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Alan H. Kaplan, Esq.
Bonnie B. Anderson, Esq.
Kleinfeld, Kaplan and Becker
1140 Nineteenth Street, N.W.
Washington, DC 20036-6601

Mr. Robert S. Milanese
President
National Association of Pharmaceutical Manufacturers
320 Old Country Road
Garden City, NY 11530

Re: Docket Nos. 95P-0262/CP1 and 96P-0317/CP1

Dear Ms. Anderson and Messrs. Kaplan and Milanese:

This is in response to your above-referenced petitions dated August 11, 1995, and August 27, 1996, respectively. The Agency is sending a combined response to your petitions because the petitions are making essentially the same request. The petition submitted by Kleinfeld, Kaplan and Becker (KKB Petition, 95P-0262/CP1) requests revisions to the Food and Drug Administration (FDA) publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*) and to the definitions of pharmaceutical equivalents and pharmaceutical alternatives at 21 CFR 320.1(c) and (d), so that bioequivalent tablets and capsules approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) would be regarded as the same dosage form. The petition submitted by the National Association of Pharmaceutical Manufacturers (NAPM Petition, 96P-0317/CP1) requests that the FDA recognize all solid oral dosage form drug products (e.g., tablets and capsules) as the same dosage form, both under the Act and for all purposes when listing them in the *Orange Book* and elsewhere, and that, upon a showing of bioequivalence, the FDA should consider such products to be pharmaceutical equivalents, rather than pharmaceutical alternatives (NAPM Petition at 2-3 and 7). The Agency has given careful consideration to your requests, including opening a public docket for comment, and for the reasons that follow, your petitions are denied.

Background

The *Orange Book* lists drug products approved by the FDA, under section 505 of the Act, on the basis of evidence of safety and effectiveness. The *Orange Book* also contains therapeutic

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equivalence evaluations for approved multisource prescription drug products. These therapeutic equivalence evaluations are intended to provide public information and advice to state health agencies, prescribers, and pharmacists, as well as to promote public education in the area of drug product selection.

The *Orange Book* provides the following explanation of the concept of therapeutic equivalence:

Therapeutic Equivalents. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents¹ and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient **in the same dosage form** and route of administration, and . . . (Emphasis added; *Orange Book*, p. viii)

Because tablets and capsules have been considered distinct dosage forms, tablets and capsules containing the same active ingredient in the same strength are regarded as pharmaceutical alternatives,² and therefore are not listed in the *Orange Book* as therapeutic equivalents even if bioequivalence has been demonstrated.

¹ FDA regulations define pharmaceutical equivalents as follows:

Pharmaceutical equivalents means drug products that contain identical amounts of the identical active 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 and/or dissolution rates. (Emphasis added; 21 CFR 320.1(c))

² Pharmaceutical alternatives are defined as follows:

Pharmaceutical alternatives means 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 and/or dissolution rates. (21 CFR 320.1(d))

Discussion

The KKB Petition asks that FDA change its policy with respect to tablets and capsules shown to be bioequivalent, and asks that the *Orange Book*:

henceforth include . . . appropriate entries that show for each tablet, capsule or other solid oral dosage form drug product approved under §505(j) of the Act that, by reason of such approval, the drug product has been demonstrated to be bioequivalent and otherwise comparable to the reference listed drug cited in its ANDA (in the manner required by §505(j)(2)(A)(i) through (v)) and that the ANDA'd drug product is therefore therapeutically equivalent to that listed drug. (KKB Petition at 1)

The KKB Petition also requests that the FDA change the *Orange Book* designations "Tablet, Oral" and "Capsule, Oral," to "Solid, Oral," and revise the definitions of "Pharmaceutical equivalents" and "Pharmaceutical alternatives" at § 320.1(c) and (d) and in the *Orange Book* to accommodate the requested changes. The petition asserts as the factual basis for this request that "the potential interchangeability between [tablets and capsules], to our knowledge, raises no medical or scientific issues whatsoever." (KKB Petition at 8)

The NAPM Petition expresses concern that some innovator firms, whose period of marketing protection is about to expire, have succeeded in delaying generic competition by voluntarily withdrawing the new drug application (NDA) for the tablet formulation of a product and submitting a second NDA for the drug product in capsule form. In order to prevent this tactic, the petition requests that the FDA consider tablets and capsules to be the same dosage form.

The NAPM Petition claims this is a problem created by FDA oversight and a now allegedly out-of-date policy of treating tablets and capsules as pharmaceutical alternatives rather than pharmaceutical equivalents. (NAPM Petition at 5 and 6) The petition argues that:

tablets and capsules are more properly regarded as a single dosage form, i.e., solid oral dosage forms. This is true as a matter of common sense and logic, and also because once bioequivalence is established, there is no scientific basis for distinguishing between tablets and capsules as a single type of oral dosage form. (NAPM Petition at 6)

In an effort to give careful consideration to the ideas put forth in your petitions, the Agency requested public comment on the petitions in the *Federal Register* of March 28, 1997 (62 FR 14917). Several comments agreed with you in advocating a limited change to the existing system

that would permit tablets and capsules with the identical active ingredient in the identical strength that have been demonstrated to be bioequivalent to be listed as therapeutically equivalent in the *Orange Book*. Other comments to the *Federal Register* notice, however, strongly indicated that patients and healthcare practitioners have expectations about the *form* of drug products, as well as expectations about the rate and extent of absorption of the drug (bioequivalence). After fully considering the claims made in both petitions and the comments received on the petitions, the Agency finds there is a sound basis for making and preserving the distinction between tablets and capsules.

Except when approved pursuant to a suitability petition, the Act requires that there be information in an abbreviated new drug application (ANDA) to show that the dosage form of the proposed generic drug is the same as that of the listed drug (21 U.S.C. 355(j)(2)(A)(iii)). This requirement is *in addition* to the requirement that the ANDA contain “information to show that the new drug is bioequivalent to the listed drug” (21 U.S.C. 355(j)(2)(A)(iv))

Although dosage form is not defined in the Act,³ FDA has consistently distinguished dosage forms on the basis of “the physical appearance of the drug and the way it is administered,” and has declined to make dosage form distinctions on the basis of pharmacologic action (FDA Docket No. 98P-0421, Aug, 12, 1997, response to petition filed by Pfizer, Inc., and FDA Docket No. 96P-0459, November 2, 1998, response to citizen petition filed by Novartis). As FDA stated in the response to Novartis’ citizen petition: “Consistent with the ideas of ‘gross’ recognition, dosing, and manner of administration, dosage form is generally determined based on the physical form of the product prior to dispensing to the patient” (Response to petition filed by Novartis, at 12). In *Warner Lambert v. Shalala*, 202 F.2d 326 (D.C. Cir. 2000), the court concluded that FDA has been consistent in its dosage form classifications and that the Agency’s distinctions among dosage forms is not arbitrary and capricious.

Dosage form implies a route of administration (one that it may share with other dosage forms) and certain physical characteristics that distinguish it from other forms using the same route of administration. The distinction between tablets and capsules, therefore, relates to physical form. This distinction is reflected in pharmaceutical texts such as *Remington’s Pharmaceutical Sciences*. Most importantly, the distinction is made in the *United States Pharmacopeia (USP)*. Chapter 1151 of the *USP 23’s* General Information section is entitled “Pharmaceutical Dosage Forms” and discusses oral tablets and capsules as distinct dosage forms. The list of dosage forms in Appendix C of the *Orange Book* is generally derived from the forms used by the *USP* in its drug monographs.

³ However, in FDA’s regulations, the term is used in the definition of “drug product,” which is defined as “a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance” (21 CFR 314.3(b))

The physical form distinction between tablets and capsules is especially significant to patients and healthcare practitioners. The most important patient/practitioner distinctions between tablets and capsules have to do with ease of swallowing and scorability. Most of the comments received on the petitions stated that capsules are easier to swallow. In fact, consumer preference for capsules has “prompted pharmaceutical manufacturers to market the product in capsule form even though the product already has been produced in tablet form” (*Remington’s Pharmaceutical Sciences* 1659 (18th ed. 1990)). However, as the American Medical Association has stated, while capsules are easier for some people to swallow, tablets are easier for others, and substitution of a nonpreferred dosage form could have a negative therapeutic outcome for those patients who are only able to swallow a specific dosage form. Tablets, especially if they are scored, can be divided to provide a smaller dose. Scored tablets are also used for titration. Some capsules, on the other hand, can be opened and sprinkled on food to make ingestion easier. These different dosage form capacities have particular significance for children and the elderly.

The choice of drug products available to patients today is affected by institutions (state formularies, HMOs, PPOs, insurance companies, hospitals) for whom cost is a primary consideration. The fact that cost is a predominant consideration means that if the dosage form is obscured or disregarded (tablets and capsules are both solid oral dosage forms), the institutions making drug selection decisions will choose, and stock or mandate, the cheapest dosage form, and patients will be deprived of a choice that may be significant to them.

Commenters stated that confusion about changing dosage forms would be a special problem for those taking many medications, such as the elderly, who may be particularly reliant on the appearance of their medications; such switches could affect patient compliance and lead to negative therapeutic outcomes.

In addition to the scientific argument that tablets and capsules are interchangeable, the KKB Petition presents the following argument based on the 1984 Drug Price Competition and Patent Term Restoration Act (1984 Amendments):

[P]rovisions of the 1984 Amendment made obsolete the exclusion from the *Orange Book* of therapeutic equivalence eligibility for approved drug products that, by reason of dosage form alone, have been considered pharmaceutical alternatives and not pharmaceutical equivalents to their reference listed drug.

Under the policy reflected in §505(j)(2)(F), an ANDA for a drug that is not pharmaceutically equivalent to a reference-listed drug, but is a pharmaceutical alternative to that drug, should be shown in the *Orange Book* as therapeutically equivalent when it is approved pursuant to a suitability petition under

§505(j)(2)(C) because of the statutory requirement that “the active ingredients of [that drug] are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and [the drug] can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph.” (KKB Petition at 4-5)

FDA disagrees with your interpretation of the intent of the 1984 Amendments. Although a generic drug approved pursuant to a suitability petition under section 505(j)(2)(C) may have the same therapeutic effect as the reference listed drug, it does not follow that these drugs would be considered therapeutically equivalent under FDA's approach to assigning therapeutic equivalence ratings. The Agency's approach to assigning therapeutic equivalence ratings is more comprehensive than the concept of therapeutic effect. To determine whether a product proposed in a suitability petition will have the same therapeutic effect as the listed drug, FDA evaluates the data submitted in the petition regarding the proposed product's effectiveness and safety. These data may include comparative bioavailability information; studies intended to rule out unlikely safety problems, such as data from acute animal studies (see 54 FR 28872 at 28880, July 10, 1989); or data showing that an alternative active ingredient in a combination product is of the same pharmacological or therapeutic class. When FDA considers whether two drug products should be rated as therapeutically equivalent, however, FDA evaluates additional factors such as whether the drugs are pharmaceutical equivalents, whether they are bioequivalent, whether they are adequately labeled, and whether they are manufactured in compliance with current good manufacturing practices.

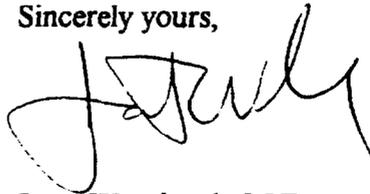
Accordingly, because pharmaceutically equivalent drug products must have identical dosage forms, two drug products with different dosage forms would not be evaluated as therapeutically equivalent. As stated above, FDA distinguishes dosage forms on the basis of the physical appearance of the drug and the way it is administered, and the Agency has sound medical reasons for making such distinctions. The significance of the distinctions between capsules and tablets is discussed above. These distinctions take into account patient compliance, ease of use, and handling by pharmacists. The importance of maintaining dosage form distinctions is also apparent with other dosage forms, such as oral liquids, rectal suppositories, or even injectables, which similarly should not be rated as therapeutically equivalent merely on the basis of their being found to have comparable bioavailability profiles or to have the same therapeutic effect.

FDA has carefully considered the policy changes suggested in your petitions and has concluded that they would not be in the public interest. In sum, the FDA has concluded that patients and healthcare practitioners have a significant interest in, and legitimate concerns regarding, the *form*

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of oral drug products, and that tablets and capsules, while similar in many respects, have special properties that may make one or the other more advantageous in the treatment of certain patients. Tablets and capsules, therefore, should not be regarded as the same dosage form. Accordingly, your petitions are denied.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Janet Woodcock". The signature is fluid and cursive, with a large initial "J" and a long, sweeping underline.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research