CFR 320.25(f).

16. U.S., Department of Health and Human Services, Food and Drug Administration, "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, September 29 - October 1, 1986" (Maryland: Dockets Management Office, January 1988) (hereinafter cited as "Task Force Report"), p. 3.

17. Although the Task Force summarized the comments of persons testifying on these matters and provided detailed rationales to support each of their respective conclusions, a systematic review of all these comments and rationales is beyond the scope of this study and the expertise of the Bureau. Those wishing to learn more about the rationales used to support certain conclusions are urged to read the Task Force's full report.

18. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, pp. 19-20

19. "Dissolution", or the act or process of dissolving, refers to the "absorption of a solid in and by a liquid". Clayton Thomas ed., Taber's Cyclopedic Medical Dictionary, 14th ed., (Pennsylvania: F.A. Davis Company, 1981), p. 421.

20. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, pp. 23-24.

21. The term, "pre-1962 drugs" refers to drugs that were marketed prior to the Drug Amendments of 1962 (P.L. 87-781).

> ...In October 1962, Congress passed these amendments [the Drug Amendments of 1962] to tighten control over drugs. Before marketing a drug, firms now had to prove not only safety, but also effectiveness for the product's intended use. The requirement was applied retroactively to 1938, when the FDC [Food, Drug, and Cosmetic] Act was passed. (Pre-1938 drugs were "grandfathered"--allowed to be sold because they were generally recognized as safe and effective--provided no evidence to the contrary developed.) To help implement the amendments, FDA contracted with the National Academy of Sciences/National Research Council to review the efficacy of drugs approved solely on the basis of safety since 1938. Firms were also required to send adverse reaction reports to FDA, and drug advertising in medical journals was required to provide complete information to doctors--the risks as well as the benefits. Dixie Farley, "Benefit vs. Risk: How FDA Approves New Drugs", in U.S., Department of Health and Human Services, Food and Drug Administration, ed. From Test Tube to Patient: New Drug Development in the United States, HHS Publication No. (FDA) 88-3168 (Maryland: January 1988), p. 30.

22. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 23.

23. The term "excipient" means "[a]ny substance added to a medicine to permit it to be formed into the proper shape and consistency; the vehicle for the drug". Thomas, Taber's Cyclopedic Medical Dictionary, supra note 19, p. 509.

24. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 24.

25. On July 9, 1984, the Pharmaceutical Manufacturers Association adopted a voluntary program under which member companies would include, in the official package insert for their oral dosage form prescription drugs, an alphabetical listing of inactive ingredients contained in the drug product. This program of industry self-regulation was intended to provide an efficient mechanism by which health care practitioners and their patients could identify the presence of inactive ingredients in prescription drugs.

    Voluntary compliance with these guidelines was to begin at the time the official package insert was next revised and reprinted. All prescription drug products packaged on or after December 1, 1985 by participating companies were to be in compliance with the guidelines, which are described below.

    1. The official package insert for an oral dosage form prescription drug product should include an alphabetical listing of inactive ingredients contained in the product.

    2. Flavorings and fragrances may be listed as "flavorings" and "fragrances".

    3. Color additives may be listed by their common names.

    4. Inactive ingredients present in trace amounts and having no functional or technical effect on the finished drug product need not be identified, unless the

inactive ingredient has been demonstrated to cause sensitivity reactions or allergic responses in some people.

5. For essentially interchangeable inactive ingredients, a statement such as "may contain one or more of the following" may be used so as not to require labeling changes for reformulations involving interchangeable ingredients.

6. An inactive ingredient or group of ingredients whose identity is a trade secret need not be disclosed if the labeling states "and other ingredients". An inactive ingredient constitutes a trade secret if its presence gives the manufacturer an advantage over competitors who do not know or use it.

7. Inactive ingredients should be listed alphabetically in either the "Description" section or the "How Supplied" section or the official package insert.

8. Labeling appearing in the Physicians' Desk Reference, should include a list of inactive ingredients in compliance with these guidelines.

9. The name of an inactive ingredient should be taken from the most current edition of the following reference works:

   (a) United States Pharmacopeia/National Formulary;

   (b) USAN and USP Dictionary of Drug Names;

   (c) CTFA (Cosmetic, Toiletry and Fragrance Association, Inc.) Cosmetic Ingredient Dictionary; and

   (d) Food Chemicals Codex.

Pharmaceutical Manufacturers Association, "Guidelines for Identification of Inactive Ingredients in Oral Dosage Form Prescription Drug Products" (Washington, D.C.: December 5, 1984), 5 pp.

In July 1985, the Generic Pharmaceutical Industry Association adopted similar guidelines for the disclosure and labeling of inactive ingredients in oral dosage form prescription products. The guidelines of the Generic Pharmaceutical Industry Association differ from those of the Pharmaceutical Manufacturers Association in that:

(1) The Generic Pharmaceutical Industry Association considers an inactive ingredient to be a trade secret if the inactive ingredient's presence "gives the manufacturer an advantage over competitors who do not know or use it and if the identity of the ingredient cannot be determined by using modern analytical technology"; and

(2) The Generic Pharmaceutical Industry Association does not specifically refer to labeling that appears in the Physicians' Desk Reference.

Oral dosage form prescription products packaged after December 31, 1985 by participating companies were to be in full compliance with these guidelines.

Generic Pharmaceutical Industry Association, "G.P.I.A. Guidelines for Disclosure and Labeling of Inactive Ingredients" (New York: undated), 2 pp.

26. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 30.

27. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 29.

28. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 31.

29. The Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417) is sometimes informally referred to as the Waxman-Hatch bill or Waxman-Hatch amendments.

30. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 31.

31. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 39.

32. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 37.

33. U.S., Department of Health and Human Services, "Task Force Report", supra note 16, p. 43.

34. Kumasaka, Letter, supra note 4.

CHAPTER 7

The "White Paper"

Introduction

> Last August [of 1989] at the height of the "generic-drug scandal", the American Academy of Family Physicians fired a salvo of its own at the beleaguered [generic drug] industry. The AAFP's [American Academy of Family Physicians] widely publicized "White Paper on Generic Drugs" attacked the scientific basis for approving generics. The FDA's test method, the AAFP claimed, lacked "credibility" among most researchers.

This chapter reviews the American Academy of Family Physicians' "White Paper on Generic Drugs" which, together with the generic drug scandal and the ongoing controversy over the substitution of four brand-name anticonvulsant drugs in Hawaii, served to heighten the Legislature's awareness of the potential risks associated with generic drug substitution. This chapter focuses on the Academy's "White Paper" not to denigrate the credibility of the Academy or the persons who wrote it; rather, this chapter focuses on the "White Paper" to illustrate the ranges of acuity and validity of the disagreements that exist over the scientific bases for approving generic drug products, and to illustrate the clash between public policy and scientific uncertainty. The Academy's "White Paper" is included in this report as Appendix B.

Methodology

Despite the inclination to accept the validity of the American Academy of Family Physicians' "White Paper on Generic Drugs" as self-evident, the Bureau sought out evaluations of the "White Paper", that either disputed or disagreed with the Academy's assertions, to obtain a different perspective on the issue of generic drug substitution. During the course of researching this issue, the Bureau happened upon several evaluations that directly challenged the credibility of the "White Paper" and, in one specific instance, the credibility of the Academy itself.[2]

While the Bureau's review of the Academy's assertions was admittedly one-sided, an exhaustive review of the literature would not have enabled the Bureau to refute or confirm the Academy's assertions with any more authority than this one-sided review of the literature. Such a review of the literature would have required specialized skills, knowledge, and ability not possessed by the Bureau, and would have ended with the Bureau being no more able to conclusively refute or confirm the Academy's assertions in any case.[3] It is important to note that while these evaluations express doubt about the validity of the "White Paper", they do not conclusively refute the Academy's assertions.

The Bureau compared a draft[4] of the "White Paper" to the version finally adopted by the Academy to ensure that criticisms of the former would still be applicable to the latter. This was necessary because some of the evaluations cited in this chapter were based on a draft of the "White Paper" and not the version adopted by the Academy. While the task of comparing the draft of the "White Paper" to the version adopted by the Academy was straightforward, deciding whether criticisms of the former were still applicable to the latter was largely a matter of researcher judgment. The Bureau, to the best of its ability, excluded

criticisms of the draft of the "White Paper" that were inapplicable to the version adopted by the Academy.

Literature Cited

A major criticism of the Academy's "White Paper" is that the literature cited do not support the report's conclusions.

Following a review of the Academy's "White Paper", the FDA made the following statement regarding the report's bibliography:[5]

> Upon first glance, the AAFP [American Academy of Family Physicians] bibliography with its 73 references seems quite impressive. The AAFP position paper on generic drugs alleges that many studies have shown inequivalence or a lack of safety and effectiveness of generic drugs, contrary to the FDA's evaluation. However, none are cited. In fact, none of the allegations are linked to the 73 references, as one would expect in a scientific paper. Thus, point by point refutation is almost impossible.[6]
>
> Many of the articles in the bibliography are letters to the editor or opinion papers. Some of the results reported in the referenced articles demonstrate bioequivalence between product findings which tend to refute, not support, the AAFP position of non-interchangability [non-interchangeability] between brand and generic drug products. A few of the conclusions made in the referenced articles have been refuted elsewhere but the subsequent articles are not part of AAFP bibliography. In addition, some of the articles are about foreign products not marketed in the United States.

In addition, the FDA stated:[7]

> ...[I]t is important to re-emphasize that the "White Paper's" "many studies" that cite products in the Orange Book that do not meet our bioequivalence criteria are not found in the "White Paper". The statement "The bioavailability of a drug in serum or urine [measurements] cannot be assumed to mean that the drug is therapeutically equivalent" is completely unsupported. No data has ever been presented to FDA and we are not aware of any literature citations that conclude that drugs that have the same rate and extent of absorption gave different clinical effects. The body does not differentiate between molecules from brand or generic sources. In fact, equivalence of rate and extent of absorption are far more sensitive in detection of differences between products than are clinical trials.

Similar criticism of the Academy's "White Paper" was voiced by the Generic Pharmaceutical Industry Association, which stated:[8]

> Many citations in the 1989 AFFP [AAFP; American Academy of Family Physicians] Committee report refer to clinical studies that have demonstrated the therapeutic equivalence or interchangeability

> of brand and generic products; other citations have been refuted in subsequent literature, without AAFP notice of the refutation; many are editorial opinions or anecdotal reports of single practitioners; some are foreign studies of foreign products not marketed in the United States; and others are in other ways not relevant to the therapeutic equivalence of brand and generic drugs....
>
> * * *
>
> The text of the AAFP Committee report has no relationship to the articles cited in the report's appendix, and there is no reference to the cited literature within the text to document the opinions of the Committee's seven members. In many instances, the articles cited refute directly the Committee's opinions and recommendations, making it highly likely that the Committee failed to read the literature cited.

Echoing similar criticism of the Academy's "White Paper" was the American Pharmaceutical Association, which stated:[9]

> ...The report states that "many studies reveal that certain test criteria (C_{max}, T_{max}, and AUC) are not met by 'orange book' equivalent products." The report implies that these studies exist but does not reference them. The FDA has often stated that there have been no documented therapeutic failures related to the use of a generic product which had been approved by the FDA as bioequivalent. The AAFP [American Academy of Family Physicians] report seems to claim otherwise but does not provide references to those studies.[10]

Criticism of the Academy's "White Paper" was simply summed up by Consumers Union, publisher of Consumer Reports magazine, in an article entitled, "The Doctor's Proclamation: White Paper or Snow Job?" Consumers Union reported:[11]

> The AAFP's [American Academy of Family Physicians'] Dr. Mann told CU [Consumers Union] that his committee reached its conclusions about generic drugs after thoroughly reviewing the 73 references listed at the end of the report. Dr. Mann said they chose references from "reliable, acceptable medical journals." They rejected letters to the editor, he said, "because we didn't feel they were appropriate."
>
> CU was able to round up 63 of those 73 references. Ten were letters to the editor. Nine were editorials. Another 10 involved drugs that are used in foreign countries. Most glaringly, CU's review failed to find a single reference that lent scientific support for the committee's key conclusion: that bioequivalence testing fails to predict clinical effectiveness.

Inert Compounds and Additives

The Academy's "White Paper" states:[12]

> ...There is much evidence in the medical literature which indicates that many so-called generic drug substitutes are not "chemically the same drug entity in the same dosage form." A generic drug must be identical to the brand name product. Many generic formulations contain different "additives" and "inert" compounds, as compared to the brand name product, and therefore must not be considered bioequivalent[.] This information applies to many of the drugs listed as class "A" in the FDA's "orange book."...

This statement was criticized by the the American Pharmaceutical Association, which stated:[13]

> ...The report incorrectly implies that for a drug to be considered bioequivalent it must contain the same inert compounds in the same amounts as the innovator product. The generally accepted definition of bioequivalence has nothing to do with the inert ingredients. Bioequivalent drug products are pharmaceuticals whose active ingredient(s) are identical chemically, present in the same amount and yield equivalent concentrations in the body over time.[14]

Similar criticism was voiced by the Generic Pharmaceutical Industry Association, which stated:[15]

> ...The very purpose of bioequivalence testing is to demonstrate that the finished dosage form of one manufacturer produces the same rate and extent of active drug absorption as the finished dosage form of another manufacturer. A finished dosage form, such as a tablet or capsule, contains the active drug ingredient and all "additives" or "inert" ingredients. A demonstration of bioequivalence is a demonstration that the inactive ingredients do not affect the absorption characteristics of the finished dosage form.[16]

Therapeutic Equivalence

The Academy's "White Paper" states:[17]

> The bioavailability of a drug in serum or urine measurements cannot be assumed to mean that the drug is therapeutically equivalent.

This statement was criticized by the Generic Pharmaceutical Industry Association, which stated:[18]

> ...When the active ingredient of a drug product is shown to enter the bloodstream at the same rate and extent as the same active ingredient from another manufacturer's product, the therapeutic effects of the two products will be the same. There is no

scientific evidence disputing this fundamental principle, which is an essential basis of approval for both brand and generic drugs.

> The formulation used by a brand-name manufacturer in its original clinical safety and effectiveness testing is not the same formulation that is eventually produced in commercial batches and marketed. This increase in scale requires a bioequivalency test to demonstrate that the marketed formulation is therapeutically equivalent to the tested one. "Thus[,] for most drugs," wrote FDA, "the generic product and the marketed brand-name product stand in the same relationship to the formulation that was originally tested for safety and effectiveness." (emphasis added)[19]
>
> Furthermore, every drug product is subject to changes in formulation throughout its product life. These formulation changes, of differing inactive ingredients, frequently result from improvements in quality of materials or changes in technology. When formulation changes occur, a brand-name manufacturer must demonstrate that its new formulation is therapeutically equivalent to the old. The scientific method used is the same bioequivalence test, with the same statistical measurements and parameters, as a generic company would use to gain approval of its formulation of the product.[20]

The Academy's statement was further criticized by the American Pharmaceutical Association, which stated:[21]

> ...The report states: "The bioavailability of a drug in serum or urine measurements cannot be assumed to mean that the drug is therapeutically equivalent." In fact, there is substantial scientific and clinical support for the use of bioequivalence as an acceptable and appropriate indicator of therapeutic equivalence.
>
> The basis of all bioequivalency testing is the assumption that therapeutic and toxic actions of drugs are directly related to the concentration of drug at the site of action and that the concentration of the drug at the site of action is proportional to the concentration of the drug in the circulating blood supply. Thus, the measurement of bioequivalency is a direct measure of potential therapeutic outcome.

Bioavailability

The Academy's "White Paper" states:[22]

> In terms of approval of a generic product, bioavailability means that the testing of the generic reveals +/-20 percent of the availability of the innovator product. The FDA has established different standards for different drugs or drug classes. Frequently noted examples in the literature are: +/- 10 percent for warfarin; +/- 25 percent for antiarrhythmic drugs; and +/- 30 percent for anti-psychotic drugs.

The "White Paper" goes on to state:[24]

> ...It is clear from our review that some drugs have an extremely narrow therapeutic window. In our opinion, even a 10 percent over or under dosage may be dangerous in our patients.

These statements were criticized by the Generic Pharmaceutical Industry Association, which stated:[25]

> ...The standard allowance of plus or minus 20 percent applies to both brand and generic drug products, and based on [limited] data available to FDA, "the product to product variability in blood levels among bioequivalent drug products on the average does not appear to be significantly greater than variability seen between different lots of the same products [product] of a single manufacturer."[26]
>
> Furthermore, the Bioequivalency Task Force report indicates that there was a consensus among the experts at the Bioequivalency Hearing that "differences of less than 20 percent in AUC and C_{max} between products in normal subjects are unlikely to be clinically significant in patients." Clinical studies of effectiveness, the experts found, have difficulty detecting differences in dose of even 50-100 percent.[27]
>
> "Moreover, current practice in the evaluation of bioequivalence makes a true difference in means as large as 20 percent very unlikely," the Bioequivalence Task Force report continues. "In the vast majority of cases, the actual difference between the means will be [much] smaller. Indeed, the observed mean difference between the bioavailability of generic and innovator products...approved over a two years period...has been only 3.5 percent."[28]

Mandated Substitution

The Academy's "White Paper" states:[29]

> ...More and more of our members are participating in state Medicaid[30] programs and health maintenance organizations, and acting as hospital physicians in facilities where there is mandated substitution of generic products for their patients....
>
> * * *
>
> ...[T]he availability of brand name products may be restricted by hospital and health maintenance organization formularies, with [sic] the bounds allowed by the state in which they function. Although these limitations affect the physician's prscribing [prescribing] of therapy for his/her patient, this issue will not be dealt with in this paper.

This statement was criticized by the Generic Pharmaceutical Industry Association, which stated:[31]

> ...The federal government does not mandate generic substitution in any federally-supported program. Prescriptions are reimbursed at brand-name prices whenever a physician prescribes that a brand is "medically necessary."[32]
>
> Further, every state's drug product selection law preserves the physician's perogative [prerogative] to prescribe branded products. Only two states - Kansas and Mississippi -- have issued regulations that set reimbursement for Medicaid prescriptions at the generic price. A branded product may still be prescribed or dispensed, but these two State Medicaid offices will pay no more than the generic price.[33]

The Bureau's review of this matter indicates that while federal Medicaid regulations governing the prescription drug program do not expressly "mandate" generic drug substitution, the aggregate upper limit requirements for multiple-source and "other" drug products provide Medicaid-participating vendors with powerful incentives to practice generic drug substitution when a physician does not indicate "Brand Medically Necessary".

The regulations, set forth at 21 CFR 447.331, 447.332, 447.333, and 447.334, specify the aggregate upper limits of payment (i.e., maximum amount) that state Medicaid agencies are permitted to reimburse Medicaid-participating vendors for the dispensing of multiple-source[34] and "other"[35] drug products.

The regulations specify the method used by the federal Health Care Financing Administration to determine specific and aggregate upper limits of payment for multiple-source drug products[36] and the method to be used by state Medicaid programs to determine the aggregate upper limits of payment for "other" drug products.[37]

The regulations expressly state that the upper limit of payment for drug products for which a specific limit has been established by the federal Health Care Financing Administration does not apply if a physician certifies in the physician's own handwriting that a brand-name drug product is medically necessary for a particular recipient.[38] Upper limits of payment for drug products so certified by a physician are determined by state Medicaid agencies in accordance with procedures set forth at 42 CFR 447.331(b) for "other" drug products.

Because reimbursement to Medicaid-participating vendors dispensing multiple-source and other drug products cannot exceed, in the aggregate, that amount which would have resulted from the application of the specific limits established for multiple-source and "other" drug products in accordance with 42 CFR 447.332(b) and 42 CFR 447.331(b) respectively, state Medicaid programs have the option (albeit limited) of establishing reimbursement schedules that are consistent with state-determined priorities and the laws governing generic drug substitution. Consequently, state Medicaid programs may choose to adjust, either upward or downward, the specific upper limits established by the federal Health Care Financing Administration for certain multiple-source drug products.[39]

If a physician in the State of Hawaii prescribes a brand-name drug product (e.g., Valium, 10mg, oral tablet) but does not indicate that the brand-name drug product is medically necessary,[40] then a pharmacy may dispense a less expensive, therapeutically

equivalent generic drug product (e.g., diazepam, 10mg, oral tablet, Parke Davis) for the prescribed brand-name drug product to ensure that the pharmacy's cost of filling the prescription will not exceed the maximum reimbursement that can be received from Medicaid.[41]

If the patient refuses to accept the therapeutically equivalent drug product dispensed and demands that the pharmacy fill the prescription with the brand-name drug product prescribed, then the patient would be required to assume the total cost of the brand-name drug product dispensed at the time of purchase. The patient receives the brand-name drug product prescribed but also assumes the total cost of the higher priced drug product.[42]

If a physician prescribes a brand-name drug product for which a therapeutically equivalent drug product can be substituted, but indicates that the brand-name drug product is medically necessary, then Medicaid pays the cost of the brand-name drug product in accordance with methods set forth at 42 CFR 447.331(b).[43]

If a physician does not prescribe a brand-name drug product (i.e., the physician prescribes "generically", e.g., diazepam, 10mg, oral tablets), then a pharmacy can dispense any drug product, whether rated as therapeutically equivalent or not, that the pharmacy may have available. If the patient refuses to accept the drug product dispensed and demands that the pharmacy fill the prescription with a specific brand-name drug product of the patient's choosing, then the patient would be required to assume the entire cost of the prescription at the time of purchase. No Medicaid reimbursement would be made to the pharmacy for dispensing the brand-name drug product since selection of the drug product to be dispensed was left entirely to the discretion of the pharmacist. The patient receives the drug product of the patient's choosing but also assumes the entire cost of having the prescription filled with a higher priced drug product.[44]

Depending on a person's point of view, Hawaii's Medicaid program provides incentives to patients who accept therapeutically equivalent drug products or disincentives to patients who refuse to accept therapeutically equivalent drug products. The Bureau also notes, however, that Hawaii's Medicaid program preserves a physician's prerogative to prohibit generic drug substitution and require the dispensing of a brand-name drug product.

Miscellaneous--Medicaid. The recently enacted Omnibus Budget Reconciliation Act of 1990, P.L. 101-508 (November 5, 1990), makes a number of changes to the Medicaid program and may have a substantial impact upon the states because of the potential penalties and recoupments possible through the late implementation of congressionally-mandated deadlines.[44a] As of this writing, the method of implementing the changes at the federal and state levels were not yet known and a discussion of the Act's impact on generic drug substitution in Hawaii could not be included in this study.

The Bureau suggests that the Legislature request the Department of Human Services to:

(1) Conduct an informational briefing for the Legislature or appropriate committees on anticipated changes to the Medicaid program before the end of the 1991 legislative session; and

(2) Submit a written report to the Legislature on the implementation of these changes before the convening of the regular session of 1992.

The informational briefing should address the substance of these changes and their anticipated outcomes. The written report should discuss the Department's implementation of these changes and any significant impacts on the ability of physicians to prohibit generic drug substitution and require the dispensing of brand-name drug products. The Department's written report should also include recommended legislation to implement these changes or to mitigate their adverse effects, if appropriate.

Critical Patients, Critical Diseases, and Critical Drugs

The Academy's "White Paper" states:[45]

> In the article "Are Generic Drugs Dangerous for the Aged[?]" (Lamy, p. 42, Journal of Gerontological Nursing, 11{4} "42, 1985 April), the author suggests a new system recognizing that there are "critical patients, critical diseases and critical drugs for which generic substitution should never be mandated." Using this model, the Committee on Drugs and Devises [Devices] modified the description of these to read as follows:
>
> Critical Patients: For example, these would include those 75 years and older, and females living alone with multiple pathology on multiple drug regimens.
>
> Critical Diseases: These would include those disease states which are difficult to stabilize. Examples of critical diseases include depression, asthma, congestive heart failure, diabetes mellitus, cardiac problems, and the psychoses.
>
> Critical Drugs: These are drugs for which the FDA allows a wide range of variance in determining bioequivalence. Examples of these critical drugs include antipsychotics and loop diuretics. Drugs listed as class "B" in the FDA "orange book" should not be substituted.

This statement was criticized by the American Pharmaceutical Association, which stated:[46]

> ...The criteria for avoiding the use of multi-source products in certain types of diseases and patients (i.e., elderly females but not elderly males) seem both arbitrary and poorly based in science. References to support these assertions are not provided.

The Bureau's impression of Lamy's article is that the author was proposing a new procedure for evaluating the therapeutic equivalence of drug products that did not require the loss of medical control over a patient and the worsening of the patient's disease state to satisfy the demand for scientific proof that two drug products were in fact bioinequivalent drug products. According to Lamy, this procedure would be based on the recognition that there were critical patients, critical diseases, and critical drugs for which generic drug substitution should never be mandated. The crux of Lamy's rationale appeared to be that no health care professional would subject a patient to existing procedures to establish scientific proof that two drug products were bioinequivalent drug products and, therefore, the requirement for clinical proof could never be met.[47] Although Lamy provided several examples to support the

adoption of this proposed system, Lamy's review was not exhaustive or extensively referenced. Lamy appeared to make no definitive statements about the risks to these "critical patients", the risks to patients suffering from "critical diseases", or the risks to patients taking "critical drugs". Rather, Lamy suggested that "critical patients", persons suffering from "critical diseases", and persons taking "critical drugs" may be at greater risk if they were indiscriminately prescribed drug products that varied too much in their degree of potency. The key assumption in Lamy's argument appeared to be that some generic drug products could vary by as much as 20 to 30 percent from an innovator's drug product (i.e., the brand-name drug product).

Lamy's reference to the 1979 Final Task Force Report of the American College of Neuropsychopharmacology may not be "timely" literature in 1990.[48] The first "Orange Book", which embodied the FDA's final rule[49] for evaluating therapeutically equivalent drug products, was not published until October 1980.[50] Consequently, the recommendations of the 1979 Task Force Report of the American College of Neuropsychopharmacology would not necessarily be relevant to drug products listed in the 1990 "Orange Book".[51]

Summary

In her book, Dose Makes the Poison, M. Alice Ottoboni states:[52]

> ...Two scientists can review the same data and interpret them differently, particularly if their educational backgrounds and professional experiences differ. And scientists, like all human beings, can have widely differing political and social value systems. Some scientists find it difficult to separate their political and social attitudes, which they hold with great sincerity and conviction, from their science. Science is objective, but scientists are not necessarily so.

Disagreements between and among physicians, pharmacists, and pharmacologists are inevitable. Whether these disagreements stem from differences over science or differences over political and social values is difficult, if not impossible, to determine. Who among us, besides other physicians, pharmacists, and pharmacologists, is capable of separating another person's science from that person's political and social values without a clear explanation of the scientific issues involved?

The Bureau believes that the Drug Product Selection Board, which is composed of physicians, pharmacists, and a pharmacologist, is the appropriate agency to which all questions regarding the therapeutic equivalence and substitutability of multiple-source drug products should be addressed. The Bureau does not possess the specialized skills, knowledge, and ability to make a technical, scientific determination as to whether "generic substitution for epileptic patients and patients with allergic sensitivities should be permitted only with authorization of both physician and patient".[53]

ENDNOTES

1. "Generic Drugs: Still Safe?", Consumer Reports, Vol. 55, No. 5 (May 1990)(hereinafter cited as "Generic Drugs"), p. 312.

   American Academy of Family Physicians, "White Paper on Generic Drugs" (Missouri: no date)(hereinafter cited as "White Paper"), 10 pp.

2. The Bureau's review of the "White Paper" did not address the matter of motivation since questions about the credibility of the Academy were speculative and not immediately relevant to the study.

   Consumers Union, publisher of Consumer Reports magazine, questioned the credibility of the Academy, in addition to the credibility of the Academy's report, because of "the group's cozy relations with brand-name drug firms that compete against generics". "Generic Drugs", Consumer Reports, supra note 1.

3. The Bureau did review and has described 60 of the 73 works listed in the bibliography of the "White Paper". An exhaustive description of the salient points in each work was not possible because of space considerations and the Academy's failure to link specific works in the bibliography to the text of the "White Paper". While some of the works listed in the bibliography of the "White Paper" were clearly relevant to the arguments advanced by the Academy, the Bureau could only speculate about how other works listed in the bibliography might have been used to advance the Academy's arguments.

   The results of the Bureau's review are included in this study as Appendix C.

4. The draft, designated only as "Appendix A, Drugs and Devices" (pp. 525-534) and "Committee on Drugs and Devices, 1988-1989 Annual Report" (pp. 519-524), was obtained from the Generic Pharmaceutical Industry Association.

5. U.S., Department of Health and Human Services, Center for Drug Evaluation and Research, Food and Drug Administration, "Review of Article entitled, 'Generic Drugs: Potential Public Health Threat', authored by Gordon MacLeod and published in Pennsylvania Medicine, January 1990, pp. 20-22" (Maryland: April 1990)(hereinafter cited as "MacLeod"), pp. 1-2.

   MacLeod cites the bibliography of the Academy's "White Paper" as evidence that the variation in generic drug equivalency has become a major health problem in Pennsylvania and elsewhere.

   The FDA provided six specific examples from the bibliography of the Academy's "White Paper" to illustrate the bibliography's deficiency.

6. The FDA's comment refers to the fact that the Academy did not cite the "White Paper's" extensive bibliography as is customarily the practice in scholarly papers. Consequently, the allegations made by the Academy could not be readily corroborated by other researchers in the scientific community.

   The Academy's failure to cite the bibliography of the "White Paper" cannot be emphasized enough since a year earlier in 1988, the Academy's Committee on Drugs and Devices had endorsed generics, concluding that "drugs approved by the FDA as generically equivalent...are as safe and effective as their brand-name counterparts." Although the Committee's 1988 report was subsequently rejected by the Academy's Congress of Delegates, the Bureau notes that several of the references cited in the Committee's 1988 report--most notably the report of the Bioequivalence Task Force (see Chapter 6)--were also listed in the bibliography of the "White Paper". Yet, as pointed out by Consumers Union, "[t]he 1989 report bore little resemblance to its predecessor."

   The Committee's 1988 report, designated only as "Appendix A, Drugs and Devices, Generic Drugs" (1988 AAFP Transactions), was obtained from the Generic Pharmaceutical Industry Association; "Generic Drugs", Consumer Reports, supra note 1.

7. U.S., Department of Health and Human Services, "MacLeod", supra note 5, p. 6.

   The FDA apparently left out the word "measurements"; American Academy of Family Physicians, "White Paper", supra note 1, p. 3.

8. Generic Pharmaceutical Industry Association, "Written comments of the Generic Pharmaceutical Industry Association regarding an early draft of the Academy's 'White Paper'" (Generic Pharmaceutical Industry Association, 200 Madison Avenue, Suite 2404, New York, N.Y. 10016, no date)(hereinafter cited as "Written comments"), pp. 1-2.

   The Generic Pharmaceutical Industry Association reviewed 26 of the references cited in the bibliography of the Academy's "White Paper" to illustrate the bibliography's deficiency.

   The Generic Pharmaceutical Industry Association represents manufacturers, distributors, and suppliers of equivalent generic drugs.

9. The statement attributed to the Academy appears to be paraphrased, i.e., the statement is not a direct quote. American Pharmaceutical Association, "Letter from John Gans, Executive Vice-President of the American Pharmaceutical Association to Robert Graham, Executive Vice President of the American Academy of Family Physicians regarding the Academy's 'White Paper'" (American Pharmaceutical Association, 2215 Constitution Avenue, NW, Washington, D.C. 20037, August 22, 1989)(hereinafter cited as "Written comments"), p. 2.

   The American Pharmaceutical Association is the national professional society of pharmacists.

10. The final version of the Academy's "White Paper" adopted by its Congress of Delegates stated:

> ...Factors considered as important by the FDA are: (1) T_{max} -- the measurement of time, after administration of the drug, at which the maximum serum concentration of a product is achieved; (2) C_{max} -- the maximum serum concentration achieved; and (3) AUC (Area Under the Curve) -- the total absorption of a single test dose. Many studies reveal that these criteria are not met by "orange book" equivalent products....

   American Academy of Family Physicians, "White Paper", supra note 1, pp. 2-3.

11. "Generic Drugs", Consumer Reports, supra note 1.

12. American Academy of Family Physicians, "White Paper", supra note 1, p. 3.

13. American Pharmaceutical Association, "Written comments", supra note 9.

14. As discussed in Chapter 2, the term "pharmaceutical equivalents" means "drug products that contain identical amounts of the identical active drug ingredient..., in identical dosage forms, but not necessarily containing the same inactive ingredients [emphasis added]...". 21 CFR 320.1.

15. Generic Pharmaceutical Industry Association, "Written comments", supra note 8, Appendix D, p. 1.

16. As discussed in Chapter 2, the Commissioner of Food and Drugs must determine whether to propose or promulgate a regulation to establish a bioequivalence requirement for pharmaceutical equivalents that are not or may not be bioequivalent drug products. One criterion for establishing a bioequivalence requirement is that specific inactive ingredients may be required for absorption of the active drug ingredient or therapeutic moiety or, alternatively, if present, may interfere with the absorption of the active drug ingredient or therapeutic moiety. 21 CFR 320.52.

17. American Academy of Family Physicians, "White Paper", supra note 1, p. 3.

18. Generic Pharmaceutical Industry Association, "Written comments", supra note 8, Appendix D, p. 1.

19. The statement attributed to the FDA comes from an article entitled, "FDA Speaks Out About Generic Drug Quality", originally printed in the April 1986 issue of the NABP

Newsletter, which is published by the National Association of Boards of Pharmacy (Illinois), pp. 53-54, and subsequently reprinted in Guide to Interchangeable Drugs and published by the Generic Pharmaceutical Industry Association (New York: 1988), p. 27.

20. The FDA has stated that:

> For such changes, FDA may require the innovator to do in vitro dissolution testing, or if considered major changes, such as in a major product reformulation, the innovator would be required to do a bioequivalence study in 20-30 normal healthy males to gain approval. What most people are not aware of is that the bioequivalence approval requirements for an ANDA [Abbreviated New Drug Application] were developed from the NDA [New Drug Application] approval requirements cited above. Thus, approving generic products without additional safety and efficacy trials is not unsound and unscientific, but is based on and entirely consistent with FDA's longstanding policy of allowing the innovator to reformulate its products based upon demonstration of bioequivalence of the active ingredient in their old and new products.

U.S., Department of Health and Human Services, "MacLeod", supra note 5, p. 4.

The Bureau's review of this matter indicates that the content of an abbreviated new drug application (ANDA) is defined in relation to the content of a new drug application (NDA), i.e., an ANDA is defined as an NDA minus certain provisions. These provisions are:

1. 21 CFR 314.50(c), relating to the summary portion of the NDA;
2. 21 CFR 314.50(d)(2), relating to nonclinical pharmacology and toxicology, i.e., data from animal and in vitro studies;
3. 21 CFR 314.50(d)(4), relating to microbiology, if the drug is an anti-infective;
4. 21 CFR 314.50(d)(5), relating to clinical data that describe clinical investigations of the drug;
5. 21 CFR 314.50(d)(6), relating to statistical evaluation of clinical data; and
6. 21 CFR 314.50(f), relating to case reports tabulation and case report forms from clinical studies.

21 CFR 314.55.

21. American Pharmaceutical Association, "Written comments", supra note 9.

22. American Academy of Family Physicians, "White Paper", supra note 1, p. 3.

23. The generic manufacturer must presently demonstrate, with 90 percent certainty in each instance, that the difference between the mean bioavailability of its product is not more than 20 percent and less than 20 percent of the mean bioavailability of the innovator's product (the 90 percent confidence interval based on the two one-sided t-test approach).

According to FDA, "[t]here are currently no products for which a 30 percent variation in the extent of absorption has been permitted." Generic Pharmaceutical Industry Association, Guide to Interchangeable Drugs, supra note 19, p. 30.

A few drugs, because of an inherent variability of both the innovator's and generic products, could not meet the FDA's statistical criteria. For these drugs, another criteria was employed, the so called 75/75 rule, which was a test to show that at least 75 percent of the people tested did not show a variation of more than 25 percent between the innovator's and generic products. For one class of drugs, the psychotropic phenothiazines, that criteria was expanded to allow 70 percent of the people tested to show a variation of 30 percent or less between the two products. FDA replaced the 75/75 rule in 1988 with a more precise statistical device, the 90 percent confidence interval. Generic Pharmaceutical Industry Association, Guide to Interchangeable Drugs, supra note 19, p. 29.

According to the FDA, the 75/75 rule was never used as the sole criteria for evaluating the bioequivalence of a generic drug or a reformulated innovator's product. U.S., Department of Health and Human Services, "MacLeod", supra note 5, p. 6.

24. American Academy of Family Physicians, "White Paper", supra note 1, p. 3.

25. Generic Pharmaceutical Industry Association, "Written comments", supra note 8, Appendix D, p. 2.

26. The passage quoted by the Generic Pharmaceutical Industry Association is from the report of the Bioequivalence Task Force. The Generic Pharmaceutical Industry Association left out the word "limited", which was used by the Bioequivalence Task Force to describe the data available to the FDA. U.S., Department of Health and Human Services, Food and Drug Administration, "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, September 29 - October 1, 1986" (Maryland: Dockets Management Office, January 1988)(hereinafter cited as "Task Force Report"), p. 32.

27. The use of the term "experts" is a characterization of the Generic Pharmaceutical Industry Association. The report of the Bioequivalence Task Force states only that there was a consensus on this issue at the Hearing. U.S., Department of Health and Human Services, "Task Force Report", supra note 26, p. 29.

Similar endorsement of the Bioequivalency Task Force's report was echoed by the American Society of Hospital Pharmacists, which stated:

> ...In 1988, the FDA Bioequivalence Task Force examined several issues on bioequivalence and generic drugs. The task force's report explored thoroughly the scientific issues raised by AAFP [American Academy of Family Physicians] and represents the best contemporary thinking of pharmaceutical scientists and well-informed clinicians. The report of this task force should be reviewed and carefully considered by AAFP.

American Society of Hospital Pharmacists, "Letter from Joseph Oddis, Executive Vice President of the American Society of Hospital Pharmacists to Morris Mellion, Speaker of the Congress of Delegates of the American Academy of Family Physicians, regarding an early draft of the Academy's 'White Paper'" (American Society of Hospital Pharmacists, 4630 Montgomery Avenue, Bethesda, MD 20814, September 6, 1989), pp. 3-4.

The American Society of Hospital Pharmacists is the national professional association representing pharmacists who practice in organized health-care settings, such as hospitals, ambulatory-care clinics, health maintenance organizations, home-care agencies, and long-term care facilities.

28. The Generic Pharmaceutical Industry Association left out the word "much", which was used to describe the actual difference between the means of generic and innovator products. The sections left out of the second sentence, as indicated by elipses, state that the 3.5 per cent observed mean difference referred to a study of post-1962 drugs approved under the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), informally referred to as the "Waxman-Hatch Act" in the report of the Bioequivalence Task Force. U.S., Department of Health and Human Services, "Task Force Report", supra note 26, p. 29.

29. American Academy of Family Physicians, "White Paper", supra note 1, p. 1.

30. Medicaid is a federally supported and state-administered assistance program providing medical care for certain low-income individuals and families. The Medicaid program is designed to provide medical assistance to persons who are eligible to receive cash payments under one of the existing welfare programs established under the Social Security Act.

Title XIX of the Social Security Act requires that every state Medicaid program offer certain basic services. In addition, the states may elect to provide a number of other services, including prescription drug services.

Under Medicaid, payments are made directly to providers of service for care rendered to eligible individuals. Participation in Medicaid is voluntary and providers who choose to participate in the Medicaid program must accept the Medicaid reimbursement levels as full payment.

Medicaid is financed jointly with state and federal funds. Federal contributions vary with states' per capita income and currently range from 50 per cent to 78 per cent of program expenditures.

State participation in the Medicaid program is voluntary and the states administer their Medicaid programs within federal requirements and guidelines. These requirements allow states discretion in determining income and other resource criteria for eligibility, covered benefits, and provider payment mechanisms. Consequently, the characteristics of Medicaid programs vary from state to state. U.S., Department of Health and Human Services, Health Care Financing Administration, HFCA Pub. No. 03270, Health Care Financing, Program Statistics, Medicare and Medicaid Data Book, 1988 (Maryland: 1989), p. 6.

31. Generic Pharmaceutical Industry Association, Written comments regarding the Academy's "White Paper", supra note 8, Appendix D, p. 2.

32. The Generic Pharmaceutical Industry Association also stated that:

> When specifying a branded product for a Medicaid recipient, the prescriber must write "brand medically necessary" in order for Medicaid to reimburse the pharmacist at the brand-name price....
>
> * * *
>
> Still, the decision to allow generic or brand-name dispensing remains solely with the prescribing physician. Pharmacists may not alter this decision without specific consultation and approval of the prescriber.

Generic Pharmaceutical Industry Association, Guide to Interchangeable Drugs, supra note 19, p. 21.

33. This statement was corroborated by the U.S. Department of Health and Human Services, Center for Drug Evaluation and Research, which stated:

> ...Although generic drugs are being promoted in an effort to contain costs, FDA strongly endorses the concept that the physician has the ultimate authority as to whether the patient receives a brand or generic drug. The Federal MAC [Maximum Allowable Cost; Medicaid] program does not mandate substitution and we are not aware of any state that requires substitution to take place without physician authorization. However, we are acutely aware that there is not uniformity among the state laws as to how the physician can prevent substitution....
>
> * * *
>
> ...Federal programs may encourage but do not mandate such [generic drug] substitution.

U.S., Department of Health and Human Services, "MacLeod", supra note 5, p. 3.

34. The federal Health Care Financing Administration establishes listings that identify and set upper limits of payment for drug products that meet the following requirements:

(1) All of the drug products have been evaluated as being therapeutically equivalent drug products in the most current edition of or supplement to Approved Drug Products with Therapeutic Equivalence Evaluations (i.e., the FDA's "Orange Book"); and

(2) At least three suppliers of these therapeutically equivalent drug products list their drug product in current editions or updates of published compendia of cost information for drug products available for sale nationally.

42 CFR 447.332(a)(1).

35. "Other" drug products are those that have been certified by a physician as being medically necessary for a recipient, and those drug products for which no specific upper limit has been established by the federal Health Care Financing Administration. 42 CFR 447.331(b).

36. 42 CFR 447.331(a); 42 CFR 447.332(b).

37. 42 CFR 447.331(b).

38. 42 CFR 447.331(c).

39. 42 CFR 447.331(a); 42 CFR 447.331(b).

While state Medicaid programs have the option of adjusting federally established upper limits for multiple-source drug products, these "adjusted" upper limits revert back to the levels established by the federal Health Care Financing Administration for the purpose of assessing compliance with the aggregate upper limit requirement. In the event of a conflict between federal and state Medicaid laws regarding the therapeutic equivalence of multiple-source drug products, federal Medicaid law takes precedence over state Medicaid law.

Telephone interview with Pete Rodler, Senior Program Analyst, U.S., Department of Health and Human Services, Health Care Financing Administration, Medicaid Bureau, Baltimore, Maryland, July 23, 1990.

40. 42 CFR 447.331(c).

41. Interview with Omel Turk, Pharmacy Consultant, Department of Human Services, Honolulu, Hawaii, May 25, 1990.

Hawaii, Department of Human Services, "Medicaid Provider Manual, Appendix 11R, MCA506/E (Trans. Bulletin: PM003, Revision Date: May 1989, Prev. Rev. Date: July 1987)", p. 7.

42. Turk, Interview, supra note 41.

43. The upper limit of payment for such a drug product would be determined by applying:

(1) The lower of the estimated acquisition costs plus reasonable dispensing fees established by the state Medicaid program; or

(2) The provider's (i.e., the vendor's) usual and customary charges to the general public.

44. Turk, Interview, supra note 41.

Realistically, it would appear to make little sense for a pharmacist to stock a generic drug product that was not rated as therapeutically equivalent to the brand-name drug product if a therapeutically equivalent generic drug product were available. Exceptions to this generalization would involve "pre-1938" drugs, and drugs and drug products still undergoing DESI review.

44a. Turk, Telephone interview, supra note 41, December 10, 1990.

45. American Academy of Family Physicians, "White Paper", supra note 1, p. 4.

46. American Pharmaceutical Association, "Written comments", supra note 9.

47. Peter Lamy, "Are Generic Drugs Dangerous for the Aged?", Journal of Gerontological Nursing, Vol. 11, No. 4 (April 1985), p. 42.

48. It should be emphasized that the recommendations of the American College of Neuropsychopharmacology are not being challenged in this discussion. Rather, the Bureau is simply pointing out the that more than 10 years have elapsed since the Task Force's final report. In 1980, the FDA stated:

> The agency agrees with the Task Force of the American College of Neuropsychopharmacology that it would be undesirable to use multisource psychotropic drug products interchangeably unless their bioequivalence had been established. The Task Force, however, did not address all psychotropic drugs, but specifically addressed the tricyclic antidepressants and phenothiazines. These drugs have been coded to indicate a known or potential bioequivalence problem. The agency has published proposed bioequivalence regulations for these two drug classes requiring both in vivo bioavailability studies and in vitro dissolution testing to establish bioequivalence....

45 FR 72599, Oct. 31, 1980.

49. 45 FR 72582.

The FDA's proposed rules for evaluating therapeutically equivalent drug products were published in the Federal Register on January 12, 1979. 44 FR 2932.

50. U.S., Department of Health and Human Services, Food and Drug Administration, Approved Drug Products with Therapeutic Equivalence Evaluations, 10th ed. (Washington, D.C.: U.S. Government Printing Office, 1990), p. 1.

51. The "Orange Book" is now in its 10th edition. The State utilizes the 9th edition of the "Orange Book", and the "Orange Book's" Cumulative Supplement 8, dated through August 1989, as the State's drug formulary of equivalent drug products. Hawaii, Department of Health, Drug Product Selection Board Meeting, Minutes of Meeting (November 17, 1989), p. 4.

Chapter 11-33, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board), indicates that the State's drug formulary of equivalent drug products is current through December 31, 1988 and not August 1989, as reflected in the November 17, 1989 minutes of the Drug Product Selection Board.

52. M. Alice Ottoboni, The Dose Makes the Poison (California: Vincente Books, 1984), pp. 182-183.

53. Senate Concurrent Resolution No. 242, S.D. 1, Fifteenth Legislature, 1989.

The Bureau notes that such a recommendation would be tantamount to recommending the removal of anticonvulsant drug products from the Hawaii Drug Formulary of Equivalent Drug Products (December 1988). Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

CHAPTER 8

Epilepsies and Allergies

Introduction

This chapter discusses the etiology of epilepsies and the relationship between the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source anticonvulsant drug products and this chronic disorder. This chapter also discusses the etiology of chemical allergies and the relationship between the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products and the onset of this rare, but potentially life-threatening, condition.

Although Senate Concurrent Resolution No. 242, S.D. 1, requests the Bureau to study the "risks and dangers of generic drug products for certain patients or conditions",[1] the Bureau believes that these risks and dangers can be generally described by using epilepsies and allergic reactions as models of the adverse reactions that can be precipitated by generic drug substitution. The individual risks and dangers of generic drug products, whether real or theoretical, are too varied and numerous to be discussed in a study of this nature since they involve the delicate interplay between personal characteristics and the severity of a condition.

This chapter focuses on those adverse reactions that involve a lack of bioavailability, bioequivalence, or therapeutic equivalence among multiple-source drug products, or a chemical allergy to an inactive ingredient. Descriptions of the individual risks and dangers of generic drug products for certain patients and conditions are included in this study as Appendix C, which briefly describes 60 of the 73 references cited in the bibliography of the American Academy of Family Physicians' "White Paper on Generic Drugs".[2]

Epilepsies

According to the American Medical Association:[3]

> Seizures are manifestations of a focal or generalized disturbance of the brain. Epilepsies are chronic seizure disorders characterized by a tendency for recurrent seizures....

Seizures and some epilepsies are caused by congenital or birth defects, degenerative disease, trauma of the central nervous system, anoxia (a lack of oxygen), fever, metabolic disturbances, anaphylaxis (an allergic reaction), infection, neoplasm (a tumor or growth), cerebrovascular (i.e., pertaining to the blood vessels of the brain) disease, poisoning, and withdrawal of alcohol and certain drugs. In some cases, seizures may occur in the absence of any diagnosable conditions (i.e., they are idiopathic in origin).[4]

Persons with epilepsy may experience a sudden loss or disturbance of consciousness in association with motor, sensory, autonomic, or inappropriate behavioral phenomena. The age-adjusted prevalence of epilepsy in the United States is reported to be 6,250 persons per 1,000,000 population.[5] According to the American Medical Association, "[t]he overall incidence of epilepsy is greatest in the first year of life, declines over fivefold in the next 10 years, reaches a minimum by age 30-40, and begins to increase again at 50".[6]

Seizures are classified by the Commission on Classification and Terminology of the International League Against Epilepsy into two broad groups: partial (focal) seizures and generalized (convulsive or nonconvulsive) seizures.[7] Epilepsies are similarly classified according to their etiology as either symptomatic (secondary) or idiopathic (primary) epilepsy; the former suggesting that the cause of a seizure is known (e.g., caused by structural lesions in the brain), the latter suggesting that the cause of the seizure is not known (i.e., taking place without any detectable brain abnormality).[8]

Epilepsies that occur during infancy are believed to result from developmental defects, metabolic disease, or birth injury. Epilepsies that begin during adulthood are believed to result from trauma, stroke, tumors, or other recognizable brain disease, but in many cases the etiology of these epilepsies cannot be determined.[9]

Since it is difficult to accurately explain the actions of antiepileptic or anticonvulsant drugs on a molecular level without entering into a lengthy discussion of nerve and nervous system physiology (e.g., the structure of nerves and the nervous system; the role of sodium, potassium, and calcium ion transport in nerve impulse transmission; and the role of neurotransmitters and neuromodulators in synaptic transmissions), it is necessary for one to accept the fact that there is a significant relationship between the serum concentration of an anticonvulsant drug and its therapeutic effect.[10]

The objective of anticonvulsant drug therapy is to control seizures as completely as possible without causing intolerable or unacceptable adverse reactions (e.g., damage to the bone marrow, liver, and kidneys). Anticonvulsant drug therapy is highly individualized since the appropriate dosage of a drug or combination of drugs depends on the size, age, and condition of the patient, the patient's response to treatment, and the interactions between concomitantly administered medication.[11]

According to the American Medical Association, most treatment failures in anticonvulsant drug therapy are caused by patient noncompliance. A sudden withdrawal of or decrease in anticonvulsant drug therapy may precipitate seizures, and uncontrolled epilepsy may lead to intractable epilepsy. Conversely, as the metabolism of the anticonvulsant drug phenytoin approaches saturation, even small dosage increases in phenytoin may cause unexpected toxicity as a result of disproportionately large increases in the serum concentration and apparent half-life of the drug.[12]

Although it may be more objective to describe the end result of therapeutic failures involving anticonvulsant drugs in terms of increased seizure frequency or some other clinical manifestation, the true magnitude of these failures cannot be properly appreciated solely in their clinical context.

It has been reported that over 80 percent of patients with seizures achieve excellent control of their seizures through faithful adherence to a regimen of anticonvulsant drug therapy.[13] Consequently, many persons with epilepsies are capable of living and do live normal, productive lives. Successful anticonvulsant drug therapy is essential to the development of a normal, productive lifestyle; therefore, therapeutic failures involving anticonvulsant drugs would most severely affect those persons who lead highly independent lives.[14]

Prior to the development of effective anticonvulsant drug therapies, comparing the lifestyles of persons with epilepsy to person's without epilepsy would have been practically meaningless; there was very little in common between the two and no reason for assuming

that the two could ever be the same. Today, except in a few cases, there is no reason to assume that persons receiving successful anticonvulsant drug therapy cannot lead lives that are comparable to persons without epilepsies. Placing the consequences of a therapeutic failure in this perspective is more meaningful (but perhaps less objective) than discussing increases in seizure frequencies since one need only visualize the outcome of a primary or secondary epileptic seizure taking place during the course of a normal day to appreciate the magnitude of this potential problem.[15]

Although it is relatively simple for a person without epilepsy to visualize the outcome of such a seizure in terms of the potential physical harm to oneself and to others, there is practically no basis for a person without epilepsy to visualize the emotional harm caused by the fear of recurrent seizures or the prejudice of co-workers, employers, and others who may have witnessed a seizure. Persons with epilepsy are not permitted to operate a motor vehicle unless they have been seizure-free for at least one year, while others have reportedly lost or come close to losing their jobs because of an "on-the-job" seizure.[16] Although persons with epilepsies are no longer viewed as being "bewitched" or "possessed", prejudices die hard among the uninformed.

Allergic Reactions

A "chemical allergy" is "an adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one".[17] These reactions are mediated by the body's immune systems.[18] A chemical allergy differs from "hypersensitivity" or "hyperreactivity" to a chemical in that the latter involves responses to a chemical that are substantially greater than the responses predicted for given doses along the dose-response continuum[19] and the former involves a situation where "a preexposure of the chemical is required to produce the toxic effect via an antibody".[20] Accordingly:[21]

> An allergic reaction does not usually exhibit a typical sigmoid dose-response curve as observed for most toxic responses. Because of this apparent lack of a dose-response, some people have not considered the allergic reaction to be a toxic response. However, since the allergic response is an undesirable, adverse, deleterious effect, it should be regarded as a toxic response. Toxicity is defined as the inherent ability of a chemical to adversely affect living organisms. Sensitization reactions are often very severe and many are fatal.

As discussed in Chapter 7, one of the questions addressed by the FDA's Bioequivalence Task Force was whether or not bioequivalence studies considered or should consider the effects of excipients or inactive ingredients on the bioavailability of drug products, and the likelihood of an inactive ingredient causing toxicity in a patient.[22]

In considering this question, the following points were made by three speakers at the bioequivalence hearing conducted by the FDA:[23]

> ...Bioequivalence testing does not measure the therapeutic consequences of excipients, e.g., allergic potential in an individual [citation deleted].
>
> The potential for adverse reaction from so-called inactive excipients is rare [citation deleted].

> The problem, is interchanging one product with another and not knowing that it may contain a different inactive ingredient which could cause toxicity or an allergic reaction in a particular person [citation deleted].
>
> The Task Force stated:[24]
>
> The first question of potential toxicity of excipients is beyond the scope of the Hearing. With respect to the second question on the effect on bioequivalence, the studies carried out address the effects of excipients and any other feature of the formulation on bioavailability....
>
> * * *
>
> The Task Force agrees that the rare incidence of allergies and toxicity to excipients may pose a problem for a few patients. Information on excipients for all drug products is currently being addressed by the Pharmaceutical Manufacturers Association (PMA) and the Proprietary Association (PA) with their voluntary labeling guidelines and this information will help enable patients to be alerted to an allergenic potential. The effect of excipients on bioavailability is assessed by current bioequivalence studies.

Summary

Because there is a significant relationship between the serum concentration of an antiepileptic or anticonvulsant drug and its therapeutic effect (i.e., a dose-response relationship), it is reasonable to conclude that there is a relationship between the bioavailability, bioequivalence, and therapeutic equivalence of anticonvulsant drug products and the precipitation of seizures and toxic effects. A decrease in the serum concentration of an anticonvulsant drug can precipitate seizures if the decrease is brought about too abruptly or results in subtherapeutic serum concentrations of the anticonvulsant drug. Conversely, an increase in the serum concentration of the anticonvulsant drug phenytoin near the limit of the body's ability to metabolize the drug can result in toxicity or reversible and irreversible adverse effects.

Ultimately, any decision regarding the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source anticonvulsant drug products must address one question: "Can a therapeutically equivalent, generic anticonvulsant drug product be substituted for the brand-name anticonvulsant drug product prescribed without precipitating epileptic seizures or toxic effects?" Arguably, an unconditional "yes" or "no" answer from the Drug Product Selection Board would have settled this matter and left very little for the Legislature to debate. By qualifying its answer and acknowledging the potential problems of substituting a therapeutically equivalent, generic anticonvulsant drug product for the brand-name anticonvulsant drug product prescribed, however, the Board broke "new ground" and, in so doing, supplied the material needed to fuel this ongoing controversy.

Using epilepsies and the anticonvulsant drugs as a general model of the relationship between the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products and the control of chronic, pathological conditions (e.g., propranolol

hydrochloride and cardiac arrhythmias, hydrochlorothiazide and hypertension, allopurinol and gout, and chlorpropamide and diabetes milletus), the risks and dangers associated with differences in the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products used to control chronic pathologies are the risks and dangers associated with toxic and subtherapeutic serum concentrations of the drug or its metabolites. In the former instance, these risks and dangers are caused by the toxic effects of the drug or its metabolites; in the latter, they are caused by the progression of the pathology and the onset of associated complications and sequelae.

Because of its etiology, there is no relationship between an allergic reaction and the bioavailability, bioequivalence, or therapeutic equivalence of multiple-source drug products. Allergic reactions are not usually dose-dependent; therefore, a lack of bioavailability, bioequivalence, or therapeutic equivalence between two or more multiple-source drug products is not likely to precipitate the onset of this potentially life-threatening condition.

An allergic reaction precipitated by generic drug substitution is most likely to be caused by an inactive (chemical) ingredient in the drug product that is substituted for the drug product prescribed. Although an allergic reaction can be precipitated by the active drug ingredient (e.g., Penicillin G benzathine), an allergic reaction precipitated by generic drug substitution is not likely to be caused by the active drug ingredient.[25]

Although the drug industry has been implementing a voluntary labeling program to help alert patients to the potential of allergic reactions, it is the pharmacist, and not the patient, who selects the therapeutically equivalent generic drug product to be substituted for the brand-name drug product prescribed. Prohibiting generic drug substitution for patients with allergic sensitivities ignores the fact that both brand-name drug products and generic drug products are periodically reformulated by their manufacturers to add or delete inactive ingredients that could precipitate allergic reactions in certain patients. The role of the pharmacist in monitoring a patient's allergic sensitivities to specific inactive ingredients and other structurally similar inactive ingredients seems pivotal.

ENDNOTES

1. Senate Concurrent Resolution No. 242, S.D. 1, Fifteenth Legislature, State of Hawaii, 1990.

2. American Academy of Family Physicians, "White Paper on Generic Drugs" (Missouri: no date), 10 pp.

3. American Medical Association, Drug Evaluations, 6th ed. (Illinois: American Medical Association, 1986), p. 169.

4. American Medical Association, Drug Evaluations, supra note 3.

5. American Medical Association, Drug Evaluations, supra note 3.

   Prevalence refers to the ratio between the number of existing cases of a condition (in this case epilepsy) and the total number of persons in a population at a point in time. The term "age-adjusted" means that the ratio has been standardized to account for differences in the prevalence of epilepsies caused by age. An age-adjusted ratio is a fictional number that is useful in making summary statements about a condition, and that permits the unbiased comparison of groups that would not otherwise be comparable because of differences in their composition. Judith Mausner and Anita Bahn, Epidemiology--An Introductory Text (Philadelphia: W.B. Saunders Company, 1974), pp. 127 and 138.

According to the Epilepsy Foundation of Hawaii, there are approximately 17,000 persons with epilepsies in the State of Hawaii. Telephone interview with Rosalind Wagner, Executive Director, Epilepsy Foundation of Hawaii, September 10, 1990.

Although the figure given by the Epilepsy Foundation of Hawaii is much greater than the figure cited by the American Medical Association, other sources report that epilepsies affect between one to two percent of the population. This would translate to a prevalence ratio of 10,000 to 20,000 per 1,000,000 population. "Nerves and Nervous Systems", 24 The New Encyclopaedia Britannica, Macropaedia, Knowledge in Depth 852, 15 ed. (1989)(hereinafter cited as "Nerves").

6. American Medical Association, Drug Evaluations, supra note 3.

7. Although there are more than 30 different types of seizures, simple partial seizures, complex partial seizures, generalized tonic-clonic seizures, and absence seizures comprise the majority of all seizures seem in persons with epilepsies. A few of the other types of seizures include infantile spasms, myoclonic seizures, and atonic seizures.

   As its name implies, partial seizures emanate from a specific portion of the brain. Generalized seizures are those in which no identifiable focus in the brain can be found; they include absence seizures, myoclonic seizures, and atonic seizures.

   Simple partial seizures (formerly known as focal motor, focal sensory, or Jacksonian seizures) are characterized by stiffening or jerking in one extremity or one side of the body. The seizure is sometimes accompanied by a tingling sensation in the affected area. While consciousness is not lost with this type of seizure, the jerking may spread to become a generalized tonic-clonic seizure in some persons.

   Complex partial seizures (formerly known as psychomotor or temporal lobe seizures) are often characterized by purposeless activity. While these seizures may vary greatly from person to person, they tend to be consistent for each person. This is the type of seizure most likely to be preceded by an aura or warning. During a seizure, a person may have a glassy stare, give no response or give a confused response to a question, move about aimlessly, make lip-smacking or chewing motions, fidget with clothes, appear drunk, drugged, or even psychotic. Emotional experiences, abnormalities in thinking and unusual sensory perceptions may also occur during a seizure, especially at the onset of the seizure. Although the person is not violent, the person may struggle or fight if restrained. While there is usually no memory of the seizure, the person is often confused after the seizure is over. A seizure will usually last one to three minutes.

   Generalized tonic-clonic seizures (formerly known as grand mal seizures) are convulsive seizures that affect the entire body. There is usually no aura or warning prior to the onset of a seizure. The person may cry out as air rushes out of the person's lungs. The person falls and becomes unconscious; the body stiffens, then the muscles begin to alternate periods of spasm and relaxation with jerking motions. The person may bite the person's tongue. Breathing is labored or jerky and stops completely at times; a pale or bluish complexion may develop if this occurs. Loss of urine or stool may also occur. Upon regaining consciousness, the person is usually confused or sleepy and may experience fatigue, headache, speech difficulty, or weakness of an arm or leg. Some persons may sleep for several hours following a seizure. A seizure will usually last one to three minutes.

   Absence seizures (formerly known as petit mal seizures) are characterized by a brief loss of consciousness (from one to ten seconds) during which there may be staring, eye blinking, or mild facial twitching. No aura or warning is associated with this type of seizure. The person usually maintains posture and does not fall. This type of seizure is most common in children and is frequently missed because the seizure is so brief and subtle. A child may experience several hundred seizures in a day. Although the seizures often stop before adulthood, they sometimes change to generalized tonic-clonic seizures.

Atonic seizures (formerly known as drop attacks) are characterized by sudden collapses and falls. After ten seconds to one minute, the person recovers, regains consciousness, and can stand and walk again.

Myoclonic seizures are characterized by sudden, brief, massive muscle jerks that may involve the whole body or part of the body. The person may spill what the person was holding or fall off a chair.

Infantile spasms are characterized by clusters of quick, sudden movements that start between three months and two years of age. If the child is sitting up, the child's head will fall forward, and the child's arms will flex forward. If the child is lying down, the child's knees will be drawn up with the child's arms and head flexed forward as if reaching for support.

"Epilepsy--Medical Aspects", Pamphlet developed by Epilepsy Education, University of Minnesota, in cooperation with MINCEP Epilepsy Care, P.A. (Minnesota: University of Minnesota, 1979)(Distributed by the Epilepsy Foundation of America and the Epilepsy Foundation of Hawaii), 6 pp.

"Seizure Recognition and First Aid", Pamphlet developed by the Epilepsy Foundation of America (Maryland: 1989)(Distributed by the Epilepsy Foundation of America and the Epilepsy Foundation of Hawaii), 7 pp.

8. "Nerves", The New Encyclopaedia Britannica, supra note 5.

9. American Medical Association, Drug Evaluations, supra note 3; "Nerves", The New Encyclopaedia Britannica, supra note 5.

10. American Medical Association, Drug Evaluations, supra note 3, p. 171.

According to the American Medical Association:

> Seizures are caused by hyperexcitable neurons. In experimental models, localized hypoxia [a deficiency of oxygen] or cooling, interference with utilization of substrate, alteration of ion permeability, or the topical application of certain chemicals to the brain (eg, cobalt, penicillin, alumina gel) may cause sudden focal hyperexcitability and electrical discharge....
>
> * * *
>
> ...Many antiepileptic drugs prevent the spread of neural excitation rather than suppressing the focus of discharge itself, and normal excitability is generally unaffected by doses that modify idiopathic and electrically or chemically induced local or systemic hyperexcitability. Therefore, the phrase, neuronal membrane stabilizing effect, often is used to describe the overall action of the antiepileptic drugs.

American Medical Association, Drug Evaluations, supra note 3, pp. 169 and 171.

11. American Medical Association, Drug Evaluations, supra note 3, pp. 176-177.

12. American Medical Association, Drug Evaluations, supra note 3, pp. 177-178.

The term "half-life" means "the length of time required for the concentration of the chemical in the body, determined at a given point in time, to be reduced by half. M. Alice Ottoboni, The Dose Makes the Poison (California: Vincente Books, 1984), p. 102.

13. "Nerves", The New Encyclopaedia Britannica, supra note 5, 853.

14. Rosalind Wagner, Telephone interview, supra note 5.

15. Rosalind Wagner, Telephone interview, supra note 5.

16. Rosalind Wagner, Telephone interview, supra note 5.

17. Curtis Klaassen and John Doull, "Evaluation of Safety: Toxicologic Evaluation" in John Doull and others, eds. Casarett and Doull's Toxicology: The Basic Science of Poisons, 2nd ed. (New York: Macmillan Publishing Co., Inc., 1980), p. 15.

    Sensitization to a chemical involves the creation of antibodies by the body's immune systems in response to an antigen. Antigens are formed by the combination of the chemical (an allergen) and an endogenous (originating from within the body) protein. Usually, at least one to two weeks are required for the synthesis of significant amounts of antibodies. Subsequent exposure to the chemical or one similar to it, even in amounts very much smaller than the original sensitizing dose or doses, results in an antigen-antibody interaction which, in turn, provokes the manifestations typically associated with an allergic reaction. Sensitization is distinguishable from irritation, which it can mimic, particularly when the skin is involved. Although irritation and sensitization can result in skin inflammation, irritation is a purely local phenomenon whereas sensitization is a systemic condition. Irritants can produce the same symptoms as allergens if contacted or inhaled; only a physician can determine if symptoms are allergic in nature. Curtis Klaassen and John Doull, "Evaluation of Safety: Toxicologic Evaluation" in John Doull and others eds. Casarett and Doull's Toxicology: The Basic Science of Poisons 2nd ed. (New York: MacMillan Publishing Co., Inc., 1980), p. 15; M. Alice Ottoboni, The Dose Makes the Poison, supra note 12, p. 27.

18. Curtis Klaassen "Principles of Toxicology", in Alfred Goodman Gilman and others eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th ed. (New York: Macmillan Publishing Co., Inc., 1980), p. 1604.

19. Simply stated, an individual's response to a chemical is a function of the dose received; response increases as dose increases. Hypersensitivity or hyperreactivity involves an individual response that is greater than the response predicted by the dose-response curve for that chemical. Overly simplified, a "dose-response curve" is a graphic representation of the relationship between the dose of a chemical administered and the effect produced in a population of "normal" individuals.

20. Klaassen and Doull, supra note 17.

21. Klaassen and Doull, supra note 17.

22. A reaction that is not addressed by the Bureau in this study, but warrants a brief explanation, is chemical idiosyncrasy. "Chemical idiosyncrasy" is:

    > [A] genetically determined abnormal reactivity to a chemical.[citation deleted] The response observed is qualitatively similar to that observed in all individuals but may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of a chemical.

    Klaassen and Doull, supra note 17.

23. U.S., Department of Health and Human Services, Food and Drug Administration, "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, September 29 - October 1, 1986" (Maryland: Dockets Management Office, January 1988)(hereinafter cited as "Task Force Report"), p. 24.

24. U.S., Department of Health and Human Services, "Task Force Report", supra note 23.

25. As discussed in Chapter 2, "pharmaceutical equivalents" are "drug products that contain identical amounts of the identical active drug ingredient, i.e., the same sat [salt] or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the

same inactive ingredients [emphasis added], 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". 21 CFR 320.1(c).

CHAPTER 9

Analyses

Drug Product Selection Board

As previously discussed in Chapter 6, the decision of the Drug Product Selection Board to "continue to allow the substitution of generic counterparts for Depakene, Dilantin, Mysoline, and Tegretol, under chapter 328, part VI [Hawaii Revised Statutes]," was ultimately based on the fact that "by statute, both a physician and/or patient is able to control the specific brand of medication she/he desires." The Board went on to state that:[1]

> Because it [the Board] recognizes the potential problems of switching anti-convulsants from one brand to another, and because anti-convulsant drugs possess an extremely narrow therapeutic range, the board realizes that constant supervision and control of a patient's medication and its manufacturer are imperative.

As also discussed in Chapter 6, the Anticonvulsant Subcommittee of the Drug Product Selection Board stated the following:[2]

> ...There are drugs that should not be substituted because they are not bioequivalent, but it is the physician's responsibility to become educated concerning these drugs.

In contrast, the FDA has stated:[3]

> 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 [emphasis added].
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> ...Evaluations of therapeutic equivalence for prescription drugs are based on scientific and medical evaluations by FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of the FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling [emphasis added]. However, these products may differ in other characteristics such as shape, scoring configuration, packaging, excipients (including colors, flavors,

> preservatives), expiration time, and, in some instances, labeling. If products with such differences are substituted for each other, there is a potential for patient confusion due to differences in color or shape of tablets, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or less patient acceptance of certain products because of flavor. There may also be better stability of one product over another under adverse conditions of storage, allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient.
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> FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician's specification of that product is appropriate [emphasis added]. Pharmacists must also be familiar with the expiration dates and labeling directions for storage of the different products, particularly for reconstituted products, to assure that patients are properly advised when one product is substituted for another.

Two different conclusions can be drawn from the statements of the Drug Product Selection Board and the FDA. The conclusion that can be drawn from the FDA's statements is that anticonvulsant drug products evaluated as therapeutically equivalent can be expected to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. According to the FDA, no adjunctive monitoring[4] of a patient's medication should be required following the substitution of one therapeutically equivalent drug product for another.[5] The conclusion that can be drawn from the Board's statements is that anticonvulsant drug products evaluated as therapeutically equivalent can be expected to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling and accompanied by the retitration of a patient's medication.

According to Melvin Kumasaka, Chairperson of the Drug Product Selection Board, Nadine Bruce, Chairperson of the Anticonvulsant Subcommittee of the Drug Product Selection Board, and Jordan Popper, Chairperson of the Professional Advisory Board of the Epilepsy Foundation of Hawaii, persons with epilepsy can be properly titrated and maintained on generic or brand-name anticonvulsant drug products with good results. According to Kumasaka, Bruce, and Popper, problems associated with toxic or subtherapeutic doses of anticonvulsant drugs can arise when patients are indiscriminately switched from one anticonvulsant drug product to another (i.e., from one manufacturer's product to another) without being retitrated on the substituted drug product. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology expressed similar concerns with respect to the anticonvulsant drugs phenytoin (Dilantin) and Carbamazepine (Tegretol).[6]

Assuming that differences in drug product 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) are

not important in the care of a particular patient, the following question is one to be properly addressed by the Legislature: "Which policy should the Drug Product Selection Board adhere to when evaluating the therapeutic equivalence of anticonvulsant drug products and drug products in other therapeutic classes?" Should the policy be one of requiring therapeutically equivalent drug products to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling? In the alternative, should the policy require therapeutically equivalent drug products to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling and accompanied by adjunctive monitoring of a patient's medication? The Bureau believes that it is this apparent difference, and not the advisability of removing anticonvulsant drug products from the State's drug formulary of equivalent drug products, which should be addressed through legislative action.

If the policy is to require therapeutically equivalent drug products to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling, then the expectation of physicians, pharmacists, and patients should be that adjunctive monitoring of the patient's medication following generic drug substitution is not necessary. If, however, the policy is to require therapeutically equivalent drug products to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling and accompanied by adjunctive monitoring of the patient's medication, then the expectation of physicians, pharmacists, and patients should be that adjunctive monitoring of the patient's medication following generic drug substitution may be necessary depending on the drug product being substituted.

Both the Department of Health[7] and the Hawaii Medical Association[8] have expressed strong reservations about the Legislature removing drug products from the State's drug formulary of equivalent drug products to address the specific concerns of groups such as the Epilepsy Foundation of Hawaii. Therapeutic equivalence evaluations, it is argued, are scientific judgments based upon evidence (albeit somewhat controversial), while generic drug substitution involves social and economic policies intended to reduce the cost of drugs to consumers.

With respect to the question of which policy controls or should control, the statutes appear to be silent on the issue; they only state that:[9]

> ...The formulary shall list all drug products that the Commissioner of Food and Drugs, United States Food and Drug Administration, has approved as safe and effective and has determined to be therapeutically equivalent. The formulary may list additional drug products that are determined by the board to meet requirements adequate to assure product quality and therapeutic equivalence. The formulary may delete approved drugs upon a finding that product quality or therapeutic equivalency or bioequivalency, as appropriate, is not adequately assured.

The standing and conference committee reports that recorded the enactment of the statute which created the State's drug formulary of equivalent drug products were inconclusive.[10] Although it would appear that some of the potential problems caused by the substitution of one therapeutically equivalent anticonvulsant drug product for another could be averted by restricting generic drug substitution when prescriptions were refilled, such a restriction would run contrary to the concepts of "bioequivalence" and "therapeutic equivalence", as articulated by the FDA in the "Orange Book".[11] The establishment of

restrictions on the refilling of certain prescriptions, whether through expressed written instructions or the creation of another formulary, would be tantamount to a statement that certain multiple-source drug products on the State's drug formulary of equivalent drug products were not, in fact, "substitutable".

If the dismissal of this seemingly fatal contradiction can be rationalized, then the Bureau believes that this dispute can be resolved by establishing restrictions on the refilling of prescriptions. These restrictions should include the following elements:

(1) A pharmacist refilling a prescription must dispense the same drug product that was previously used to fill or refill the prescription if the phrase "do not substitute" or "brand medically necessary" has been hand written on the prescription; switching manufacturers is not permitted if substitution has been prohibited;

(2) To prohibit substitution (i.e., the switching of manufacturers) when a prescription is refilled, the prescriber (e.g., a physician) must hand write the phrase "do not substitute" or "brand medically necessary". With respect to a prescription written for a brand-name drug product, this means that only the brand-name drug product can be used to refill the prescription. With respect to a prescription written "generically", i.e., without reference to a proprietary name or specific manufacturer, this means that all subsequent prescriptions must be refilled using the same manufacturer of the drug product that was initially dispensed;

(3) A pharmacist must indicate on the label of the container in which the drug product is sold to the consumer:

(a) The manufacturer of the drug product dispensed; and

(b) The fact that substitution has been prohibited when refilling the prescription;

and

(4) If a pharmacist is unable to refill a prescription using the same manufacturer of the drug product that was previously dispensed, then the pharmacist must obtain permission from the prescriber to substitute or refuse to refill the prescription.

If a separate, additional formulary were created for the purpose of identifying those drug products that could not be substituted when a prescription was refilled, then there would be no need for a prescriber to hand write the phrase "do not substitute" or "brand medically necessary" except where Medicaid prescriptions were concerned. In addition, there would be no need for a pharmacist to indicate the fact that substitution was prohibited when refilling the prescription. A prescriber would, however, have to hand write instructions to the effect that substitution was permitted if, in fact, the prescriber wished to permit substitution when the prescription was refilled.

Two-line Prescription Pad Format

As previously discussed in Chapter 3, a prescriber must write the phrase "do not substitute" to prohibit generic drug substitution on a written prescription. The phrase cannot be preprinted or stamped on the prescription pad. Likewise, a prescriber or an authorized employee of the prescriber must orally order "do not substitute" to prohibit generic drug substitution on a prescription that is ordered orally.[12]

Both the Hawaii Medical Association and the Drug Product Selection Board indicated an interest in adopting a two-signature prescription pad format where a prescriber would sign one line on the prescription pad to prohibit generic drug substitution and another to permit it.[13] The Hawaii Medical Association favors a two-signature prescription pad format over the present prescription pad format since it does not require a prescriber to write the phrase "do not substitute" to prohibit generic drug substitution on written prescriptions. Convenience and recognizing the principal role of the physician in matters of patient care are the primary reasons cited by the Hawaii Medical Association for a two-signature prescription pad format. The Drug Product Selection Board's interest in the two-signature prescription pad format represents an attempt to reach a compromise with the Epilepsy Foundation of Hawaii over the removal of the anticonvulsant drugs from the State's drug formulary of equivalent drug products.

While a two-signature prescription pad format would relieve prescribers from having to write the phrase "do not substitute" to prohibit generic drug substitution on written prescriptions, it would not relieve prescribers from having to write the phrase "brand medically necessary" to meet federal Medicaid requirements. According to the U.S. Department of Health and Human Services,[14] the phrase "brand medically necessary" or "medically necessary" must be written in the prescriber's own hand to be valid. The phrase cannot be preprinted or stamped on the prescription pad, nor can it abbreviated. As previously discussed in Chapter 7, where state and federal Medicaid requirements differ, it is the federal requirement that takes precedence.

While a two-signature prescription pad format would alleviate prescribers from having to write the phrases "do not substitute" and "brand medically necessary" to meet state and federal requirements when prohibiting generic drug substitution on prescriptions written for Medicaid patients, the same result can be obtained by amending the State's generic drug substitution law to permit prescribers to write either "do not substitute" or "brand medically necessary" to prohibit generic drug substitution on written prescriptions. Of the arguments advanced in favor of a two-signature prescription pad format, none is more compelling than recognizing the principal role of the prescriber in matters of patient care. The FDA has stated that "[t]he 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".[15]

If prescribers are ultimately responsible for the drug products dispensed to their patients, should the onus be on the prescriber to write the phrase "do not substitute" to prohibit generic drug substitution, or should the prescriber have the right to permit or prohibit generic drug substitution by signing one of two preprinted signature lines on a prescription pad?[16]

Arguably, if a prescriber is ultimately responsible for the drug products dispensed to the prescriber's patients, then the prescriber should have the ultimate authority to either

permit or prohibit generic drug substitution. The choice of a two-signature prescription pad represents the "middle ground" between antisubstitution legislation, where generic drug substitution is prohibited unless otherwise noted, and prosubstitution legislation, where generic drug substitution is permitted unless otherwise noted.

Unlike those decisions regarding the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products, the choice of prescription pad formats is a decision that should be made by the Legislature and not left the Drug Product Selection Board.

The Bureau believes that convenience, by itself, does not warrant the adoption of a two-signature prescription pad format. Rather, the Bureau believes that a two-signature prescription pad format would be warranted if it were being adopted to preclude charges of negligence arising out of acts of omission. For example, in the State of Ohio:[17]

> (D) The failure of a prescriber to restrict a prescription by specifying "dispense as written," or "D.A.W.," pursuant to division (A)(1) of this section shall not constitute evidence of the prescriber's negligence unless the prescriber had reasonable cause to believe that the health condition of the patient for whom the drug was intended warranted the prescription of a specific brand name drug and no other. No licensed prescriber shall be liable for civil damages or in any criminal prosecution arising from the interchange of a generically equivalent drug for a prescribed brand name drug by a pharmacist, unless the prescribed brand name drug would have reasonably caused the same loss, damage, injury, or death.

An advantage of a two-signature prescription pad format is that it would preclude charges of negligence arising out of acts of omission since a prescriber would have to sign one of the two preprinted lines on the prescription pad to make the prescription valid, i.e., the prescriber signs either on the line that prohibits generic drug substitution or on the line that permits generic drug substitution, but not both. The Bureau notes, however, that a two-signature prescription pad format would not necessarily preclude charges of negligence arising out of acts of commission, i.e., signing the line that permits generic drug substitution when, in fact, the prescriber intended to sign the line that prohibits generic drug substitution. Again, the same results (i.e., protecting prescribers from charges of negligence arising out of acts of omission) could be obtained by amending the State's generic drug substitution law to protect prescribers from these charges unless the prescriber had reasonable cause to believe that the health condition of the patient for whom the drug product was intended warranted the dispensing of a brand-name drug product and not a therapeutically equivalent generic drug product. The adoption of a two-signature prescription pad format would not be necessary to provide prescribers with this kind of protection if, in fact, it were needed.

The Bureau believes that the most compelling reason for not adopting a two-line prescription pad format is that "[a] very low percentage of prescriptions include prohibition of substitution with explicit handwritten instructions such as 'D.A.W.' [Dispense As Written] or 'N.S.' [No Substitution]; however, two-signature line methods result in substantial prohibition of substitution".[18]

It follows logically that the more often prescribers prohibit generic drug substitution, the fewer opportunities pharmacists have to practice generic drug substitution. Assuming

that the amount of generic prescribing (i.e., prescribing without specifying a proprietary name or manufacturer) remains constant as prescribers prohibit generic drug substitution with increasing frequency, total cost-savings due to generic drug use would decrease.[19]

The Bureau believes that the relevant policy-related issues that warrant further consideration by the Legislature at this time are:

(1) Whether or not recognizing the principal role of a prescriber in matters of patient care is sufficient reason for adopting a two-signature prescription pad format. If not, then;

(2) Whether or not the State's generic drug substitution law should be amended to permit prescribers to write either "do not substitute" or "brand medically necessary" to prohibit generic drug substitution on written prescriptions; and

(3) Whether or not the State's generic drug substitution law should be amended to protect prescribers from charges of negligence arising out of acts of omission, unless the prescriber had reasonable cause to believe that the health condition of the patient for whom the drug product was intended warranted the dispensing of a brand-name drug product and not a therapeutically equivalent generic drug product.

The Bureau believes that amending the State's generic drug substitution law for the convenience of prescribers is not warranted at this time, and that amending the State's generic drug substitution law to reach a compromise with a particular group would be ill-advised as public policy.

Allergies

As previously discussed in Chapter 8, allergic reactions are not usually dose-dependent; therefore, a lack of bioavailability, bioequivalence, or therapeutic equivalence between two or more multiple-source drug products is not likely to precipitate the onset of this potentially life-threatening condition. Although allergic reactions can be precipitated by chemicals that are structurally dissimilar (i.e., not structurally identical), allergic reactions precipitated by generic drug substitution would most likely be caused by inactive ingredients in the drug products that were substituted for the drug products prescribed, and not the active ingredients in either drug product. As previously discussed in Chapter 2, pharmaceutical equivalents do not necessarily contain the same inactive ingredients.

Allergic reactions can be very rare or very common depending on the allergen involved. As pointed out by M. Alice Ottoboni:[20]

> It is probable that any chemical is capable of causing an allergic reaction in some rare individual somewhere in the world, but there are some chemicals that cause sensitization in a significant portion of the people with whom they come in contact. Examples of such substances are pollens of all varieties, epoxy resin components, orris root, and formaldehyde. Orris root was used many years ago as a base for face powder until its allergenic properties were recognized. Formaldehyde has long been recognized as a sensitizer in occupational settings, but it was not known that

> the general public had any significant exposure to formaldehyde until its relatively recent identification as a component of indoor air pollution....
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> As pointed in the report of the FDA's Bioequivalence Task Force:[21]
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> ...The potential for adverse reaction from so-called inactive excipients is rare [citation deleted].
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> The Task Force agrees that the rare incidence of allergies and toxicity to excipients may pose a problem for a few patients. Information on excipients for all drug products is currently being addressed by the Pharmaceutical Manufacturers Association (PMA) and the Proprietary Association (PA) with their voluntary labeling guidelines and this information will help enable patients to be alerted to an allergenic potential.

Because allergic and other toxic reactions to inactive excipients or inactive ingredients are reportedly rare, and because allergic reactions are not usually dose-dependent or necessarily chemical-specific, the Bureau believes that the risks posed by allergic and other toxic reactions should be handled on an individual, case-by-case, basis. For example, the Bureau believes that the drug industry's voluntary labeling program[22] to help alert patients to the potential of allergic reactions should be integrated with the State's generic drug substitution law since pharmacists, and not their patients, ultimately select the therapeutically equivalent generic drug products to be substituted for the brand-name drug products prescribed.

A pharmacist in the State of New Jersey, with the permission of the prescriber, is required to substitute a therapeutically equivalent drug product for the drug product prescribed if "the pharmacist's patient profile record discloses drug sensitivity, allergies or adverse reactions to the drug product prescribed".[23] Utilizing the concept of patient profile records, it would appear that integration of the drug industry's voluntary labeling program and the State's generic drug substitution law can be accomplished if, at the very minimum, pharmacists are permitted to refuse to substitute when the pharmacist's patient profile record discloses the potential for an allergic or other adverse reaction to an inactive ingredient in the therapeutically equivalent generic drug product to be substituted for the brand-name drug product prescribed.

If one accepts a pharmacist's decision to refuse to substitute in the foregoing situation as a prudent exercise in professional judgment, then one must ask: "Should a pharmacist be permitted to refuse to substitute only in situations where the pharmacist's patient profile record discloses the potential for an allergic or other adverse reaction to an inactive ingredient in the therapeutically equivalent generic drug product to be substituted for the brand-name drug product prescribed?" If the answer to the foregoing is "no", then one must next ask: "Should a pharmacist be permitted to refuse to substitute under other circumstances if, in the pharmacist's professional judgment, generic drug substitution is not in the best interest of the consumer?"

The Bureau notes that generic drug substitution may not be in the best interest of a consumer or a pharmacist if the pharmacist and the consumer are unable to effectively

communicate with one another. If a pharmacist and a consumer cannot effectively communicate with one another, how does the pharmacist obtain an informed consent to substitute? Effective communication would seem to be a prerequisite to informed consent. The Bureau notes that pharmacists are not fluent in all languages, whether written, spoken, or signed, and that there are a substantial number of persons in Hawaii who are illiterate in English. In addition, the Bureau notes that the concept of generic drug substitution may be totally incomprehensible and, consequently, unacceptable to other persons. The State's generic drug substitution law assumes, perhaps incorrectly, that everyone in Hawaii is either fluent or literate in English and capable of comprehending the concept of therapeutic equivalence.

At the very minimum, the Bureau believes that a pharmacist refusing to substitute should be required to:

(1) Inform the consumer of the pharmacist's decision not to substitute, including an explanation of why the pharmacist is refusing to substitute;

(2) Notify the prescriber of the pharmacist's decision not to substitute, including an explanation of why the pharmacist refused to substitute;

(3) Keep a separate record of the pharmacist's decisions not to substitute, including an explanation of why the pharmacist refused to substitute, and to make this record available for inspection by the Drug Product Selection Board or the Department of Health; and

(4) Make periodic reports to the Drug Product Selection Board or the Department of Health concerning the pharmacist's decisions not to substitute, as either may require.

At the very minimum, the Bureau also believes that the Drug Product Selection Board, in consultation with the Board of Pharmacy, should be required to:

(1) Adopt rules to standardize recordkeeping and reporting requirements concerning a pharmacist's decision not to substitute;

(2) Periodically review records or reports concerning a pharmacist's decision not to substitute; and

(3) Inform pharmacists and prescribers of changes in the State's generic drug substitution law and the recordkeeping and reporting requirements established by administrative rule.

Based on the foregoing discussion, the following policy question should be addressed: "Should a pharmacist be permitted to refuse to substitute when the pharmacist's patient profile record discloses the potential for an allergic or other adverse reaction to an inactive ingredient in the therapeutically equivalent generic drug product to be substituted for the brand-name drug product prescribed?" If the answer to the foregoing is "yes", then the next policy question to be addressed is: "Should a pharmacist be permitted to refuse to substitute under other circumstances if, in the pharmacist's professional judgment, generic drug substitution is not in the best interest of the consumer?"

Admittedly, such a change in the State's generic drug substitution law may create conflicts between pharmacists who refuse to substitute, consumers who do not want to pay for higher priced brand-name drug products, prescribers who are not accepting of pharmacists who question their professional judgment, and third-party insurers who have established upper limits of payment for certain prescription reimbursements or incentive programs to promote generic drug substitution (e.g., Medicaid, the Hawaii Dental Service, and the Hawaii Medical Service Association).

With respect to conflicts between pharmacists who refuse to substitute and consumers who do not want to pay for higher priced brand-name drug products, the Bureau believes that consumers are free to take their business to another pharmacist and will do so if the cost of purchasing a more expensive brand-name drug product outweighs the potential risks of generic drug substitution.

With respect to conflicts between pharmacists who refuse to substitute and prescribers who are not accepting of pharmacists who question their professional judgment, the Bureau believes that prescribers can avoid conflicts over generic drug substitution by prescribing "generically", or hand writing the phrase "do not substitute". As previously discussed in Chapter 1, drug product selection leaves the choice of the drug product dispensed (whether a brand-name or a generic) to the pharmacist. In the case where a prescriber hand writes the phrase "do not substitute", the pharmacist can either dispense the prescription as written or refuse to dispense the prescription if dispensing the prescription would not be in the consumer's best interest.

With respect to conflicts between consumers and pharmacists, and private third-party insurers caused by pharmacists who refuse to substitute, the Bureau believes that it is in the best interest of the insurer and the pharmacist and the consumer if an allergic or other adverse reaction precipitated by generic drug substitution can be reasonably avoided. Private insurers are in a position to decide whether or not a pharmacist's decision not to substitute was warranted and to make exceptions to their reimbursement schedules. Private insurers are also in a position to decide which pharmacies are eligible to participate in their respective prescription drug programs and to disqualify participating pharmacies that abuse or misuse the law and mislead consumers.[24]

With respect to conflicts between pharmacists who refuse to substitute and the State's Medicaid prescription drug program (a public third-party insurer that has established upper limits of payment for certain prescription reimbursements to promote generic drug substitution), the Bureau believes that pharmacists can avoid losses in income due to federal upper limits[25] by informing Medicaid patients of the pharmacist's decision to refuse to substitute and instructing the patient to return to the prescriber for a prescription that prohibits generic drug substitution. As previously discussed in Chapter 7, the federal Medicaid rules require prescribers to hand write the phrase "brand medically necessary" or "medically necessary" to prohibit substitution. Pharmacists who insist on dispensing more expensive brand-name drug products in the absence of such a prohibition are reimbursed at the same rate as pharmacists who substitute less expensive, therapeutically equivalent generic drug products for the brand-name drug products prescribed.

Generic Drug Approval

As previously discussed in Chapter 5, the Bureau believes that legislation which duplicates the FDA's generic drug approval process should be considered in light of what is to be gained by such an endeavor. While the generic drug scandal has undoubtedly tarnished the FDA's image and raised justifiable questions about the agency's ability to effectively carry out its appointed duties, the Bureau does not believe that a wholesale condemnation of the agency's credibility and competence is warranted. Unless it can be clearly demonstrated that the State of Hawaii is willing and able to establish a generic drug approval process on its own, the Bureau does not believe that legislation which duplicates the FDA's generic drug approval process would be in the best interest of the State.

In addition to diverting valuable resources away from other health programs, such a program, if understaffed or underfunded, could become the source of another generic drug scandal. As previously discussed in Chapter 5, with the power and authority to regulate an activity comes the responsibility for appropriating and allocating the necessary resources to enable government to effectively carry out its appointed duties. In arguing the merits of this particular point, it may be helpful to remember that the acceptance of illegal gratuities was just one aspect of the generic drug scandal. The other aspects of the generic drug scandal appeared to be attributable in one way or another to a lack of adequate resources and personnel.

Cause of Action. If the ultimate goal of the Legislature is to deter fraud and deceit or to award reparations to persons who purchase a drug product approved through fraud or deceit, then the Bureau recommends that the Legislature consider establishing a cause of action[26] to enable persons who consume a drug product approved through fraud or deceit to seek reparations from the company that perpetrated the fraud or deceit. At the very minimum, the cause of action should:

(1) Enable persons, including third parties, to initiate an action in a circuit court and to seek reparations from a company without having to demonstrate that any material harm resulted from the consumption of the drug product;

(2) Establish a minimum award, in addition to attorneys' fees and court costs, for persons who can demonstrate that they purchased the drug product, even if they cannot demonstrate that any material harm resulted from the consumption of the drug product;

(3) Enable persons to initiate an action based on a finding by the FDA or the State of Hawaii that a company obtained approval for the drug product through fraud or deceit; and

(4) Require a company to establish and maintain a trust fund to indemnify the State of Hawaii against future claims which may arise from the fraud or deceit.

Establishing such a cause of action may act as a deterrent to companies that contemplate fraud or deceit by exposing them to potentially ruinous litigation precipitated by many individual lawsuits. The proceeds from the judgments would be paid to the consumers themselves, unlike a fine which would be paid to the State, and the liability of the drug company would increase in direct proportion to the commercial success of the product for which approval was obtained through fraud or deceit--the greater the sales, the greater the potential liability. The establishment of such a cause of action would also have the added

advantage of indemnifying the State against claims for material harm resulting from the consumption of the drug product.

The Board and the Hawaii Administrative Procedure Act. As previously discussed in Chapter 3, the Board is presently allowed, without regard to chapter 91, Hawaii Revised Statutes (the Hawaii Administrative Procedure Act), to establish in the State's drug formulary of equivalent drug products those equivalent drug products that the Commissioner of Food and Drugs of the United States Food and Drug Administration, has approved as safe and effective and has determined to be therapeutically equivalent. Although the State's drug formulary is allowed to:

(1) List additional drug products that are determined by the Board to meet requirements adequate to assure product quality and therapeutic equivalence; and

(2) Delete approved drug products upon a finding that product quality or therapeutic equivalency or bioequivalency, as appropriate, is not adequately assured;

it is unclear whether or not these actions are also exempt from chapter 91.

Aside from the question of which Board actions are exempt from the requirements of chapter 91, Hawaii Revised Statutes, are the potential problems of notice and information to the public caused by that blanket exemption. While considerations of speed, efficiency, and convenience make it appropriate to exempt certain Board rulemaking actions regarding the State's drug formulary of equivalent drug products from the relatively time consuming public notice, public hearing, and (possibly) gubernatorial approval requirements of chapter 91, it is less clear what function is served by exempting these actions from the requirement of filing the rules in their final form in the Office of the Lieutenant Governor.

Generally, state agency rules must be on file at the Lieutenant Governor's office in order to have the force and effect of law. The filing requirement provides an element of certainty: a particular version of the rules is either on file at the Lieutenant Governor's office or it is not. The fact that the Board presently files copies of the State's drug formulary of equivalent drug products at the Lieutenant Governor's office does not provide any certainty other than the existence of that particular version of the State's drug formulary. Because certain rulemaking actions regarding the State's drug formulary are completely exempt from chapter 91, Hawaii Revised Statutes, and hence the filing requirements, a more current version of the State's drug formulary adopted by the Board, located elsewhere, would be controlling whether or not anyone outside the Board knew of its existence. The Legislature can allow rules or changes thereto to be adopted in an expedited manner without these conceptual difficulties by limiting exemptions from chapter 91 to exemptions from the public notice, public hearing, gubernatorial approval, and waiting period requirements.

The Board presently conducts "meetings" before deciding whether or not to delete drug products from the State's drug formulary of equivalent drug products. (For reasons to be discussed in this chapter, the listing of additional drug products not contained in the FDA's "Orange Book" is presently a moot point.) At these meetings, interested persons are afforded the opportunity to present testimony concerning the bioavailability, bioequivalence, and therapeutic equivalence of drug products. The meetings are not conducted in accordance with chapter 91, Hawaii Revised Statutes.[27] The Senate standing committee report accompanying the enactment that exempted certain Board actions from chapter 91 indicates

that this exemption may have only been intended to "eliminate the requirement that public hearings be held when the Board is merely adopting the recommendations of the Federal Food and Drug Administration...", and that "hearings would still be held for cases in which the Board chooses to delete or add drugs contrary to FDA recommendations".[28]

Because of questions regarding the extent to which the State's drug formulary of equivalent drug products is allowed to list additional drug products and to delete approved drug products without regard to chapter 91, Hawaii Revised Statutes, the Bureau recommends that the Legislature use this opportunity to:

(1) Clarify whether or not the listing of additional drug products and the deletion of approved drug products is subject to chapter 91, totally exempt from chapter 91, or exempt from the public notice and public hearing requirements of chapter 91; and

(2) Amend the State's generic drug substitution law to permit the Board to establish in the State's drug formulary those drug products that the Commissioner of Food and Drugs has approved as safe and effective and has determined to be therapeutically equivalent, without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, rather than exempting the Board from all the requirements of chapter 91. To avoid untimely delays in the implementation and enforcement of these amendments to the State's drug formulary, the Bureau recommends that the Legislature permit the amendments to become effective immediately upon filing with the Office of the Lieutenant Governor without the need for gubernatorial approval.

Federal Inaction. The Bureau believes that if the Drug Product Selection Board continues to list in the State's drug formulary of equivalent drug products only those drug products contained in the FDA's "Orange Book", then there may be no need for legislation that provides for "the removal of pharmaceutical companies from the State Drug Formularies, where approval from the FDA has been obtained improperly, until the safety and effectiveness of their generic drug products can be proven".[29] Assuming that the FDA would take prompt action to remove these pharmaceutical companies from the "Orange Book" as soon as the pharmaceutical companies admitted their guilt or were found guilty in administrative hearings, it is unclear what, if anything, this legislation would accomplish.

If the Legislature is concerned that the FDA may fail to take prompt action to remove these pharmaceutical companies or their drug products from the "Orange Book" once the pharmaceutical companies admit their guilt or are found guilty in administrative hearings, the Bureau recommends that the Drug Product Selection Board be allowed to remove improperly approved (i.e., approved through fraud or deceit) drug products from the State's drug formulary of equivalent drug products without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, Hawaii Revised Statutes, and that the Legislature allow the removals to take effect upon filing with the Office of the Lieutenant Governor.

The Bureau recommends that the Drug Product Selection Board's authority under these circumstances be limited to the removal of individual drug products since the removal of pharmaceutical companies and entire lines of drug products from the State's drug formulary of equivalent drug products could potentially affect drug products that were not approved through fraud or deceit, and subject persons who rely on the availability of less expensive, therapeutically equivalent generic drug products to personal hardships. The

Bureau notes that the State's Medicaid program could be particularly affected by the removal of entire lines of drug products from the State's drug formulary since the federal Health Care Financing Administration utilizes the FDA's "Orange Book", and not the State's drug formulary, when it determines the aggregate upper limits of payment for multiple source drug products.

While the generic drug scandal has raised justifiable concerns about the FDA's ability and willingness to act swiftly to remove drug products from the "Orange Book" where approval was obtained improperly, the Bureau believes that the question to be asked here is: "Can the State do a better job of regulating the generic drug approval process than the FDA?" The Bureau is aware of at least two bills, H.R. 4810 (Dingell) and S. 2683 (Hatch),[30] that were introduced in the Congress to impose sanctions and other penalties for illegal activities involving the approval of drugs under section 505(j) of the Federal Food, Drug, and Cosmetic Act (relating to Abbreviated New Drug Applications).[31]

Addition of Drug Products not in the "Orange Book". If the Drug Product Selection Board is contemplating the addition of drug products to the State's drug formulary of equivalent drug products that are not contained in the FDA's "Orange Book" (i.e., pre-1938 drugs and drugs still undergoing DESI review),[32] the Bureau recommends that the State's generic drug substitution law be amended to give the Board explicit authority to remove these drug products from the State's drug formulary in cases of fraud or deceit, without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, Hawaii Revised Statutes, and that these removals be allowed to become effective immediately upon filing with the Office of the Lieutenant Governor.

Defrauding or Deceiving the Board. Another compelling reason for adopting legislation to remove drug products from the State's drug formulary of equivalent drug products in cases of fraud or deceit would be that the Board must periodically conduct meetings to determine whether or not a drug product contained in the FDA's "Orange Book" should be removed from the State's drug formulary. Because an action before the Board may be initiated by any person, the Board could conceivably hear testimony from the manufacturer of the drug product in question, the manufacturers' competitors, pharmacologists, pharmacists, patient advocacy and consumer groups, insurance companies, government agencies, professional associations, physicians and their patients.

Because every decision of the Board has the potential to cause adverse health and economic impacts, the Bureau believes that the Board should be given the authority to:

(1) Remove a drug product from the State's drug formulary of equivalent drug products, whether or not the drug product is contained in the FDA's "Orange Book", without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, Hawaii Revised Statutes; and

(2) Bar a person from addressing the Board or bringing actions before the Board in the future;

if the Board, a county prosecuting attorney, or the Attorney General finds that the person knowingly made false or misleading statements to the Board either in support of or opposition to the removal or addition of a drug product to the State's drug formulary. The Bureau believes that all persons who knowingly make false or misleading statements to the Board should be subject to similar sanctions.

Summary. Based on the foregoing discussion, the following policy questions should be addressed:

(1) Should the Drug Product Selection Board be allowed to remove drug products from the State's drug formulary of equivalent drug products where approval from the FDA has been obtained through fraud or deceit, without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, Hawaii Revised Statutes?

(2) Should a cause of action be established to deter fraud and deceit or to award reparations to persons who consume drug products approved through fraud or deceit?

(3) Should the Drug Product Selection Board be given the authority to:

(a) Remove a drug product from the State's drug formulary of equivalent drug products, whether or not the drug product is contained in the FDA's "Orange Book", without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91; and

(b) Bar a person from addressing the Board or bringing actions before the Board in the future;

if the Board, a county prosecuting attorney, or the Attorney General finds that the person knowingly made false or misleading statements to the Board?

ENDNOTES

1. Letter from Melvin Kumasaka, Chairperson of the Drug Product Selection Board to various individuals informing them of the Board's decision to continue to allow the substitution of anticonvulsant drugs, November 30, 1989, p. 1.

2. Hawaii, Department of Health, Drug Product Selection Board, "Anticonvulsant Subcommittee Report for the Drug Product Selection Board" (no date), 1 p.

3. U.S., Department of Health and Human Services, Food and Drug Administration, Approved Drug Products with Therapeutic Equivalence Evaluations, 10th ed. (Washington, D.C.: U.S. Government Printing Office, 1990)(hereinafter cited as "Orange Book"), pp. 1-1 to 1-3.

4. The Bureau's use of the term "adjunctive monitoring" is intended to denote monitoring of a patient that is in addition to or in excess of monitoring that would normally be required had generic drug substitution not occurred.

5. Telephone interview with Tom McGinnis, Special Assistant to the Director, Office of Generic Drugs, U.S., Department of Health and Human Services, Food and Drug Administration, August 28, 1990.

6. Telephone interview with Melvin Kumasaka, Chairperson, Drug Product Selection Board, August 24, 1990.

   Telephone interview with Nadine Bruce, Member, Drug Product Selection Board, August 27, 1990.

   Interview with Jordan Popper, Chairperson, Professional Advisory Board, Epilepsy Foundation of Hawaii; David Hornshuh, President, Hawaii Pharmaceutical Association; and Rosalind Wagner, Executive Director, Epilepsy Foundation of Hawaii, August 13, 1990.

"Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology", Neurology, Vol. 40 (November 1990), p. 1642.

7. Interview with Peter Sybinsky, Deputy Director of Health Resources, Department of Health, and member of the Drug Product Selection Board (representing John Lewin, Director of Health), July 26, 1990.

8. Interview with Rebecca Kendro, Assistant Executive Director, Hawaii Medical Association, Steve Wallach, Frederick Reppun, and John Kim, President, Hawaii Medical Association, August 14, 1990.

9. Hawaii Rev. Stat., sec. 328-96(a).

10. Senate Standing Committee Report No. 15-80 on Senate Bill No. 2134, Journal of the Senate of the Tenth Legislature (1980), pp. 1027-1028.

    House Standing Committee Report No. 504-80 on Senate Bill No. 2134-80, H.D. 1, Journal of the House of Representatives of the Tenth Legislature (1980), pp. 1498-1499.

    Conference Committee Report No. 4-80 on Senate Bill No. 2134-80, H.D. 1, Journal of the Senate of the Tenth Legislature (1980), pp. 938-940.

    House Standing Committee Report No. 513-82 on House Bill No. 2057, H.D. 1, Journal of the House of Representatives of the Eleventh Legislature (1982), pp. 1125-1126.

    Senate Standing Committee Report No. 695-82 on House Bill No. 2057-82, Journal of the Senate of the Eleventh Legislature (1982), p. 1243.

    Conference Committee Report No. 28-82 on House Bill No. 2057-82, H.D. 1, S.D. 1, Journal of the House of Representatives of the Eleventh Legislature (1982), p. 829.

    House Standing Committee Report No. 292-86 on House Bill No. 1995-86, H.D. 1, Journal of the House of Representatives of the Thirteenth Legislature (1986), p. 1122.

    Senate Standing Committee Report No. 541-86 on House Bill No. 1995-86, H.D. 1, Journal of the Senate of the Thirteenth Legislature (1986), pp. 1024-1025.

11. U.S., Department of Health and Human Services, "Orange Book", supra note 3, p. v. See Chapter 4, The "Orange Book".

12. Hawaii Rev. Stat., sec. 328-92(b).

13. Kendro, Wallach, Reppun, and Kim, Interview, supra note 8.

    Meeting of the Drug Product Selection Board, July 6, 1990.

14. Telephone interview with Pete Rodler, Senior Program Analyst, Medicaid Bureau, U.S., Department of Health and Human Services, Health Care Financing Administration, September 4, 1990.

15. 44 FR 2937, Jan. 12, 1979.

    The FDA has also stated that "FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients". U.S., Department of Health and Human Services, "Orange Book", supra note 3, p. 1-2.

16. It is important to note that the Hawaii Medical Association is not opposed to generic drug substitution; the Hawaii Medical Association, in fact, supports generic drug substitution and

efforts to contain the cost of health care in Hawaii. Kendro, Wallach, Reppun, and Kim, Interview, supra note 8.

17. Ohio Rev. Code, sec. 4729.38(D).

18. Carolee Devito and others, "A Summary of What We Know and Don't Know About Generic Drug Substitution Laws", in Theodore Goldberg and others, eds. Generic Drug Laws: A Decade of Trial--A Prescription for Progress. U.S., Department of Health and Human Services, National Center for Health Services Research and Health Care Technology Assessment, NCHSR Report No. 86-30 (Virginia: National Technical Information Service, 1986), p. 492.

According to the Federal Trade Commission:

> A recent summary of results from four states surveyed by the Goldberg team [1981] draws the following conclusions [footnote deleted]:
>
> 1. The two-signature-line prescription form leads to much more frequent physician prohibition of substitution than when prescribers are required to write out a phrase such as "Dispense as Written." In Rhode Island, with a two-line form, physicians prohibited substitution 38 percent of the time, in contrast to a rate of 5 percent or less in states requiring a handwritten statement of prohibition (about 5 percent of multi-source prescriptions in Michigan, about 1.5 percent in Wisconsin, and less than 1.5 percent in Vermont.)
>
> * * *
>
> A second cross-state analysis has been reported by Richard Zeich [1984] who uses data from 1000 retail pharmacies nationwide sampled in the Market Measures National Substitution Audit [footnote deleted]. Some of Zeich's results are at odds with those of Goldberg and Devito [1981]:
>
> 1. Substitution took place on 6.7 percent of new prescriptions in states with single-line prescription forms but on only 4 percent in states with two-line forms. (Substitution was also found to be increasing over time in one-line states but not as much in two-line states.) This appeared to be the result of the difference in the incidence of physician prohibition of substitution: 5 percent of new prescriptions in one-line states but 60 to 70 percent in two-line states [footnote deleted].
>
> * * *
>
> These studies are in agreement with respect to the effects of the two-line prescription pad; they disagree about the effects of mandatory provisions and about the superiority of a positive formulary.
>
> * * *
>
> The format of the prescriber's prescription pad is very powerful; a format which makes it very convenient for the physician to prohibit substitution is associated with significantly lower levels of substitution....

Alison Mason and Robert Steiner, Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws, Staff Report of the Bureau of Economics, Federal Trade Commission (Washington, D.C.: U.S. Government Printing Office, October 1985), pp. 106-107.

According to Market Measures, Inc., physician's prohibited generic drug substitution 43 percent of the time in "two-line" states (i.e., states that allow physicians to prohibit substitution by signing on the appropriate line or checking a box), as opposed to 12 percent of the time in states where the phrase "D.A.W." (Dispense As Written), or other similar

phrases, had to be hand written to prohibit generic drug substitution. Market Measures, "National Substitution Audit--12 Months Ending March 1990" (Market Measures, Inc., 449 Mt. Pleasant Avenue, West Orange, New Jersey 07052).

According to the National Pharmaceutical Council, the following states and the District of Columbia require a prescriber to hand write the phrase "do not substitute", "dispense as written, "medically necessary", or some other similar phrase or abbreviation of a similar phrase, to prohibit generic drug substitution: Connecticut; Florida; Georgia; Hawaii; Kentucky; Maryland; Massachusetts; Michigan; Minnesota; Montana; Nebraska; New Hampshire; New Mexico; New York; North Dakota; Ohio; Oregon; Pennsylvania; Vermont; West Virginia; and Wisconsin.

The states of Alabama, Arizona, Delaware, Idaho, Indiana, Iowa, Kansas, Louisiana, Mississippi, Missouri, North Carolina, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Washington, and Wyoming permit a prescriber to sign on a "Dispense As Written" line to prohibit generic drug substitution.

The states of Alaska, Arkansas, California, Colorado, Illinois, Maine, Nevada, and New Jersey permit a prescriber to initial or check a box next to an appropriately worded statement to prohibit generic drug substitution.

The states of Alaska, Arkansas, California, Colorado, Iowa, Kansas, Louisiana, Maryland, Mississippi, and North Carolina permit a prescriber to prohibit generic drug substitution through more than one mechanism. The state of Oklahoma prohibits substitution without the permission of either prescriber or purchaser.

"How to Protect Your Prescriptions From Substitution (Effective as of April 1990)", pamphlet published by the National Pharmaceutical Council (1894 Preston White Drive, Reston, Virginia 22091), 8 pp.

19. A decrease in cost-savings due to generic drug substitution could be partially offset by an increase in the amount of generic prescribing since generic prescribing leaves the selection of the drug product to be dispensed to the discretion of the pharmacist.

20. M. Alice Ottoboni, The Dose Makes the Poison (California: Vincente Books, 1984), p. 27.

21. U.S., Department of Health and Human Services, Food and Drug Administration, "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, September 29 - October 1, 1986" (Maryland: Dockets Management Office, January 1988)(hereinafter cited as "Task Force Report"), p. 24.

22. Pharmaceutical Manufacturers Association, "Guidelines for Identification of Inactive Ingredients in Oral Dosage Form Prescription Drug Products" (Washington, D.C.: December 5, 1984), 5 pp.; Generic Pharmaceutical Industry Association, "G.P.I.A. Guidelines for Disclosure and Labeling of Inactive Ingredients" (New York: no date), 2 pp. See Chapter 6, note 25.

23. New Jersey Stat. Ann., sec. 24:6E-8.

The statute, which is entitled **"Prescriptions; dispensation of substitute drug for drug not on latest list of interchangeable drug products; reasons; approval of prescriber"**, states:

> Notwithstanding any other law, where a different brand name or nonbrand name drug product of the same established name shall reflect a lower cost to the consumer and no drug product of such established name is included in the latest list of interchangeable drug products published by the council, or where in the professional judgment of the pharmacist there is no valid proof of efficacy for the drug product prescribed, or the pharmacist's patient profile record discloses drug sensitivity, allergies or adverse reactions to the drug product prescribed [emphasis added], or there exists a more appropriate drug product than the drug product prescribed, a

> different brand name or nonbrand name drug product shall be dispensed by the pharmacist, provided, however, that such action by a pharmacist shall be authorized only if in each case the pharmacist notifies the prescriber of the drug product to be dispensed and the name of the manufacturer thereof, and receives the approval of the prescriber to substitute such drug product for the drug product prescribed. The pharmacist shall be required to indicate on the prescription the date and time of the prescriber's approval and whether the approval was communicated orally or in writing.

24. According to the Hawaii Medical Service Association (HMSA), the Association will be implementing a post-claim drug utilization review program to monitor the past prescribing and dispensing activities of HMSA-participating prescribers and pharmacists. Telephone interview with Roy Yamauchi, Manager of Pharmacy Benefits, Hawaii Medical Service Association, September 17, 1990.

25. 42 CFR 447.331, 447.332, 447.333, and 447.334. See Chapter 7, Mandated Substitution.

26. The term "cause of action" means:

> The fact or facts which give a person a right to judicial relief. The legal effect of an occurrence in terms of redress to a party to the occurrence. A situation or state of facts which would entitle [a] party to sustain action and give him [a] right to seek a judicial remedy in his behalf.

Henry Black, Black's Law Dictionary, Abridged 5th ed. (Minnesota: West Publishing Co., 1983), p. 114.

27. Telephone interview with Peter Sybinsky, supra note 7, December 4, 1990.

28. Senate Standing Committee Report No. 541-86 on House Bill No. 1995-86, H.D. 1, Journal of the Senate of the Thirteenth Legislature (1986), pp. 1024-1025.

29. Senate Concurrent Resolution No. 242, S.D. 1, Fifteenth Legislature, 1990, State of Hawaii.

30. H.R. 4810, 101st Congress, 2nd Session; S. 2683, 101st Congress, 2nd Session.

31. Congress reportedly did not approve either bill. Representative Dingell's bill (H.R. 4810) would have provided the FDA, through the U.S. Secretary of Health and Human Services, with additional enforcement authority over misconduct relating to approvals of generic drugs. Representative Dingell and the bill's other sponsors limited the scope of the bill to generic drugs. The Administration's bill (S. 2683), in contract, would have given the FDA additional enforcement authority over manufacturers of all products subject to its jurisdiction. Lewis Engman and others, Generic Medicines: Restoring Public Confidence, Report of the Blue Ribbon Committee on Generic Medicines (received from the Generic Pharmaceutical Industry Association, New York) (November 15, 1990), pp. 57-58.

32. See Chapter 6, note 21.

CHAPTER 10

Dollars or Cents?

Introduction

This chapter discusses the Bureau's attempt to quantify the "economic benefits that Hawaii's [emphasis added] consumers have derived from the use of generic drug products".[1] The chapter discusses the methodology used by the Bureau to collect and, in some cases, generate the data needed to compute cost-savings attributable to the use of generic drug products. The Bureau's estimates of cost-savings, along with the assumptions upon which they are based, are also discussed in this chapter. The chapter concludes by discussing the cost-savings estimates made by the Hawaii Medical Service Association, Hawaii Dental Service, and the Department of Human Services, for the purpose of assisting the Bureau with this study.

The Bureau has neither the technical expertise nor the access to the data needed to quantify cost-savings attributable to the use of generic drug products. Funds were not available to hire independent pharmaceutical marketing firms that have the necessary skills, knowledge, and ability to conduct this kind of study. This portion of the study would not have been possible without the generous assistance of Market Measures, Inc. (West Orange, New Jersey), which spent countless hours on the telephone providing the Bureau with advice that it typically provides for a fee to paying customers, and the assistance of the Hawaii Medical Service Association, Longs Drug Stores, the Hawaii Dental Service, the Department of Human Services, and the Federal Trade Commission. The Bureau could not have generated the information and analyses in this chapter without the assistance of this group.

This study attempts to quantify cost-savings attributable to the use of generic drug products at the level of the community pharmacy. Cost-savings realized by hospital pharmacies and other non-retail institutional pharmacies were not examined in this study since the prescribing and dispensing of prescription drugs in these institutions are generally governed by their respective drug and therapeutics committees. Consequently, this study most likely underestimates the economic benefits that Hawaii's consumers have derived from the use of generic drug products.

Finally, the Bureau notes that this study does not distinguish between "direct" cost-savings, i.e., cost-savings realized at the time of purchase in the form of cash, and "indirect" cost-savings, i.e., cost-savings realized at a future date in the form of lower insurance premiums or insurance premiums that do not increase with inflation.

Survey of Prescription Drug Prices

To determine the economic benefits that Hawaii's consumers have derived from the use of generic drug products, the Bureau surveyed all "community pharmacies" in the State for the prices of 31 frequently dispensed generic drug products and their brand-name counterparts.[2] Because the Bureau did not originally plan to compute the cost-savings attributable solely to generic drug substitution, the survey instrument employed by the Bureau was designed only to quantitatively measure the difference between the price of filling a prescription with a brand-name drug product and the price of filling that same prescription with a generic drug product.[3] The survey instrument employed by the Bureau is included in

this report as Appendix D. The Bureau's list of 31 frequently dispensed generic drug products was based on prescription claims data provided by the Hawaii Medical Service Association for the 1989 calender year.[4]

The Bureau's survey was limited to 31 frequently dispensed generic drug products since the Bureau believed that a lengthy survey would generate a poor response because it would be too burdensome and time consuming to be answered by busy pharmacists. The survey was also limited to what the Bureau considered to be non-proprietary information (e.g., the retail price of a prescription) since the Bureau believed that requests for proprietary information (e.g., total retail sales from prescription drugs and the number of prescriptions dispensed) might discourage pharmacists from responding to the survey. Questions that the Bureau believed might lead to guessing because of insufficient data (e.g., the rate of generic drug substitution versus the rate of drug product selection) were also omitted since the reliability of these data would be questionable.[5]

Although studies comparing generic drug product prices and brand-name drug product prices are frequently based on comparisons involving quantities of 100 tablets or capsules, the Bureau chose to survey for quantities that were typically dispensed by pharmacists. The Bureau chose to survey for quantities that were typically dispensed by pharmacists since surveying for quantities of 100 in all instances would have exaggerated the dollar difference between the price of generic drug products and brand-name drug products typically dispensed in lesser quantities (e.g., 28 tablets). The quantities surveyed by the Bureau were provided by Melvin Kumasaka, Chief Pharmacist for Longs Drug Stores in Hawaii.[6]

The Bureau's survey was mailed to 135 licensed, community pharmacies in the State. A list of the 135 pharmacies surveyed by the Bureau is included in this report as Appendix E. To create its list of licensed, community pharmacies in the State, the Bureau obtained a list of licensed pharmacies from the Department of Commerce and Consumer Affairs, Professional and Vocational Licensing Division.[7] Pharmacies that possessed licenses which were classified as "forfeited" or "closed/cancelled" as of March 17, 1990, were immediately deleted from the list. Non-retail pharmacies (e.g., hospital and institutional pharmacies) were likewise deleted from the list. Finally, those pharmacies not listed in the February 1, 1990, "GTE Hawaiian Tel" directory were deleted from the list. The last step in this elimination process was deemed necessary since the list of licensed pharmacies obtained from the Department of Commerce and Consumer Affairs included a number of pharmacies whose licenses were classified as "delinquent" as of March 17, 1990.

In those few instances where the Bureau was unable to determine from the telephone directory whether or not a pharmacy was a non-retail pharmacy, the Bureau phoned the pharmacy to clarify its status. If the Bureau was unable to contact the pharmacy after several attempts, the pharmacy was deleted from the list. The remaining pharmacies on the list were classified by the Bureau as "community pharmacies" or retail pharmacies that service the general public.

The Bureau mailed out 137 surveys on September 12, 1990, and received a total of 45 responses by September 31, 1990. Two responses were received too late to be included in the analyses of data; one survey was returned to the Bureau with a note that the pharmacy was not currently in business; and one was returned with a note that another survey had been sent to the pharmacy at a different address. Response to the Bureau's survey was 45 of 135 or 33 percent.

Analyses of Data

The data received by the Bureau were grouped according to drug product and are included in this report as Appendix F. To facilitate the interpretation of the data received by the Bureau, the following descriptive statistics were computed:

(1) Mean Price - Generic Product. This statistic described the "average" price of a generic drug product. It was computed by taking the arithmetic mean of all prices for a generic drug product, except where data were suppressed[8] or missing.[9]

(2) Mean Price - Brand-name Product. This statistic described the "average" price of a brand-name drug product. It was computed by taking the arithmetic mean of all prices for a brand-name drug product, except where data were suppressed or missing.

(3) Mean Price - Paired Generic Product. This statistic described the "average" price of a generic drug product. It was computed by taking the arithmetic mean of generic drug product prices from pharmacies that reported a generic drug product price and a brand-name drug product price (hence the term "paired"). It did not include suppressed or missing data.

(4) Mean Price - Paired Brand-name Product. This statistic described the "average" price of a brand-name drug product. It was computed by taking the arithmetic mean of brand-name drug product prices from pharmacies that reported a generic drug product price and a brand-name drug product price. It did not include suppressed or missing data.

The abovementioned statistics were then used to compute the following figures.

(1) The dollar difference between the mean price of a brand-name drug product and the mean price of a generic drug product.

(2) The percentage difference between the mean price of a generic drug product and the mean price of a brand-name drug product. The figures derived from these computations completed the statement: "The mean price of the generic drug product was ____ percent less than the mean price of the brand-name drug product".[10]

(3) The dollar difference between the mean price of a paired brand-name drug product and the mean price of a paired generic drug product.

(4) The percentage difference between the mean price of a paired generic drug product and the mean price of a paired brand-name drug product. The figures derived from these computations completed the statement: "The mean price of the paired generic drug product was ____ percent less than the mean price of the paired brand-name drug product".

The computation of separate statistics for paired responses was undertaken to determine whether or not paired responses would yield a more conservative estimate of cost-savings when compared to data that included paired and unpaired responses. The results of these computations are summarized in Tables 1, 2, and 3.

Table 1

Summary of Mean Drug Product Prices and Assorted Statistics

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) Mean Price- Generic Product ($)**	(3) Mean Price- Brand-name Product ($)	(4) $ Difference Between (2) & (3)	(5) % Difference Between (2) & (3)***	(6) Mean Price- Paired Generic Product ($)****	(7) Mean Price- Paired Brand-name Product ($)	(8) $ Difference Between (6) & (7)	(9) % Difference Between (6) & (7)	(10) $ Difference Between (4) & (8)
1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension -100 ml	6.57	7.20	0.63	9	6.60	7.59	0.99	13	0.36
2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension - 100 ml	8.31	10.18	1.87	18	8.44	10.63	2.19	21	0.32
3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules - 30 Capsules	8.90	10.01	1.11	11	8.07	10.01	1.94	19	0.83
4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules - 30 Capsules	13.44	15.53	2.09	13	11.44	15.53	4.09	26	2.00
5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets - 30 Tablets	6.53	10.08	3.55	35	6.52	10.08	3.56	35	0.01
6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablets - 28 Tablets	5.55	8.25	2.70	33	5.19	8.25	3.06	37	0.36
7. Penicillin V Potassium (V-Cillin K) - *500 mg Tablets - 28 Tablets*	7.14	12.73	5.59	44	6.92	12.73	5.81	46	0.22
8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	5.98	8.95	2.97	33	5.96	8.95	2.99	33	0.02
9. Allopurinol (Zyloprim) - 100 mg Tablets - 100 Tablet	11.38	17.97	6.59	37	11.43	17.97	6.54	36	0.05
10. Allopurinol (Zyloprim) - 300 mg Tablets - 100 Tablets	22.87	43.79	20.92	48	23.21	43.79	20.58	47	0.34
11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets - 30 Tablets	10.67	17.55	6.88	39	10.64	17.55	6.91	39	0.03
12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets - 20 Tablets	8.43	22.54	14.11	63	8.22	22.59	14.37	64	0.26
13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets - 10 Tablets	7.29	31.38	24.09	77	7.13	31.38	24.25	77	0.16
14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspension - 100 ml	8.60	10.84	2.24	21	8.87	11.42	2.55	22	0.31
15. Cephalexin (Keflex) - 250 mg Capsules - 28 Capsules	17.00	32.77	15.77	48	16.99	33.10	16.11	49	0.34
16. Cephalexin (Keflex) - 500 mg Capsules - 28 Capsules	30.35	60.64	30.29	50	30.30	61.27	30.97	51	0.68
17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules - *30 Capsules*	10.62	12.76	1.94	15	10.72	12.76	2.04	16	0.10

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) Mean Price- Generic Product ($)**	(3) Mean Price- Brand-name Product ($)	(4) $ Difference Between (2) & (3)	(5) % Difference Between (2) & (3)***	(6) Mean Price- Paired Generic Product ($)****	(7) Mean Price- Paired Brand-name Product ($)	(8) $ Difference Between (6) & (7)	(9) % Difference Between (6) & (7)	(10) $ Difference Between (4) & (8)
18. Hydroxyzine Hydrochloride (Atarax) - 10 mg Tablets - 30 Tablets	6.02	17.08	11.06	65	5.72	17.08	11.36	67	0.30
19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets - 100 Tablets	5.18	15.04	9.86	66	5.18	15.18	10.00	66	0.14
20. Diazepam (Valium) - 5 mg Tablets - 30 Tablets	6.90	18.19	11.29	62	6.94	18.19	11.25	62	0.04
21. Chlorpropamide (Diabinese) - 250 mg Tablets - 100 Tablets	11.62	62.12	50.5	81	11.67	62.12	50.45	81	0.40
22. Ibuprofen (Motrin) - 400 mg Tablets - 30 Tablets	6.74	9.04	2.30	25	6.67	9.09	2.42	27	0.12
23. Dipyridamole (Persantine) - 50 mg Tablets - 100 Tablets*	9.97	42.12	32.15	76	9.97	42.10	32.13	76	0.02
24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream - 30 Grams	6.04	15.04	9.00	60	6.08	15.04	8.96	60	0.04
25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	6.21	9.09	2.88	32	6.07	9.11	3.04	33	0.16
26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets - 12 Tablets	5.96	7.76	1.80	23	5.98	7.81	1.83	23	0.03
27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid - 120 ml*	6.70	13.63	6.93	51	6.60	13.49	6.89	51	0.04
28. Dextromethorphan/Iodinated Glycerol (Tussi-Organidin DM) Liquid - 120 ml*	6.34	12.97	6.63	51	6.26	12.97	6.71	52	0.08
29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets - 24 Tablets*	6.66	15.98	9.32	58	6.66	16.29	9.63	59	0.31
30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets - 30 Tablets	7.89	14.67	6.78	46	7.98	14.67	6.69	46	0.09
31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets - 100 Tablets	10.42	35.68	25.26	71	10.37	35.68	25.31	71	0.05

* Not rated as "therapeutically equivalent" in the Hawaii Drug Formulary of Equivalent Drug Products (December 1988).

** "Mean Price - ( ) Product" means the arithmetic mean of the prices reported for that drug product. It does not include suppressed or missing data.

*** "% Difference" means that the mean price of the generic drug product was ____ per cent less than the mean price of the brand-name drug product.

**** "Mean Price - Paired ( ) Product" means the arithmetic mean of the prices reported for that drug product. It excludes data from pharmacies that only reported a generic drug product price or a brand-name drug product price (hence the term "paired"). It does not include suppressed or missing data.

Table 2

Determination of Cost-Savings Using Mean Prices and Claims Data Provided by HMSA*

(1) DRUG NAME ( ) DOSAGE AND UNITS	(2) $ Difference Between Mean Price of Generic and Brand-name Product	(3) Number of Claims Paid at Generic Product Price	(4) Calculated Cost-savings ($)	(5) Cost-savings Reported by HMSA ($)	(6) $ Difference Between (4) & (5)**	(7) $ Difference as a Percentage of (5)
1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension -100 ml	0.63	10,883	6,856	37,071	30,215	82
2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension - 100 ml	1.67	27,240	50,939	55,748	4,809	9
3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules - 30 Capsules	1.11	22,376	24,837	70,604	45,767	65
4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules - 30 Capsules	2.09	13,706	28,646	69,122	40,476	59
5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets - 30 Tablets	3.55	18,786	66,690	46,717	19,973	43
6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablets - 28 Tablets	2.70	12,222	32,999	43,138	10,139	24
7. Penicillin V Potassium (V-Cillin K) - 500 mg Tablets - 28 Tablets	5.59	9,780	54,670	52,898	1,772	3
8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	2.97	9,629	28,598	34,987	6,389	18
9. Allopurinol (Zyloprim) - 100 mg Tablets - 100 Tablet	6.59	5,234	34,492	19,828	14,664	74
10. Allopurinol (Zyloprim) - 300 mg Tablets - 100 Tablets	20.92	9,406	196,774	93,558	103,216	110
11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets - 30 Tablets	6.88	7,727	53,162	40,908	12,254	30
12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets - 20 Tablets	14.11	7,822	110,368	82,332	28,036	34
13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets - 10 Tablets	24.09	6,705	161,523	249,218	87,695	35
14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspension - 100 ml	2.24	5,758	12,898	13,998	1,100	8
15. Cephalexin (Keflex) - 250 mg Capsules - 28 Capsules	15.77	5,646	89,037	63,677	25,360	40
16. Cephalexin (Keflex) - 500 mg Capsules - 28 Capsules	30.29	4,134	125,219	85,192	40,027	47
17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules - 30 Capsules	1.94	5,644	10,949	4,998	5,951	119

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) $ Difference Between Mean Price of Generic and Brand-name Product	(3) Number of Claims Paid at Generic Product Price	(4) Calculated Cost-savings ($)	(5) Cost-savings Reported by HMSA ($)	(6) $ Difference Between (4) & (5)**	(7) $ Difference as a Percentage of (5)
18. Hydroxyzine Hydrochloride (Atarax) - 10 mg Tablets - 30 Tablets	11.06	5,382	59,525	72,467	12,942	18
19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets - 100 Tablets	9.86	5,305	52,307	26,209	26,098	100
20. Diazepam (Valium) - 5 mg Tablets - 30 Tablets	11.29	4,953	55,919	51,541	4,378	8
21. Chlorpropamide (Diabinese) - 250 mg Tablets - 100 Tablets	50.50	4,625	233,563	158,385	75,178	47
22. Ibuprofen (Motrin) - 400 mg Tablets - 30 Tablets	2.30	4,133	9,506	9,034	472	5
23. Dipyridamole (Persantine) - 50 mg Tablets - 100 Tablets	32.15	4,091	131,526	110,698	20,828	19
24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream - 30 Grams	9.00	3,916	35,244	23,875	11,369	48
25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	2.88	3,899	11,229	13,907	2,678	19
26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets - 12 Tablets	1.80	3,747	6,745	10,545	3,800	36
27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid - 120 ml	6.93	3,472	24,061	24,871	810	3
28. Dextromethorphan/Iodinated Glycerol (Tussi-Organidin DM) Liquid - 120 ml	6.63	3,304	21,906	23,836	1,930	8
29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets - 24 Tablets	9.32	3,142	29,283	24,214	5,069	21
30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets - 30 Tablets	6.78	3,083	20,903	17,454	3,449	20
31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets - 100 Tablets	25.26	3,108	78,508	57,842	20,666	36
Summary - all data	--	238,858	1,858,882	1,688,872	170,010	10
Summary - excluding data from #23, #27, #28, and #29	--	224,849	1,652,106	1,505,253	146,853	10

* Hawaii Medical Service Association

** Positive and negative signs omitted; summary not equal to sum of figures.

Table 3

Determination of Cost-Savings Using Mean Prices-Paired and Claims Data Provided by HMSA*

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) $ Difference Between Mean Price-Paired of Generic & Brand-name Product	(3) Number of Claims Paid at Generic Product Price	(4) Calculated Cost-savings ($)	(5) Cost-savings Reported by HMSA ($)	(6) $ Difference Between (4) & (5)**	(7) $ Difference as a Percentage of (5)
1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension -100 ml	0.99	10,883	10,774	37,071	26,297	71
2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension - 100 ml	2.19	27,240	59,656	55,748	3,908	7
3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules - 30 Capsules	1.94	22,376	43,409	70,604	27,195	39
4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules - 30 Capsules	4.09	13,706	56,058	69,122	13,064	19
5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets - 30 Tablets	3.56	18,786	66,878	46,717	20,161	43
6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablets - 28 Tablets	3.06	12,222	37,399	43,138	5,739	13
7. Penicillin V Potassium (V-Cillin K) - 500 mg Tablets - 28 Tablets	5.81	9,780	56,822	52,898	3,924	7
8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	2.99	9,629	28,791	34,987	6,196	18
9. Allopurinol (Zyloprim) - 100 mg Tablets - 100 Tablet	6.54	5,234	34,230	19,828	14,402	73
10. Allopurinol (Zyloprim) - 300 mg Tablets - 100 Tablets	20.58	9,406	193,575	93,558	100,017	107
11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets - 30 Tablets	6.91	7,727	53,394	40,908	12,486	31
12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets - 20 Tablets	14.37	7,822	112,402	82,332	30,070	37
13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets - 10 Tablets	24.25	6,705	162,596	249,218	86,622	35
14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspenion - 100 ml	2.55	5,758	14,683	13,998	685	5
15. Cephalexin (Keflex) - 250 mg Capsules - 28 Capsules	16.11	5,646	90,957	63,677	27,280	43
16. Cephalexin (Keflex) - 500 mg Capsules - 28 Capsules	30.97	4,134	128,030	85,192	42,838	50
17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules - 30 Capsules	2.04	5,644	11,514	4,998	6,516	130

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) $ Difference Between Mean Price-Paired of Generic & Brand-name Product	(3) Number of Claims Paid at Generic Product Price	(4) Calculated Cost-savings ($)	(5) Cost-savings Reported by HMSA ($)	(6) $ Difference Between (4) & (5)**	(7) $ Difference as a Percentage of (5)
18. Hydroxyzine Hydrochloride (Atarax) - 10 mg Tablets - 30 Tablets	11.36	5,382	61,140	72,467	11,327	16
19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets - 100 Tablets	10.00	5,305	53,050	26,209	26,841	102
20. Diazepam (Valium) - 5 mg Tablets - 30 Tablets	11.25	4,953	55,721	51,541	4,180	8
21. Chlorpropamide (Diabinese) - 250 mg Tablets - 100 Tablets	50.45	4,625	233,331	158,385	74,946	47
22. Ibuprofen (Motrin) - 400 mg Tablets - 30 Tablets	2.42	4,133	10,002	9,034	968	11
23. Dipyridamole (Persantine) - 50 mg Tablets - 100 Tablets	32.13	4,091	131,444	110,698	20,746	19
24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream - 30 Grams	8.96	3,916	35,087	23,875	11,212	47
25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	3.04	3,899	11,853	13,907	2,054	15
26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets - 12 Tablets	1.83	3,747	6,857	10,545	3,688	35
27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid - 120 ml	6.89	3,472	23,922	24,871	949	4
28. Dextromethorphan/Iodinated Glycerol (Tussi-Organidin DM) Liquid - 120 ml	6.71	3,304	22,170	23,836	1,666	7
29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets - 24 Tablets	9.63	3,142	30,257	24,214	6,043	25
30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets - 30 Tablets	6.69	3,083	20,625	17,454	3,171	18
31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets - 100 Tablets	25.31	3,108	78,663	57,842	20,821	36
Summary - all data	--	238,658	1,935,290	1,688,872	246,418	15
Summary - excluding data from #23, #27, #28, and #29	--	224,649	1,727,497	1,505,253	222,244	15

* Hawaii Medical Service Association

** Positive and negative signs omitted; summary not equal to sum of figures.

In addition to computing the abovementioned statistics, the Bureau computed skewness coefficients[11] for all price distributions to quantify the effect that extremely high or extremely low prices might have exerted on mean prices. The results of these computations are included in this report as Appendix G. Because there is no generally agreed upon point at which a distribution becomes "skewed", the Bureau computed the median[12] of each price distribution to determine whether or not the median would yield a more conservative estimate of cost-savings when compared to the mean.

The median prices were used to compute the following figures.

(1) Median Price - Generic Product. This statistic described the median price of a generic drug product. It was computed by taking the median of all prices for a generic drug product, except where data were suppressed or missing.

(2) Median Price - Brand-name Product. This statistic described the median price of a brand-name drug product. It was computed by taking the median of all prices for a brand-name drug product, except where data were suppressed or missing.

(3) Median Price - Paired Generic Product. This statistic described the median price of a generic drug product. It was computed by taking the median of generic drug product prices from pharmacies that reported a generic drug product price and a brand-name drug product price (hence the term "paired"). It did not include suppressed or missing data.

(4) Median Price - Paired Brand-name Product. This statistic described the median price of a brand-name drug product. It was computed by taking the median of brand-name drug product prices from pharmacies that reported a generic drug product price and a brand-name drug product price. It did not include suppressed or missing data.

The abovementioned statistics were then used to compute the following figures.

(1) The dollar difference between the median price of a brand-name drug product and the median price of a generic drug product.

(2) The percentage difference between the median price of a generic drug product and the median price of a brand-name drug product. The figures derived from these computations completed the statement: "The median price of the generic drug product was ____ percent less than the median price of the brand-name drug product".[13]

(3) The dollar difference between the median price of a paired brand-name drug product and the median price of a paired generic drug product.

(4) The percentage difference between the median price of a paired generic drug product and the median price of a paired brand-name drug product. The figures derived from these computations completed the statement: "The median price of the paired generic drug product was ____ percent less than the median price of the paired brand-name drug product".

The computation of separate statistics for paired responses was undertaken to determine whether or not paired responses would yield a more conservative estimate of cost-savings when compared to data that included paired and unpaired responses. The results of these computations are summarized in Tables 4, 5, and 6.

Ultimately, the Bureau's decision to use the median (unpaired) prices of drug products to compute cost-savings was based on the following considerations.

(1) The median (unpaired) prices of the drug products sampled provided the most conservative estimate of cost-savings when compared to estimates of cost-savings based on the mean prices of the drug products, the median paired prices of the drug products, and the mean paired prices of the drug products (refer to Table 7).

(2) The median prices of the drug products sampled provided the most conservative estimate of cost-savings when compared to the cost-savings computed by the Hawaii Medical Service Association, which were based on average wholesale prices.

(3) Although the dollar differences between the mean and median prices for most generic drug products and brand-name drug products were relatively small, cost-savings is a function of the dollar difference between the price of a generic drug product and the price of a brand-name drug product. Consequently, even a small difference between the mean and median price of a generic drug product or a brand-name drug product, or both, could substantially affect cost-savings, especially if the dollar difference between the generic drug product and the brand-name drug product were already small to begin with.

Conversely, the larger the dollar difference between the price of a generic drug product and the price of a brand-name drug product, the smaller the effect on cost-savings attributable to the difference between the mean and median price of the generic drug product or the brand-name drug product.

During the course of preparing the data for analyses, the Bureau came upon four prices that appeared to be based on a 30-day supply of tablets or capsules instead of the 100 tablets or capsules specified for those drug products in the survey. In addition, the Bureau came upon two prices that were definitely written for quantities not specified in the survey. Finally, the Bureau came upon two prices that appeared to be transposed through transcribing errors. After conferring with Melvin Kumasaka, Chief Pharmacist for Longs Drug Stores in Hawaii, on these data, the Bureau decided that these data would be suppressed and excluded from the study.[14] The eight drug products affected by the suppression of these prices are identified in Appendix G.

The suppression of the two prices that appeared to be transposed through transcribing errors was supported by the fact that several other pharmacists committed the same error. In the latter instances, however, these pharmacists rectified their errors by indicating that certain prices had, in fact, been transposed.

Table 4

Summary of Median Drug Product Prices and Assorted Statistics

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) Median Price- Generic Product ($)**	(3) Median Price- Brand-name Product ($)	(4) $ Difference Between (2) & (3)	(5) % Difference Between (2) & (3)***	(6) Median Price- Paired Generic Product ($)****	(7) Median Price- Paired Brand-name Product ($)	(8) $ Difference Between (6) & (7)	(9) % Difference Between (6) & (7)	(10) $ Difference Between (4) & (8)
1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension -100 ml	6.40	6.42	0.02	< 1	6.36	7.16	0.80	11	0.78
2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension - 100 ml	8.32	9.85	1.53	16	8.25	9.95	1.70	17	0.17
3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules - 30 Capsules	8.95	9.73	0.78	8	8.10	9.73	1.63	17	0.85
4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules - 30 Capsules	13.90	14.65	0.75	5	11.26	14.65	3.39	23	2.64
5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets - 30 Tablets	6.46	9.84	3.38	34	6.46	9.84	3.38	34	0
6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablets - 28 Tablets	5.32	8.62	3.30	38	5.18	8.62	3.44	40	0.14
7. Penicillin V Potassium (V-Cillin K) - 500 mg Tablets - 28 Tablets	6.95	13.76	6.81	49	6.80	13.76	6.96	51	0.15
8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	5.91	9.00	3.09	34	5.84	9.00	3.16	35	0.07
9. Allopurinol (Zyloprim) - 100 mg Tablets - 100 Tablet	11.90	17.94	6.04	34	11.90	17.94	6.04	34	0
10. Allopurinol (Zyloprim) - 300 mg Tablets - 100 Tablets	22.95	42.33	19.38	46	23.43	42.33	18.90	45	0.48
11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets - 30 Tablets	10.72	17.16	6.44	38	10.72	17.16	6.44	38	0
12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets - 20 Tablets	8.15	21.93	13.78	63	7.98	21.93	13.95	64	0.17
13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets - 10 Tablets	6.96	31.44	24.48	78	6.63	31.44	24.81	79	0.33
14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspenion - 100 ml	8.32	10.77	2.45	23	8.69	11.00	2.31	21	0.14
15. Cephalexin (Keflex) - 250 mg Capsules - 28 Capsules	17.29	32.37	15.08	47	17.22	32.50	15.28	47	0.20
16. Cephalexin (Keflex) - 500 mg Capsules - 28 Capsules	29.89	60.15	30.26	50	29.40	60.39	30.99	51	0.73
17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules - 30 Capsules	11.02	12.44	1.42	11	10.90	12.44	1.54	12	0.12

(1) DRUG NAME ( ) DOSAGE AND UNITS	(2) Median Price-Generic Product ($)**	(3) Median Price-Brand-name Product ($)	(4) $ Difference Between (2) & (3)	(5) % Difference Between (2) & (3)***	(6) Median Price-Paired Generic Product ($)****	(7) Median Price-Paired Brand-name Product ($)	(8) $ Difference Between (6) & (7)	(9) % Difference Between (6) & (7)	(10) $ Difference Between (4) & (8)
18. Hydroxyzine Hydrochloride (Atarax) - 10 mg Tablets - 30 Tablets	5.67	17.16	11.49	67	5.50	17.16	11.66	70	0.17
19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets - 100 Tablets	4.85	15.75	10.90	69	4.69	15.77	11.08	70	0.18
20. Diazepam (Valium) - 5 mg Tablets - 30 Tablets	6.70	18.26	11.56	63	6.70	18.26	11.56	63	0
21. Chlorpropamide (Diabinese) - 250 mg Tablets - 100 Tablets	11.70	61.69	49.92	81	11.75	61.69	49.94	81	0.02
22. Ibuprofen (Motrin) - 400 mg Tablets - 30 Tablets	6.82	8.80	1.98	23	6.73	8.80	2.07	24	0.09
23. Dipyridamole (Persantine) - 50 mg Tablets - 100 Tablets*	9.60	41.39	31.79	77	9.60	41.39	41.39	31.79	0
24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream - 30 Grams	5.99	14.56	8.57	59	5.95	14.56	8.61	59	0.04
25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	5.99	9.03	3.04	34	5.80	9.21	3.41	37	0.37
26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets - 12 Tablets	5.64	7.83	2.19	28	5.64	7.85	2.21	28	0.02
27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid - 120 ml*	6.51	13.75	7.24	53	6.37	13.63	7.26	53	0.02
28. Dextromethorphan/Iodinated Glycerol (Tussi-Organidin DM) Liquid - 120 ml*	6.20	13.0	6.80	52	6.10	13.03	6.93	53	0.13
29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets - 24 Tablets*	6.47	16.50	10.03	61	6.47	16.50	10.03	61	0
30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets - 30 Tablets	7.92	14.48	6.56	45	8.00	14.48	6.48	45	0.08
31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets - 100 Tablets	9.90	35.23	25.33	72	9.90	35.23	25.33	72	0

* Not rated as "therapeutically equivalent" in the Hawaii Drug Formulary of Equivalent Drug Products (December 1988).

** "Median Price - ( ) Product" means the median of the prices reported for that drug product. It does not include suppressed or missing data.

*** "% Difference" means that the median price of the generic drug product was ___ per cent less than the median price of the brand-name drug product.

**** "Median Price - Paired ( ) Product" means the median of the prices reported for that drug product. It excludes data from pharmacies that only reported a generic drug product price or a brand-name drug product price (hence the term "paired"). It does not include suppressed or missing data.

Table 5

Determination of Cost-Savings Using Median Prices and Claims Data Provided by HMSA*

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) $ Difference Between Median Price of Generic and Brand-name Product	(3) Number of Claims Paid at Generic Product Price	(4) Calculated Cost-savings ($)	(5) Cost-savings Reported by HMSA ($)	(6) $ Difference Between (4) & (5)**	(7) $ Difference as a Percentage of (5)
1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension -100 ml	0.02	10,883	218	37,071	36,853	99
2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension - 100 ml	1.53	27,240	41,677	55,748	14,071	25
3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules - 30 Capsules	0.78	22,376	17,453	70,604	53,151	75
4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules - 30 Capsules	0.75	13,706	10,280	69,122	58,842	85
5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets - 30 Tablets	3.38	18,786	63,497	46,717	16,780	36
6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablets - 28 Tablets	3.30	12,222	40,333	43,138	2,805	7
7. Penicillin V Potassium (V-Cillin K) - 500 mg Tablets - 28 Tablets	6.81	9,780	66,602	52,898	13,704	26
8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	3.09	9,629	29,754	34,987	5,233	15
9. Allopurinol (Zyloprim) - 100 mg Tablets - 100 Tablet	6.04	5,234	31,613	19,828	11,785	59
10. Allopurinol (Zyloprim) - 300 mg Tablets - 100 Tablets	19.38	9,406	182,288	93,558	88,730	95
11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets - 30 Tablets	6.44	7,727	49,762	40,908	8,854	22
12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets - 20 Tablets	13.78	7,822	107,787	82,332	25,455	31
13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets - 10 Tablets	24.48	6,705	164,138	249,218	85,080	34
14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspenion - 100 ml	2.45	5,758	14,107	13,998	109	1
15. Cephalexin (Keflex) - 250 mg Capsules - 28 Capsules	15.08	5,646	85,142	63,677	21,465	34
16. Cephalexin (Keflex) - 500 mg Capsules - 28 Capsules	30.26	4,134	125,095	85,192	39,903	47
17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules - 30 Capsules	1.42	5,644	8,014	4,998	3,016	60

(1) DRUG NAME ( ) DOSAGE AND UNITS	(2) $ Difference Between Median Price of Generic and Brand-name Product	(3) Number of Claims Paid at Generic Product Price	(4) Calculated Cost-savings ($)	(5) Cost-savings Reported by HMSA ($)	(6) $ Difference Between (4) & (5)**	(7) $ Difference as a Percentage of (5)
18. Hydroxyzine Hydrochloride (Atarax) - 10 mg Tablets - 30 Tablets	11.49	5,382	61,839	72,467	10,628	15
19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets - 100 Tablets	10.90	5,305	57,825	26,209	31,616	121
20. Diazepam (Valium) - 5 mg Tablets - 30 Tablets	11.56	4,953	57,257	51,541	5,716	11
21. Chlorpropamide (Diabinese) - 250 mg Tablets - 100 Tablets	49.92	4,625	230,880	158,385	72,495	46
22. Ibuprofen (Motrin) - 400 mg Tablets - 30 Tablets	1.98	4,133	8,183	9,034	851	9
23. Dipyridamole (Persantine) - 50 mg Tablets - 100 Tablets	31.79	4,091	130,053	110,698	19,355	17
24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream - 30 Grams	8.57	3,916	33,560	23,875	9,685	41
25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	3.04	3,899	11,853	13,907	2,054	15
26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets - 12 Tablets	2.19	3,747	8,206	10,545	2,339	22
27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid - 120 ml	7.24	3,472	25,137	24,871	266	1
28. Dextromethorphan/Iodinated Glycerol (Tussi-Organidin DM) Liquid - 120 ml	6.80	3,304	22,467	23,836	1,369	6
29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets - 24 Tablets	10.03	3,142	31,514	24,214	7,300	30
30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets - 30 Tablets	6.56	3,083	20,224	17,454	2,770	16
31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets - 100 Tablets	25.33	3,108	78,726	57,842	20,884	36
Summary - all data	--	238,858	1,815,484	1,688,872	126,612	8
Summary - excluding data from #23, #27, #28, and #29	--	224,649	1,606,313	1,505,253	101,060	7

* Hawaii Medical Service Association

** Positive and negative signs omitted; summary not equal to sum of figures.

Table 6

Determination of Cost-Savings Using Median Prices-Paired and Claims Data Provided by HMSA*

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) $ Difference Between Median Price of Paired Generic & Brand-name Product	(3) Number of Claims Paid at Generic Product Price	(4) Calculated Cost-savings ($)	(5) Cost-savings Reported by HMSA ($)	(6) $ Difference Between (4) & (5)**	(7) $ Difference as a Percentage of (5)
1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension -100 ml	0.80	10,883	8,706	37,071	28,365	77
2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension - 100 ml	1.70	27,240	46,308	55,748	9,440	17
3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules - 30 Capsules	1.63	22,376	36,473	70,604	34,131	48
4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules - 30 Capsules	3.39	13,706	46,463	69,122	22,659	33
5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets - 30 Tablets	3.38	18,786	63,497	46,717	16,780	36
6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablets - 28 Tablets	3.44	12,222	42,044	43,138	1,094	3
7. Penicillin V Potassium (V-Cillin K) - 500 mg Tablets - 28 Tablets	6.96	9,780	68,069	52,898	15,171	29
8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	3.16	9,629	30,428	34,987	4,559	13
9. Allopurinol (Zyloprim) - 100 mg Tablets - 100 Tablet	6.04	5,234	31,613	19,828	11,785	59
10. Allopurinol (Zyloprim) - 300 mg Tablets - 100 Tablets	18.90	9,406	177,773	93,558	84,215	90
11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets - 30 Tablets	6.44	7,727	49,762	40,908	8,854	22
12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets - 20 Tablets	13.95	7,822	109,117	82,332	26,785	33
13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets - 10 Tablets	24.81	6,705	166,351	249,218	82,867	33
14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspension - 100 ml	2.31	5,758	13,301	13,998	697	5
15. Cephalexin (Keflex) - 250 mg Capsules - 28 Capsules	15.28	5,646	86,271	63,677	22,594	35
16. Cephalexin (Keflex) - 500 mg Capsules - 28 Capsules	30.99	4,134	128,113	85,192	42,921	50
17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules - 30 Capsules	1.54	5,644	8,692	4,998	3,694	74

(1) DRUG NAME ( )- DOSAGE AND UNITS	(2) $ Difference Between Median Price of Paired Generic & Brand-name Product	(3) Number of Claims Paid at Generic Product Price	(4) Calculated Cost-savings ($)	(5) Cost-savings Reported by HMSA ($)	(6) $ Difference Between (4) & (5)**	(7) $ Difference as a Percentage of (5)
18. Hydroxyzine Hydrochloride (Atarax) - 10 mg Tablets - 30 Tablets	11.66	5,382	62,754	72,467	9,713	13
19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets - 100 Tablets	11.08	5,305	58,779	26,209	32,570	124
20. Diazepam (Valium) - 5 mg Tablets - 30 Tablets	11.56	4,953	57,257	51,541	5,716	11
21. Chlorpropamide (Diabinese) - *250 mg Tablets - 100 Tablets*	49.94	4,625	230,973	158,385	72,588	46
22. Ibuprofen (Motrin) - 400 mg Tablets - 30 Tablets	2.07	4,133	8,555	9,034	479	5
23. Dipyridamole (Persantine) - 50 mg Tablets - 100 Tablets	41.39	4,091	169,326	110,698	58,628	53
24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream - 30 Grams	8.61	3,916	33,717	23,875	9,842	41
25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	3.41	3,899	13,296	13,907	611	4
26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets - 12 Tablets	2.21	3,747	8,281	10,545	2,264	21
27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid - 120 ml	7.26	3,472	25,207	24,871	336	1
28. *Dextromethorphan/Iodinated* Glycerol (Tussi-Organidin DM) Liquid - 120 ml	6.93	3,304	22,897	23,836	939	4
29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets - 24 Tablets	10.03	3,142	31,514	24,214	7,300	30
30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets - 30 Tablets	6.48	3,083	19,978	17,454	2,524	14
31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets - 100 Tablets	25.33	3,108	78,726	57,842	20,884	36
Summary - all data	--	238,858	1,934,241	1,688,872	245,369	15
Summary - excluding data from #23, #27, #28, and #29	--	224,849	1,685,297	1,505,253	180,044	12

* Hawaii Medical Service Association

** Positive and negative signs omitted; summary not equal to sum of figures.

Although the Bureau came upon two instances where the generic drug product was more expensive than the brand-name drug product, the Bureau decided that these data would not be suppressed and excluded from the study. After consulting with Melvin Kumasaka and Roy Yamauchi, Manager of Pharmacy Benefits for the Hawaii Medical Service Association, the Bureau came to the conclusion that while these occurrences were probably rare, they were not implausible.[15]

Finally, the Bureau came upon several prices that were entered on the survey under the "Brand" heading but identified by that (one) pharmacist as being for "Brand-name generics". The Bureau treated these data as "Generic" prices since the pharmacist expressly indicated that the prices were for "branded generic drug products". The alternative would have been to suppress these data and to exclude them from the study.

Computation of Cost-Savings

The computation of cost-savings attributable to the use of generic drug products relies on several important assumptions. These assumptions have been underscored to emphasize their importance and to remind the reader that the estimates provided by the Bureau are only as good as the assumptions upon which they are based. If it can be assumed that statistics which describe the practice of pharmacy across the United States are applicable to the practice of pharmacy in the State of Hawaii, then the Bureau's figures should provide the reader with a conservative estimate of cost-savings attributable to the use of generic drug products.

To determine cost-savings attributable to the use of generic drug products, and to separate these cost-savings according to generic drug substitution and drug product selection, the Bureau computed the following figures.

(1) The "average" (i.e., arithmetic mean) cost-saving per prescription dispensed using a generic drug product based on various prices (e.g., mean prices, mean prices-paired, median prices, and median prices-paired) and claims data provided by the Hawaii Medical Service Association. For the purpose of this study, the Bureau assumed that cost-savings per claim "paid" at a generic price was equal to cost-savings per prescription "dispensed" using a generic drug product.

(2) The average cost-saving per prescription dispensed using a generic drug product based on various prices and claims data provided by the Hawaii Medical Service Association, but excluding data from four drug products that were not rated as therapeutically equivalent in the Hawaii Drug Formulary of Equivalent Drug Products (December 1988).[16]

The results of these computations are summarized in Table 7. Because these figures are based only on data from the Bureau's list of 31 frequently dispensed generic drug products, it must be assumed that these figures are representative of the cost-savings attributable to the use of generic drug products not included in the Bureau's survey.

Table 7

Determination of Average Cost-Savings Per Claim for 31 Frequently Dispensed Generic Drug Products Based on Various Prices and Claims Data Provided by HMSA*

Characteristics of Data Used to Compute Cost-savings	Number of Claims Paid at Generic Price	Calculated Cost-savings ($)	Average Cost-savings per Claim Paid at Generic Price ($)
Mean prices, all data	238,858	1,858,882	7.78
Mean prices-paired, all data	238,858	1,935,290	8.10
Median prices, all data	238,858	1,815,484	7.60
Median prices-paired, all data	238,858	1,934,241	8.10
Mean prices, excluding #23, #27, #28, and #29	224,849	1,652,106	7.35
Mean prices-paired, excluding #23, #27, #28, and #29	224,849	1,727,497	7.68
Median prices, excluding #23, #27, #28, and #29	224,849	1,606,313	7.14
Median prices-paired, excluding #23, #27, #28, and #29	224,849	1,685,297	7.50
HMSA, all data	238,858	1,688,872	7.07
HMSA, excluding #23, #27, #28, and #29	224,849	1,505,253	6.69

*Hawaii Medical Service Association

The Bureau estimated the number of prescriptions dispensed in 1989 by extrapolating from the number of prescriptions dispensed in 1977 by 87 community pharmacies to the number of prescriptions dispensed by the 135 community pharmacies surveyed by the Bureau as part of this study. According to the 1977 Census of Retail Trade, 2,911,000 prescriptions were dispensed by 87 community pharmacies in 1977.[17] Based on these data, the Bureau assumed that approximately 4,500,000 prescriptions were dispensed in 1989 through community pharmacies.

Next, the Bureau estimated the portion of all prescriptions (new and refills) dispensed in Hawaii during 1989 using generic drug products. According to Consumers Union, publisher of Consumer Reports magazine, generic drug products accounted for approximately "one-third" of all new prescriptions dispensed in the United States during 1989.[18] Lacking representative data on the portion of all prescriptions dispensed in Hawaii during 1989 using generic drug products, the Bureau assumed that generic drug products accounted for approximately 33 per cent of all prescriptions dispensed in Hawaii during 1989.[19]

Next, the Bureau estimated the rate at which pharmacists in Hawaii substituted generic drug products for brand-name drug products on all prescriptions dispensed in 1989. Assuming a 33 per cent generic drug product market share and using data from the "National Substitution Audit" provided by Market Measures, Inc., the Bureau estimated that pharmacists substituted generic drug products for brand-name drug products on approximately 19 per cent of all new prescriptions dispensed in states where physicians were required to handwrite the phrase "dispense as written" or "brand medically necessary" (including "do not substitute") to prohibit generic drug substitution. For the purpose of this study, the Bureau assumed that the substitutions made by these pharmacists involved the dispensing of therapeutically equivalent drug products. The data and computations used to derive this figure are included in this study as Appendix H.[20] For the purpose of this study, the Bureau also assumed that pharmacists in Hawaii (a state which requires physicians to handwrite the phrase "do not substitute" to prohibit generic drug substitution) substituted generic drug products for brand-name drug products on 19 per cent of all prescriptions dispensed in 1989.

Using these data, the Bureau computed cost-savings attributable to the use of generic drug products, whether rated as therapeutically equivalent in the Hawaii Drug Formulary of Equivalent Drug Products (December 1988) or not.[21] The Bureau then computed the cost-savings attributable to generic drug substitution, excluding data from the four generic drug products that were not rated as therapeutically equivalent in the Hawaii Drug Formulary of Equivalent Drug Products (December 1988).[22] Finally, the Bureau computed the cost-savings attributable to drug product selection. The results of these computations are summarized in Appendix I.

Results

Based on its survey of 31 frequently dispensed generic drug products, the Bureau found that:

(1) The median prices of prescriptions dispensed using generic drug products were $0.02 to $49.92 less than the prices of corresponding brand-name drug products; and

(2) The median prices of prescriptions dispensed using generic drug products were between under one per cent to 81 per cent less than the median prices of corresponding brand-name drug products.

Assuming that:

(1) 4,500,000 prescriptions were dispensed by community pharmacies in 1989;

(2) Generic drug products accounted for 33 per cent of all prescriptions dispensed in 1989;

(3) Pharmacists substituted therapeutically equivalent generic drug products for the brand-name drug products prescribed on 19 per cent of all prescriptions dispensed in 1989;

(4) The average cost-savings per prescription dispensed using a generic drug product, whether rated as therapeutically equivalent or not, was $7.60; and

(5) The average cost-savings per prescription dispensed using a therapeutically equivalent generic drug product was $7.14;[23]

then in Hawaii in 1989, cost-savings attributable to the use of generic drug products were equal to $11,286,000. This figure can be broken down into:

(1) Cost-savings attributable to generic drug substitution (i.e., substitution involving therapeutically equivalent drug products) that were equal to $6,105,000; and

(2) Cost-savings attributable to drug product selection that were equal to $5,181,000.

Hawaii Medical Service Association

Using average wholesale prices and prescription claims data for 1989, the Hawaii Medical Service Association estimated that the Association saved $4,441,035 on 491,119 prescriptions (or approximately $9.05 per prescription) through the use of generic drug products.[24] The $4,441,035 in savings reported by the Association represented 58 per cent of the savings that were possible in 1989. The methodology and data used by the Association to compute these figures are included in this study as Appendix J.

Hawaii Dental Service

Using the average amount paid for, and the number of prescription claims dispensed using, single-source (brand-name) drug products, generic drug products, and multiple-source brand-name drug products (i.e., brand-name drug products that could have been, but were not, substituted with generic drug products), the Hawaii Dental Service estimated that it saved $327,505 on 58,163 prescriptions (or approximately $5.63 per prescription) through the use of therapeutically equivalent generic drug products.[25] The $327,505 in savings reported by the Service represented 52 per cent of the savings that were possible in 1989. The methodology and data used by the Service to compute these figures are included in this study as Appendix K.

The Bureau notes that the differences between the cost-savings reported by the Bureau and the Hawaii Medical Service Association, and the Hawaii Dental Service are probably attributable to differences in the methodologies used to estimate cost-savings.[26]

Department of Human Services--Medicaid Program

Using number of prescriptions, average number of doses per prescription, number (and amount) of dispensing fees, cost per dose, and prescription claims data for 1989, the Department of Human Services estimated that the State's Medicaid program saved the following amounts on the following six drug products through the utilization of generic drug products. The methodology and data used by the Department of Human Services to compute these figures are included in this study as Appendix L.

(1) **Drug product:** Phenytoin Sodium (Dilantin), 100 mg extended release capsules.
Pharmacologic class: anticonvulsant.
Cost-savings: $1,595 saved on 864 prescriptions, or $1.85 per prescription.

(2) **Drug product:** Carbamazepine (Tegretol), 200 mg tablets.
Pharmacologic class: anticonvulsant.
Cost-savings: $5,231 saved on 468 prescriptions, or $11.18 per prescription.

(3) **Drug product:** Propranolol Hydrochloride (Inderal), 40 mg tablets.
Pharmacologic class: cardiac drug.
Cost-savings: $3,627 saved on 450 prescriptions, or $8.06 per prescription.

(4) **Drug product:** Procainamide Hydrochloride (Procan SR), 500 mg sustained release tablets.
Pharmacologic class: cardiac drug.
Cost-savings: $478 saved on 82 prescriptions, or $5.83 per prescription.

(5) **Drug product:** Chlorpromazine Hydrochloride (Thorazine), 50 mg tablets.
Pharmacologic class: psychotropic.
Cost-savings: $3,629 saved on 236 prescriptions, or $15.38 per prescription.

(6) **Drug product:** Haloperidol (Haldol), 10 mg tablets.
Pharmacologic class: psychotropic.
Cost-savings: $8,224 saved on 318 prescriptions, or $25.86 per prescription.

Summary

The Bureau believes that generic drug products can save consumers substantial sums of money as long as chemical allergies to inert ingredients, adverse psychosomatic reactions, and differences in the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products do not excessively complicate patient care or compromise patient health to the point where medical intervention becomes necessary.

Determining whether or not the use of a generic drug product is in the best interest of a patient is largely a matter of professional judgment. Arguably, physicians know comparatively little about prescription drug prices, pharmacists know comparatively little

about the current mental and physical state of their customers, third-party insurers know comparatively little about the prescribing practices of physicians and the pricing practices of pharmacists, and patients know comparatively little about bioavailability, bioequivalence, and therapeutic equivalence. Consequently, the Bureau believes that no one individual, including a physician, a pharmacist, or a third-party insurer, can unequivocally claim to know what is in the overall best interest of a patient.

Being the best clinician in the State will not benefit a patient who cannot afford the cost of the medications prescribed for the patients's ailments. Likewise, being the most successful pharmacist in the State at generic drug substitution will not benefit a patient who:

(1) Must be retitrated and monitored when the patient is switched from the drug product of one manufacturer to the drug product of another manufacturer;

(2) Does not understand bioavailability, bioequivalence, and therapeutic equivalence, and stops taking the medication prescribed by the patient's physician because the medication dispensed looks or tastes different; or

(3) Stops taking the medication prescribed by the patient's physician because the medication dispensed precipitates an allergic or other toxic reaction.

Finally, being the most efficient third-party insurer in the State at cost-containment will not benefit a patient if the prescribing practices of the patient's physician, the dispensing practices of the patient's pharmacist, and the purchasing practices of the patient, are adversely influenced by overly restrictive cost-containment policies.

The cost of performing a blood test to retitrate a patient switched from the drug product of one manufacturer to the drug product of another manufacturer could range from $40 to $70, depending on the drug product in question.[27] This, of course, does not include the cost of additional visits to the physician or time away from work. As pointed out by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology:[28]

> ...Loss of work time can occur both for breakthrough seizures and for drug toxicity. Seizures and toxicity also lead to increased physician visits, increased ordering of blood level tests, and additional loss of work hours for each of these. The increased visits and blood level tests will happen for many patients even without clinically apparent toxicity or breakthrough seizures, simply in the attempt to prevent such problems [emphasis added]. These hidden costs represent a serious flaw in the economic incentive for generic substitution, which can result in additional costs that far outweigh any small cost savings accruing from use of generic medications. In particular, a $10 to $100 annual cost savings by using generics would be canceled out many times over by just a few extra physician visits and blood level tests during that year. Although the patient will bear the risk for seizures, he or she will gain little in cost savings even when no new expenses are incurred.

Physicians, pharmacists, and third-party insurers all play an important role in making quality health care accessible to the people of Hawaii. In the end there is only one true

"loser"--the patient--when adversarial and confrontational attitudes between and among physicians, pharmacists, and third-party insurers prevail.

ENDNOTES

1. Senate Concurrent Resolution No. 242, S.D. 1, Fifteenth Legislature, 1990, State of Hawaii.

2. The delineation of generic drug products and brand-name drug products is relatively simple when the issues being discussed concern bioavailability, bioequivalence, and therapeutic equivalence. Unfortunately, the delineation of generic drug products and brand-name drug products becomes more complex when the issues being discussed concern the pricing of drug products. Depending on the average wholesale price of a drug product, a brand-name drug product could be classified as a generic drug product. This situation is particularly true where the antibiotic drug products are concerned. Adding to an already confused situation are the third-party insurers who, for the purposes of reimbursement, may consider all therapeutically equivalent drug products whether brand-name or generic, to be generic drug products for the purposes of paying prescription claims.

   Assuming that most pharmacies would not stock more than one brand-name drug product and one generic drug product for any given multiple-source drug product, and assuming that most pharmacies would not stock a brand-name drug product and a generic drug product if a third-party insurer had designated both products as either generic drug products or brand-name drug products for the purpose of reimbursing prescription claims, the Bureau believed that it would not be practical to strictly define "generic drug product" and "brand-name drug product" in the survey. For the purpose of this study, the Bureau considered "branded generic drug products" to be "generic drug products" and not "brand-name drug products".

   For the purpose of this study, the Bureau assumed that most pharmacists, and the information marketing companies that collect data from them, generally agree on the delineation of generic drug products and brand-name drug products. The Bureau also assumed that any discrepancies among or between pharmacists and information marketing companies involving the delineation of generic drug products and brand-name drug products would not substantially affect the outcome of this study.

3. Four of the 31 drug products surveyed by the Bureau were not rated as "therapeutically equivalent" in the Hawaii Drug Formulary of Equivalent Drug Products (December 1988). Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

   The four drug products were: dipyridamole (Persantine) - 50 mg tablets; codeine/iodinated glycerol (Tussi-Organidin) liquid; dextromethorphan/iodinated glycerol (Tussi-Organidin DM) liquid; and guaifenesin/phenylpropanolamine (Entex) - 400/75 mg SA tablets. The other 27 drug products surveyed by the Bureau were rated as "therapeutically equivalent".

   The dispensing of generic drug products not rated as therapeutically equivalent is possible through "generic prescribing", i.e., prescribing without regard to a proprietary name or a specific manufacturer.

   "Pre-1938" drugs, and drugs and drug products that have not completed DESI review, are excluded from the FDA's "Orange Book" but permitted to be marketed. U.S., Department of Health and Human Services, Food and Drug Administration, Approved Drug Products with Therapeutic Equivalence Evaluations, 10th ed. (Washington, D.C.: U.S. Government Printing Office, 1990), p. v.

4. Hawaii Medical Service Association, "Top 50 Generic Categories" (Unpublished data prepared by Edward Heon, Senior Information Coordinator), September 5, 1990.

   The Association provided the Bureau with a list of the 50 most frequently dispensed generic drug products in 1989. The Association's list was based on the number of prescription

claims paid "generically" or at a rate commensurate with the cost of less-expensive generic drug products. Although the Bureau's list was supposed to be composed of the 32 most frequently dispensed generic drug products, an inadvertent error caused the omission of one generic drug product from this list. The omission of the 31st most frequently dispensed generic drug product was unfortunate but would not appear to be significant since the difference between the 31st most frequently dispensed generic drug product and the 32nd most frequently dispensed generic drug product was only 16 prescriptions.

5. Telephone interviews with Melvin Kumasaka, Chairperson of the Drug Product Selection Board, Chief Pharmacist for Longs Drug Stores in Hawaii, and Vice-President of the Hawaii Pharmaceutical Association, August 22 - September 10, 1990.

6. Kumasaka, Telephone interviews, supra note 5.

   While it could be argued that more than one chain of drugstores should have been consulted to derive these data, the Bureau notes that only one quantity for each drug product would have been surveyed in the end. Ultimately, the decision to consult with only one chain of drugstores was a practical one since consulting with more than one chain of drugstores would have required the use of additional survey instruments and delayed the completion of this study.

7. Hawaii, Department of Commerce and Consumer Affairs, Professional and Vocational Licensing Division, "Printout of licensed pharmacists and pharmacies" (Unpublished data), March 17, 1990, 94 pp.

8. The issue of data suppression is discussed in the following paragraphs.

9. For the purpose of this study, missing data were treated as "NA" (not applicable) responses. A "NA" response meant that a pharmacist did not customarily stock a generic drug product or a brand-name drug product, or both.

10. These figures were calculated using the following formula:

$$\text{Percent difference} = \frac{100 \times (|\text{Cost of Generic} - \text{Brand}|)}{\text{Cost of Brand}}$$

    This formula applies only if the mean price of a generic drug product is less than the mean price of a brand-name drug product.

11. Skewness coefficients generally range from -3 to +3, with zero indicating a perfectly symmetrical distribution. For the purpose of this study, the coefficients were used to measure the effect that extremely high or extremely low values were exerting on the mean. In a perfectly symmetrical distribution, the mean and median are equal to one another.

12. The median is the "middlemost" observation; half of the values exceed it and half are below it.

    Theoretically, a skewness coefficient not equal to zero denotes a lack of symmetry. Skewness, however, does not automatically make the use of the median preferable to the mean; skewed or not, the mean for a particular distribution is the "average" value for that distribution.

13. These figures were calculated using the following formula:

$$\text{Percent difference} = \frac{100 \times (|\text{Cost of Generic} - \text{Brand}|)}{\text{Cost of Brand}}$$

    This formula applies only if the median price of a generic drug product is less than the median price of a brand-name drug product.

14. Kumasaka, Telephone interviews, supra note 5, September 24 - September 28, 1990.

15. Kumasaka, Telephone interviews, supra note 5, September 24 - September 28, 1990; Telephone interviews with Roy Yamauchi, Manager of Pharmacy Benefits for the Hawaii Medical Service Association, October 1 - October 2, 1990.

16. Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

17. U.S., Department of Commerce, Bureau of the Census, 1977 Census of Retail Trade, Subject Series: Miscellaneous Subjects (Washington, D.C.: U.S. Government Printing Office, 1985), p. 2-76.

    The Bureau had originally planned to derive the number of prescriptions dispensed in 1989 by extrapolating from data in the 1987 Census of Retail Trade published by the U.S. Department of Commerce, Bureau of the Census. Unfortunately, data from the 1987 Census of Retail Trade were not available from the Bureau of the Census in time for the completion of this study. Briefly, the Bureau planned to increase the number of prescriptions dispensed in 1987 by 1.2 per cent to obtain the number of prescriptions dispensed in 1988, and then to increase the number of prescriptions dispensed in 1988 by 0.6 per cent to obtain the number of prescriptions dispensed in 1989.

    According to Pharmacy Times, these figures represented the change in the number of prescriptions dispensed between 1987 and 1989 in the United States. Laura La Piana Simonsen, "Top 200 Drugs of 1989--What Are Pharmacists Dispensing Most Often?", Pharmacy Times, Vol. 56, No. 4 (April 1990)(hereinafter cited as "Top 200 Drugs of 1989), p. 56; Laura La Piana Simonsen, "Top 200 Drugs of 1988--Branded New Rxs Rise 4.0% and Total Rxs Move Up 1.2%", Pharmacy Times, Vol. 55, No. 4 (April 1989), p. 40.

    Although the Census of Retail Trade is published every five years by the U.S. Department of Commerce, data for the State of Hawaii were withheld in 1982 because the estimates did not meet publication standards on the basis of either response rate, associated standard error, or a consistency review. U.S., Department of Commerce, Bureau of the Census, 1982 Census of Retail Trade, Industry Series: Miscellaneous Series, Document no. C 3.255/2-2: RC82-I (Washington, D.C.: U.S. Government Printing Office, 1985), pp. v and 4-105.

    Because the fate of data collected for the 1987 Census of Retail Trade could not be predicted at the time this study was being written, the Bureau chose to rely on data extrapolated from the 1977 Census of Retail Trade.

18. "Generic Drugs: Still Safe?", Consumer Reports, Vol. 55, No. 5 (May 1990), p. 310.

    According to Hemmant Shah of HKS & Co., Inc., the figure cited by Consumers Union was based on data collected from retail pharmacies. (HKS & Co., Inc., provided Consumers Union with the figures that appeared in Consumer Reports' April 1990 article on generic drugs. Shah's figures were based on data from Pharmaceutical Data Service of Phoenix, Arizona.) Telephone interview with Hemmant Shah, HKS & Co., Inc. (Bound Brook, New Jersey), October 4, 1990.

    The issue of generic drug market share is a potentially controversial topic since various figures for generic market share are cited by different sources. For example, using prescription data for 1980, Mason and Steiner reported that "[g]eneric market share varies from state to state, ranging from 12.1 percent to 33.5 per cent". Generic market share for the entire United States in 1980 was computed to be between 23.3 and 25.1 per cent. Alison Mason and Robert Steiner, Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws, Staff Report of the Bureau of Economics, Federal Trade Commission (Washington, D.C.: U.S. Government Printing Office, October 1985), pp. 112-113.

    Using data provided by Market Measures, Inc., the Bureau determined that generic drug market share could theoretically range from a low of 14 per cent to a high of 37 per cent

depending upon the assumptions made. Market Measures, Inc., "Unpublished data from the National Substitution Audit--12 Months Ending March 1990" (hereinafter cited as "Unpublished data"), 3 pp. Market Measures, Inc., is a pharmaceutical marketing research firm that measures generic drug substitution as part of its National Substitution Audit (Market Measures, 449 Mt. Pleasant Avenue, West Orange, New Jersey 07052).

In contrast, Pharmacy Times reported that the generic market share of new prescriptions dispensed in 1989 was approximately 14 per cent. Simonsen, "Top 200 Drugs of 1989", supra note 17.

Despite discussions with Laura La Piana Simonsen, Senior Editor for Pharmacy Times, Gary Endlein, Senior Product Manager for IMS America (publisher of the National Prescription Audit), Anne Neff, Project Director for Market Measures, Inc., and Hemmant Shah of HKS & Co., Inc., the Bureau was not able to explain the disparity between the figures reported by Pharmacy Times, Masson and Steiner, and Consumer Reports magazine. Telephone interview with Laura La Piana Simonsen, Senior Editor, Pharmacy Times (Port Washington, New York), October 9, 1990; Telephone interviews with Gary Endlein, Senior Project Manager, IMS America (Plymouth Meeting, Pennsylvania), October 9 - 10, 1990; Telephone interview with Anne Neff, Project Director, Market Measures, Inc. (West Orange, New Jersey), October 9, 1990; and Shah, Telephone interview, supra note 18, October 10, 1990.

19. Data provided by the Hawaii Medical Service Association suggest that generic drug products accounted for approximately 55 per cent of the prescription claims paid out during 1989. Letter from Edward Heon, Senior Information Coordinator, Hawaii Medical Service Association, to Keith Fukumoto, September 12, 1990.

    In contrast, data from the Hawaii Dental Service suggest that generic drug products accounted for approximately 34 per cent of the prescription claims paid out during 1989. Memorandum from Chandra Yamane, Administrative Coordinator, Hawaii Dental Service, to Keith Fukumoto, October 15, 1990.

20. Market Measures, Inc., "Unpublished data", supra note 18.

    Neff, Telephone interviews, supra note 18, July 27, 1990 and October 8, 1990.

21. Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

22. Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

23. It was the general opinion of the three pharmacists consulted that the Bureau's estimates for number of prescriptions dispensed, generic drug product market share, and rate of generic drug substitution were "on the conservative side". Consequently, unless the price data obtained by the Bureau through its survey of community pharmacies were substantially biased, the Bureau's estimates of cost-savings should be conservative. Kumasaka, Telephone interview, supra note 5, October 10, 1990; Yamauchi, Telephone interview, supra note 15, October 9, 1990; and Telephone interview with Omel Turk, Pharmacy Consultant, Department of Human Services, October 10, 1990.

24. Heon, Letter, supra note 19.

25. Yamane, Memorandum, supra note 19.

26. Yamane, Memorandum, supra note 19, November 19, 1990.

27. The figures cited are patient billing list prices and do not reflect the potential discounts that are available to some clients through contractual arrangements. Telephone interview with Carl Linden, Supervisor of Toxicology, Accupath/Smith Kline Bioscience Laboratories (Honolulu), December 3, 1990.

28. "Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology", Neurology, Vol. 40 (November 1990), p. 1641.

CHAPTER 11

Summary of Findings and Recommendations

Introduction

As discussed in Chapter 1, Senate Concurrent Resolution No. 242, S.D. 1, requests the Bureau to:[1]

(1) Study the economic benefits that Hawaii's consumers have derived from the use of generic drug products;

(2) Study the risk and dangers of generic drug products for certain patients or conditions;

(3) Recommend whether generic drug substitution for brand-name anticonvulsant drug products prescribed for persons with epilepsies should be permitted only with the authorization of both the physician and the patient;

(4) Recommend whether generic drug substitution for brand-name drug products prescribed for persons with allergic sensitivities should be permitted only with the authorization of both the physician and the patient; and

(5) Recommend legislation and policies that allow for the assessment of fines and the removal of pharmaceutical companies from the Hawaii Drug Formulary of Equivalent Drug Products,[2] where approval from the FDA has been obtained improperly, until the safety and effectiveness of their generic drug products can be proven.

This chapter summarizes, as directly as possible, the Bureau's response to each request made by the Legislature. In the interest of brevity, this chapter does not contain the preparatory explanations or background information that have been discussed in preceding chapters. Because of the technical nature of the generic drug substitution controversy, the use of idiomatic expressions to describe key concepts and principles could not be avoided.

Findings

Economic benefits. Based on its survey of 31 frequently dispensed generic drug products, the Bureau found that:

(1) The median prices of prescriptions dispensed using generic drug products were $0.02 to $49.92 less than the prices of corresponding brand-name drug products; and

(2) The median prices of prescriptions dispensed using generic drug products were between under one per cent to 81 per cent less than the median prices of corresponding brand-name drug products.

In Hawaii in 1989, cost-savings attributable to the use of generic drug products were equal to $11,286,000. This figure can be broken down into:

(1) Cost-savings attributable to generic drug substitution (i.e., substitution involving therapeutically equivalent drug products) that were equal to $6,105,000; and

(2) Cost-savings attributable to drug product selection that were equal to $5,181,000.

Using average wholesale prices and prescription claims data for 1989, the Hawaii Medical Service Association estimated that the Association saved $4,441,035 on 491,119 prescriptions (or approximately $9.05 per prescription) through the use of generic drug products. The $4,441,035 in savings reported by the Association represented 58 per cent of the savings that were possible in 1989.

Using the average amount paid for, and the number of prescription claims dispensed using, single-source (brand-name) drug products, generic drug products, and multiple-source brand-name drug products (i.e., brand-name drug products that could have been, but were not, substituted with generic drug products), the Hawaii Dental Service estimated that it saved $327,505 on 58,163 prescriptions (or approximately $5.63 per prescription) through the use of therapeutically equivalent generic drug products. The $327,505 in savings reported by the Service represented 52 per cent of the savings that were possible in 1989.

Using number of prescriptions, average number of doses per prescription, number (and amount) of dispensing fees, cost per dose, and prescription claims data for 1989, the Department of Human Services estimated that the State's Medicaid program saved the following amounts on the following six drug products through the utilization of generic drug products.

(1) **Drug product:** Phenytoin Sodium (Dilantin), 100 mg extended release capsules.
Cost-savings: $1,595 saved on 864 prescriptions, or $1.85 per prescription.

(2) **Drug product:** Carbamazepine (Tegretol), 200 mg tablets.
Cost-savings: $5,231 saved on 468 prescriptions, or $11.18 per prescription.

(3) **Drug product:** Propranolol Hydrochloride (Inderal), 40 mg tablets.
Cost-savings: $3,627 saved on 450 prescriptions, or $8.06 per prescription.

(4) **Drug product:** Procainamide Hydrochloride (Procan SR), 500 mg sustained release tablets.
Cost-savings: $478 saved on 82 prescriptions, or $5.83 per prescription.

(5) **Drug product:** Chlorpromazine Hydrochloride (Thorazine), 50 mg tablets.
Cost-savings: $3,629 saved on 236 prescriptions, or $15.38 per prescription.

(6) **Drug product:** Haloperidol (Haldol), 10 mg tablets.
Cost-savings: $8,224 saved on 318 prescriptions, or $25.86 per prescription.

Risks and dangers. Because there is a significant relationship between the serum concentration of an antiepileptic or anticonvulsant drug and its therapeutic effect, it is reasonable to conclude that there is a relationship between the bioavailability, bioequivalence, and therapeutic equivalence of anticonvulsant drug products and the precipitation of seizures and toxic effects. A decrease in the serum concentration of an anticonvulsant drug can precipitate seizures if the decrease is brought about too abruptly or results in subtherapeutic

serum concentrations of the anticonvulsant drug. Conversely, an increase in the serum concentration of the anticonvulsant drug phenytoin near the limit of the body's ability to metabolize the drug can result in toxicity or reversible and irreversible adverse effects.

Using epilepsies and the anticonvulsant drugs as a general model of the relationship between the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products and the control of chronic, pathological conditions (e.g., propranolol hydrochloride and cardiac arrhythmias, hydrochlorothiazide and hypertension, allopurinol and gout, and chlorpropamide and diabetes milletus), the risks and dangers associated with differences in the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products used to control chronic pathologies are the risks and dangers associated with toxic and subtherapeutic serum concentrations of the drug or its metabolites. In the former instance, these risks and dangers are caused by the toxic effects of the drug or its metabolites; in the latter, they are caused by the progression of the pathology and the onset of associated complications or sequelae.

Because of its etiology, there is no relationship between an allergic reaction and the bioavailability, bioequivalence, or therapeutic equivalence of multiple-source drug products. Allergic reactions are not usually dose-dependent; therefore, a lack of bioavailability, bioequivalence, or therapeutic equivalence between two or more multiple-source drug products is not likely to precipitate the onset of this potentially life-threatening condition. An allergic reaction precipitated by generic drug substitution is most likely to be caused by an inactive ingredient in the drug product that is substituted for the drug product prescribed.

Recommendations

Persons with epilepsies. The Bureau believes that therapeutic equivalence evaluations should be scientific judgments based upon evidence, and that these judgments should be made by the Drug Product Selection Board based on policies established by the Legislature. Consequently, the Bureau does not recommend that the Legislature enact legislation to permit generic drug substitution for brand-name anticonvulsant drug products only with the authorization of both the physician and the patient.

A physician can presently prohibit generic drug substitution by handwriting the words "Do Not Substitute" on a written prescription or orally instructing a pharmacist not to substitute on an oral prescription. A patient can refuse generic drug substitution by exercising the patient's right to refuse generic drug substitution before a pharmacist dispenses the patient's prescription.

In addition, the Bureau believes that decisions regarding generic drug substitution should be based on social and economic policies intended to reduce the cost of drugs to consumers without unduly endangering their health or compromising the quality of health care, and that these policies should be determined by the Legislature and implemented by the Drug Product Selection Board. Assuming that differences in drug product characteristics such as shape, scoring configuration, packaging, excipients (including colors, flavors, preservatives), expiration time and minor aspects of labeling are not important in the care of a particular patient, the following question is one to be properly addressed by the Legislature: "Which policy should the Drug Product Selection Board adhere to when evaluating the therapeutic equivalence of anticonvulsant drug products and drug products in other therapeutic classes?"

Should the policy be one of requiring therapeutically equivalent drug products to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling? In the alternative, should the policy require therapeutically equivalent drug products to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling and accompanied by adjunctive monitoring of a patient's medication? According to Melvin Kumasaka, Chairperson of the Drug Product Selection Board, Nadine Bruce, Chairperson of the Anticonvulsant Subcommittee of the Drug Product Selection Board, and Jordan Popper, Chairperson of the Professional Advisory Board of the Epilepsy Foundation of Hawaii, persons with epilepsy can be properly titrated and maintained on generic or brand-name anticonvulsant drug products with good results. According to Kumasaka, Bruce, and Popper, problems associated with toxic or subtherapeutic doses of anticonvulsant drugs can arise when patients are indiscriminately switched from one anticonvulsant drug product to another without being retitrated on the substituted drug product. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology expressed similar concerns with respect to the anticonvulsant drugs phenytoin (Dilantin) and carbamazepine (Tegretol).

The Bureau recommends that the Legislature establish a policy on generic drug substitution that can be implemented by the Drug Product Selection Board, and that the Legislature otherwise leave to the Drug Product Selection Board the technical decisions involved in administering the State's generic drug substitution law.

Persons with allergic sensitivities. Because allergic and other toxic reactions to inactive ingredients are reportedly rare, and because allergic reactions are not usually dose-dependent or necessarily chemical-specific, the Bureau believes that the risks posed by allergic and other toxic reactions should be handled on an individual, case-by-case, basis. Consequently, the Bureau does not recommend that the Legislature enact legislation to permit generic drug substitution for brand-name drug products prescribed for persons with allergic sensitivities only with the authorization of both the physician and the patient.

The Bureau believes that the drug industry's voluntary labeling program to help alert patients to the potential of allergic reactions should be integrated with the State's generic drug substitution law since pharmacists, and not their patients, ultimately select the therapeutically equivalent generic drug products to be substituted for the brand-name drug products prescribed. Utilizing the concept of patient profile records, it would appear that integration of the drug industry's voluntary labeling program and the State's generic drug substitution law can be accomplished if, at the very minimum, pharmacists are permitted to refuse to substitute when the pharmacist's patient profile record discloses the potential for an allergic or other adverse reaction to an inactive ingredient in the therapeutically equivalent generic drug product to be substituted for the brand-name drug product prescribed.

At the very minimum, the Bureau believes that a pharmacist refusing to substitute should be required to:

(1) Inform the consumer of the pharmacist's decision not to substitute, including an explanation of why the pharmacist is refusing to substitute;

(2) Notify the prescriber of the pharmacist's decision not to substitute, including an explanation of why the pharmacist refused to substitute;

(3) Keep a separate record of the pharmacist's decisions not to substitute, including an explanation of why the pharmacist refused to substitute, and to make this record available for inspection by the Drug Product Selection Board or the Department of Health; and

(4) Make periodic reports to the Drug Product Selection Board or the Department of Health concerning the pharmacist's decisions not to substitute, as either may require.

At the very minimum, the Bureau also believes that the Drug Product Selection Board, in consultation with the Board of Pharmacy, should be required to:

(1) Adopt rules to standardize recordkeeping and reporting requirements concerning a pharmacist's decision not to substitute;

(2) Periodically review records or reports concerning a pharmacist's decision not to substitute; and

(3) Inform pharmacists and prescribers of changes in the State's generic drug substitution law and the recordkeeping and reporting requirements established by administrative rule.

Based on the foregoing discussion, the following policy question should be addressed: "Should a pharmacist be permitted to refuse to substitute when the pharmacist's patient profile record discloses the potential for an allergic or other adverse reaction to an inactive ingredient in the therapeutically equivalent generic drug product to be substituted for the brand-name drug product prescribed?" If the answer to the foregoing is "yes", then the next policy question to be addressed is: "Should a pharmacist be permitted to refuse to substitute under other circumstances if, in the pharmacist's professional judgment, generic drug substitution is not in the best interest of the consumer?"

The Bureau recommends that the Legislature address these policy issues and their implementation by the Drug Product Selection Board, and that the Legislature leave to prescribers and pharmacists the assessment and management of the risks posed by allergic and other toxic reactions to inactive ingredients.

Fines and administrative actions. The Legislature requested that the Bureau recommend legislation and policies that allow for the assessment of fines and the removal of pharmaceutical companies from the Hawaii Drug Formulary of Equivalent Drug Products,[3] where approval from the FDA has been obtained improperly, until the safety and effectiveness of their generic drug products can be proven. If the ultimate goal of the Legislature is to deter fraud and deceit or to award reparations to persons who purchase a drug product approved through fraud or deceit, then the Bureau recommends that the Legislature consider establishing a cause of action to enable persons who consume a drug product approved through fraud or deceit to seek reparations from the company that perpetrated the fraud or deceit. At the very minimum, the cause of action should:

(1) Enable persons, including third parties, to initiate an action in a circuit court and to seek reparations from a company without having to demonstrate that any material harm resulted from the consumption of the drug product;

(2) Establish a minimum award, in addition to attorneys' fees and court costs, for persons who can demonstrate that they purchased the drug product, even if they cannot demonstrate that any material harm resulted from the consumption of the drug product;

(3) Enable persons to initiate an action based on a finding by the FDA or the State of Hawaii that a company obtained approval for the drug product through fraud or deceit; and

(4) Require a company to establish and maintain a trust fund to indemnify the State of Hawaii against future claims which may arise from the fraud or deceit.

Because of questions regarding the extent to which the State's drug formulary of equivalent drug products is allowed to list additional drug products and to delete approved drug products without regard to chapter 91, Hawaii Revised Statutes (the Hawaii Administrative Procedure Act), the Bureau recommends that the Legislature use this opportunity to:

(1) Clarify whether or not the listing of additional drug products and the deletion of approved drug products is subject to chapter 91, totally exempt from chapter 91, or exempt from the public notice and public hearing requirements of chapter 91; and

(2) Amend the State's generic drug substitution law to permit the Board to establish in the State's drug formulary those drug products that the Commissioner of Food and Drugs has approved as safe and effective and has determined to be therapeutically equivalent, without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, rather than exempting the Board from all the requirements of chapter 91. To avoid untimely delays in the implementation and enforcement of these amendments to the State's drug formulary, the Bureau recommends that the Legislature permit the amendments to become effective immediately upon filing with the Office of the Lieutenant Governor without the need for gubernatorial approval.

The Bureau believes that if the Drug Product Selection Board continues to list in the Hawaii Drug Formulary of Equivalent Drug Products[4] only those drug products contained in the FDA's "Orange Book", then there may be no need for legislation that provides for the removal of pharmaceutical companies from the State's drug formulary, where approval from the FDA has been obtained improperly. Assuming that the FDA would take prompt action to remove these pharmaceutical companies from the "Orange Book" as soon as the pharmaceutical companies admitted their guilt or were found guilty in administrative hearings, it is unclear what, if anything, this legislation would accomplish.

If the Legislature is concerned that the FDA may fail to take prompt action to remove these pharmaceutical companies or their drug products from the "Orange Book" once the pharmaceutical companies admit their guilt or are found guilty in administrative hearings, the Bureau recommends that the Drug Product Selection Board be allowed to remove improperly approved drug products from the State's drug formulary of equivalent drug products without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, Hawaii Revised Statutes, and that the Legislature allow the removals to take effect upon filing with the Office of the Lieutenant Governor.

The Bureau recommends that the Drug Product Selection Board's authority under these circumstances be limited to the removal of individual drug products since the removal of pharmaceutical companies and entire lines of drug products from the State's drug formulary of equivalent drug products could potentially affect drug products that were not approved through fraud or deceit, and subject persons who rely on the availability of less expensive, therapeutically equivalent generic drug products to personal hardships. The Bureau notes that the State's Medicaid program could be particularly affected by the removal of entire lines of drug products from the State's drug formulary since the federal Health Care Financing Administration utilizes the FDA's "Orange Book", and not the State's drug formulary, when it determines the aggregate upper limits of payment for multiple source drug products.

If the Drug Product Selection Board is contemplating the addition of drug products to the State's drug formulary of equivalent drug products that are not contained in the FDA's "Orange Book", the Bureau recommends that the State's generic drug substitution law be amended to give the Board explicit authority to remove these drug products from the State's drug formulary in cases of fraud or deceit, without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, Hawaii Revised Statutes, and that these removals be allowed to become effective immediately upon filing with the Office of the Lieutenant Governor.

Another compelling reason for adopting legislation to remove drug products from the State's drug formulary of equivalent drug products in cases of fraud or deceit would be that the Board must periodically conduct meetings to determine whether or not a drug product contained in the FDA's "Orange Book" should be removed from the State's drug formulary. Because every decision of the Board has the potential to cause adverse health and economic impacts, the Bureau believes that the Board should be given the authority to:

(1) Remove a drug product from the State's drug formulary, whether or not the drug product is contained in the FDA's "Orange Book", without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, Hawaii Revised Statutes; and

(2) Bar a person from addressing the Board or bringing actions before the Board in the future;

if the Board, a county prosecuting attorney, or the Attorney General finds that the person knowingly made false or misleading statements to the Board either in support of or opposition to the removal or addition of a drug product to the State's drug formulary.

Based on the foregoing discussion, the Bureau recommends that the following policy questions be addressed:

(1) Should the Drug Product Selection Board be allowed to remove drug products from the State's drug formulary of equivalent drug products where approval from the FDA has been obtained through fraud or deceit, without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91, Hawaii Revised Statutes?

(2) Should a cause of action be established to deter fraud and deceit or to award reparations to persons who consume drug products approved through fraud or deceit?

(3) Should the Drug Product Selection Board be given the authority to:

(a) Remove a drug product from the State's drug formulary of equivalent drug products, whether or not the drug product is contained in the FDA's "Orange Book", without regard to the public notice, public hearing, and gubernatorial approval requirements of chapter 91; and

(b) Bar a person from addressing the Board or bringing actions before the Board in the future;

if the Board, a county prosecuting attorney, or the Attorney General finds that the person knowingly made false or misleading statements to the Board?

Miscellaneous--physician prerogative. Both the Hawaii Medical Association and the Drug Product Selection Board indicated an interest in adopting a two-signature prescription pad format where a prescriber would sign one line on the prescription pad to prohibit generic drug substitution and another to permit it. The Hawaii Medical Association favors a two-signature prescription pad format over the present prescription pad format since it does not require a prescriber to write the phrase "do not substitute" to prohibit generic drug substitution on written prescriptions. Convenience and recognizing the principal role of the physician in matters of patient care are the primary reasons cited by the Hawaii Medical Association for a two-signature prescription pad format. The Drug Product Selection Board's interest in the two-signature prescription pad format represents an attempt to reach a compromise with the Epilepsy Foundation of Hawaii over the removal of the anticonvulsant drugs from the State's drug formulary of equivalent drug products.

While a two-signature prescription pad format would relieve prescribers from having to write the phrase "do not substitute" to prohibit generic drug substitution on written prescriptions, it would not relieve prescribers from having to write the phrase "brand medically necessary" to meet federal Medicaid requirements. While a two-signature prescription pad format would alleviate prescribers from having to write the phrases "do not substitute" and "brand medically necessary" to meet state and federal requirements when prohibiting generic drug substitution on prescriptions written for Medicaid patients, the same result can be obtained by amending the State's generic drug substitution law to permit prescribers to write either "do not substitute" or "brand medically necessary" to prohibit generic drug substitution on written prescriptions.

An advantage of a two-signature prescription pad format is that it would preclude charges of negligence arising out of acts of omission since a prescriber would have to sign one of the two preprinted lines on the prescription pad to make the prescription valid. Again, the same results could be obtained by amending the State's generic drug substitution law to protect prescribers from these charges unless the prescriber had reasonable cause to believe that the health condition of the patient for whom the drug product was intended warranted the dispensing of a brand-name drug product and not a therapeutically equivalent generic drug product.

The Bureau believes that the relevant policy-related issues that warrant further consideration by the Legislature at this time are:

(1) Whether or not recognizing the principal role of a prescriber in matters of patient care is sufficient reason for adopting a two-signature prescription pad format. If not, then;

(2) Whether or not the State's generic drug substitution law should be amended to permit prescribers to write either "do not substitute" or "brand medically necessary" to prohibit generic drug substitution on written prescriptions; and

(3) Whether or not the State's generic drug substitution law should be amended to protect prescribers from charges of negligence arising out of acts of omission, unless the prescriber had reasonable cause to believe that the health condition of the patient for whom the drug product was intended warranted the dispensing of a brand-name drug product and not a therapeutically equivalent generic drug product.

Miscellaneous--Medicaid. The recently enacted Omnibus Budget Reconciliation Act of 1990, P.L. 101-508 (November 5, 1990), makes a number of changes to the Medicaid program and may have a substantial impact upon the states because of the potential penalties and recoupments possible through the late implementation of congressionally-mandated deadlines.

The Bureau suggests that the Legislature request the Department of Human Services to:

(1) Conduct an informational briefing for the Legislature or appropriate committees on anticipated changes to the Medicaid program before the end of the 1991 legislative session; and

(2) Submit a written report to the Legislature on the implementation of these changes before the convening of the regular session of 1992.

The informational briefing should address the substance of these changes and their anticipated outcomes. The written report should discuss the Department's implementation of these changes and any significant impacts on the ability of physicians to prohibit generic drug substitution and require the dispensing of brand-name drug products. The Department's written report should also include recommended legislation to implement these changes or to mitigate their adverse effects, if appropriate.

Summary

The Bureau believes that generic drug products can save consumers substantial sums of money as long as chemical allergies to inert ingredients, adverse psychosomatic reactions, and differences in the bioavailability, bioequivalence, and therapeutic equivalence of multiple-source drug products do not excessively complicate patient care or compromise patient health to the point where medical intervention becomes necessary. The Bureau notes that the cost of performing a blood test to retitrate a patient switched from the drug product of one manufacturer to the drug product of another manufacturer could range from $40 to $70, depending on the drug product in question. As pointed out by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, these costs represent a flaw in the economic incentive for generic substitution, which can result in additional costs that outweigh any small cost savings accruing from use of generic medications.

The Bureau believes that physicians, pharmacists, and third-party insurers all play an important role in making quality health care accessible to the people of Hawaii. The Bureau

also believes that in the end there is only one true "loser"--the patient--when adversarial and confrontational attitudes between and among physicians, pharmacists, and third-party insurers prevail. The role of the Legislature in the generic drug substitution controversy should be to establish policies that can be implemented by the Drug Product Selection Board. The role of the Drug Product Selection Board in the generic drug substitution controversy should be to faithfully implement those policies established by the Legislature. The Legislature should leave the technical decisions required for the administration of the State's generic drug substitution law to the Drug Product Selection Board, and the Drug Product Selection Board should leave the establishment of broad policies to the Legislature.

ENDNOTES

1. Senate Concurrent Resolution No. 242, S.D. 1, Fifteenth Legislature, State of Hawaii, 1990.

2. Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

3. Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

4. Section 11-33-3, Hawaii Administrative Rules (Department of Health, Drug Product Selection Board).

THE SENATE
FIFTEENTH LEGISLATURE, 1990
STATE OF HAWAII

S.C.R. NO. 242 S.D. 1

SENATE CONCURRENT RESOLUTION

REQUESTING THE LEGISLATIVE REFERENCE BUREAU TO CONDUCT A STUDY ON THE USE OF GENERIC DRUG PRODUCTS.

WHEREAS, the Hawaii Food, Drugs, and Cosmetics Act was amended in 1980 to allow generic drug substitution for brand name drugs; and

WHEREAS, the Legislature's intent was to extend cost savings to consumers; and

WHEREAS, the recent scandal of falsified lab results by several pharmaceutical companies in order to gain Federal Drug Administration (FDA) approval of their generic drugs indicates that enhanced regulation in this area may be needed; and

WHEREAS, although the FDA has suspended these pharmaceutical companies from distributing particular generic drug products, no reparations have been made available to patients; and

WHEREAS, there are some drugs for which the FDA allows a wide range of variance in determining bioequivalence and, in some cases, these drugs reportedly have been found not to be chemically identical to brand name products and not to have the same therapeutic effect; and

WHEREAS, the American Academy of Family Physicians in a publication entitled "White Paper on Generic Drugs" found that bioavailability does not necessarily equal therapeutic equivalence in certain groups of patients; and,

WHEREAS, there are concerns for certain high risk groups, such as those who are allergic to certain products, or those with critical diseases such as epilepsy who apparently are more affected by the substitution of generic drugs for brand name drugs and for whom generic substitution should only be made with extreme caution; now, therefore,

BE IT RESOLVED by the Senate of the Fifteenth Legislature of the State of Hawaii, Regular Session of 1990, the House of Representatives concurring, that the Legislative Reference Bureau, in consultation with the Department of Health, the Hawaii

RFS1654 SCR242 SD1 SMA

Medical Association, the Hawaii Medical Service Association, and other interested parties, is requested to conduct a study of the economic benefits that Hawaii's consumers have derived from the use of generic drug products, and the risks and dangers of generic drug products for certain patients or conditions; and

BE IT FURTHER RESOLVED that the study recommend whether generic substitution for brand name anticonvulsant drug products prescribed for epileptic patients and patients with allergic sensitivities should be permitted only with authorization of both physician and patient; and

BE IT FURTHER RESOLVED that the study recommend legislation and policies that allow for the assessment of fines and the removal of pharmaceutical companies from the State Drug Formularies, where approval from the FDA has been obtained improperly, until the safety and effectiveness of their generic drug products can be proven; and

BE IT FURTHER RESOLVED that the Legislative Reference Bureau report its findings and recommendations to the Legislature not later than twenty days before the convening of the Regular Session of 1991; and

BE IT FURTHER RESOLVED that certified copies of this Concurrent Resolution be transmitted to the Director of the Legislative Reference Bureau and the Director of Health.

Appendix B

AMERICAN ACADEMY OF FAMILY PHYSICIANS

WHITE PAPER ON GENERIC DRUGS

PART I — INTRODUCTION

An organization which represents as many physicians as the American Academy of Family Physicians must take a stand on the issue of generic substitution of prescription drugs. Generic products are here and they are not going to go away. More and more of our members are participating in state Medicaid programs and health maintenance organizations, and acting as hospital physicians in facilities where there is mandated substitution of generic products for their patients. The Committee on Drugs and Devices was created to maintain surveillance and make recommendations on legislative, regulatory and public activities relating to drugs and devices.

"Generic substitution" is defined as "the act of dispensing a different drug or an unbranded drug product for the drug product prescribed (i.e. chemically the same drug entity in the same dosage form, but distributed by different companies)." The Academy has taken a position of being opposed to "therapeutic substitution," which is the utilization of drug products containing different therapeutic moieties, but which are of the same pharmacologic and/or therapeutic class that can be expected to have similar therapeutic effects when administered to patients in therapeutically equivalent doses.

PART II — FEDERAL AND STATE REGULATION

The Pure Food and Drug Act of 1906 allowed the Food and Drug Administration to seize drug products which were mislabeled or adulterated, if the Agency had received complaints. The Food, Drug and Cosmetic Act of 1938 required manufacturers to submit proof of a drug's safety prior to marketing, and allowed the FDA a 60-day period to review the documentation before the drug could be marketed. In 1962 the Kefauver-Harris Amendment increased the FDA's authority by requiring that "adequate and controlled studies" demonstrate "substantial evidence" of safety and efficacy before a drug could be approved for marketing. Randomized clinical trials have generally been the required studies for such proof. Since 1970, a complete New Drug Application, including data from clinical trials, has not been required to market a product chemically the same as one marketed before 1962. Instead, such approval could be obtained by filing an Abbreviated New Drug Application (ANDA) containing evidence of the bioequivalence of the new drug to the original product. There was and is no provision that there be proof of therapeutic equivalence.

In 1984 the United States Congress enacted the Drug Price Competition and Patent Term Restoration Act. This legislation, known as the Waxman-Hatch Act, encouraged the development of new innovator drugs and facilitated the FDA's approval process for generic drugs. The law established an ANDA

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process for post-1962 drug products. Products chemically equivalent to previously approved products need only be proved bioequivalent, not clinically or therapeutically equivalent, to the original product. Specific regulations will be discussed in PART III of this report.

The individual states maintain much of the authority to regulate drug substitution. Most states had anti-substitution laws in the 1950s, but all of these had been modified or repealed by 1982. Most states use the FDA's "orange book," as the guide by which their Medicaid formularies are developed. States can set different regulations from the FDA. California (Bioequivalence Advisory Panel) and New Jersey (Drug Utilization Review Council) have rated generic thioridazine and nitrofurantoin products as "not bioequivalent." In addition to this, the availability of brand name products may be restricted by hospital and health maintenance organization formularies, with the bounds allowed by the state in which they function. Although these limitations affect the physician's prescribing of therapy for his/her patient, this issue will not be dealt with in this paper.

The family physicians of the United States of America share the concern of other specialty groups of physicians, particularly as it relates to the use of generic drug products in children and the elderly of our nation. Bioavailability does not necessarily equal therapeutic equivalence in these groups of patients.

PART III — THE FDA APPROVAL PROCESS

A manufacturer must meet three general requirements to obtain FDA approval for the marketing of a generic drug. First, the generic product must have the same amount of active ingredients in the same dosage form and with the same route of administration, as the innovator product. The same manufacturing standards must be met by the generic, as are required by the innovator product. All prescription drugs are subject to the FDA Good Manufacturing Practices regulations governing manufacture and quality. Lastly, a manufacturer must show that the product is bioequivalent to the innovator product.

In some instances, the FDA requires only in vitro tests for drug identity, strength, quality, purity, disintegration, or dissolution to establish bioequivalence. For the majority of generic products, a study with human subjects (in vivo) must be done. These in vivo studies of bioavailability generally measure the extent and rate of absorption of the drug in the systemic circulation, rather than the drug's actual effect. The FDA specifies that testing be conducted in approximately 18-24 (one study noted only six subjects were tested) healthy persons between the ages of 21 and 35, who are within 10 percent of their ideal body weight, under fasting conditions. The study shall be one with a single-dose, randomized, crossover design. These FDA guidelines attempt to minimize the effect of inter- and intra-subject variability. Factors considered as important by the FDA are: (1) Tmax — the measurement of time, after administration of the drug, at which the maximum serum concentration of a product is achieved; (2) Cmax — the maximum serum concentration achieved;

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and (3) AUC (Area Under the Curve) — the total absorption of a single test dose. Many studies reveal that these criteria are not met by "orange book" equivalent products. There is much debate, which must be acknowledged, concerning the absence of proof that the availability of the therapeutic chemical in a drug equates with the effects, side-effects, or toxicity of additives and inert materials in a drug product.

In terms of approval of a generic product, bioavailability means that the testing of the generic reveals +/-20 percent of the availability of the innovator product. The FDA has established different standards for different drugs or drug classes. Frequently noted examples in the literature are: +/-10 percent for warfarin; +/-25 percent for antiarrhythmic drugs; and +/-30 percent for anti-psychotic drugs.

PART IV — CONCLUSION

The findings of the committee in its review of the medical literature and of the definitions and claims of the FDA have raised serious concerns about generic drugs which can no longer be ignored. There is much evidence in the medical literature which indicates that many so-called generic drug substitutes are not "chemically the same drug entity in the same dosage form." A generic drug must be identical to the brand name product. Many generic formulations contain different "additives" and "inert" compounds, as compared to the brand name product, and therefore must not be considered bioequivalent This information applies to many of the drugs listed as class "A" in the FDA's "orange book." The bioavailability of a drug in serum or urine measurements cannot be assumed to mean that the drug is therapeutically equivalent. It is clear from our review that some drugs have an extremely narrow therapeutic window. In our opinion, even a 10 percent over or under dosage may be dangerous in our patients.

If a family physician, participating in a health maintenance organization or a hospital setting, is required to prescribe a generic product and his/her patient's condition worsens, we would recommend close monitoring of serum drug levels, rather than assuming that the patient's disease state has changed or that the patient's degree of compliance with the treatment regimen has changed. Investigation may prove that the real problem is related to switching from a brand name drug to a generic product or from one generic to another generic without the physician's knowledge. Although measuring serum blood levels may obviate any cost benefit to the total health management plan, we have no other alternative to suggest.

The FDA methodology of testing a generic product, using 18-24 healthy volunteers between the ages of 21 and 35 years of age, whose weight is within 10 percent of normal, is lacking in credibility by most researchers. The methodology fails to consider first pass metabolism, active metabolites of the chemical, age, sex, dissolution, absorption, gastric pH, influence of other diseases and drugs, and effects of ingestion with food, alcohol or in a tobacco user. One study revealed that two FDA supported laboratories did not agree on serum levels in a study of one generic drug.

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In the article "Are Generic Drugs Dangerous for the Aged" (Lamy, p. 42, Journal of Gerontological Nursing, 11(4) "42, 1985 April), the author suggests a new system recognizing that there are "critical patients, critical diseases and critical drugs for which generic substitution should never be mandated." Using this model, the Committee on Drugs and Devises modified the description of these to read as follows:

Critical Patients: For example, these would include those 75 years and older, and females living alone with multiple pathology on multiple drug regimens.

Critical Diseases: These would include those disease states which are difficult to stabilize. Examples of critical diseases include depression, asthma, congestive heart failure, diabetes mellitus, cardiac problems, and the psychoses.

Critical Drugs: These are drugs for which the FDA allows a wide range of variance in determining bioequivalence. Examples of these critical drugs include antipsychotics and loop diuretics. Drugs listed as class "B" in the FDA "orange book" should not be substituted.

PART V — RECOMMENDATIONS

As patient advocate, the family physician has the ultimate responsibility for the treatment prescribed for any given disease process. That responsibility includes securing safe, efficacious, and cost-effective medications. A review of the medical literature reveals that generic drugs approved by the FDA are not chemically identical (the same drug entity in the same dosage form) to the brand name product in many well documented cases. In addition, the testing required by the FDA does not document that bioequivalency equals therapeutic equivalency. All drugs approved by the FDA as generically equivalent (i.e. listed as class "A" in the FDA "orange book") frequently have not been found to be as safe and effective as their brand name counterparts.

There are "Critical Patients," "Critical Drugs," and "Critical Diseases" in which there should never be mandatory substitution of a generic drug.

Critical Patients: For example, these would include those 75 years and older, and females living alone with multiple pathology on multiple drug regimens.

Critical Diseases: These would include those disease states which are difficult to stabilize. Examples of critical diseases include depression, asthma, congestive heart failure, diabetes mellitus, cardiac problems, and the psychoses.

Critical Drugs: These are drugs for which the FDA allows a wide range of variance in determining bioequivalence. Examples of these critical drugs include antipsychotics and loop diuretics. Drugs listed as class "B" in the FDA "orange book" should not be substituted.

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(a) The Academy encourages the FDA to revise or enforce its current definition of a generic drug, and enact regulations requiring scientifically reliable methodology to insure therapeutic equivalency, rather than bioequivalency.

(b) The Academy recommends that the FDA streamline the procedures for reporting of drug toxicity and ineffectiveness. The present method is burdensome and often without positive results. This does not encourage the reporting of problems related to brand name or generic substitutes.

(c) The Academy supports the position that there should be no blanket approval of generic substitution. If substitution is mandated, the Academy encourages members to carefully monitor patients.

(d) The Academy should encourage family practice residency programs to institute original and ongoing research in the area of therapeutic equivalency versus bioavailability, with emphasis on toxicity and side effects, as well as efficacy of generic products.

(e) The American Academy of Family Physicians urges its members to be their patient's advocate, as a source of objective scientific information concerning brand name and generic drugs. The Academy supports the concept of prescribing the least costly medication, if safety and efficacy are not compromised.

(f) The American Academy of Family Physicians is committed to continually reviewing the issue of safety and efficacy of generic drugs and to make appropriate changes in policy as new information becomes available. The Academy further encourages its constituent chapters to monitor the issue of generic drugs in each state.

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Appendix C

Review of Bibliography

Introduction

This appendix briefly describes 60 of the 73 articles, editorials, commentaries, and other publications referenced in the bibliography of the American Academy of Family Physicians' "White Paper on Generic Drugs". The descriptions discuss what the Bureau believed to be the most relevant aspects of each reference insofar as the Bureau's study was concerned. The purpose of this review is not to provide the reader with enough information to draw conclusions about the validity of each reference and its relevance to the Academy's "White Paper"; rather, the purpose of this review is to illustrate the complex scientific and philosophical issues surrounding the generic drug substitution controversy, and to illustrate the disagreements over these and other issues. Readers interested in drawing conclusions about the validity of these references and their relevance to the Academy's "White Paper" should read each reference in its entirety instead of relying on the Bureau's descriptions. These references are available at the Hawaii Medical Library and the University of Hawaii's Hamilton Library.

(1) Medical Letter on Drugs & Therapeutics, "Generic topical corticosteroids", Vol. 30, No. 765 (May 6, 1988), pp. 49-50.

Description: Reports differences in the potency of brand-name topical corticosteroids and their generic counterparts. Reports no difference in the potency of three different concentrations of the same brand-name topical corticosteroid.

(3) Sheila Richton-Hewett, Elyse Foster and Carl Apstein, "Medical and Economic Consequences of a Blinded Oral Anticoagulant Brand Change at a Municipal Hospital", Archives of Internal Medicine, Vol. 148, No. 4 (April 1988), pp. 806-808.

Description: Reports an increase in the number of patients whose anticoagulation was poorly controlled following a change in the brand of warfarin sodium used in the Boston City Hospital. Reports that there was a concomitant increase in the number of clinic visits and an increased frequency of prothrombin time test to regulate the dosage in such patients. Reports that a significant increase in morbidity and overall health care costs resulted from this attempt to economize by changing brands of medication.

(4) Alexander Fisher, "The Significance of Ethylenediamine Hydrochloride Dermatitis Caused by a 'generic' Nystatin-Triamcinolone II Cream", Cutis, Vol. 41, No. 4 (April 1988), p. 241.

Description: Reports the allergic reaction (contact dermatitis) of a 42-year old male to ethylenediamine hydrochloride, an inert ingredient and sensitizer found in Myco-Triacet II Cream but not its supposed equivalent, Mycolog II Cream.

(6) Alexander Fisher, "Problems Associated with 'Generic' Topical Medications", Cutis, Vol. 41, No. 5 (May 1988), pp. 313-314.

Description: Discusses potential allergic problems (sensitivity) with generic formulations of two different topical medications because of the inert ingredients used to preserve these medications. Discusses the problem of identifying sensitizing inert ingredients in topical dermatologic medications. Reports differences in the potency of brand-name topical corticosteroids and their generic counterparts.

(8) Mark Manzo, "A drug by any other name. Your guide to generic and brand names", Nursing 88, Vol. 18, No. 1 (January 1988), pp. 113-120.

Description: Lists over 800 brand-name drug products by their established names.

(10) E. Kallstrom, M. Heikinheimo and H. Quiding, "Bioavailability of three commercial preparations of ibuprofen 600 mg.", Journal of International Medical Research, Vol. 16, No. 1 (January-February 1988), pp. 44-49.

Description: Reports that different brands of ibuprofen may not be pharmacokinetically interchangeable, and that Brufen is superior to either Burana or Ibumetin when considering both the rate and extent of absorption.

(11) Allan Barreuther, "Problems with generic theophylline and indiscriminate brand switching", Annals of Allergy, Vol. 60, No. 3 (March 1988), pp. 275-276.

Description (Letter to the Editor): Discusses an article entitled, "Problems with generic theophylline and indiscriminate brand switching", authored by Gerald Klein. States that "[m]y greatest concern with this article is that it bears a misleading title and is passed off as a 'scientific' article rather than pure misguided opinion". States that the author (Klein) resorts to using obscure references to confirm his impression of what might happen in some patients if indiscriminate switching were to happen.

(12) Richard Stoughton, "Are generic topical glucocorticosteroids equivalent to the brand name?", Journal of the American Academy of Dermatology, Vol. 18, No. 1 Part 1 (January 1988), pp. 138-139.

Description (Editorial): Discusses differences in the potency of brand-name topical corticosteroids and their generic counterparts using the vasoconstrictor assay method. States that it is common knowledge among those who work with problems in percutaneous absorption that minor differences in formulation

can lead to major differences in penetration by glucocorticosteroids. Suggests that the vasoconstrictor assay method be used to compare the equivalence of generic drugs with their brand-name equivalents before the generic drugs are released for prescription use.

(14) John Aita, "Generic vs branded carbamazepine", Nebraska Medical Journal, Vol. 73, No. 11 (November 1988), pp. 322-323.

Description (Letter to the Editor): Expresses the author's displeasure with the Nebraska Department of Social Services' decision to pay for a generic anticonvulsant (carbamazepine) rather than the brand-name anticonvulsant (Tegretol) unless prior authorization for the brand-name product is obtained by the physician.

(15) R. Faser Triplett, "Generic substitution: a dilemma for the allergist", Annals of Allergy, Vol. 61, No. 5 (November 1988), pp. 323a-323b.

Description: Discusses the bioinequivalence of theophylline sustained-released formulations and other generic drugs. States that there is an accumulating literature describing reports of patients adequately controlled with a brand-name product and who either had subtherapeutic or toxic responses when switched to a generic drug.

(16) Joanne Rogin, "Generic anticonvulsants", Minnesota Medicine, Vol. 71, No. 3 (March 1988), p. 120.

Description (Letter to the Editor): Expresses the concerns of the Epilepsy Foundation of America regarding the mandatory substitution of generic anticonvulsants. Suggests that rule-making bodies--including those at the federal and state levels, as well as prepaid medical plans, institutions such as hospitals, correctional facilities, residential facilities, and others who make decisions about the availability of certain medications--be made aware of the potential adverse effects of changing from one formulation of an anticonvulsant to another without the prior expressed permission of the treating physician and the agreement of the patient.

(17) Fred Baughman, Jr., "Substituting of Generic Drugs", Western Journal of Medicine, Vol. 148, No. 4 (April 1988), p. 469.

Description (Letter to the Editor): Expresses the author's concerns about Medi-Cal, health maintenance organizations, and independent practice associations mandating substitution with generic preparations in cases where a brand-name drug has previously been used by a patient. States that because there is no proof of the equivalency of a generic anticonvulsant to the brand-name drug or, for that matter, to other generic preparations of the same drug, any change from the preparation with which seizure control was obtained must be viewed as a therapeutic trial and, as such, one attended by the slight but real possibility that seizure control could be lost.

(19) Stephen Curry, John Gums, Lisa Williams, R. Whitney Curry and Bernard Wolfson, "Levothyroxine sodium tablets: chemical equivalence and

bioequivalence", Drug Intelligence & Clinical Pharmacy, Vol. 22, No. 7/8 (July-August 1988), pp. 589-591.

Description: Discusses the bioequivalence of two brands of levothyroxine sodium tablets compared in a study using hypothyroid patients. Discusses past reports of bioequivalence and bioinequivalence with respect to levothyroxine products. States that some of the subpotency data may have arisen because an inappropriate assay method has traditionally been used in tablet standardization. States that most of the bioequivalence studies have suffered from poor design, i.e., they were anecdotal, involved too few patients, were not randomized or blinded, failed to involve compliance checks or to standardize blood drawing times, and used healthy volunteers. States that nonhypothyroid patients (healthy volunteers) can adjust to variable levothyroxine intake, yielding normal test results from relatively inactive or superpotent tablets. States that the two brands of levothyroxine are bioequivalent.

(20) Howard Netz, "Generic Drugs: Therapeutic Effectiveness and Interchangeability", Colorado Medicine, Vol. 85, No. 16 (September 1, 1988), pp. 347-348.

Description: Discusses the position of the Colorado Medical Society with respect to generic substitution. Discusses the Colorado Law of Drugs and Druggists. States that many pharmacists are not knowledgeable regarding equivalence issues, and in fact many pharmacists do not own or are not aware of the Federal Food and Drug List (the FDA's "Orange Book"). States that many physicians are not knowledgeable nor can be expected to be knowledgeable regarding the many manufacturers and their generic substitution products. Makes seven recommendations regarding generic substitution.

(21) Lial Kofoed and Martha Nelson, "Psychological Issues in the Use of Generic Drugs", American Journal of Psychiatry, Vol. 145, No. 10 (October 1988), pp. 1315-1316.

Discussion (Letter to the Editor): Discusses the case history of an elderly paranoid male whose condition deteriorated as a result of subtherapeutic serum phenytoin and carbamazepine levels. Explains that the pharmacy at which the patient obtained his medication had changed its supplier of carbamazepine, and that the patient noticed the change in shape and color of the carbamazepine tablets from those he had been previously taking. States that the patient became reluctant to take the carbamazepine and then refused to take the phenytoin as well. States that the patient's baseline suspiciousness was aggravated by the unexpected and unexplained change in the color and shape of the carbamazepine tablets, and that subsequent reductions in the patient's serum drug levels and the associated symptom escalation were the result of noncompliance with his regimen rather than lack of bioequivalence of the new tablets.

(22) Andre Jackson and Mei-Ling Chen, "Application of Moment Analysis in Assessing Rates of Absorption for Bioequivalence Studies", Journal of Pharmaceutical Sciences, Vol. 76, No. 1 (January 1987), pp. 6-9.

Description: Discusses the use of moment analysis in the evaluation of equivalency between test and reference formulations with respect to the rate of absorption for four drugs having different pharmacokinetic characteristics. States that currently, the most common procedure for comparing rates of absorption is to use peak plasma concentration (C_{max}) and time to peak (t_{max}), both of which have been pointed out to be rather rough estimates containing minimal information about the absorption process. States that these parameters (C_{max} and t_{max}) are not well defined for drugs that show multiple peak concentrations and, thus, no uniform methods are available for assessing the rate of absorption. States that mean absorption time has utility as a parameter in assessing equivalency for the classes of drugs in this study, especially when used in conjunction with C_{max}.

(23) Paul Doering, Oscar Araujo and Franklin Flowers, "Generic equivalence of dermatologic products. How equivalent is equivalent?", Journal of the American Academy of Dermatology, Vol. 16, No. 5 Part 1 (May 1987), pp. 1068-1070.

Description (Commentary): Discusses the case history of a 66-year old white male who purchased a generic form of fluocinolone ointment in a petroleum base despite instructions from his physician to the contrary. Discusses the problem of inactive ingredients that are found in the generic substitute, some of which are known topical sensitizers, but are not found in the brand-name drug product (Synalar). States that the events in this case unfolded in a time sequence that made patch tests impractical. States that the evidence that the inactive ingredients worsened the condition is strictly circumstantial, and that the worsening could likely have been the normal variation of the disease process itself.

(24) Louis Keith and Michael Method, "Generic Drugs in Reproductive Medicine: Is the Value Anticipated the Value Obtained?", International Journal of Fertility, Vol. 32, No. 4 (July/August 1987), pp. 268-278.

Description: Discusses some of the potential clinical problems that may arise when generic drugs are substituted in reproductive medicine. States that generic substitution in reproductive medicine is beset with potentially serious clinical problems arising from the extremely narrow margin for dosage error, highly individual dosage requirements, and adverse economic and psychological consequences following generic failure. States that current FDA guidelines may allow an unacceptably high degree of variation in bioavailability, and that the policy of testing in males those drugs designed to be given with virtual exclusivity to females may introduce other, as yet unknown, problems. States that generic substitution may also engender reductions in patient compliance since, with oral contraceptives, for example, the major compliance problem is likely to arise from faulty tablet taking due to differing colors, sizes, and packaging. States that regardless of the medication prescribed, any change in the appearance of dispensed medications may lead to confusion, especially when patients are unaware of the generic substitution, have been receiving a familiar medication for months, are elderly and, perhaps, set in their habits, do not speak or read English, or are functionally illiterate.

(25) Daniel Dreyfuss, Richard Shader, Jerold Harmatz and David Greenblatt, "Bioequivalence Studies in the Elderly: A Pilot Study of Two Oxazepam Dosage Forms", Journal of Clinical Psychopharmacology, Vol. 7, No. 3 (June 1987), pp. 200-201.

Description (Letter to the Editor): Describes the results of a pilot bioequivalence study using elderly individuals. States that the study demonstrates the bioequivalence of two oral dosage forms of oxazepam in elderly individuals. States that bioequivalence studies should not necessarily exclude elderly subjects as long as they are medically suitable for participation, and that for some medications that are primarily administered to elderly persons in clinical practice, elderly volunteers may constitute the most appropriate subject group for bioequivalence studies.

(26) Brian Strom, "Generic drug substitution revisited", New England Journal of Medicine, Vol. 316, No. 23 (June 4, 1987), pp. 1456-1462.

Description: Discusses the uncertainty over which pharmacokinetic factors are needed to ensure bioequivalence, the affect that individual differences can have on bioavailability, the problem of first-pass metabolism, the clinical activity of major metabolites, the problems involved in extrapolating from a single-dose test to a steady state, and the overall utility of bioavailability testing as a means of predicting therapeutic equivalence. Reports that a recent study found that two laboratories, both run by the FDA, did not agree completely on any set of trials for four different drug products. States that in the absence of evidence to the contrary, the FDA's current method of approving new generic products, on the basis of bioavailability data, seems to be an acceptable interim approach. States that the FDA's method should be improved as the technology evolves. Suggests that in the meantime, physicians and patients can continue to consider using generic drugs, bearing in mind that their use may result in financial savings and that a few generic drugs have been found to be clinically inequivalent to their brand-name counterparts.

(27) Gerald Faich, James Morrison, Edwin Dutra, Donald Hare and Peter Rheinstein, "Reassurance about generic drugs", New England Journal of Medicine, Vol. 316, No. 23 (June 4, 1987), pp. 1473-1475.

Description (Letter to the Editor): Discusses an article entitled, "Generic Drug Substitution Revisited", authored by Brian Strom. Discusses the FDA's procedure and rationale for evaluating the bioequivalence of generic drugs. Discusses the criticisms of the FDA's procedure and the basis for refuting these criticisms. States that clinicians and patients should find reassurance in the fact that although hundreds of new generic products have been approved since 1984, the FDA has yet to receive a documented instance of a serious problem with a generic drug.

(28) Daniel Greenblatt and Richard Shader, "Bioequivalence of Generic Drugs in Clinical Psychopharmacology", Journal of Clinical Psychopharmacology, Vol. 7, No. 1 (February 1987), pp. A21-A23.

Description (Editorial): Discusses a study on mean plasma trazodone concentrations in six healthy volunteers following administration of 50 mg as an

oral solution, the film-sealed tablet, and the Dividose tablet. States that this is not a comparison of a brand-name versus a generic preparation, but rather a comparison of two dosage forms of the same manufacturer. States that in the vast majority of cases, generically available equivalents of brand-name psychotropic drugs can be assumed to be bioequivalent and therapeutically equivalent, and that given the large number of generic drug prescriptions, there are few well-documented problems. Suggests, however, that thought and attention to the problem of therapeutic inequivalence are always appropriate.

(30) Gerald Klein, "Problems with generic theophylline and indiscriminate brand switching", Annals of Allergy, Vol. 58, No. 5 (May 1987), pp. 350-352.

Description: States that substitution of theophylline brands without careful monitoring can result in toxic levels. Discusses the findings and recommendations of other researchers with respect to fluctuations in theophylline serum levels, suggesting that patients should not be routinely switched from one theophylline product to another without adequate monitoring and that indiscriminate serum sampling should be discouraged. States that the problems associated with the use of generic theophylline will probably increase.

(31) Gloria Koch and John Allen, "Untoward Effects of Generic Carbamazepine Therapy", Archives of Neurology, Vol. 44, No. 6 (June 1987), pp. 578-579.

Description: Discusses the case history of a 30-year old women who exhibited significant clinical deterioration while receiving generic carbamazepine therapy for a short period of time. Discusses the results of assays to determine the patient's serum carbamazepine levels. States that a physician must consider decreased bioavailability or altered metabolism of generic carbamazepine in compliant patients who have been under good control but whose condition subsequently deteriorates.

(32) American Academy of Pediatrics Committee on Drugs, "Generic Prescribing, Generic Substitution and Therapeutic Substitution", Pediatrics, Vol. 79, No. 5 (May 1987), p. 835.

Description: Discusses the American Academy of Pediatrics' position on generic prescribing, generic substitution, and therapeutic substitution. States that "there is little evidence to support the assumption of bioequivalence for most therapeutic agents in infants and children" and "[t]herefore, the Committee [on Drugs] does not support a blanket recommendation for generic substitution". States that the Committee strongly opposes therapeutic substitution. Makes four recommendations regarding generic prescribing, generic substitution, and therapeutic substitution.

(33) Elaine Wyllie, C.E. Pippenger and A. David Rothner, "Increased Seizure Frequency With Generic Primidone", JAMA (Journal of the American Medical Association), Vol. 258, No. 9 (September 4, 1987), pp. 1216-1217.

Discussion: Discusses the case history of a 16-year old girl who twice exhibited problems when she was switched from primidone (Mysoline) to generic primidone (Bolar). States that seizure frequency increased in both episodes and that trough serum primidone and phenobarbital concentrations

dropped precipitously during the second episode. States that the two primidone preparations were clearly not bioequivalent in this patient, even though both were approved by the FDA. Discusses the results of assays to determine the patient's serum primidone and phenobarbital levels during the second of these two episodes.

(34) Stephen Olsen, Michael Eldon, Roger Toothaker, James Ferry and Wayne Colburn, "Controversy II: Bioequivalence as an Indicator of Therapeutic Equivalence: Modeling the Theoretic Influence of Bioinequivalence on Single-Dose Drug Effect", Journal of Clinical Pharmacology, Vol. 27, No. 5 (May-June 1987), pp. 342-345.

Description: Reports that inherent interindividual variability in pharmacodynamic response can have a more dramatic impact on effect duration than a change in bioavailability. States that inherent variability in response to a targeted plasma drug concentration has the potential to produce greater therapeutic failures than those produced through variation in bioavailability. States that "the results from our limited simulations indicate that therapeutic failures within the current FDA bioequivalence criteria are not likely to be a result of bioavailability differences".

(35) Bruce Diamond and J. William Albrecht, "Medical and Psychiatric Implications of Generic Drugs", Psychopathology, Vol. 20, Supplement No. 1 (1987), pp. 92-93.

Description: Discusses the economic, scientific, social, political, and legal implications of generic drug use. States that bioequivalence does not necessarily translate into therapeutic equivalence and that, in some cases, because of the broad interpretation of drug equivalence, patients may not be receiving adequate amounts of medication, while others may be receiving toxic doses. States that resolving the generic drug standard issue by adopting stricter guidelines for generic drug approval based on clinical efficacy and toxicity data rather than on the bioequivalence standard currently being used would more likely result in safer, more effective patient care.

(37) John MacDonald, "Breakthrough seizure following substitution of Depakene capsules (Abbott) with a generic product", Neurology, Vol. 37, No. 12 (December 1987), p. 1885.

Description: Discusses the case history of a 19-year old female who apparently experienced breakthrough seizures after a generic brand of valproic acid was substituted for Depakene capsules (Abbott), which the patient had been taking continuously for many years and which had allowed the patient to remain seizure-free for three years. States that this previously well-controlled epileptic patient's breakthrough seizure most likely resulted from the abrupt substitution of a different commercial preparation of valproic acid, possibly resulting in a significant change in plasma AED (antiepileptic drug) levels. States that acute plasma AED levels were not available in this case.

(38) Richard Stoughton, "Are Generic Formulations Equivalent to Trade Name Topical Glucocorticoids?", Archives of Dermatology, Vol. 123, No. 10 (October 1987), pp. 1312-1314.

Description: Reports differences in the potency of brand-name topical corticosteroids and their generic counterparts. Reports no difference in the potency of three different concentrations of the same brand-name topical corticosteroid.

(39) David Greenblatt and Richard Shader, "Drug Absorption Rate: A Critical Component of Bioequivalence Assessment in Psychopharmacology", Journal of Clinical Pharmacology, Vol. 27, No. 2 (February 1987), pp. 85-86.

Description (Commentary): Discusses the importance of rate and extent of drug absorption in bioequivalence studies of psychotropic drugs. Cites the benzodiazepines as an example.

(42) Harold Dettelbach, "A time to speak out on bioequivalence and therapeutic equivalence", Journal of Clinical Pharmacology, Vol. 26, No. 5 (May-June 1986), pp. 307-308.

Description (Editorial): Suggests that the present system for evaluating generic drugs be revised to include patients, the group in whom therapeutic and pharmacodynamic differences can be of critical importance.

(43) Peter Lamy, "Generic equivalents: Issues and concerns", Journal of Clinical Pharmacology, Vol. 26, No. 5 (May-June 1986), pp. 309-316.

Description: Discusses concerns regarding substitution without the knowledge of the physician or patient, mandated substitution and the switching of generic and brand-name products, and the restriction of product availability through state formularies. Discusses the favorable treatment of generic manufacturers and products, legal challenges to the abbreviated new drug application process, and liability for injuries arising from substitution. Discusses the lack of "due process" in the procedure for evaluating bioequivalency and the unilateral nature of the FDA's internal "guidances", and the disagreement over statistical evaluation. Discusses special concerns regarding elderly patients and critical drugs, critical diseases, and critical patients. States that "[i]n one instance a generic product received approval even though there was a difference of 30% from the reference compound (not allowed for this class of drug), and a power range of 55% to 81%". States that "examination of IND [investigational new drug application] 15-087 for a generic thioridazine, which was approved, shows that of 24 study subjects, four dropped out (unexplained) and that 45% failed the test for AUC, 40% failed C_{max}, and 75% failed t_{max}".

(44) Richard Shader and David Greenblatt, "'Look-alikes' and generics", Journal of Clinical Psychopharmacology, Vol. 6, No. 2 (April 1986), pp. A17-A18.

Description (Editorial): Discusses the problem of "look alike" drug products, or different chemical entities whose pharmaceutical dosage forms appear identical. Discusses the FDA's list of approved prescription drug products with therapeutic equivalence evaluations and the limitations of the FDA's current procedure for evaluating bioequivalence.

(45) Robert Wolen, "The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence", Journal of Clinical Pharmacology, Vol. 26, No. 6 (July-August 1986), pp. 419-424.

Description: Reports that the application of stable isotope methodology to the problems of bioavailability and bioequivalence has proved extremely versatile and useful, and that the technique is simple and powerful and results in extremely low risk to the subject. Suggests the use of stable isotope methods for routine and difficult bioavailability problems. States that the use of stable isotopes could, according to other researchers, reduce the number of subjects in a bioequivalence trial by at least 50 percent. States that in addition to reducing the cost of a trial, the use of stable isotopes reduces the time, number of samples collected, and subject discomfort when compared to conventional cross over designs while providing superior data.

(46) John Colaizzi and David Lowenthal, "Critical Therapeutic Categories: A Contradiction to Generic Substitutions?", Clinical Therapeutics, Vol. 8, No. 4 (1986), pp. 370-379.

Description: Discusses the FDA's policy for the approval of generic drugs, the basis for professional criticism of the FDA's bioequivalence policies, the therapeutic categories in which generic substitution may alter clinical outcome, and other potential problem areas. States that in certain critical therapeutic categories and for certain patient populations, each substitution poses the risk of treatment failure and of increased toxicity. States that these therapeutic categories include cardiovascular drugs, psychotropic agents, and anticonvulsants. States that the populations at risk include debilitated or elderly patients with abnormal gastrointestinal, renal, or hepatic function. States that the FDA's approach to approval of generic drugs, based primarily on the demonstration of bioequivalence, is considered by many professionals as likely to result in excessive variability among treated patients. States that indiscriminate switching among generic products should be avoided, especially for drugs in these critical therapeutic categories and for drugs prescribed for elderly or debilitated patients.

(49) John Colaizzi and Joseph Barone, "Physicians and pharmacist attitudes toward a generic incentive program," New Jersey Medicine, Vol. 83, No. 3 (March 1986), pp. 153-156.

Description: Discusses the results of a survey to assess the attitudes of New Jersey's physicians and pharmacists toward a dual copay prescription drug program designed to stimulate generic dispensing. States that although programs designed to enhance the use of generic drugs might have a valuable intent of reducing health care costs, it is alarming that so many physicians and pharmacists harbor substantial reservations about such efforts to increase the rate of generic substitution. States that the results presented in this study demonstrate that many pharmacists and physicians have concerns about the consequences of programs to contain and reduce health care costs. States that the response rate to the questionnaire was 29 percent and 31 percent for physicians and pharmacists, respectively.

(50) Miles Weinberger and Gary Milavetz, "Influence of formulation on oral drug delivery: considerations for generic substitution and selection of slow-release products", Iowa Medicine, Vol. 76, No. 1 (January 1986), pp. 24-28.

Description: States that despite improved standards for known problem drugs and considerable effort expended by the FDA to disseminate information regarding the bioequivalency of different formulations of the same drug, documented bioinequivalency remains common, and concerns remain regarding the adequacy of bioavailability data for many medications without established inequivalence. Discusses the effect of variations in formulation on the bioavailability of digoxin, phenytoin, and theophylline. States that the potential for a formulation to affect drug delivery requires careful consideration on the part of the prescribing physician and dispensing pharmacist.

(51) Betty Dong, Victoria Young and Basil Rapoport, "The nonequivalence of levothyroxine products", Drug Intelligence & Clinical Pharmacy, Vol. 20, No. 1 (January 1986), pp. 77-78.

Description (Letter to the Editor): Describes the results of assays to determine the levothyroxine content of several brand-name and generic products using high performance liquid chromatography. States that generic products had variable hormone contents ranging from ± 30 percent of their stated content. States that Levothyroid (a brand-name product) had 99 percent of its stated content and that, prior to its reformulation in 1982, Synthroid (a brand-name product) contained 25 percent less levothyroxine than its stated content. States that according to other authors, Synthroid now contains 100 percent of its stated content. States that these data clearly show that there is a wide variability between brand and generic products with regard to actual versus stated levothyroxine content.

(53) Paul Groth and James Dunn, "Bioavailability of indomethacin tablets in men volunteers", Clinical Pharmacy, Vol. 5, No. 10 (October 1986), pp. 820-824.

Description: Compares the bioavailability of indomethacin in 22 healthy men who received two tablet dosage formulations and a capsule formulation. Reports that the results of this bioequivalency study demonstrate that the extent of absorption of indomethacin from the two tablet formulations studied is similar to that of the reference capsule formulation, and that a trend toward earlier and higher peak serum concentrations with the capsule was observed.

(54) Craig White, "Generic Distributors Should Not Assume Bioequivalency", American Pharmacy, Vol. NS26, No. 11 (November 1986), pp. 6 and 16.

Description (Letter to the Editor): Expresses the author's concern over the substitution of one generic version of chlorthalidone for another generic version of this drug by a distributor of generic drug products. States that after reading various reports in the literature, it can be deduced that FDA approval of generic products is not necessarily an indication that the products are equivalent in all instances. States that generic distributors should be as accountable for the products they sell as a pharmacist is accountable for the products that the pharmacist dispenses.

(55) Benjamin Calesnick, Lloyd Kreider and Annette Dinan, "Genesis of generic drugs," Pennsylvania Medicine, Vol. 89, No. 12 (December 1986), pp. 32, 34 and 36.

Description: Discusses the Pennsylvania Generic Drug Law. States that the law's protection of physicians and pharmacists from increased liability (when substitution is authorized) is complemented by an exhaustive scientific review of drug products to ensure that the drug products are bioequivalent before being admitted to the state formulary. States that under these safeguards, prescribing physicians may be satisfied when they permit generic drug substitution for a patient's prescription.

(56) Sheldon Stoffer, "Will generic substitution affect quality of generic care?", Geriatrics, Vol. 41, No. 12 (December 1986), pp. 21 and 23-24.

Description: Discusses the FDA's procedure for evaluating the bioequivalence of generic drugs and the potential problems that the procedure can pose for elderly patients. States that although people over the age of 65 currently account for more than 30 percent of this country's drug sales, very few drug companies have tested their products extensively in the geriatric population. States that old people take more drugs than young people, creating greater opportunity for adverse drug reactions, and that an adverse drug reaction may be masked by both the diseases that afflict the elderly and the normal ravages of aging. Makes six recommendations regarding generic substitution.

(57) Joseph Barone and Wesley Byerly, "Determination of Bioequivalence of Psychotropic Drugs and Concerns Involving Product Interchange", Journal of Clinical Psychiatry, Vol. 47 (Supplement)(September 1986), pp. 28-32.

Description: Discusses concerns regarding Medicaid and Medicare, the pharmacokinetics of phenothiazines, the design and interpretation of bioequivalence studies, and the clinical significance of anecdotal reports of therapeutic failures. States that with many of the psychotropic drugs, there is evidence of a history of bioequivalence problems. States that in the case of thioridazine, most of the generically equivalent products that have received a therapeutically equivalent designation from the FDA have been found to have deficiencies in the tests that the FDA itself has specified as indicators of bioequivalence. States that these deficiencies have been noted for numerous products for both statistical power and the 70/70 rule. Discusses concerns regarding the validity of assay techniques for drugs in biologic fluids, statistical power analysis, the appropriateness of the 70/70 rule, and the relevance of bioequivalence studies using healthy normal volunteers.

(58) Louis Gottschalk, "Clinical Relevance of the Bioavailability/Bioequivalence Controversy", Journal of Clinical Psychiatry, Vol. 47 (Supplement)(September 1986) Supplement, pp. 3-5.

Description: Suggests that the bioavailability and bioequivalence of psychotropic drugs should be tested carefully, and that studies of their pharmacokinetics should be supplemented by pharmacodynamic procedures, such as the quantitative electroencephalogram. Suggests that the testing of psychotropic drugs should be supplemented with clinical trials. States that an

awareness of the importance of the bioavailability and bioequivalence of psychotropic drugs can alert the clinician to the necessity of having useful guidelines to monitor treatment and prevent the development of adverse events.

(59) Larry Ereshefsky, Michael Jann, Stephen Saklad and Chester Davis, "Bioavailability of psychotropic drugs: historical perspective and pharmacokinetic overview", Journal of Clinical Psychiatry, Vol. 47 (Supplement)(September 1986), pp. 6-15.

Description: States that the use of blood sampling for bioavailability testing of central nervous system (CNS)-active compounds is rational. States that brain concentrations for most CNS-active lipophilic agents are well correlated to blood concentrations. States that two drugs judged to be bioequivalent based on plasma concentrations should yield comparable therapeutic and adverse effects. Suggests that concurrent pharmacodynamic measurements might be the best overall strategy for agents with low plasma concentrations and wider inter- and intrasubject variability. States that many of the issues related to the bioequivalence of antipsychotic agents will not be resolved until a better understanding of the pharmacokinetics and pharmacodynamics of psychotropic medications is developed.

(60) Turan Itil and Kurtz Itil, "The Significance of Pharmacodynamic Measurements in the Assessment of Bioavailability and Bioequivalence of Psychotropic Drugs Using CEEG and Dynamic Brain Mapping", Journal of Clinical Psychiatry, Vol. 47 (Supplement)(September 1986), pp. 20-27.

Description: Reports that the quantitative pharmaco-electroencephalogram (QPEEG) method, using the computer-analyzed electroencephalogram, fulfills most of the requirements of an ideal bioavailability method. Reports that the QPEEG method is a noninvasive procedure, and that single-dose drug administration is free of any risk to the subjects. States that using the QPEEG method, the acute pharmacologic effect of a psychotropic drug is studied at its site of action--the brain--as is or should be required by an "ideal" bioequivalence procedure, rather than by extrapolating from circulating levels in the blood.

(61) W.W. Mapelson, "The use of GLIM and the bootstrap in assessing a clinical trial of two drugs," Statistics in Medicine, Vol. 5, No. 4 (July-August 1986), pp. 363-374.

Description: Discusses the use of generalized linear interactive modelling (GLIM) to rationally determine equipotent doses of two different drugs. Explains that in many clinical trials of a new drug against an old one, there is a well-established dose of the old drug. States that this dose is presumably thought to provide the best compromise between the levels of desirable and undesirable effects and therefore, often cannot ethically be departed from. Explains that if the potency of the new drug is not known, it is reasonable to try a range of doses around the value thought most likely to be appropriate on the basis of results from other applications or in other species. States that in these circumstances, an informative way of comparing the new drug with the old one is to determine the equipotent dose of the new drug for each response of

interest. Explains that if the doses for the desirable effects are all less than any of those for the undesirable effects, then the new drug is clearly preferred and vice versa; if there is overlap, any decision will depend on clinical judgment.

(62) Marjorie Sun, "Generic Valiums Clear Another Hurdle at FDA", Science, Vol. 229, No. 4710 (July 26, 1985), p. 369.

Description: Discusses the FDA's rejection of arguments made by Hoffman-La Roche that the FDA is using the wrong tests to evaluate generic versions of Valium (diazepam). Reports that Hoffman-La Roche stated that generic diazepams available in Canada and Turkey did not produce the same central nervous effects as Valium. Discusses Hoffman-La Roche's argument that the FDA should require computerized brain-wave tests in addition to blood sampling as a measure of bioequivalency. Reports that the FDA stated that the study which compared the foreign generics to Valium was so seriously flawed that it invalidated Hoffman-La Roche's argument that brain-wave tests can distinguish important differences between generics and Valium. Discusses the changes in bioequivalency testing procedures for diazepams agreed to by the FDA as a result of Hoffman-La Roche's challenge.

(63) Richard Levy, "Therapeutic inequivalence of pharmaceutical alternates", American Pharmacy, Vol. NS25, No. 4 (April 1985), pp. 28-39.

Description: Discusses the therapeutic inequivalence of "pharmaceutical alternatives", i.e., different salts, esters, dosage forms, or physicochemical forms of the same active moiety.

(64) Leroy Schwartz, "The Debate over Substitution Policy. Its Evolution and Scientific Basis", American Journal of Medicine, Vol. 79, No. 2B (August 23, 1985), pp. 38-44.

Description: Discusses considerations about the differences in bioavailability between brand-name drugs and generic formulations, the meaning of drug quality, the national regulatory situation concerning generic substitution, and state-to-state variations in product selection laws. Discusses the actual and potential problems with generic substitution with regard to current and future prescribing practices. Discusses proposed regulations permitting or mandating substitution of generic alternatives and therapeutic substitutes. States that although there is no consensus on the proper use of generic drugs, physicians should be aware of potential differences in bioavailability and therapeutic effectiveness that may arise when one drug product is substituted for another. States that these differences are of particular concern for certain therapeutic categories such as psychotropic, cardiovascular, and endocrine/metabolic drugs, as well as for special population groups, such as the elderly, infants, and children.

(65) James Hennessey, Kenneth Burman and Leonard Wartofsky, "The Equivalency of Two L-Thyroxine Preparations", Annals of Internal Medicine, Vol. 102, No. 6 (June 1985), pp. 770-773.

Description: Reports the bioinequivalency of Synthroid and Levothroid, two brand-name L-thyroxine (levothyroxine) preparations, in patients with healthy thyroid gland function (euthyroid). Reports that although no significant differences were seen in routine thyroid hormone measurements, these data showed a significantly higher free thyroxine level in the patients treated with Synthroid, as well as lower thyrotropin values at 15 and 30 minutes after administration of thyrotropin-releasing hormone. States that although the current formulations of these two preparations appear to give comparable blood levels of thyroid hormone and have similar clinical effects, they are not strictly speaking bioequivalent.

(66) Mark Powell, Miryam Weisberger, Richard Gural, Menger Chung, James Patrick, Elaine Radwanski and Samson Symchowicz, "Cooperative Bioavailability and Pharmacokinetics of Three Formulations of Albuterol", Journal of Pharmaceutical Sciences, Vol. 74, No. 2 (February 1985), pp. 217-219.

Description: Discusses the bioavailability of two 4 mg tablet formulations of albuterol, differing in their inactive excipients, and a syrup formulation of albuterol. Concludes that the results of this study demonstrate that following single oral 4 mg doses, two albuterol tablet formulations, differing in their inactive excipients, are bioequivalent. States that in addition, each tablet formulation is bioequivalent to the syrup formulation of albuterol.

(67) Gerald Yakatan, Clayton Rasmussen, Patricia Feis and Stanley Wallen, "Bioinequivalence of Erythromycin Ethylsuccinate and Enteric-Coated Erythromycin Pellets Following Multiple Oral Doses", Journal of Clinical Pharmacology, Vol. 25, No. 1 (January-February 1985), pp. 36-42.

Description: Reports that erythromycin ethylsuccinate is not bioequivalent to an enteric-coated erythromycin base pellet product. States that although pharmaceutical alternatives of erythromycin are used as if they were therapeutic equivalents, the extent of absorption of these products can vary significantly.

(68) Joseph Barone and John Colaizzi, "Critical evaluation of thioridazine bioequivalence", Drug Intelligence & Clinical Pharmacy", Vol. 19, No. 11 (November 1985), pp. 847-858.

Description: States that significant concerns remain within the scientific, pharmaceutical, and medical communities regarding the bioequivalence of generic forms of thioridazine products as well as other phenothiazines. States that although the numerous bioequivalency problems reviewed in this article represent legitimate concerns, the most significant issues relating to thioridazine bioequivalence include the appropriateness of the analytical process used to determine plasma levels of thioridazine and its metabolites, the correct method for calculating statistical power, adherence to 70/70 rule and the appropriateness of that rule, the significance of and adherence to the Pitman-Morgan test for comparing variability, and the validity of using therapeutic equivalency as the criterion for interchangeability, rather than bioequivalency. Reports that several generic brands of thioridazine tablets apparently have a designation of therapeutic equivalence even though there is

an apparent failure to meet the usual bioequivalency guidelines, such as the 70/70 rule and the statistical power test.

(69) Peter Lamy, "Are generic drugs dangerous for the aged?," Journal of Gerontological Nursing, Vol. 11, No. 4 (April 1985), p. 42.

Description: See Chapter 7.

(70) Joseph DeVeaugh-Geiss, "Informed Consent and Generic Drug Substitution", Clinical Therapeutics, Vol. 7, No. 5 (1985), pp. 544-548.

Description: Suggests that when physicians cannot determine that only bioequivalent products may be substituted for the drugs prescribed, a special aspect of informed consent should be considered. Suggests that in addition to following the guidelines of informed consent, i.e., informing patients of the potential risks and benefits of any treatment the patient is to receive, physicians should also consider discussing the possibility that a bioinequivalent generic drug may be dispensed. States that psychiatric patients frequently do not have the opportunity or the ability to freely choose a generic substitute and to evaluate and report the outcome. States that important differences between medical and psychiatric disorders dictate that informed consent for psychiatric therapies should be considered a special case. States that the most obvious difference is that psychiatric disorders often involve impairment in judgment, insight, rationality, and perception, whereas most medical illnesses impair physical function without altering mental function.

(71) Allan Detsky and David Sackett, "Establishing Therapeutic Equivalency. What Is a Clinically Significant Difference?", Archives of Internal Medicine, Vol. 146, No. 5 (May 1986), pp. 861-862.

Description (Editorial): Asks the question, "How small should differences in outcomes be before therapeutic equivalence is established?" States that to consider two therapies equivalent, the difference between them must be smaller that the minimum "clinically significant difference", which is defined as that difference in outcomes that would induce clinicians (or policymakers) to adopt (or promote) a better therapy. States that the most appropriate way to formally define a clinically significant difference is to perform a detailed cost-benefit (risk-benefit) calculation. States that the choice of a clinically significant difference for establishing negativity or therapeutic equivalency is an "economic" one, requiring a set of formal analytical techniques that have not frequently been used by statisticians and clinicians in either the planning or interpreting stages of clinical trials.

(72) Laurie DeLeve, Laslo Endrenyi and Frans Leenen, "Plasma Concentration-Response Relationships of Two Formulations of Propranolol", Journal of Clinical Pharmacology, Vol. 25, No. 3 (April 1985), pp. 182-186.

Description: States that dissociation between serum concentrations and effects points out the clinical relevance of complementing kinetic studies of propranolol with pharmacodynamic studies. Reports that the two formulations of propranolol have a very similar bioavailability, not just by kinetic parameters, but also by dynamic equivalence. States that variability in the actual biologic

response--degree of beta blockade--was, if anything, less than variability in plasma propranolol concentrations. Concludes that in the case of propranolol, bioavailability studies are therefore sufficient to establish bioequivalence.

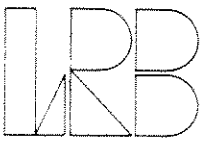
(73) U.S., Department of Health and Human Services, Food and Drug Administration, "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, September 29 - October 1, 1986" (Maryland: Dockets Management Office, January 1988), 49 pp.

Description: See Chapter 6.

Appendix D

Survey of Prescription Drug Prices-- Letter and Survey Instrument

Samuel B. K. Chang
Director



LEGISLATIVE REFERENCE BUREAU
State of Hawaii
State Capitol
Honolulu, Hawaii 96813
Phone (808) 548-6237

September 11, 1990

4351A

Dear Pharmacist:

This is to request your cooperation in completing a survey to assist the Legislature in determining the economic benefits that Hawaii's consumers have derived from the use of generic drug products.

Pursuant to Senate Concurrent Resolution No. 242, S.D. 1 (see enclosed), the Legislative Reference Bureau is currently conducting a study on the use of generic drug products in Hawaii. Among the issues that the Bureau has been directed to address in its report to the Legislature is that of cost-containment. As a pharmacist in a licensed, retail establishment, you have prescription drug price information that can be used to objectively illustrate the potential economic benefits that consumers can realize through the substitution of less-costly, therapeutically equivalent, generic drug products for more-expensive, therapeutically equivalent, brand-name drug products.

Please take a few minutes to complete and return the enclosed survey of 31 multiple-source, prescription drug product prices. Your responses will be combined with those of other licensed, retail pharmacies throughout the State and presented to the Legislature along with the Bureau's report shortly before the convening of the 1991 legislative session. All individual resonses will be kept confidential. To allow the Bureau sufficient time to analyze the results of this survey, we ask that you mail your completed survey to the Bureau by Friday, September 21, 1990 or you may FAX the survey to the Bureau at 531-6650. If this survey was mistakenly sent to you, i.e., you are not a licensed, retail pharmacy, please return it to the Bureau in the enclosed envelope and call this error to our attention.

If you have any questions or need additional information, please feel free to call Keith Fukumoto at 548-6237. Thank you very much for your assistance.

Sincerely,

Samuel B. K. Chang
Director

SBKC:at
Encs.

INSTRUCTIONS

Part I

Calculate the present retail prices of each prescription listed below using first the generic (including branded generic) product that you customarily stock and then the brand-name product that you customarily stock. If you are temporarily out of stock of a particular product, use the last retail price figure available for that product. If you do not customarily stock a particular product or customarily stock only the generic or brand-name product, then indicate this fact by writing the initials "NA" to signify that a particular retail price is "not applicable".

Please return this survey to: Legislative Reference Bureau, State Capitol, Room 004, Honolulu, Hawaii 96813 (or FAX it to 531-6650).

1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension
   100 ml Generic $_____ Brand $_____

2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension
   100 ml Generic $_____ Brand $_____

3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules
   30 Capsules Generic $_____ Brand $_____

4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules
   30 Capsules Generic $_____ Brand $_____

5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets
   30 Tablets Generic $_____ Brand $_____

6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablet
   28 Tablets Generic $_____ Brand $_____

7. Penicillin V Potassium (V-Cillin K) - 500 mg Tablet
   28 Tablets Generic $_____ Brand $_____

8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/5 ml Syrup
   120 ml Generic $_____ Brand $_____

9. Allopurinol (Zyloprim) - 100 mg Tablets
   100 Tablets Generic $_____ Brand $_____

10. Allopurinol (Zyloprim) - 300 mg Tablets
    100 Tablets Generic $_____ Brand $_____

OVER

11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets
30 Tablets Generic $_____ Brand $_____

12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets
20 Tablets Generic $_____ Brand $_____

13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets
10 Tablets Generic $_____ Brand $_____

14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspenion
100 ml Generic $_____ Brand $_____

15. Cephalexin (Keflex) - 250 mg Capsules
28 Capsules Generic $_____ Brand $_____

16. Cephalexin (Keflex) - 500 mg Capsules
28 Capsules Generic $_____ Brand $_____

17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules
30 Capsules Generic $_____ Brand $_____

18. Hydroxyzine Hydrochloride (Atarax) - 10 mg Tablets
30 Tablets Generic $_____ Brand $_____

19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets
100 Tablets Generic $_____ Brand $_____

20. Diazepam (Valium) - 5 mg Tablets
30 Tablets Generic $_____ Brand $_____

21. Chlorpropamide (Diabinese) - 250 mg Tablets
100 Tablets Generic $_____ Brand $_____

22. Ibuprofen (Motrin) - 400 mg Tablets
30 Tablets Generic $_____ Brand $_____

23. Dipyridamole (Persantine) - 50 mg Tablets
100 Tablets Generic $_____ Brand $_____

24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream
30 Grams Generic $_____ Brand $_____

25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup
120 ml Generic $_____ Brand $_____

26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets
12 Tablets Generic $_____ Brand $_____

27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid
120 ml Generic $_____ Brand $_____

28. Dextromethorphan/Iodinated Glycerol (Tussi-Organidin DM) Liquid
120 ml Generic $_____ Brand $_____

29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets
24 Tablets Generic $_____ Brand $_____

30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets
30 Tablets Generic $_____ Brand $_____

31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets
100 Tablets Generic $_____ Brand $_____

Appendix E

Pharmacies Surveyed

Shoreview Pharmacy
P. O. Box 1113
Kapaa, Hawaii 96746

Apothecary Shop, Ltd.
P. O. Box 7068
Honolulu, Hawaii 96721

Wailuku Professional Pharmacy
1900 Main St., Space 3
Wailuku, Hawaii 96793

North Shore Pharmacy
and Health Emporium
P. O. Box 759
Kilauea, Hawaii 96754

Beretania Prescription Pharmacy
848 S. Beretania St., Ste. 100-B
Honolulu, Hawaii 96713

North Shore RX Pharmacy
P. O. Box 91
Kahuku, Hawaii 96731

Center Pharmacy, Inc.
302 California Ave.
Wahiawa, Hawaii 96786

City Pharmacy
966 Kaheka St.
Honolulu, Hawaii 96814

Honolulu Pharmacy
634 Kalihi St.
Honolulu, Hawaii 96819

Hilo Medical Group Pharmacy
1292 Waianuenue Ave.
Hilo, Hawaii 96720

Ka'u Community Pharmacy
Ka'u Medical Clincal
Pahala, Hawaii 96777

Waipahu Family Pharmacy
94-916 Waipahu St.
Waipahu , Hawaii 96797

Maui Pharmacy-Kihei
1325 S. Kihei Rd., #110
Kihei, Hawaii 96753

Lahaina Pharmacy
880 Front St., #118
Lahaina, Hawaii 96761

Straub Pharmacy Aiea
Newtown Square
98-1247 Kaahumanu St.
Aiea, Hawaii 96701

Haleiwa Pharmacy
66-145 Kam Hwy.
Haleiwa, Hawaii 96712

Maui Clinic Pharmacy
53 Puunene Ave.
Kahului, Hawaii 96732

Medical Center Pharmacy
1086 Kamahele St.
Kailua, Hawaii 96734

Costco Pharmacy
4410 Lawehana St.
Honolulu, Hawaii 96818

Holiday Mart Drugs
801 Kaheka St.
Honolulu, Hawaii 96814

Holiday Mart Drugs
345 Hahani St.
Kailua, Hawaii 96734

Enchanted Lake Pharmacy
1020 Keolu Drive
Kailua, Hawaii 96734

Westside Pharmacy
1-3845 Kaumualii Hwy.
Hanapepe, Hawaii 96716

Kalaheo Pharmacy
P. O. Box 249
Hanapepe, Hawaii 96716

Hibiscus Pharmacy
1411 S. King St., #207
Honolulu, Hawaii 96814

Southshore Pharmacy
P. O. Box 160
Koloa, Hawaii 96756

Rainbow Pharmacy
P. O. Box 1000
Kalaheo, Hawaii 96741

HPI Pharmacy
P. O. Box 3265
Lihue, Hawaii 96766

HPI Pharmacy
P. O. Box 669
Waimea, Hawaii 96796

College Pharmacy
2015 S. King St.
Honolulu, Hawaii 96826

IPC Pharmacy/Pearl
98-150 Kaonohi St.
Aiea, Hawaii 96701

IPC Pharmacy/Hon Med
550 S. Beretania St.
Honolulu, Hawaii 96813

IPC Pharmacy/Waianae
86-260 Farrington Hwy.
Waianae, Hawaii 96792

IPC Fronk Clinic Pharmacy
839 S. Beretania St.
Honolulu, Hawaii 96813

IPC Pharmacy/Kamuela
P. O. Box 2337
Kamuela, Hawaii 96743

IPC Pharmacy/Liliha
1027 Hala Dr.
Honolulu, Hawaii 96817

IPC Pharmacy/Nuuanu
1374 Nuuanu Ave.
Honolulu, Hawaii 96817

IPC Pharmacy/LCCOH
944 W. Kawailani St.
Hilo, Hawaii 96720

IPC Pharmacy/LMC
1712 Liliha St., #101
Honolulu, Hawaii 96817

IPC/Wailuku Professional Pharmacy
1900 Main St.
Wailuku, Hawaii 96793

IPC Pharmacy
Kihei Professional Pharmacy
41 E. Lipoa Space 23A
Kihei, Hawaii 96753

Johnson's Sunny Pharmacy
2225 N. School St.
Honolulu, Hawaii 96819

Karwacki Professional Pharmacy
30 Aulike St.
Kailua, Hawaii 96734

Kona Coast Drugs, Inc.
75-5759 Kuakini Hwy., #104
Kailua, Hawaii 96740

Haleiwa Pharmacy
66-125 Kam Hwy.
Haleiwa, Hawaii 96712

Plaza Pharmacy
321 N. Kuakini St.
Honolulu, Hawaii 96817

Liu's Pharmacy
P. O. Box 1348
Honokaa, Hawaii 96727

Waipahu Drug
94-748A Hikimoe St.
Waipahu, Hawaii 96797

Waianae Drug
85-1058 Farrington Hwy.
Waianae, Hawaii 96792

Longs Drugs
1330 Pali Highway
Honolulu, Hawaii 96818

Longs Drugs
1088 Bishop St., Ste. 113
Honolulu, Hawaii 96813

Longs Drugs
1450 Ala Moana Blvd.
Honolulu, Hawaii 96814

Longs Drugs
4211 Waialae Ave.
Honolulu, Hawaii 96816

Longs Drugs-Pearl City
850 Kam Hwy.
Pearl City, Hawaii 96782

Longs Drugs
555 Kilauea Ave.
Hilo, Hawaii 96720

Longs Drugs
1620 No. School St.
Honolulu, Hawaii 96817

Longs Drugs
Maui Mall Shopping Center
Kahului, Hawaii 96732

Longs Drugs-Kaneohe
46-047 Kam Hwy.
Kaneohe, Hawaii 96744

Longs Drugs Store #92
440 Pearlridge Center
Aiea , Hawaii 96701

Longs Drugs Store #10
591 Kailua Road
Kailua, Hawaii 96734

Longs Drugs Store #11
2750 Woodlawn Dr.
Honolulu, Hawaii 96822

Longs Drugs Store #16
3221 Waialae Ave.
Honolulu, Hawaii 96816

Longs Drugs Store #18
377 Keahole St.
Honolulu, Hawaii 96825

Longs Drugs Store
377 Keahole St.
Honolulu, Hawaii 96825

Longs Drugs Store
2000 Kukui Grove Center
Lihue, Hawaii 96766

Longs Drugs Store #20
94-780A Meheula Pkwy.
Mililani, Hawaii 96789

Longs Drugs Store #22
111 East Puainako St.
Hilo, Hawaii 96720

Longs Drugs Store #2
Lahaina Cannery
1221 Honoapilani Hwy.
Lahaina, Hawaii 96761

Longs Drugs Store #25
94-1249-D Meheula Pkwy.
Mililani, Hawaii 96789

Longs Drugs Store #24
75-5595 Palani Road
Kailua, Hawaii 96734

Longs Drugs Store #25
94-060 Farrington Hwy.
Waipahu, Hawaii 96797

The Pillbox Pharmacy
1133 Eleventh Ave.
Honolulu, Hawaii 96816

Medicine Man, Inc.
1113 Kapahulu Ave.
Honolulu, Hawaii 96816

Molokai Drugs, Inc.
P. O. Box 558
Kaunakakai, Hawaii 96748

Olson Apothecary
407 Uluniu St., #107
Kailua, Hawaii 96734

Oshima Drug
P. O. Box 48
Kealakekua, Hawaii 96750

Kuhio Pharmacy
2330 Kuhio Ave.
Honolulu, Hawaii 96815

Outrigger Pharmacy
2335 Kalakaua Ave.
Honolulu, Hawaii 96815

Food Fair Supermarket
1990 Kinoole St.
Hilo, Hawaii 96720

Medical Arts Pharmacy
1010 S. King St., #106
Honolulu, Hawaii 96814

Pali Drugs Inc.
49 Oneawa St.
Kailua, Hawaii 96734

Pay 'n Save #122
200 E. Kamehameha Ave.
Kahului, Hawaii 96732

Pay 'n Save #115
45-480 Kaneohe Bay Dr.
Kaneohe, Hawaii 96744

Pay 'n Save #114
94-300 Farrington Hwy.
Waipahu, Hawaii 96797

Pay 'n Save #113
98-1277 Kaahumanu St.
Aiea, Hawaii 96701

Pay 'n Save #112
2220 S. King St.
Honolulu, Hawaii 96826

Pay 'n Save #110
54-316 Kam Hwy.
Hauula, Hawaii 96717

Pay 'n Save #109
1505 Dillingham Blvd.
Honolulu, Hawaii 96817

Pay 'n Save #097
2100 Kanoelehua Ave.
Hilo, Hawaii 96720

Pay 'n Save #096
4100 Rice St.
Lihue, Hawaii 96766

Pay 'n Save #080
95-221 Kipapa Dr.
Mililani, Hawaii 96789

Pay 'n Save #076
47-388 Hui Iwa St.
Kaneohe, Hawaii 96744

Pay 'n Save #073
86-120 Farrington Hwy.
Waianae, Hawaii 96792

Pay 'n Save #072
74-5584 Palani Road
Kailua-Kona, Hawaii 96740

Pay 'n Save #059
848 Ala Lilikoi St.
Honolulu, Hawaii 96818

Pay 'n Save #143
4-831 Kuhio Hwy.
Kapaa, Hawaii 96746

Professional Plaza Pharmacy
1520 Liliha St., #201
Honolulu, Hawaii 96813

KTA Keauhou Pharmacy
Keauhou Kona Shopping Village
Kailua-Kona, Hawaii 96740

KTA Puainako Pharmacy
50 East Puainako St.
Hilo, Hawaii 96720

KTA Kamuela Pharmacy
50 East Puainako St.
Hilo, Hawaii 96720

Queen's Physicians Office
Building Pharmacy
1380 Lusitana St.
Honolulu, Hawaii 96813

Aiea Medical Pharmacy
99-128 Aiea Hts. Dr., #103
Aiea, Hawaii 96701

Royal Pharmacy Ewa
91-919 Ft. Weaver Road
Ewa Beach, Hawaii 96706

Kihei Drug & Pharmacy
1881 So. Kihei Road
Kihei, Hawaii 96753

Safeway Pharmacy #12
200 Hamakua Dr.
Kailua, Hawaii 96734

Safeway Pharmacy #12
831 Kuhio Hwy.
Kapaa, Hawaii 96746

Kalihi Pharmacy
2055 No. King St.
Honolulu, Hawaii 96819

Sav-Mor Drugs #2
Kalihi Shopping Center
2295 No. King St.
Honolulu, Hawaii 96819

Shiigi Drug Co.
777 Kilauea Ave.
Hilo, Hawaii 96720

Kamehameha Pharmacy
P. O. Box 610
Kapaau, Hawaii 96755

St. Francis Medical
Plaza West Pharmacy
2230 Liliha St.
Honolulu, Hawaii 96817

Queen Emma Pharmacy
1270 Queen Emma St., #101
Honolulu, Hawaii 96813

Windward Pharmacy
46-056 Kam Hwy.
Kaneohe, Hawaii 96744

Times Pharmacy #11
1425 Liliha St.
Honolulu, Hawaii 96817

Times Pharmacy #16
1199 Dillingham Blvd.
Honolulu, Hawaii 96817

Times Pharmacy #15
94-144 Farrington Hwy.
Waipahu, Hawaii 96797

Times Pharmacy #8
1290 S. Beretania St.
Honolulu, Hawaii 96814

Times Pharmacy #9
99-115 Aiea Hts. Dr.
Aiea, Hawaii 96701

Times Pharmacy #2
1173 21st Ave.
Honolulu, Hawaii 96816

Times Pharmacy #12
98-1264 Kaahumanu St.
Pearl City, Hawaii 96782

Times Pharmacy #4
45-934 Kam Hwy.
Kaneohe, Hawaii 96744

Times Pharmacy #6
94-766 Farrington Hwy.
Waipahu, Hawaii 96797

Toda Drug
Kahului Shopping Center
Kahului, Hawaii 96732

Pukalani Drugs
Pukalani Terrace Center
55 Pukalani, #1512
Pukalani, Hawaii 96768

Paradise Pharmacy
81-21 Makawao Ave.
Pukalani, Hawaii 96768

Valley Isle Pharmacy
2180 Main St.
Wailuku, Hawaii 96793

Valley Isle Pharmacy
130 Prison St.
Lahaina, Hawaii 96761

Wailuku Town Pharmacy
99 S. Market St.
Wailuku, Hawaii 96793

Valley Isle Pharmacy
2349 S. Kihei Road
Kihei, Hawaii 96753

Village Pharmacy, Inc.
P. O. Box 340
Kamuela, Hawaii 96743

Chinatown Pharmacy
70 N. Hotel St.
Honolulu, Hawaii 96817

Wahiawa Pharmacy
823 California Ave.
Wahiawa, Hawaii 96786

Waimanalo Pharmacy
41-1610 Kalanianaole Hwy.
Waimanalo, Hawaii 96795

Castle Professional Center
46-001 Kam Hwy.
Kaneohe, Hawaii 96744

Wilder Avenue Drugs
1233 Wilder Ave.
Honolulu, Hawaii 96822

Appendix F

Raw Data

1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension
   100 ml Generic $_____ Brand $_____

[7.45/NA]*	5.74/NA	7.75/NA	5.47/NA	5.00/NA	4.95/NA
3.99/NA	NA/NA	5.50/NA	8.25/NA	6.40/8.00	4.95/NA
8.45/8.45	7.50/NA	NA/4.95	NA/NA	NA/NA	7.73/NA
7.37/NA	7.75/7.75	6.57/6.57	5.95/NA	5.32/NA	5.99/NA
5.50/5.50	7.17/NA	6.32/10.63	6.25/6.27	4.86/NA	8.99/NA
5.50/5.50	NA/5.49	8.95/12.70	5.30/NA	7.53/NA	5.61/NA
9.19/NA	4.27/4.57	7.53/NA	7.70/NA	6.54/NA	5.90/NA
7.00/NA	8.09/NA	7.30/NA			

*Suppressed; 80 ml price

2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension
   100 ml Generic $_____ Brand $_____

5.77/NA	6.80/NA	9.40/NA	7.38/NA	6.40/NA	5.55/14.55
6.19/NA	NA/NA	7.00/NA	10.40/14.15	7.75/9.85	8.50/NA
9.95/9.95	9.00/NA	NA/6.35	NA/NA	5.00/NA	11.00/NA
10.60/NA	9.95/9.95	9.25/NA	6.50/NA	7.12/NA	6.39/NA
7.50/7.50	10.12/NA	8.78/13.68	8.25/8.43	5.65/NA	8.99/NA
7.50/7.50	NA/8.99	9.95/12.90	6.30/NA	9.92/NA	9.96/NA
[10.91/NA]*	7.27/8.49	8.38/NA	9.80/NA	7.68/NA	6.76/NA
11.70/NA	9.89/NA	12.01/NA			

* Suppressed; 150 ml price

3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules
   30 Capsules Generic $_____ Brand $_____

14.15/NA	11.70/NA	6.30/NA	12.01/NA	6.50/NA	7.55/NA
8.29/NA	NA/NA	9.65/NA	10.95/14.65	6.90/9.50	8.95/NA
9.15/9.15	12.00/NA	4.90/6.45	NA/NA	8.00/NA	9.85/NA
12.05/NA	10.35/10.35	8.36/NA	10.05/NA	7.40/NA	7.39/NA
8.10/8.10	11.42/NA	9.58/14.32	7.00/9.57	4.47/NA	9.69/NA
8.10/8.10	7.69/9.89	5.99/9.99	6.80/NA	9.65/NA	9.16/NA
8.08/NA	8.09/10.09	9.33/NA	10.50/NA	6.90/NA	11.25/NA
12.10/NA	9.59/NA	6.68/NA			

NA - Not available or missing datum

4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules
30 Capsules Generic $_____ Brand $_____

18.01/NA	18.20/NA	8.10/NA	17.57/NA	9.60/NA	11.95/25.95
14.39/NA	NA/NA	16.30/NA	15.85/22.50	11.50/14.50	13.95/NA
13.90/13.90	15.00/NA	10.15/10.45	NA/NA	6.25/9.50	12.25/NA
19.70/NA	15.50/15.50	12.92/NA	15.03/NA	9.55/NA	11.39/NA
10.80/10.80	19.80/NA	11.01/23.85	9.25/14.80	6.99/NA	16.69/NA
10.80/10.80	12.59/16.39	8.99/12.99	9.35/NA	16.45/NA	13.97/NA
15.62/NA	11.59/15.49	16.45/NA	19.50/NA	9.30/NA	20.71/NA
17.15/NA	14.99/NA	9.06/NA			

5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets
30 Tablets Generic $_____ Brand $_____

7.20/11.52	7.13/10.75	7.25/9.35	5.60/NA	5.65/9.00	4.85/9.85
6.29/9.79	7.15/11.89	5.40/8.40	8.95/11.25	7.00/10.50	4.50/7.95
6.35/8.15	7.50/10.00	5.55/7.10	5.50/7.85	6.25/9.50	7.25/10.48
6.55/11.30	9.70/11.23	6.34/10.35	6.24/9.76	7.44/10.31	4.99/12.99
6.54/9.83	7.48/8.53	6.09/9.79	5.65/9.47	4.29/7.80	6.99/10.99
6.54/9.83	6.19/13.19	8.99/14.00	4.80/8.55	6.46/9.52	6.54/NA
7.67/NA	5.99/9.39	6.46/9.52	7.40/10.40	5.93/NA	7.27/NA
7.85/11.90	5.49/10.19	6.69/11.17			

6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablet
28 Tablets Generic $_____ Brand $_____

8.27/NA	6.24/NA	6.15/9.30	5.92/NA	4.20/8.65	3.95/8.55
6.39/NA	NA/NA	5.00/NA	6.75/9.80	5.65/6.95	4.50/8.95
5.15/6.85	7.50/NA	4.50/NA	4.50/7.45	3.80/6.45	6.30/NA
6.65/NA	6.67/9.95	5.21/9.15	5.14/NA	5.24/NA	5.99/9.69
4.72/4.72	5.94/NA	5.26/8.11	5.12/9.54	3.65/7.75	5.59/8.59
4.72/4.72	3.99/8.79	5.99/8.99	4.85/NA	5.06/NA	5.34/NA
6.46/NA	5.89/10.19	5.06/NA	6.70/8.45	4.98/NA	5.66/NA
7.15/NA	5.29/NA	7.29/NA			

NA - Not available or missing datum

7. Penicillin V Potassium (V-Cillin K) - 500 mg Tablet
28 Tablets Generic $_____ Brand $_____

11.76/NA	7.76/NA	8.00/13.80	6.09/NA	6.95/14.40	5.85/14.95
8.09/NA	NA/NA	6.80/NA	8.75/14.55	6.65/8.75	6.95/15.50
6.80/7.05	9.00/NA	4.80/NA	NA/NA	6.60/12.60	7.79/NA
7.50/NA	9.29/14.35	7.37/13.75	5.62/NA	6.63/NA	7.99/15.69
5.62/5.62	7.69/NA	6.73/13.29	6.44/12.81	3.65/13.76	6.59/13.99
5.62/5.62	5.39/13.69	8.99/12.00	5.95/NA	5.06/NA	6.80/NA
8.21/NA	7.39/15.19	6.65/NA	7.65/15.90	6.66/NA	7.47/NA
9.85/NA	7.89/NA	7.86/NA			

8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/ 5 ml Syrup
120 ml Generic $_____ Brand $_____

6.35/9.79	6.48/NA	6.65/9.10	7.20/10.27	4.60/7.75	5.35/7.55
6.19/7.79	NA/NA	4.85/9.20	6.75/9.75	6.25/9.75	5.50/7.95
4.85/8.15	6.00/9.00	5.70/7.90	4.90/7.20	3.80/8.25	6.65/9.12
6.95/9.10	9.79/9.79	5.74/7.32	6.55/10.10	5.80/9.49	4.69/9.99
6.22/9.00	6.80/7.07	5.79/7.07	5.45/8.12	4.72/7.31	5.99/9.69
6.22/9.00	5.39/10.99	4.99/8.99	6.95/13.40	5.84/7.92	5.97/9.74
7.32/NA	4.87/9.09	5.84/7.92	4.85/8.40	5.09/NA	6.17/8.58
7.45/9.10	7.89/11.79	5.82/9.41			

9. Allopurinol (Zyloprim) - 100 mg Tablets
100 Tablets Generic $_____ Brand $_____

12.91/19.50	10.09/18.22	11.90/17.40	13.13/19.83	9.80/16.90	10.55/19.95
13.89/15.69	13.05/18.30	11.55/19.05	12.50/17.95	10.25/21.50	11.95/17.95
11.95/NA	8.00/NA	12.60/18.20	11.15/13.50	12.00/17.45	11.90/17.43
[5.50/7.50]*	15.00/17.79	12.15/17.94	8.64/16.76	8.80/18.13	10.99/20.39
10.58/16.78	16.44/20.58	12.66/18.43	8.35/16.43	6.01/16.82	8.99/18.99
10.58/16.78	10.99/16.69	9.20/20.00	7.65/17.35	12.46/17.57	10.96/17.79
12.27/NA	7.49/15.77	12.46/17.57	14.00/19.80	11.50/17.18	12.86/17.94
14.20/18.30	12.69/16.79	13.57/19.50			

*Suppressed; price for 30-day supply?

10. Allopurinol (Zyloprim) - 300 mg Tablets
100 Tablets Generic $_____ Brand $_____

26.75/46.38	14.08/48.24	30.75/40.30	17.56/46.16	21.00/42.35	22.85/46.90
20.89/39.09	25.65/39.70	19.20/49.50	23.25/40.85	21.00/55.00	26.95/39.95
15.45/NA	20.00/NA	24.00/42.60	24.50/35.05	21.65/47.00	27.55/42.13
[9.65/14.60]*	41.00/45.47	27.23/41.21	23.61/40.17	19.03/44.30	23.99/48.96
11.41/39.68	41.39/53.38	13.94/45.83	12.00/39.33	16.42/44.30	23.99/48.69
11.41/39.68	28.19/42.29	27.50/46.00	17.35/44.75	27.63/40.59	21.67/41.40
23.05/NA	13.09/39.17	27.63/40.51	34.20/54.15	24.75/40.63	21.30/42.30
19.35/NA	20.19/39.69	31.70/47.88			

*Suppressed; price for 30-day supply?

11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets
30 Tablets Generic $_____ Brand $_____

9.88/18.50	9.84/16.97	11.85/16.85	11.27/19.19	10.30/16.05	9.35/18.95
9.69/14.59	11.07/18.95	12.65/18.30	11.95/13.50	9.00/35.00	11.50/18.95
10.70/16.50	12.00/18.00	11.75/17.00	9.75/12.95	10.30/16.50	11.75/16.88
10.05/18.95	15.00/18.95	11.65/17.38	10.46/17.35	11.72/17.42	9.39/18.99
9.66/16.23	13.90/19.23	7.84/16.75	5.95/15.88	8.65/15.40	11.99/19.69
9.66/16.23	12.79/19.59	8.00/12.00	8.20/15.40	10.71/17.08	10.72/17.23
11.81/NA	7.49/15.69	10.88/17.08	12.50/19.10	11.50/16.63	11.25/15.73
9.05/17.55	11.99/18.19	12.53/18.89			

12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets
20 Tablets Generic $_____ Brand $_____

8.61/23.81	11.69/NA	8.80/12.40	5.88/24.16	8.15/21.35	6.60/22.95
10.29/19.69	14.05/25.70	7.65/21.85	9.35/21.75	7.60/26.50	7.95/23.95
7.80/25.40	NA/20.00	6.95/22.45	5.55/21.55	NA/23.00	8.80/21.20
13.05/25.70	13.99/20.50	6.84/21.79	10.29/22.96	8.00/21.19	6.99/26.39
8.18/20.55	8.85/26.76	6.88/22.70	5.25/20.20	3.65/20.67	5.99/23.99
8.18/20.55	4.59/20.89	9.79/24.80	8.95/21.80	7.58/30.54	7.85/20.27
9.22/NA	5.57/20.57	10.20/20.17	6.60/22.00	5.60/21.21	12.66/NA
14.50/25.70	9.29/22.79	8.23/24.31			

NA - Not available or missing datum

13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets
10 Tablets Generic $_____ Brand $_____

6.34/34.39	7.52/NA	8.05/22.25	6.42/34.67	7.25/29.90	6.50/32.85
9.99/29.09	NA/NA	5.85/37.95	8.50/30.85	5.80/NA	7.50/28.95
7.20/NA	12.00/NA	5.80/29.10	5.20/31.95	6.75/33.00	7.92/NA
9.30/NA	12.10/36.53	5.93/31.60	5.57/33.63	6.04/32.31	6.69/40.39
7.10/29.69	7.75/40.64	6.49/35.83	6.45/16.29	4.36/29.84	6.99/36.99
7.10/29.69	4.19/NA	11.00/22.00	5.45/30.75	6.56/31.44	6.93/NA
8.34/30.76	5.59/27.04	9.94/31.44	8.40/27.10	9.06/NA	6.84/NA
8.80/NA	7.29/NA	6.08/35.39			

14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspenion
100 ml Generic $_____ Brand $_____

9.35/NA	7.27/9.57	8.30/NA	8.85/17.65	NA/11.65	6.55/NA
NA/10.79	NA/NA	NA/11.75	10.95/11.60	7.25/NA	7.50/10.50
9.50/10.75	NA/12.00	6.50/10.50	8.80/9.40	NA/9.00	8.33/NA
NA/7.90	9.05/13.19	7.66/NA	8.64/11.32	NA/11.77	8.69/12.69
7.25/7.25	NA/7.91	NA/NA	7.00/10.10	NA/9.80	NA/7.69
7.25/7.25	8.29/11.89	12.00/20.00	7.35/10.00	9.53/9.53	9.52/11.77
10.92/12.00	NA/9.47	13.50/11.87	7.85/11.00	NA/11.33	7.76/NA
NA/7.70	8.09/NA	8.57/NA			

15. Cephalexin (Keflex) - 250 mg Capsules
28 Capsules Generic $_____ Brand $_____

21.78/35.05	18.19/NA	16.70/30.95	21.75/35.39	20.45/32.15	15.40/36.15
18.19/29.79	21.11/33.39	20.30/37.05	17.35/31.50	10.50/NA	17.95/31.95
16.65/32.05	NA/20.00	13.50/33.25	17.40/32.50	17.75/35.00	16.71/30.96
21.95/NA	26.33/37.40	19.77/32.24	21.36/34.33	17.22/33.05	13.39/39.39
9.48/30.31	26.58/41.58	14.31/36.46	8.57/29.96	7.52/33.05	13.69/36.59
9.48/30.31	9.29/34.09	12.00/20.00	12.80/33.50	18.74/32.00	16.68/31.74
17.18/31.38	12.67/30.97	21.57/32.00	26.40/35.00	15.90/30.96	15.92/NA
18.70/NA	19.69/31.39	19.14/36.05			

16. Cephalexin (Keflex) - 500 mg Capsules
28 Capsules Generic $_____ Brand $_____

36.96/67.63	31.00/NA	29.40/56.75	40.93/65.06	35.75/59.90	28.75/65.65
43.09/53.39	31.70/60.39	36.75/71.35	29.95/57.30	21.50/NA	30.95/62.95
28.60/54.70	NA/36.00	21.90/61.55	31.75/64.10	28.45/56.00	29.40/59.39
31.70/NA	50.68/68.25	39.98/58.55	41.05/64.54	23.63/64.01	21.99/70.99
14.80/56.11	44.66/76.37	24.71/67.75	14.07/55.54	11.17/64.01	25.59/65.69
14.80/56.11	15.09/65.89	27.00/40.00	23.60/64.40	33.07/59.08	28.59/52.50
29.82/57.18	13.69/57.27	37.85/59.09	56.00/67.00	27.66/57.03	38.63/NA
31.25/NA	34.39/58.39	43.31/67.64			

17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules
30 Capsules Generic $_____ Brand $_____

12.70/13.68	10.46/12.83	11.55/12.44	13.07/14.09	10.20/11.00	8.70/12.40
9.29/10.59	12.00/15.16	8.80/12.40	11.95/12.95	7.75/15.00	7.50/11.95
11.45/12.30	NA/15.00	10.45/10.95	7.80/11.15	NA/12.00	11.55/12.44
12.00/14.45	13.13/14.75	11.43/NA	12.18/12.94	10.41/12.92	9.99/13.69
10.90/11.79	13.46/13.90	10.86/12.52	NA/11.44	9.53/10.83	10.99/11.99
10.90/11.79	11.09/11.79	8.99/13.50	9.90/12.15	NA/11.96	7.29/12.44
12.88/NA	11.09/12.39	11.79/NA	NA/13.60	11.30/12.19	11.05/12.65
13.30/15.20	10.89/13.29	12.31/13.60			

18. Hydroxyzine Hydrochloride (Atarax) - 10 mg Tablets
30 Tablets Generic $_____ Brand $_____

5.73/12.79	6.04/17.53	6.70/10.10	5.02/19.09	7.05/15.90	4.15/18.45
8.59/15.09	NA/NA	5.15/19.00	7.25/17.30	5.55/NA	5.50/15.95
6.20/13.55	7.50/NA	5.20/16.10	5.50/15.40	5.65/19.50	6.89/16.79
5.45/17.45	8.80/18.80	5.12/17.28	5.35/17.94	5.79/17.30	4.99/20.39
5.50/16.14	7.09/20.05	5.07/17.78	4.05/15.78	3.80/16.05	5.69/19.59
5.50/16.14	3.99/16.59	5.99/18.00	6.70/16.55	5.84/17.00	13.00/NA
7.09/NA	5.87/16.29	5.84/17.00	5.30/16.00	5.39/17.16	4.07/17.29
8.90/NA	5.69/16.19	5.46/18.79			

NA - Not available or missing datum

19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets
100 Tablets Generic $_____ Brand $_____

5.37/NA	4.85/NA	6.20/15.30	5.04/17.38	4.60/14.90	3.95/NA
6.69/NA	NA/NA	4.15/NA	6.25/15.80	6.50/NA	5.95/12.95
4.65/NA	NA/12.00	4.35/16.05	4.55/13.50	5.00/NA	3.95/1530
4.42/NA	7.40/16.57	4.11/15.77	7.15/16.31	4.33/NA	4.69/15.99
4.27/14.65	6.96/NA	3.92/15.80	4.26/14.30	3.74/NA	4.69/NA
4.27/14.65	3.99/NA	5.99/16.99	4.70/NA	6.16/NA	5.85/NA
5.47/15.72	4.59/7.69	6.16/NA	5.50/16.00	6.50/NA	5.68/NA
4.45/NA	5.39/NA	6.19/17.16			

20. Diazepam (Valium) - 5 mg Tablets
30 Tablets Generic $_____ Brand $_____

6.39/19.61	6.69/18.33	7.75/17.45	4.98/19.87	7.50/17.25	4.85/19.95
7.69/15.79	6.70/19.85	11.65/19.20	8.35/18.05	5.25/NA	7.50/16.95
6.70/19.85	[NA/7.50]*	7.30/18.30	4.50/12.65	6.85/19.80	7.68/17.53
6.70/19.85	9.35/19.93	4.99/17.98	5.80/18.69	6.17/18.26	4.69/20.39
6.49/16.88	7.68/21.09	6.81/18.47	5.00/16.53	4.01/14.81	5.99/20.69
6.49/16.88	5.19/20.49	9.00/12.99	7.15/17.40	6.61/17.66	6.70/17.89
8.09/17.95	4.97/15.37	4.78/17.66	11.25/20.00	6.70/17.20	15.45/18.05
6.70/19.85	6.69/19.09	5.91/19.61			

*Suppressed; transcribing error?

21. Chlorpropamide (Diabinese) - 250 mg Tablets
100 Tablets Generic $_____ Brand $_____

8.33/63.63	13.16/69.16	12.25/47.30	10.40/68.30	11.75/51.85	17.95/60.85
15.09/53.59	15.04/60.90	6.30/78.80	12.75/60.10	7.75/NA	13.50/59.50
11.45/77.45	[NA/12.00]*	10.60/56.95	12.90/58.70	10.70/73.00	12.25/62.35
12.30/60.90	16.00/62.80	12.16/NA	11.79/58.50	10.35/67.40	9.99/58.39
12.20/58.93	14.18/65.56	5.96/70.58	9.51/58.58	8.60/56.40	9.99/61.69
12.20/58.93	8.89/66.29	13.00/62.59	11.15/50.85	18.17/62.25	11.47/67.96
12.59/NA	7.27/48.77	11.79/59.27	10.45/78.00	12.00/62.59	18.98/61.94
9.15/66.45	11.59/55.29	8.08/63.63			

*Suppressed; transcribing error?

NA - Not available or missing datum

22. Ibuprofen (Motrin) - 400 mg Tablets
30 Tablets Generic $_____ Brand $_____

6.34/10.38	6.96/9.65	7.20/9.45	5.57/10.64	6.10/7.30	5.55/7.55
NA/7.09	8.65/9.25	6.70/7.45	7.75/7.75	6.25/NA	7.50/NA
7.35/20.60	7.50/9.00	5.20/6.75	4.75/7.15	6.90/6.90	7.22/9.44
6.75/9.25	11.34/10.07	5.49/9.29	7.41/8.89	5.24/8.93	4.69/8.69
6.88/8.80	6.95/7.86	6.29/8.74	4.45/5.77	4.24/7.24	6.69/8.69
6.88/8.80	3.99/5.29	8.99/11.99	11.30/16.80	7.15/8.37	6.71/10.20
7.64/NA	6.19/6.97	7.37/8.62	5.20/8.20	5.33/9.48	6.26/8.89
8.65/NA	7.29/8.49	7.81/10.05			

23. Dipyridamole (Persantine) - 50 mg Tablets
100 Tablets Generic $_____ Brand $_____

8.56/45.64	8.76/47.49	11.70/27.90	11.24/45.35	8.45/42.20	9.85/45.95
12.39/38.39	NA/NA	7.10/40.40	12.25/40.15	NA/50.00	11.95/39.95
10.25/46.10	NA/40.00	9.60/40.15	7.65/34.40	13.00/47.00	11.69/41.39
6.70/41.75	13.80/40.37	10.12/41.07	11.88/37.95	9.00/43.44	8.69/48.39
8.90/38.97	16.26/53.20	7.43/45.12	9.20/38.61	5.72/43.44	7.99/47.99
8.90/38.97	9.49/41.39	11.99/45.36	8.55/41.75	7.28/39.79	10.71/40.67
NA/40.04	6.67/31.57	[4.78/15.26]*	11.50/53.40	10.54/39.87	7.78/41.58
NA/38.95	14.39/37.79	10.87/47.14			

*Suppressed; price for 30-day supply?

24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream
30 Grams Generic $_____ Brand $_____

6.56/16.13	5.99/NA	6.55/6.55	9.08/24.68	4.10/4.75	5.75/NA
5.79/11.09	NA/NA	4.15/NA	7.25/22.15	7.75/NA	4.95/11.95
4.30/NA	8.00/NA	5.90/19.45	NA/NA	4.25/15.00	6.58/NA
7.00/13.70	7.98/15.50	6.02/22.24	5.88/13.25	6.15/20.88	4.69/4.69
4.70/13.31	6.93/NA	4.75/14.86	7.25/14.25	4.45/4.45	5.99/5.99
4.70/13.31	3.99/13.89	7.99/24.99	7.15/21.45	7.91/21.82	5.63/13.85
5.60/NA	4.99/22.99	7.91/21.82	5.90/15.00	4.62/NA	6.26/NA
7.00/7.30	4.69/NA	6.63/NA			

NA - Not available or missing datum

25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup
120 ml Generic $_____ Brand $_____

6.64/10.46	6.79/NA	4.95/5.60	7.55/10.73	4.70/8.10	5.95/7.95
6.59/7.89	NA/NA	5.25/9.75	7.75/9.95	6.50/NA	5.50/7.50
5.15/8.05	8.00/NA	5.40/8.50	5.25/7.65	NA/NA	NA/NA
7.60/10.30	10.17/10.17	6.04/NA	6.96/9.95	6.07/9.03	4.69/10.39
5.11/8.87	6.41/8.69	5.79/6.53	4.00/8.51	4.85/8.03	5.99/10.59
5.11/8.87	5.39/11.69	5.99/9.99	5.80/8.30	NA/NA	6.13/10.17
7.32/NA	5.49/9.39	NA/8.50	4.70/7.50	5.80/9.76	7.27/NA
7.60/10.30	9.19/10.29	6.77/10.14			

26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets
12 Tablets Generic $_____ Brand $_____

6.56/8.44	6.05/7.96	6.40/7.85	6.91/8.81	5.80/7.45	3.95/5.95
5.49/6.19	NA/NA	5.30/7.55	6.95/8.35	5.65/NA	8.95/13.50
5.25/6.00	6.00/8.00	5.45/6.60	4.50/6.05	NA/NA	6.39/7.85
7.80/8.00	6.75/8.50	5.50/7.16	6.30/8.11	5.40/7.80	6.39/8.99
7.20/8.26	6.51/7.24	5.25/6.91	5.05/9.39	NA/5.80	5.59/7.69
7.20/8.26	6.59/9.79	4.99/6.99	NA/NA	5.58/6.70	5.62/7.64
5.64/8.27	5.39/7.79	5.09/6.70	4.95/6.00	5.42/7.10	5.61/NA
7.50/8.05	5.19/8.59	6.21/8.07			

27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid
120 ml Generic $_____ Brand $_____

7.24/14.45	6.94/NA	7.85/10.00	6.51/14.89	6.30/12.45	7.95/13.95
7.09/11.09	NA/NA	5.50/13.35	8.50/13.75	7.75/NA	6.95/12.95
5.70/13.35	8.00/NA	5.70/13.40	NA/NA	NA/15.00	7.86/13.14
7.60/14.60	NA/16.03	5.99/NA	7.83/13.93	6.27/13.85	4.99/15.99
6.22/12.49	NA/14.50	5.74/13.23	6.44/12.14	5.01/12.85	7.59/13.99
6.22/12.49	6.29/14.19	5.99/8.99	NA/NA	6.52/13.39	6.87/14.23
8.28/NA	5.79/13.69	5.44/13.39	5.95/14.00	5.95/15.74	6.10/13.57
7.60/16.35	8.09/14.39	6.71/14.35			

28. Dextromethorphan/Iodinated Glycerol (Tussi-Organidin DM) Liquid
120 ml Generic $_____ Brand $_____

7.01/13.99	6.29/12.50	7.60/12.70	6.99/14.41	5.90/13.05	5.95/13.25
6.59/10.69	NA/NA	5.95/12.75	6.75/13.25	7.25/NA	6.95/12.95
5.30/12.70	9.00/NA	5.85/13.00	NA/NA	NA/12.75	7.57/12.72
4.80/NA	8.95/15.25	5.56/NA	6.60/13.47	5.71/13.29	5.39/15.39
6.20/12.07	NA/13.86	5.31/12.80	5.85/11.72	NA/12.29	6.69/12.69
6.20/12.07	4.69/12.09	5.99/8.99	NA/NA	6.27/13.80	6.99/13.75
7.99/NA	5.67/13.29	5.80/13.80	5.55/10.30	5.54/13.26	5.67/13.14
5.37/15.65	7.29/12.19	6.27/13.90			

29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets
24 Tablets Generic $_____ Brand $_____

6.93/17.91	8.65/16.69	7.30/16.00	7.18/18.17	5.20/15.70	NA/18.25
NA/9.59	8.10/19.58	NA/10.85	8.25/16.50	6.25/16.50	6.50/17.50
7.50/17.60	8.00/15.00	5.50/16.75	NA/NA	NA/18.00	7.30/15.99
NA/9.65	9.27/17.60	4.91/11.09	5.93/17.06	5.91/16.26	4.69/18.39
6.75/15.34	NA/18.85	5.28/16.48	5.23/10.21	NA/NA	5.99/17.69
6.75/15.34	3.99/14.79	5.99/17.08	NA/NA	6.04/14.89	7.34/16.32
7.72/16.41	6.47/17.19	6.04/16.28	5.50/13.20	5.49/13.73	NA/NA
8.10/19.60	10.59/17.29	6.43/17.91			

30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets
30 Tablets Generic $_____ Brand $_____

7.64/15.36	7.64/14.45	9.20/13.95	8.33/15.85	7.80/13.35	7.55/14.95
10.19/11.79	10.60/15.80	6.55/14.45	9.75/14.50	5.50/17.50	8.50/14.50
8.45/14.60	6.00/NA	6.95/14.25	7.25/14.20	7.20/14.00	9.18/13.97
5.00/15.80	10.55/14.59	6.86/13.91	9.10/14.84	8.72/14.96	6.69/15.69
8.18/13.32	9.11/15.77	6.49/14.06	8.00/12.97	6.53/18.96	9.59/15.59
8.18/13.32	7.99/12.69	8.85/15.00	NA/NA	7.92/13.79	8.19/14.21
5.99/NA	8.19/15.39	7.92/13.79	8.40/14.15	6.35/13.72	6.84/14.41
8.85/17.75	6.59/14.69	7.74/15.25			

31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets

100 Tablets Generic $_____ Brand $_____

8.56/36.37	10.40/40.02	12.60/35.85	6.09/41.04	12.10/32.50	4.75/34.05
20.99/29.39	12.70/39.55	7.70/35.05	13.25/35.15	6.75/28.50	12.50/32.50
11.10/37.80	[NA/12.00]*	6.45/30.35	12.65/30.40	11.15/38.00	12.60/37.46
6.30/39.55	17.97/39.85	4.41/27.99	11.83/34.73	5.72/38.96	12.99/32.99
9.90/35.23	19.66/47.18	5.32/41.38	8.37/33.61	7.54/38.96	8.69/34.60
9.90/35.23	4.89/35.59	16.50/35.00	NA/NA	8.37/33.29	14.86/36.81
13.02/NA	5.49/27.27	16.51/36.43	6.45/35.00	9.80/36.13	9.62/37.76
9.70/NA	10.59/33.99	11.34/41.21			

*Suppressed; price for 30-day supply?

Appendix G

Summary of Population Sizes and Skewness Coefficients

DRUG NAME ( )- DOSAGE AND UNITS	Number Generic Product Prices	Skewness Coefficient	Number Brand-name Product Prices	Skewness Coefficient	Number Paired Generic Product Prices	Skewness Coefficient	Number Paired Brand-name Product Prices	Skewness Coefficient	Number Data Points Suppressed
1. Amoxicillin Trihydrate (Polymox) - 125 mg/5 ml Oral Suspension -100 ml	39	+0.14	12	+1.05	10	+0.23	10	+0.83	1
2. Amoxicillin Trihydrate (Polymox) - 250 mg/5 ml Oral Suspension - 100 ml	40	+0.10	13	+0.43	11	-0.30	11	+0.32	1
3. Amoxicillin Trihydrate (Polymox) - 250 mg Capsules - 30 Capsules	43	+0.19	12	+0.86	12	-0.05	12	+0.86	0
4. Amoxicillin Trihydrate (Polymox) - 500 mg Capsules - 30 Capsules	43	+0.08	14	+0.85	14	+0.01	14	+0.85	0
5. Acetaminophen; Codeine Phosphate (Tylenol w/Codeine No. 3) - 300 mg/30 mg Tablets - 30 Tablets	45	+0.45	40	+0.42	40	+0.47	40	+0.42	0
6. Penicillin V Potassium (V-Cillin K) - 250 mg Tablets - 28 Tablets	44	+0.35	22	-1.03	22	+0.06	22	-1.03	0
7. Penicillin V Potassium (V-Cillin K) - 500 mg Tablets - 28 Tablets	43	+0.50	21	-1.34	21	-0.29	21	-1.34	0
8. Codeine Phosphate; Promethazine Hydrochloride (Phenergan w/Codeine) - 10 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	44	+0.93	41	+1.03	41	+1.01	41	+1.03	0
9. Allopurinol (Zyloprim) - 100 mg Tablets - 100 Tablet	44	-0.31	41	-0.11	41	-0.30	41	-0.11	1
10. Allopurinol (Zyloprim) - 300 mg Tablets - 100 Tablets	44	+0.59	40	+0.72	40	+0.49	40	+0.72	1
11. Acetaminophen; Propoxyphene Napsylate (Darvocet-N 100) - 650 mg; 100 mg Tablets - 30 Tablets	45	-0.24	44	+3.51	44	-0.21	44	+3.51	0
12. Sulfamethoxazole; Trimethoprim (Bactrim DS) - 800 mg; 160 mg Tablets - 20 Tablets	43	+0.71	42	-0.34	40	+0.89	40	-0.38	0
13. Doxycycline Hyclate (Vibra - Tabs) EQ - 100 mg Base Tablets - 10 Tablets	44	+0.94	32	-0.72	32	+1.19	32	-0.72	0
14. Erythromycin Ethylsuccinate (Eryped - 200) - 200 mg/5 ml Oral Suspenion - 100 ml	30	+1.28	34	+1.54	21	+0.98	21	+1.46	0
15. Cephalexin (Keflex) - 250 mg Capsules - 28 Capsules	44	-0.05	40	-1.19	39	-0.01	39	-0.82	0
16. Cephalexin (Keflex) - 500 mg Capsules - 28 Capsules	44	+0.18	40	-1.01	39	+0.20	39	-0.48	0

DRUG NAME ( )- DOSAGE AND UNITS	Number Generic Product Prices	Skewness Coefficient	Number Brand-name Product Prices	Skewness Coefficient	Number Paired Generic Product Prices	Skewness Coefficient	Number Paired Brand-name Product Prices	Skewness Coefficient	Number Data Points Suppressed
17. Erythromycin (Eryc) Enteric-coated Pellets - 250 mg EC Capsules - 30 Capsules	40	-0.50	42	+0.39	37	-0.41	37	+0.34	0
18. *Hydroxyzine Hydrochloride (Atarax)* - 10 mg Tablets - 30 Tablets	44	+2.11	39	-1.15	39	+0.79	39	-1.15	0
19. Hydrochlorothiazide (Hydrodiuril) - 25 mg Tablets - 100 Tablets	43	+0.48	22	-2.05	21	+0.63	21	-2.41	0
20. Diazepam (Valium) - 5 mg Tablets - 30 Tablets	44	+1.95	43	-1.00	43	+1.93	43	-1.00	1
21. Chlorpropamide (Diabinese) - 250 mg Tablets - 100 Tablets	44	+0.47	41	+0.38	41	+0.50	41	+0.38	1
22. Ibuprofen (Motrin) - 400 mg Tablets - 30 Tablets	44	+0.87	41	+2.67	40	+1.00	40	+2.65	0
23. Dipyridamole (Persantine) - 50 mg Tablets - 100 Tablets	39	+0.49	43	-0.10	39	+0.49	39	-0.19	1
24. Triamcinolone Acetonide (Kenalog) - 0.1% Cream - 30 Grams	43	+0.23	30	-0.15	30	+0.26	30	-0.15	0
25. Codeine Phosphate; Phenylephrine Hydrochloride; Promethazine Hydrochloride (Phenergan VC with Codeine) - 10 mg/5 ml; 5 mg/5 ml; 6.25 mg/5 ml Syrup - 120 ml	40	+0.96	35	-0.46	34	+1.25	34	-0.49	0
26. Acetaminophen; Hydrocodone Bitartrate (Vicodin) - 500 mg/5 mg Tablets - 12 Tablets	41	+0.78	40	+1.80	39	+0.72	39	+1.91	0
27. Codeine/Iodinated Glycerol (Tussi-Organidin) Liquid - 120 ml	39	+0.16	37	-0.91	34	+0.27	34	-0.92	0
28. Dextromethorphan/Iodinated *Glycerol (Tussi-Organidin DM)* Liquid - 120 ml	39	+0.90	37	-0.61	34	+0.96	34	-0.60	0
29. Guaifenesin/Phenylpropanolamine (Entex) - 400 mg/75 mg SA Tablets - 24 Tablets	35	+0.61	41	-1.20	35	+0.61	35	-1.20	0
30. Acetaminophen; Butalbital; Caffeine (Fioricet) - 325 mg; 50 mg; 40 mg Tablets - 30 Tablets	44	+0.03	42	+0.99	42	-0.01	42	+0.99	0
31. Propranolol Hydrochloride (Inderal) - 20 mg Tablets - 100 Tablets	43	+0.63	41	+0.13	41	+0.66	41	+0.13	1

Appendix H

Computation of Generic Drug Market Share Using Data from the National Substitution Audit (Market Measures, Inc.)

208,042 prescriptions in sample*

34,824 prescriptions were written "generically"

28,207 prescriptions were dispensed using a generic drug product (80 per cent of the prescriptions written generically were dispensed using a generic drug product).

6,617 prescriptions were dispensed using a brand-name drug product (20 per cent of the prescriptions written generically were dispensed using a brand-name drug product).

173,218 prescriptions were written for brand-name drug products.

(1) Assuming a generic drug market share of 33 per cent;

(2) Given that 28,207 prescriptions were dispensed using a generic drug product; and

(3) Assuming that a portion of the 173,218 prescriptions written for brand-name drug products were dispensed using generic drug products;

then 68,654 prescriptions were dispensed using generic drug products. This figure can be broken down into 40,447 prescriptions written for brand-name drug products and dispensed using generic drug products, and 28,207 prescriptions written generically and dispensed using generic drug products.

Generic drug substitution occurred on 40,447 or 19 per cent of the 208,042 prescriptions in the sample.

**These data were for prescriptions written in "DAW" states, or states where a physician is required to handwrite the phrase "dispense as written" or "brand medically necessary" (including "do not substitute") to prohibit generic drug substitution.*

Appendix I

Determination of Cost-Savings Attributable to Generic Drug Products, Generic Drug Substitution, and Drug Product Selection

Assuming that:

(1) 4,500,000 prescriptions were dispensed by community pharmacies in 1989;

(2) Generic drug products accounted for 33 per cent of all prescriptions (new and refills) dispensed in 1989;

(3) Pharmacists substituted therapeutically equivalent generic drug products for the brand-name drug products prescribed on 19 per cent of all prescriptions dispensed in 1989;

(4) The average cost-savings per prescription dispensed using a generic drug product, whether rated as therapeutically equivalent or not, was $7.60; and

(5) The average cost-savings per prescription dispensed using a therapeutically equivalent generic drug product was $7.14;

then in Hawaii in 1989 cost-savings attributable to the use of generic drug products were equal to (4,500,000)(0.33)($7.60) or $11,286,000. This figure can be broken down into:

(1) Cost-savings attributable to generic drug substitution (i.e., substitution involving therapeutically equivalent drug products) that were equal to (4,500,000)(0.19)($7.14) or $6,105,000; and

(2) Cost-savings attributable to drug product selection that were equal to $11,286,000 - $6,105,000 or $5,181,000.

Appendix J

Letter from Edward Heon

HAWAII MEDICAL SERVICE ASSOCIATION

818 Keeaumoku St., Honolulu, HI 96814 | P.O. Box 860, Honolulu, HI 96808

(808) 944-2110

September 12, 1990

Mr. Keith Fukumoto
Legislative Reference Bureau
State Capitol
Room 004
Honolulu, HI 96813

Dear Keith,

Attached you will find a summary report with respect to cost comparisons between brand name products and their generic equivalents. This information supports data which was previously sent to you via FAX on September 6, 1990. Before this information is officially released, it is important to realize the foundation of the supporting data.

All totals and averages have been calculated based on frequencies and quantities from actual claims utilization data for 1989 and BlueBook Average Wholesale Prices as of September 1, 1990. Also, **COSTS** are a measure of ingredient costs only and do not account for additional service charges or dispensing fees.

It is also important to note that the utilization data may be incomplete since members would not need to file claims for products which are billed for less than or equal to their copayment. Typically, this would mean that brand drugs charged less than $7.00 and generic drugs charged less than $2.00 may be absent from our data.

Finally, the data excludes the following:

- Repackaged products
- Obsolete dated products
- Products not covered on an out-patient basis (i.e. Supplies, Injectibles, Over-the-counter drugs, etc.)
- Prescriptions which were not filled by brand products as well as generically at least twelve times each during 1989

If you have any questions or additional requests please call me at 944-2482.

Sincerely,

Edward C. Heon

Edward C. Heon
Senior Information Coordinator

Attachment

BRANCHES

670 PONAHAWAI ST., SUITE 121
HILO, HI 96720
TEL 935-5441

75-167 HUALALAI ROAD
KAILUA-KONA, HI 96740
TEL 329-5291

33 LONO AVE., SUITE 350
KAHULUI, HI 96732
TEL 871-6295

4366 KUKUI GROVE ST., SUITE 103
LIHUE, HI 96766
TEL 245-3393

SUMMARY OF GENERICALLY AVAILABLE PRODUCTS
BRAND vs GENERIC ANALYSIS
1989 UTILIZATION DATA
and AWPs AS OF 9/1/90

VARIABLE	BRAND	GENERIC	% DIFF
NUMBER OF PRESCRIPTIONS	400,940	491,119	
NUMBER OF UNITS OF DRUG	22,265,953	29,894,506	
WEIGHTED AVERAGE AWP	0.27047	0.09268	191.8%
WEIGHTED AVERAGE QTY/Rx	59	61	
WEIGHTED AVERAGE COST/Rx	$ 15.96	$ 5.65	182.5%

The total cost of the generic products dispensed was $2,770,571.04 while the brand replacement cost would have been $7,211,606.49. Therefore, the net cost savings experienced through generic substitution was $4,441,035.45.

The total cost which could have occurred through 100% generic substitution amounts to $5,608,403.10 while the total brand cost which could have occurred through 0% generic substitution amounts to $13,233,372.31. Therefore, the maximum potential cost savings which could have occurred was $7,624,969.21.

D E F I N I T I O N S O F T I T L E S

OBS	Ranking of generic categories by total claims count
G_NAME	Generic name of the drug
FORM	Form of the drug
STRENGTH	Strength of the drug
B_NAME	Trade name or Brand name of the drug
T_FREQ	Total number of prescriptions/claims received in 1989
G_FREQ	Generically paid prescriptions/claims
B_FREQ	Brand name paid prescriptions/claims
T_QTY	Total number of units of drug dispensed in 1989
G_QTY	Number of units of drug dispensed Generically
B_QTY	Number of units of a Brand name drug dispensed
W_AWP_G	Weighted Average Wholesale Price of Generic units
W_AWP_B	Weighted Average Wholesale Price of Brand units
GEN_COST	Total ingredient cost of generically dispensed units (ie. W_AWP_G x G_QTY)
BNDREPLC	Brand Replacement costs of generically dispensed units (ie. W_AWP_B x G_QTY)
NET_SAVE	Savings incurred through generic substitution (ie. BNDREPLC - GEN_COST)

OBS	G_NAME	FORM	STRENGTH	B_NAME	T_FREQ	G_FREQ
1	ESTROGENS,CONJUGATED	TABLET	0.625MG	PREMARIN	34,435	2,038
2	AMOXICILLIN TRIHYDRATE	CAPSULE	250MG	POLYMOX	27,962	27,943
3	AMOXICILLIN TRIHYDRATE	ORAL SUSP	250MG/5ML	AMOXICILLIN	27,403	27,240
4	CODEINE PHOSPHATE/APAP	TABLET	30/300	TYLENOL W/CODEINE NO.3	25,397	18,786
5	AMOXICILLIN TRIHYDRATE	CAPSULE	500MG	POLYMOX	17,793	17,770
6	CODEINE/PROMETH	SYRUP		PHENERGAN W/CODEINE	14,696	9,629
7	ERYTHROMYCIN BASE	CAPSULE EC	250MG	ERYC	13,664	5,644
8	PENICILLIN V POTASSIUM	TABLET	250MG	V-CILLIN K	13,348	12,913
9	PENICILLIN V POTASSIUM	TABLET	500MG	V-CILLIN K	12,808	12,508
10	PROPOXYPHENE NAPSYLATE/APAP	TABLET	100-650	DARVOCET-N 100	12,105	7,727
11	ALLOPURINOL	TABLET	300MG	ZYLOPRIM	11,080	9,406
12	AMOXICILLIN TRIHYDRATE	ORAL SUSP	125MG/5ML	AMOXICILLIN	10,917	10,883
13	SULFAMETHOXAZOLE/TRIMETHOPRIM	TABLET	800-160MG	BACTRIM DS	9,958	7,822
14	THEOPHYLLINE ANHYDROUS	TABLET SA	300MG	THEO-DUR	9,122	1,065
15	CODEINE/IODINATED GLYCEROL	LIQUID		TUSSI-ORGANIDIN	8,823	3,472
16	MEDROXYPROGESTERONE ACET	TABLET	10MG	PROVERA	8,572	2,385
17	DIPYRIDAMOLE	TABLET	50MG	PERSANTINE	7,826	4,091
18	GUAIFENESIN/PHENYLPROP	TABLET SA	400/75	ENTEX LA	7,639	3,169
19	LEVOTHYROXINE SODIUM	TABLET	0.1MG	SYNTHROID	7,615	1,447
20	DIAZEPAM	TABLET	5MG	VALIUM	7,570	4,953
21	CEPHALEXIN	CAPSULE	250MG	KEFLEX	7,347	5,512
22	DOXYCYCLINE HYCLATE	TABLET	100MG	VIBRA-TABS	7,308	6,705
23	CHLORPROPAMIDE	TABLET	250MG	DIABINESE	7,146	4,625
24	D-METHORPHAN/IOD GLYCEROL	LIQUID		TUSSI-ORGANIDIN DM	7,126	3,304
25	P-EPHEDRINE/COD/CHLORPHENIR	LIQUID		NOVAHISTINE DH	6,953	2,624

OBS	B_FREQ	T_QTY	G_QTY	B_QTY	W_AWP_G	W_AWP_B	GEN_COST	BNDREPLC	NET_SAVE
1	32,397	1,233,152	122,966	1,110,186	0.19093	0.27923	23,478.41	34,335.47	10,857.06
2	19	686,843	686,348	495	0.21203	0.32478	145,524.63	222,910.65	77,386.02
3	163	3,522,867	3,491,826	31,041	0.04562	0.06193	159,286.38	216,236.58	56,950.20
4	6,611	559,104	396,941	162,163	0.07777	0.19547	30,869.02	77,588.12	46,719.10
5	23	410,353	409,791	562	0.39067	0.58701	160,094.57	240,551.41	80,456.84
6	5,067	1,962,220	1,289,988	672,232	0.01567	0.04286	20,213.76	55,284.04	35,070.28
7	8,020	396,394	163,664	232,730	0.24194	0.27248	39,597.14	44,595.25	4,998.11
8	435	399,856	387,917	11,939	0.06077	0.17771	23,575.52	68,937.54	45,362.02
9	300	310,048	303,489	6,559	0.12063	0.33956	36,610.25	103,051.96	66,441.71
10	4,378	374,799	227,114	147,685	0.23448	0.41460	53,254.13	94,161.94	40,907.81
11	1,674	604,363	547,602	56,761	0.18911	0.36002	103,558.19	197,146.50	93,588.31
12	34	1,425,886	1,419,836	6,050	0.02618	0.05239	37,170.57	74,387.44	37,216.87
13	2,136	178,977	141,569	37,408	0.22999	0.81155	32,558.90	114,889.96	82,331.06
14	8,057	575,084	73,949	501,135	0.13641	0.22351	10,087.38	16,528.00	6,440.62
15	5,351	1,196,964	465,735	731,229	0.02069	0.07410	9,637.85	34,509.77	24,871.92
16	6,187	206,989	54,509	152,480	0.24504	0.51408	13,356.82	28,021.77	14,664.95
17	3,735	686,059	378,634	307,425	0.05728	0.34964	21,686.72	132,384.82	110,698.10
18	4,470	154,478	59,657	94,821	0.07979	0.48899	4,760.05	29,171.66	24,411.61
19	6,168	379,923	98,890	281,033	0.02031	0.14567	2,008.26	14,405.12	12,396.86
20	2,617	244,377	152,132	92,245	0.10358	0.44238	15,757.97	67,299.62	51,541.65
21	1,835	202,324	149,883	52,441	0.54367	0.95468	81,486.59	143,090.42	61,603.83
22	603	119,186	110,562	8,624	0.36158	2.60775	39,976.93	288,318.56	248,341.63
23	2,521	451,216	328,644	22,572	0.06270	0.54466	20,606.34	178,998.67	158,392.33
24	3,822	994,701	447,153	547,548	0.01727	0.07058	7,723.43	31,559.09	23,835.66
25	4,329	1,044,978	370,193	674,785	0.01764	0.04471	6,532.01	16,551.81	10,019.80

OBS	G_NAME	FORM	STRENGTH	B_NAME	T_FREQ
26	DIGOXIN	TABLET	0.25MG	LANOXIN	6,943
27	HYDROXYZINE HYDROCHLORIDE	TABLET	10MG	ATARAX	6,831
28	PE/PHENYLPROP/PHENYLTOLOX/CPM	TABLET SA		NALDECON	6,569
29	ERYTHROMYCIN ETHYLSUCCINATE	ORAL SUSP	200MG/5ML	ERYPED-200	6,395
30	ALLOPURINOL	TABLET	100MG	ZYLOPRIM	6,385
31	ACETAMINOPHEN/CAFFEINE/BUTALB	TABLET		FIORICET	6,242
32	PE/PHENYLPROP/PHENYLTOLOX/CPM	SYRUP	1/2	NALDECON	5,951
33	HCTZ/TRIAMTERENE	TABLET	50/75	MAXZIDE	5,937
34	ESTROGENS,CONJUGATED	TABLET	1.25MG	PREMARIN	5,856
35	THEOPHYLLINE ANHYDROUS	TABLET SA	200MG	THEO-DUR	5,611
36	OXYCODONE HCL/ACETAMINOPHEN	CAPSULE	5/500	TYLOX	5,565
37	HYDROCODONE BITARTRATE/APAP	TABLET	5/500	VICODIN	5,546
38	ERYTHROMYCIN/SULFISOXAZOLE	ORAL SUSP		PEDIAZOLE	5,475
39	PRAZOSIN HCL	CAPSULE	1MG	MINIPRESS	5,451
40	HYDROCHLOROTHIAZIDE	TABLET	25MG	HYDRODIURIL	5,445
41	GUAIFENESIN/CODEINE PHOSPHATE	SYRUP		ROBITUSSIN A-C	5,277
42	IBUPROFEN	TABLET	400MG	MOTRIN	5,103
43	PSEUDOEPHEDRINE/CHLORPHENIR	CAPSULE SA	120/8	DECONAMINE SR	5,081
44	PHENYLEPHRINE/CODEINE/PROMETH	SYRUP		PHENERGAN VC W/CODEINE	5,053
45	ESTROGENS,CONJUGATED	TABLET	0.3MG	PREMARIN	5,040
46	PROPRANOLOL HYDROCHLORIDE	TABLET	20MG	INDERAL	5,031
47	CEPHALEXIN	CAPSULE	500MG	KEFLEX	4,989
48	LEVOTHYROXINE SODIUM	TABLET	0.15MG	SYNTHROID	4,804
49	TRIAMCINOLONE ACETONIDE	CREAM	0.1PC	KENALOG	4,660
50	GUAIFENESIN/P-EPHEDRINE/COD	SYRUP	10MG	ROBITUSSIN-DAC	4,347

OBS	G_FREQ	B_FREQ	T_QTY	G_QTY	B_QTY	W_AWP_G	W_AWP_B	GEN_COST	BNDREPLC	NET_SAVE
26	301	6,642	423,343	16,856	406,487	0.02524	0.07709	425.36	1,299.44	874.08
27	5,382	1,449	257,018	206,955	50,063	0.06364	0.41318	13,171.49	85,509.83	72,338.34
28	1,422	5,147	158,426	37,377	121,049	0.03050	0.64304	1,140.00	24,034.84	22,894.84
29	5,758	637	739,350	661,280	78,070	0.04995	0.07116	33,029.53	47,058.85	14,029.32
30	5,234	1,151	408,491	355,351	53,140	0.07545	0.13126	26,812.35	46,642.42	19,830.07
31	3,083	3,159	212,827	96,600	116,227	0.14507	0.32576	14,014.01	31,468.18	17,454.17
32	1,525	4,426	887,785	223,214	664,571	0.01359	0.07171	3,032.98	16,006.68	12,973.70
33	1,332	4,605	176,989	48,542	128,447	0.18631	0.55721	9,043.86	27,047.90	18,004.04
34	262	5,594	204,649	14,551	190,098	0.24791	0.38362	3,607.39	5,582.08	1,974.69
35	634	4,977	365,916	41,916	324,000	0.11272	0.18690	4,724.86	7,834.14	3,109.28
36	267	5,298	149,611	8,118	141,493	0.30511	0.47520	2,476.85	3,857.69	1,380.84
37	3,747	1,799	136,435	84,936	51,499	0.15401	0.27919	13,080.57	23,712.88	10,632.31
38	1,876	3,599	759,286	265,028	494,258	0.11141	0.13851	29,526.86	36,708.65	7,181.79
39	234	5,217	302,115	14,595	287,520	0.20859	0.30438	3,044.42	4,442.42	1,398.00
40	5,305	140	314,421	308,451	5,970	0.02038	0.10542	6,285.10	32,517.97	26,232.87
41	3,099	2,178	723,697	419,679	304,018	0.01717	0.05717	7,205.54	23,992.15	16,786.61
42	4,133	970	179,538	134,800	44,738	0.09809	0.16514	13,223.12	22,260.85	9,037.73
43	549	4,532	128,116	12,605	115,511	0.20430	0.41490	2,575.25	5,229.85	2,654.60
44	3,899	1,154	681,843	521,345	160,498	0.01852	0.04521	9,653.13	23,568.08	13,914.95
45	205	4,835	188,958	12,344	176,614	0.13605	0.20119	1,679.42	2,483.50	804.08
46	3,108	1,923	385,344	252,319	133,025	0.08348	0.31275	21,063.89	78,913.87	57,849.98
47	4,028	961	127,943	104,035	23,908	1.08755	1.87665	113,143.10	195,237.16	82,094.06
48	435	4,369	194,701	26,646	168,055	0.02743	0.17425	730.94	4,643.07	3,912.13
49	3,916	744	225,863	185,786	40,077	0.05018	0.18008	9,322.84	33,457.17	24,134.33
50	1,168	3,179	584,096	155,648	428,448	0.02149	0.04968	3,344.34	7,732.02	4,387.68

Appendix K

Memorandum from Chandra Yamane

HDS Medical

700 BISHOP STREET SUITE 777
HONOLULU HAWAII 96813-4196
PHONE (808) 536-0020

MEMORANDUM

DATE: October 15, 1990

TO: Keith Fukumoto

FROM: Chandra Yamane, HDS

RE: Revised Report

Enclosed is the revised report requested in our October 11, 1990 telephone conversation.

The report now excludes data falling into the "other" nondrug item category and includes HDS' system definition of the three remaining categories -- brand, generic, and substitutable.

HDS would appreciate receiving a copy of your final report. If you have any questions, please call.

HDS MEDICAL - RX DISPENSED IN 1989

CATEGORY	NUMBER OF PRESCRIPTIONS	AMOUNT PAID	AVERAGE AMOUNT PAID
BRAND	56,545	$1,273,060	$22.51
GENERIC	58,163	$378,066	$6.50
SUBSTITUTABLE	54,594	$662,276	$12.13
TOTAL	169,302	$2,313,402	$13.66

SAVINGS	58,163 GENERIC RX PAID @ $12.13=	$705,571
less	ACTUAL GENERIC PAID=	$378,066
	AMOUNT SAVED=	$327,505
	AMOUNT SAVED AS % OF TOTAL PD=	14.2%
POTENTIAL SAVINGS	54,594 SUBSTITUTABLE PAID=	$662,276
less	54,594 SUBST. RX PAID @ $6.50=	$354,867
	POTENTIAL SAVINGS=	$307,409
	POTENTIAL SAVINGS AS % TOTAL PD=	13.3%

Note:

Brand - A single source trade named product

Generic - A multisource non-trade named product dispensed under its chemical name

Substitutable - A multisource trade name product

Department of Human Services-Medicaid Program

DEC - 5 1990

JOHN WAIHEE
GOVERNOR

WINONA E. RUBIN
DIRECTOR

ALFRED K. SUGA
DEPUTY DIRECTOR

MERWYN S. JONES
DEPUTY DIRECTOR

STATE OF HAWAII
DEPARTMENT OF HUMAN SERVICES
Health Care Administration Division
P. O. Box 339
Honolulu, Hawaii 96809

December 4, 1990

Samuel B. K. Chang
Director
Legislative Reference Bureau
State of Hawaii
State Capitol
Honolulu, Hawaii 96813

Dear Mr. Chang:

The attached information completes the ongoing request for data involving Medicaid Program savings due to the use of generic drugs.

Included in the attachments are the methodologies, data collection methods, calculations, findings and conclusions. It is interesting that the range of savings varies with each pharmacologic class of drugs from as little as 2.12% for anticonvulsants to as much as 53.5% with the psychotropics.

Any further questions should be directed to our Pharmacy Consultant, Omel Turk at 548-8917.

Sincerely,

Winona E. Rubin
Director

Attachments

DATA COLLECTION FOR LEGISLATIVE REFERENCE BUREAU REPORT ON GENERIC DRUG SUBSTITUTION BY DHS-HCAD

METHODOLOGY

INTRODUCTION

Due to constraints of available resources, a programwide study of all drugs in the Medicaid Program was not possible. The evaluation of savings due to the encouraged use of generic drug products was focused on three pharmacologic groups: anticonvulsant, psychotropic and cardiac drugs. These groups were not chosen randomly but because controversy exists about the bioequivalency in these pharmacologic categories and a wide choice of multiple choice generic drug products is available. An assumption was made that any savings identified in these classes where careful if not reluctant substitution for brands occurs would indicate a high probability of greater programwide savings in all other drug products.

DATA COLLECTION

Two medications were randomly selected from each of these three classes:

1. Anticonvulsants: phenytoin 100 mg and carbamazepine 200 mg.
2. Psychotropics: chlorpromazine 50 mg and haloperidol 10 mg.
3. Cardiac Drugs: propranolol 40 mg and procainamide sustained release 500 mg.

Three pharmacy chains with pharmacies in locales statewide were polled to determine which generic equivalents they utilized. Since the brand name of each drug product was known, the chains were asked to identify only the National Drug Code (NDC) number of the chosen generic equivalents they used. These chain pharmacies were Longs Drug Stores, Pay'N Save Drug Stores Inc. and Clinical Pharmacy Consultants (CPC).

From Hawaii MMIS Medicaid Drug Usage Frequency Analysis annual report for the period of 01/01/89 - 12/31/89 provided by the Medicaid fiscal agent, Hawaii Medical Service Association (HMSA), showing annual Medicaid expenditures for drugs during the calendar year 1989, the following information for each generic equivalent and brand name product was extracted.

1. Total dollar payment.
2. Average number of doses per prescription (Rx).
3. Total number of prescriptions (Rx).

CALCULATIONS

A. Total Number of Doses

The total number of doses of each NDC number was determined by multiplying the total number of prescriptions by the average doses per prescription.

B. Cost Per Dose

The cost per dose was calculated by deducting out the number of dispensing fees (Total Rx's multiplied by the dispensing fee) from total payment and dividing that remainder by the total number of doses.

C. Total Cost If Only Brand Used

The cost per dose of the brand name drug was multiplied times the total doses of brand and generic used. To that product was added the dispensing fee cost (Total prescriptions multiplied by the dispensing fee).

D. Savings Due To Generic Use

The actual 1989 total payment cost was subtracted from the total cost that would have been incurred had only the brand name been paid for.

E. Percent Savings Due To Use Of Generic Drugs

The savings due to generic use was divided by the total cost if only brand used and converted to a percent number.

FINDINGS

As might have been predicted, generic substitution was lowest in the anticonvulsant category ranging from a savings of 2.12% with Phenytoin to 4.54% with Carbamazepine. (Please see the attached spreadsheets.) This is due to the reluctance of physicians and pharmacists to change patients from one brand to another because of differences in absorption and other bioequivalency phenomena. The price differential between the widely use generic is not as great as with some other therapeutic classes.

The savings on the psychotropic drugs studied was surprising. While titration and patient compliance factors

substantially influence patient response, substitution was considerable with savings ranging from 53.5% on Chlorpromazine to 42.17% for Haloperidol 10 mg. The larger savings is also attributed largely to the wide difference in price of the generic brands compared to the brand. The range for Chlorpromazine is $0.3171 and $0.0292 per tablet for the brand and generic respectively. The range in prices between brand and generic for the Haloperidol 10 mg ranges from $0.5417 per tablet downward to $0.0957 per tablet.

Of the cardiac drugs, propranalol with prices ranging from $0.1269 downward to $0.0141 show a savings of 50.14%. A wide difference in cost of the various manufacturers and an extremely high use of generic drug products contribute to this savings. Almost 8 times as many generic doses as brand name doses are used. Procainamide SR 500 was not substituted as often nor enjoyed the wide difference in price between generic and brand product. Savings was 9.61%.

CONCLUSIONS

Substantial savings have been realized by the Medicaid Program through the use of generic drug products. Physicians and pharmacists are less likely to substitute medications that must be closely titrated to the patient needs or that have documented bioequivalency problems.

This limited study would not indicate the exact percent savings, but would allow an assumption of "substantial savings" in the $17,000,000 pharmacy portion of Medicaid. The Department has provided strong incentives for the participating providers and recipients to utilize generic medications where possible. This policy is partly responsible for the Hawaii Medicaid Pharmacy Program being the fourth lowest cost such program nationally in terms of dollars spent per patient for drug therapy.

GENERIC SUBSTITUTION COST SAVINGS STUDY
DEPARTMENT OF HUMAN SERVICES
HEALTH CARE ADMINISTRATION DIVISION
Omel Turk, MBA, Pharmacy Consultant
DRUG NAME:Phenytoin 100 mg. PHARMACOLOGIC CLASS:Anticonvulsant

MANUFACTURER OF DRUG	NATIONAL DRUG CODE	COST PER DOSE	TOTAL # OF DOSES	TOTAL Rx's	AVERAGE DOSES PER Rx	TOTAL PAYMENT
P-D (BRAND)	00071-0362	$0.0708	551,530	6,101	90.4	$65,942
BARR (GENERIC)	00725-0084	$0.0500	76,464	864	88.5	$7,627
		$0.0000	0			
		$0.0000	0			
		$0.0000	0			
			627,994	6,965		$73,569

TOTAL COST IF ONLY BRAND USED $75,164
ACTUAL 1989 COST(BRAND + GEN.) $73,569

SAVINGS DUE TO GENERIC USE $1,595

PER CENT SAVINGS DUE TO USE OF GENERIC DRUGS 2.12%

GENERIC SUBSTITUTION COST SAVINGS STUDY
DEPARTMENT OF HUMAN SERVICES
HEALTH CARE ADMINISTRATION DIVISION
Omel Turk, MBA, Pharmacy Consultant
DRUG NAME:Carbamazepine 200mg PHARMACOLOGIC CLASS:Anticonvulsant

MANUFACTURER OF DRUG	NATIONAL DRUG CODE	COST PER DOSE	TOTAL # OF DOSES	TOTAL Rx's	AVERAGE DOSES PER Rx	TOTAL PAYMENT
GEIGY (BRAND)	00028-0027	$0.2293	380,990	3,248	117.3	$101,654
FOREST (GENERIC	00258-3587	$0.1222	18,957	178	106.5	$3,101
PUREPAC (GENERI	00228-2143	$0.1271	16,345	149	109.7	$2,734
URL (GENERIC)	00677-1099	$0.1273	15,017	141	106.5	$2,532
		$0.0000	0			
			431,309	3,716		$110,021

TOTAL COST IF ONLY BRAND USED $115,252
ACTUAL 1989 COST (BRAND+GEN) $110,021

SAVINGS DUE TO GENERIC USE $5,231

PER CENT SAVINGS DUE TO USE OF GENERIC DRUGS 4.54%

GENERIC SUBSTITUTION COST SAVINGS STUDY
DEPARTMENT OF HUMAN SERVICES
HEALTH CARE ADMINISTRATION DIVISION
Omel Turk, MBA, Pharmacy Consultant
DRUG NAME:Propranalol 40 mg. PHARMACOLOGIC CLASS: Cardiac Drug

MANUFACTURER OF DRUG	NATIONAL DRUG CODE	COST PER DOSE	TOTAL # OF DOSES	TOTAL Rx's	AVERAGE DOSES PER Rx	TOTAL PAYMENT
AYERST(BRAND)	00046-0424	$0.1269	5,695	85	67	$1,097
LEDERLE(GENERIC	00005-3111	$0.0174	19,794	299	66.2	$1,661
BARR(GENERIC)	00555-0367	$0.0141	12,941	151	85.7	$848
		$0.0000	0			
		$0.0000	0			
			38,430	535		$3,606

TOTAL COST IF ONLY BRAND USED $7,233
ACTUAL 1989 COST (BRAND+GEN) $3,606
SAVINGS DUE TO GENERIC USE $3,627

PER CENT SAVINGS DUE TO USE OF GENERIC DRUGS 50.14%

GENERIC SUBSTITUTION COST SAVINGS STUDY
DEPARTMENT OF HUMAN SERVICES
HEALTH CARE ADMINISTRATION DIVISION
Omel Turk, MBA, Pharmacy Consultant
DRUG NAME:Procainamide SR 500 mg. PHARMACOLOGICAL CLASS:Cardiac Drug

MANUFACTURER OF DRUG	NATIONAL DRUG CODE	COST PER DOSE	TOTAL # OF DOSES	TOTAL Rx's	AVERAGE DOSES PER Rx	TOTAL PAYMENT
P-D (BRAND)	00071-0204	$0.1804	14,964	151	99.1	$3,365
GENEVA(GENERIC)	00781-2315	$0.0505	166	4	41.5	$26
BOLAR(GENERIC)	00725-0153	$0.1148	3,062	33	92.8	$497
SIDMAK(GENERIC)	50111-0340	$0.1108	3,663	45	81.4	$604
		$0.0000	0			
			21,856	233		$4,492

TOTAL COST IF BRAND ONLY USED $4,970
ACTUAL 1989 COST (BRAND+GEN) $4,492
SAVINGS DUE TO GENERIC USE $478

PER CENT SAVINGS DUE TO USE OF GENERIC DRUGS 9.61%

GENERIC SUBSTITUTION COST SAVINGS STUDY
DEPARTMENT OF HUMAN SERVICES
HEALTH CARE ADMINISTRATION DIVISION
Omel Turk, MBA, Pharmacy Consultant
DRUG NAME: Chlorpromazine 50 mg. PHARMACOLOGIC CLASS: Psychotropic

MANUFACTURER OF DRUG	NATIONAL DRUG CODE	COST PER DOSE	TOTAL # OF DOSES	TOTAL Rx's	AVERAGE DOSES PER Rx	TOTAL PAYMENT
SKF (BRAND)	00007-5076	$0.3171	4,374	81	54	$1,744
GENEVA(GENERIC)	00781-1717	$0.0292	12,602	236	53.4	$1,407
		$0.0000	0			
		$0.0000	0			
		$0.0000	0			
			16,976	317		$3,151

TOTAL COST IF ONLY BRAND USED $6,780
ACTUAL 1989 COST (BRAND+GEN.) $3,151
SAVINGS DUE TO GENERIC USE $3,629

PER CENT SAVINGS DUE TO USE OF GENERIC DRUGS 53.53%

GENERIC SUBSTITUTION COST SAVINGS STUDY
DEPARTMENT OF HUMAN SERVICES
HEALTH CARE ADMINISTRATION DIVISION
Omel Turk, MBA, Pharmacy Consultant
DRUG NAME: :Haloperidol 10 mg PHARMACOLOGIC CLASS: Psychotropic

MANUFACTURER OF DRUG	NATIONAL DRUG CODE	COST PER DOSE	TOTAL # OF DOSES	TOTAL Rx's	AVERAGE DOSES PER Rx	TOTAL PAYMENT
MCNEIL (BRAND)	00045-0246	$0.5417	11,753	211	55.7	$7,296
GENEVA(GENERIC)	00781-1397	$0.1525	7,753	118	65.7	$1,702
BARR(GENERIC)	00555-0481	$0.0957	8,166	128	63.8	$1,345
RUGBY(GENERIC)	00536-3880	$0.1533	4,025	72	55.9	$934
		$0.0000	0			
			31,697	529		$11,277

TOTAL COST IF BRAND ONLY USED $19,501
ACTUAL 1989 COST (BRAND+GEN) $11,277
SAVINGS DUE TO GENERIC USE $8,224

PER CENT SAVINGS DUE TO USE OF GENERIC DRUGS 42.17%