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ATTORNEY GENERAL OPINION NO. 90- 50

The Honorable Roy M. Ehrlich
State Senator, 35th District
State Capitol, Room 138-N
Topeka, Kansas 66612

Re: Public Health -- Examination and Registration of
Pharmacists -- Pharmacists Required to be in Charge
of Pharmacy; Brand Exchange

Synopsis: Drugs which were generally recognized as safe prior to the enactment of the federal food, drug and cosmetic act of 1938 were not considered new drugs within the meaning of that act, and were therefore given approval through the grandfather provisions of the act. As long as those grandfathered drugs do not become new drugs, there will be a lack of sufficient data, and an absence of an opportunity to determine bioequivalence between other drugs and the grandfathered drug. In light of this lack of information, the grandfathered drugs are not subject to brand exchange as are drugs for which bioequivalence has been determined. Cited herein: K.S.A. 1989 Supp. 65-1626; 65-1637; 21 U.S.C.S. § 355 (Cum. Supp. 1989); 21 U.S.C.S. § 358 (1984); 34 Stat. 768 (1906), 37 Stat. 416 (1912), 52 Stat. 1040 (1938); Pub. L. 87-781 (1962), Pub. L. 98-417 (1984).

* * *

Dear Senator Ehrlich:

As State Senator for the Thirty-Fifth District, you have requested our opinion concerning the brand exchange provisions of the Kansas pharmacy act, K.S.A. 1989 Supp. 65-1637(a). Specifically, you ask whether certain drugs which have not been rated for bioequivalency by the food and drug administration (FDA) are considered bioequivalent.

The FDA has published a list of equivalent drugs entitled, Approved Prescription Drug Products with Therapeutic Equivalence Evaluations. This book, otherwise called the "Orange Book," categorizes some drug products in either list "A" or "B". A drug product is given an "A" listing if it is considered therapeutically equivalent, and a "B" listing if it is considered not therapeutically equivalent. Fink, Pharmacy Law Digest, at CL-44 (Facts and Comparisons, July, 1988). Application of K.S.A. 1989 Supp. 65-1637(a)(4), set out in greater detail below, is easy if a drug product is listed in the Orange Book in category "B". The difficulty is when a drug is not listed in either category. It is these unlisted drugs about which you have requested our opinion. As will be discussed in greater detail, the FDA lacks sufficient data for those unlisted drugs to make a determination of equivalency or non-equivalency. Kansas State Board of Pharmacy Newsletter, Volume 10, No. 3, November, 1989 at page 1.

Pharmacists are generally required to fill prescriptions in strict conformity with the prescription order. However, a pharmacist may exercise brand exchange for brand name products listed on a prescription order within the guidelines of K.S.A. 1989 Supp. 65-1637. That statute states in relevant part:

"(a) All prescriptions shall be filled in strict conformity with any directions of the prescriber, except that a pharmacist who receives a prescription order for a brand name drug product may exercise brand exchange with a view toward achieving a lesser cost to the purchaser unless:

. . . .

"(4) the federal food and drug administration has determined that a drug product of the same generic name is not

bioequivalent to the prescribed brand name prescription medication." K.S.A. 1989 Supp. 65-1637(a).

The term "brand exchange" is defined as "the dispensing of a different drug product of the same dosage form and strength and of the same generic name than the brand name drug product prescribed." "Brand name" is defined as "the registered trademark name given to a drug product by its manufacturer, labeler or distributor." The term "generic name" is defined as "the established chemical name or official name of a drug or drug product." K.S.A. 1989 Supp. 65-1626(d), (e), and (1). The chemical name describes the chemical structure of the drug's active ingredient, and the official name is that name assigned by the secretary of the FDA for use in any official compendium. 21 U.S.C.S. § 358(a) (1984). The term "official name" is sometimes used synonymously with the term "generic name." Wheaton, Generic Competition and Pharmaceutical Innovation: The Drug Price Competition and Patent Term Restoration Act of 1984, 35 Cath. U.L. Rev. 433, 442 (1986). Generic drugs are products containing the same active ingredients, but not necessarily the same inactive ingredients, as the pioneer or name brand drug. These inactive ingredients, or "excipients," may effect the safety and efficacy of the generic product by affecting the rate at which the active ingredient is absorbed or delivered. United States v. Generix Drug Corp., 460 U.S. 453, 454-55; 103 S.Ct. 1298; 75 L.Ed.2d 198, 201-02 (1983).

The statute makes no provision for limiting a pharmacist's discretion if the physician specifies a prescription-only drug by generic name instead of a brand name. Presumably, the pharmacist would have greater flexibility in selecting the drug dispensed when the prescription order is not for a brand name drug. Wheaton, 35 Cath. U.L. Rev. at 437.

The evolution of the federal drug acts explains why FDA lacks sufficient data for determining that certain drugs are bioequivalent. This history as well as the history of the state statute, also explains why certain drugs may not be brand-exchanged, even though FDA has not made a negative finding on the issue of bioequivalency. The federal food and drug act of 1906, 34 Stat. 768 (1906), was the first nationwide legislation regulating drugs. Some purity standards and accurate labeling requirements were imposed by the law. False claims of efficacy were made unlawful by the 1912 amendments to the act. See 37 Stat. 416 (1912). These laws did not provide a premarket review for safety of the

drug. Following the "Elixir of Sulfanilamide" disaster, the 1906 act and the 1912 amendments were repealed and replaced with a new law in 1938. This tragedy involved nearly 100 deaths as the result of the drug's toxicity, for which no premarket tests were apparently required, or performed. Note, Drug Efficacy and the 1962 Drug Amendments, 60 Georgetown L.J. 185, 186 (1971).

The federal food, drug, and cosmetic act of 1938, 52 Stat. 1040 (1938), required an effective new drug application (NDA) for any "new drug" prior to introducing the new drug into commerce. § 505(a), 52 Stat. 1052. Section 201(p)(1) of the act defined "new drug" as one "not generally recognized by qualified experts as safe for its intended use." Weinberger v. Hynson, Wescott & Dunning, 412 U.S. 609, 612; 93 S.Ct. 2469; 37 L.Ed.2d 207, 213 (1973). The basis for this recognition was the drug's many years of use and its having been well tested. If there was any dispute among experts, a drug was considered a new drug, requiring FDA review and approval. Premo Pharmaceutical Laboratories, Inc. v. U.S., 629 F.2d 795, 802 (2d Cir. 1980).

The 1938 act was amended in 1962 by Pub. L. 87-781, Title I (1962) to include efficacy as a factor for approval of an NDA. Therefore, a drug must be proven effective as well as safe, and previously approved drugs were to be withdrawn if substantial evidence of efficacy was lacking. Hynson, 412 U.S. at 613, 37 L.Ed.2d at 214. However, section 107(c)(4) of the 1962 act contained a grandfather clause, exempting from the efficacy requirement a drug which,

"on the day preceding enactment (1) was commercially used or sold in the United States, (2) was not a 'new drug' as defined in the 1938 Act (it being generally recognized as safe), and (3) 'was not covered by an effective application' for a new drug under the 1938 Act." Hynson, 412 U.S. at 614, 37 L.Ed.2d at 214.

With the exception of these "grandfathered" drugs, other drugs already on the market were given transitional protection, and pending NDA's were deemed approved for the transitional period. U.S. v Pharmaceutical Corporation v. Weinberger, 412 U.S. 655, 662-63; 93 S.Ct. 2498; 37 L.Ed.2d 244, 250 (1973). In order to expedite the evaluation process, the FDA contracted with the National Academy of Sciences -

National Research Council to review the potential new drugs for efficiency of the product. The Drug Efficacy Study Implementation was published, stating the FDA's findings of whether certain drugs were considered effective for use. U.S. v. Undetermined Quantities of Various Article of Drug, 675 F.2d 994, 998 (8th Cir. 1982). See also, Note, 60 Georgetown L.J. at 207-14. Also, as part of the efficacy review, the FDA formulated an abbreviated new drug application (ANDA) procedure whereby those seeking to market generic versions of safe and effective pre-1962 drugs could obtain approval by showing the generic drug is identical to the pioneer drug. Burroughs Wellcome Co. v. Schweiker, 649 F.2d 221, 223 (4th Cir. 1981); Wheaton, 35 Cath. Univ. L.R. at 439. This abbreviated application had only to show bioequivalence ("the action of two drugs that, 'when administered to the same individual in the same dosage regimen, result in equivalent concentrations of drug in blood and tissue'"), and bioavailability ("the rate at which and the extent to which the drug enters the general circulation"). Tri-Bio Laboratories, Inc. v. U.S., 836 F.2d 135, 137-38 nn. 3, 6 (3rd Cir. 1987), cert. denied, 102 L.Ed.2d 35 (1988). Post-1962 pioneer drugs could not be so easily copied without fear of expropriation of the data prepared by the pioneer drug manufacturers. 836 F.2d at 138. Therefore, a "paper NDA" was acceptable to avoid wasteful duplicative drug testing. U.S. v. Atropine Sulfate 1.0 MG. (Article of Drug), 843 F.2d 860, 861 (5th Cir. 1988); 649 F.2d at 223.

With the adoption of the drug price competition and patent restoration act, Pub. L. 98-417 (1984) codified at 21 U.S.C.S. § 355 (Cum. Supp. 1989) [1984 act], post-1962 pioneer drugs were allowed to be "copycatted" in the same manner as the pre-1962 drugs. This act eliminated the need for independent clinical research data, allowing the copiers to use the abbreviated new drug application. Mead Johnson Pharmaceutical Group v. Bowen, 838 F.2d 1332, 1333 (D.C. Cir. 1988). The congressional purpose behind the 1984 amendments was to facilitate the entry of generic drugs into the market. Inwood Laboratories, Inc. v. Young, 723 F.Supp. 1523, 1524 (D.D.C. 1989).

The upshot of this historical background is that most drugs are approved as documented for being safe and efficient by FDA. Pioneer drugs documented in this manner may be copied and approved through the ANDA procedure by a showing of bioequivalency. Such is not the case with those drugs grandfathered by the 1938 act. This narrow category of

drugs is the focus of your request. For the reasons stated below, we agree with the Board of Pharmacy that these drugs may not be brand exchanged.

As previously noted, the pre-1938 drugs were grandfathered if generally recognized as being safe for their intended use. Other drugs were considered new drugs, and underwent new drug applications. These new drugs, or pioneer drugs, were then copied by generic drugs, also called "me-too" drugs. It is the post-1938 drugs, both the pioneers and the generics, for which data is available for comparisons of bioequivalency. As long as the pre-1938 drugs continue to be "grandfathered," they will not be new drugs within the meaning of the federal acts, as amended. The drugs would cease to become grandfathered, i.e. they would become new drugs, when "insufficient data exists upon which qualified experts can reach a consensus that the drug is safe and effective." U.S. v. Seven Cardboard Cases of an Article of Drug, 716 F.Supp. 1221, 1223 (E.D. Mo. 1989). The statutory emphasis in this regard is on safety and efficacy, not on bioequivalency. As long as those drugs do not become new drugs, there will not be cause or sufficient data for the FDA to determine bioequivalency.

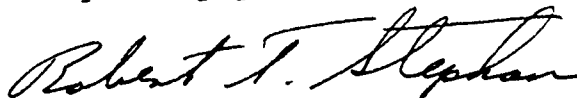
The issue of bioequivalence was at least partially discussed before the Kansas legislature when the brand-exchange law was being considered. The minutes of the House Committee on Public Health and Welfare, March 15, 1977, reflect testimony on 1976 Senate Bill 108, which eventually became K.S.A. 1989 Supp. 65-1637, stating that the physician controlled brand exchange, as proposed in Senate Bill 108, would not involve all drugs on the market. Rather, "[b]rand exchange involved only those products which [had] been protected by patent for 17 years and now are on the open market." Minutes, Attachment 1, Testimony of Doug Johnson, conferee, at page 2. Additionally, it was stated that brand exchange would involve products which the FDA allows to remain on the market after the efficacy review and publication of potential bioequivalence problems. The FDA had stressed that "it does not intend to allow drug products with bioequivalence problems to remain on the market." Minutes, Attachment 2, Testimony of Harold Godwin, conferee, at page 2.

Without data upon which to determine bioequivalency, and without a reason to prompt such a determination, we believe that the pre-1938 drugs cannot be presumed brand-exchangeable under the current Kansas statutes. The pharmacy act was intended to protect the public health, safety and

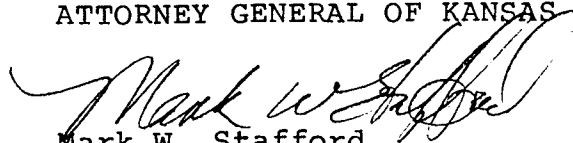
welfare. Kansas State Board of Pharmacy v. Wilson, 8 Kan.App.2d 359, 362 (1983). Administrative construction of a statute is to be given great weight, unless such construction is clearly erroneous. DSG Corp. v. Shelor, 239 Kan. 312, 315 (1986). Given the lack of data available to determine bioequivalency, and the absence of an event prompting review to find a drug not bioequivalent, it is our opinion that the construction of K.S.A. 1989 Supp. 65-1637 announced by the board of pharmacy does not conflict with the legislative intent behind the brand exchange amendment. Literally applying the current statutes according to the plain language of K.S.A. 1989 Supp. 65-1637(a)(4) would make subsection (a)(4) excess language because of the FDA's intent to keep non-bioequivalent generics off the market. Therefore, a finding by the FDA that a generic is not bioequivalent would have, at the time the brand exchange statute was enacted, resulted in the drug's withdrawal from the market.

In conclusion, it is our opinion that drugs which were generally recognized as safe prior to the enactment of the federal food, drug and cosmetic act of 1938 were not considered new drugs within the meaning of that act, and were therefore given approval through the grandfather provisions of the act. As long as those grandfathered drugs do not become new drugs, there will be a lack of sufficient data, and an absence of an opportunity to determine bioequivalence between other drugs and the grandfathered drug. In light of this lack of information, the grandfathered drugs are not subject to brand exchange as are drugs for which bioequivalence has been determined.

Very truly yours,



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