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VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: *Comments of Abbott Laboratories (FDA Docket 01P-0323)*

Dear Madam or Sir:

On behalf of Abbott Laboratories (Abbott),1/ we submit the following comments under 21 CFR 10.30(d) in support of the citizen petition filed jointly by Pharmacia Corporation and Pfizer, Inc. on July 30, 2001 (the Joint Petition).

Abbott supports generally the arguments in the Joint Petition and believes that the interpretation of section 505(b)(2) of the Food, Drug, and Cosmetic Act (the FDCA), as proposed by the Food and Drug Administration (FDA), exceeds the agency's legal authority.2/ In addition, a core issue raised in the Joint Petition concerns FDA's lack of legal authority to assign therapeutic equivalence (TE) ratings to applications submitted under section 505(b)(2). Joint Petition at 25-29. The purpose of these comments is to provide Abbott's support for, and to elaborate upon, this argument. As discussed in these comments, the assignment of "A-level" ratings to 505(b)(2) products is procedurally and substantively flawed under the Administrative Procedure Act (the APA) and the FDCA.

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1/ Abbott is an international corporation involved in research, development, and marketing of pharmaceuticals, nutritionals, hospital products, and diagnostic products.

2/ *See FDA Guidance for Industry: Applications Covered by Section 505(b)(2)* (Oct. 1999) (the *Draft Guidance*).

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On the procedural side, the Office of Management and Budget (OMB) recently cautioned agencies about the practice of using "guidance documents" to carry out programs that, as a matter of law, require notice and comment rulemaking. *See Draft Report to Congress on the Costs and Benefits of Federal Regulations*, 67 FR 15014, 15034 (Mar. 28, 2002) (discussing *Appalachian Power. Co. v. EPA*, 208 F.3d 1015 (D.C. Cir. 2000)). As OMB observed,

> Through guidance documents, agencies sometimes have issued or extended their "real rules," *i.e.*, interpretative rules and policy statements, quickly and inexpensively–particularly with the use of the Internet–and without following procedures prescribed under statutes or Executive orders.

The assignment of TE ratings to 505(b)(2) products falls squarely within OMB's concerns.

On the substantive side, there is the outstanding question raised in the Joint Petition regarding FDA's statutory authority to rate as "equivalent" products approved on the basis of a 505(b)(2) application. The TE rating system closely follows the findings made under section 505(j) for drugs that are the subject of abbreviated new drug applications (ANDAs). There is no statutory basis, however, for stretching the TE system beyond section 505(j).

We join in the petitioners' request that FDA refrain from assigning TE ratings to 505(b)(2) products, until the agency addresses the substantive and procedural issues discussed in these comments. As shown below, many state governments rely on FDA's TE ratings to carry out their programs. FDA must refrain from triggering a cascade of legal obligations, each time it assigns a TE rating to a 505(b)(2) product, until all pending issues have been resolved.

I. BACKGROUND

A. The *Orange Book*

In the late 1970s, FDA began to receive requests for assistance from state governments developing prescription drug "formularies." The formularies, among other things, had begun to list lower cost generic substitutes for brand-name drugs. Physicians and pharmacists were also asking FDA for authoritative

recommendations on product selection. The agency, however, lacked the resources to respond separately to each request. *See generally* 44 FR 2932 (Jan. 12, 1979). Instead, FDA developed a list of approved drug products with "therapeutic equivalence evaluations" to be made available for public inspection. *Id.; see* 21 CFR 20.117. This list is now published annually (with monthly supplements) under the title *Approved Drug Products with Therapeutic Equivalence Evaluations* (generally known as the "*Orange Book*").

A therapeutic equivalence (TE) evaluation represents FDA's judgment that two drug products "are pharmaceutical equivalents and . . . can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." *Id.* at viii. According to the *Orange Book,* FDA will classify one drug as therapeutically equivalent to another *only if*:

- Both products are approved as safe and effective;
- Both are pharmaceutically equivalent in that they contain identical amounts of the same active ingredient in the same dosage form and route of administration, and meet compendial or other applicable standards of strength, quality, purity, and identity;
- Both are bioequivalent 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 such a known or potential problem, they are shown to meet an appropriate bioequivalence standard;
- Both are adequately labeled; and
- Both are manufactured in compliance with current good manufacturing practice regulations.

Orange Book at 1.2. Two products that are determined by FDA to be therapeutic equivalents are assigned an "A" rating, along with one of six possible "sub-codes." *See id.* at 1.7. Products that have not been shown to be equivalent to a reference drug are assigned a "B" rating, along with one of ten sub-codes. *Id.* Procedures for changing a TE rating are described in sections 1.9 and 1.10 of the *Orange Book.*

According to FDA, TE ratings confer no rights or responsibilities on sponsors, consumers, or health professionals. They do not mandate substitution; rather, they only provide "information and advice." *Orange Book* at 1.5; *see* 45 FR 72582, 72587 (Oct. 31, 1980). Based on this reasoning, FDA has not memorialized through notice and comment rulemaking its standard for assigning TE ratings, its coding system, or the procedures for changing TE ratings.3/ Rather, the assignment of TE ratings to generic drugs is regarded by FDA as an "unofficial" act of no legal significance. *Id.* at v; 45 FR at 72587.4/

B. The Role of TE Ratings

Over the last two decades, TE ratings have become the decisive factor in many states for determining whether and on what terms one drug may be substituted for another. At least 16 states have adopted the *Orange Book* as binding for purposes of permitting or mandating substitution of generic drugs. *See* National Assoc. of Boards of Pharmacy, *2000-2001 Survey of Pharmacy Law* at 50-51 (attached as Tab 1). Also, certain states incorporate references to the *Orange Book* directly into their state codes. For example, products assigned an A-rating by FDA are by statute included automatically on the Massachusetts List of Interchangeable Drug Products. *See* 105 Code Mass. Regs. 720.050 (2002). Similarly, products are eligible for inclusion on New York's list of interchangeable products only if FDA "has evaluated such drug product as pharmaceutically and therapeutically equivalent" (*i.e.*, A-rated), but ineligible if FDA "has identified the product as having an actual or potential bioequivalence problem" (*i.e.*, B-rated). *See* N.Y. Pub. Health Law § 206(o)(2) (2002).

3/ The only reference to TE ratings in an FDA regulation is in 21 CFR 20.117, which lists the availability of certain computer printouts for public inspection. The regulation does not include a process or a standard for conducting a TE evaluation.

4/ *See Pharm. Mfrs. Ass'n v. Kennedy*, 471 F. Supp. 1224, 1229 (D. Md. 1979) (finding that TE ratings are not "agency actions" because they merely "compile data which has already been obtained via statutory procedure or solicited informally through survey and other sampling techniques"). The court, however, relied on the idea that TE ratings would be issued only after public comment. *Id.* at 1231 ("PMA, however will have an opportunity to dispute any findings on equivalency both at the proposal stage and after the FDA has made its final determination."). Whatever may have been contemplated in 1979, no such process for assigning TE ratings exists today. Moreover, as the same court recently recognized, "given the increased significance attributed to an *Orange Book* listing over the years since this Court decided *Pharmaceutical Mfrs.*, it would appear that an *Orange Book* designation constitutes a final agency action." *Zeneca Inc. v. Shalala*, 1999 WL 728104, at *11 n.13 (D. Md. Aug. 11, 1999), *aff'd* 213 F.3d 161 (4th Cir. 2000).

Other states permit or mandate substitution for brand name products with a "generic equivalent," implicitly incorporating FDA's *Orange Book* ratings into the definition of "generic equivalent." *See, e.g.*, Arizona Rev. Stat. Ann. § 32-1963.01(L)(3) (2002) ("Generic equivalent . . . does not include a drug that is listed by [FDA] as having unresolved bioequivalence concerns according to the administration's most recent publication of approved drug products with therapeutic equivalence evaluations."); Indiana Code § 16-42-22-4(b) (2002) ("A drug does not constitute a generically equivalent drug product if it is listed by [FDA] . . . as having actual or potential bioequivalence problems."). Thus, a B-rated product – "for which actual or potential bioequivalence problems have not been resolved"(*Orange Book* at xviii) – would not be substitutable in these states.

The designation of a drug as "A" rated to another drug also has been incorporated into the federal Medicaid program. *See* 42 USC 1396r-8(e)(4) (setting standard for upper limits on payment for multiple source drugs based on FDA's therapeutic equivalence evaluations); 42 CFR 447.332(a) (defining upper limit on payment based on whether at least three suppliers of a drug "have been classified by FDA as category 'A' in its publication [the *Orange Book*]"). Finally, the significance of the *Orange Book's* therapeutic equivalence ratings has been accepted and recognized by the courts. *See, e.g., Geneva Pharms. Tech. Corp. v. Barr Labs., Inc.*, 201 F. Supp.2d (S.D.N.Y. 2002) ("The *Orange Book* gives an AB rating to all generic warfarin sodium product[s] available today. Consequently, generic warfarin sodium is eligible for unrestricted substitution for Coumadin under most state pharmacy regulations.").

II. COMMENTS

In addition to the arguments presented in the Joint Petition, Abbott has the following comments on the issue of assigning A-level ratings to products marketed on the basis of 505(b)(2) applications.

A. It is Contrary to the Statutory and Regulatory Scheme to Assign "A" Ratings to 505(b)(2) Products

As interpreted by FDA, section 505 of the FDCA establishes four types of marketing applications. Two are described in section 505(b), and two are described in section 505(j). Assignment of A-ratings, however, is consistent with only one of these four types of applications.

Section 505(b)(1) describes a "full NDA." Under 505(b)(1), an applicant must provide "full reports of investigations" showing that the drug is safe and effective. 21 USC 355(b)(1)(A). In addition, the applicant must have full rights to all of the investigations. That is, the applicant either must have conducted the investigations herself or obtained permission to use the investigations from the person who conducted them. Section 505(b)(1) is intended for original products, not "equivalents" to approved products.

Section 505(b)(2), according to FDA, describes a "hybrid NDA." A 505(b)(2) application is the same as a 505(b)(1) application except that the investigations relied upon by the applicant are being used without "a right of reference" (*i.e.,* without permission). 21 USC 355(b)(2). As interpreted by FDA, section 505(b)(2) should be used for new products (*i.e.,* new molecular entities) or products that incorporate a significant change from a previously approved product. *Draft Guidance* at 3 (describing the two types of applications that may be submitted under section 505(b)(2)).5/ Based on FDA's interpretation, there should be no expectation that a 505(b)(2) product would be "equivalent" to an approved drug. Indeed, FDA has established by regulation that an application submitted under section 505(b)(2) for a duplicate product should be re-filed under section 505(j), as a generic drug. *See* 21 CFR 314.101(d)(9); *see also Draft Guidance* at 2 ("Section 505(b)(2) permits approval of applications *other than those for duplicate products* . . . ." (emphasis added)).

Section 505(j) describes two types of abbreviated new drug applications (ANDAs). Both rely on the concept of showing "sameness" to an approved or "listed" drug product. The first type of ANDA, defined in section 505(j)(2)(A) describes what is commonly referred to as a generic drug – *i.e.*, a "pharmaceutically equivalent" and "bioequivalent" product that can be expected to be as safe and effective as an already-approved listed drug. *See* 21 CFR 320.1(c) and (e). Drug products approved as pharmaceutical equivalents are, according to the *Orange Book*, the only products that are eligible to receive A-ratings. *See Orange Book* at 1.2 (stating that two drugs can be considered "therapeutic equivalents" only if they are "pharmaceutical equivalents").

5/ *See also* 54 FR 28872, 28891 (July 10, 1989) (noting that 505(b)(2) applications "will generally be submitted *for never before approved changes in already approved products*" and for products that "could not be approved under section 505(j)" of the FDCA) (emphasis added).

The second type of ANDA, defined in section 505(j)(2)(C), describes an ANDA for a drug that differs from the listed drug – *i.e.,* a "pharmaceutically alternative" drug product (*see* 21 CFR 320.1(d)). If FDA determines that the difference does not require additional clinical investigations, then FDA may approve the drug under section 505(j). If, however, FDA determines that the difference is significant enough to require clinical studies, the applicant must proceed under section 505(b). Products approved under section 505(j) as "pharmaceutical alternatives" are, by definition, ineligible for an A-rating. *Orange Book* at 1.2 (limiting definition of "therapeutic equivalents" to products that are "pharmaceutical equivalents").

In all, the assignment of A-ratings applies only to products approved as *pharmaceutical equivalents under section 505(j).* This is so for several reasons.

First, the A-rating communicates to the public that the drug product has been determined by FDA to be a substitutable generic. Section 505(j) contains the exclusive standard established by Congress for the approval of substitutable generic products. *See* www.fda.gov/ogd ("A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. . . . Drug companies must submit an abbreviated new drug application (ANDA) for approval to market a generic product."). State regulators, among others, associate A-ratings with the "pharmaceutical equivalence" and "bioequivalence" standards that are contained solely in section 505(j). *See* section I.B, above.

Second, FDA's own argument that TE ratings are of "no legal significance" is plausible only when the ratings are applied within the context of section 505(j). The ratings arguably represent a short-hand way of communicating the findings that FDA must make under section 505(j). In that sense, Abbott believes the ratings themselves are "fairly encompassed" within section 505(j). *See Air Transport Ass'n of America, Inc. v. FAA*, 291 F.3d 49 (D.C. Cir. 2002). The same cannot be said, however, for products reviewed under sections 505(b) and 505(c). The standard for assigning A-ratings specifically tracks section 505(j), not sections 505(b) or 505(c). *Compare* 21 USC 355(j)(2)(A) and (j)(4) (setting forth listed drug, pharmaceutical equivalence, bioequivalence, labeling, and manufacturing standards

for generic drugs) with *Orange Book* at 1.2 (setting forth nearly identical list of requirements as that found in section 505(j)).6/

Third, when Congress amended the FDCA in 1984, it incorporated FDA's *Orange Book* into the statute, as a means of facilitating the approval of generic drugs under section 505(j). *See* 21 USC 355(j)(7). Moreover, Congress essentially incorporated the agency's TE standard into section 505(j), as the standard for the approval of generic drugs. No such foundation exists for section 505(b)(2) applications, and Congress made no parallel enactment for products approved on the basis of 505(b)(2) applications. To the extent that Congress implicitly adopted the agency's TE rating program, it did so only for equivalent products approved under section 505(j).

B. FDA Must Use Notice and Comment Rulemaking to Extend the TE System to 505(b)(2) Products

The TE system as applied to generic drugs has been in place for nearly 25 years, and has been a part of the generic drug approval system under section 505(j) for nearly 20 years. The standard in the *Orange Book* for assigning TE ratings closely tracks the standard for approving equivalent products under section 505(j). For those reasons, Abbott believes that the TE rating system, as applied to generic drugs approved under section 505(j), is consistent with the APA (5 USC 551 *et seq.*). *Cf. Alaska Professional Hunters Assoc., Inc. v. FAA,* 177 F.3d 1030, 1035 (D.C. Cir. 1999) (recognizing the concept of "administrative common law" based on authoritative interpretations provided over a 30 year period).

6/ In the government's *amicus* brief to the United States Court of Appeals for the Eleventh Circuit in *Florida Breckenridge, Inc. v. Solvay Pharms., Inc.*, 1999 WL 292667 (11th Cir. 1999), FDA emphasized the need for a single standard for determining generic equivalence:

> Nor is there any room in federal law for a standard that defines generic equivalence in a manner inconsistent with the FDA's therapeutic equivalence standard. *The statutory requirement of bioequivalence* is an essential component of that standard and is a bulwark in the system of drug preclearance regulations designed to ensure the safety and efficacy of drugs on the market today.

Brief for the United States of America as *Amicus Curiae* (filed July 23, 1998) at 10-11; *accord id.* at 20-22. The "statutory requirement of bioequivalence" is found only in section 505(j) of the FDCA, not section 505(b).

There is, however, little doubt that under current law, the TE system is a "rule" within the meaning of the APA. 5 USC 551(4) (defining "rule" as "the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy . . . ."). Moreover, the assignment of a TE rating lays down an authoritative interpretation or conclusion that, likewise, would be regarded as a rule. *See Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1020-21 (D.C. Cir. 2000); *see also Tozzi v. U.S. Dept. of Health and Human Services (DHHS)*, 271 F.3d 301 (D.C. Cir. 2001) (holding that DHHS's listing of chemicals as carcinogens is subject to APA review because the listing triggers binding obligations under federal and state laws).7/

FDA's TE ratings reflect a judgment that, when applied outside of section 505(j), go beyond the findings FDA is required to make for premarket approval purposes for a given product. *See, e.g., American Hosp.* Ass'*n*, 834 F.2d at 1047 (inquiry as to whether rule is substantive asks broadly whether agency action "encodes a substantive value judgment or puts a stamp of approval or disapproval on a given type of behavior"). The standard for assigning A-ratings (*Orange Book* at 1.2), for coding different categories of products (*id.* at 1.7), and for making changes to TE ratings (*id.* at 1.9 and 1.10), all fall well beyond the scope of what can reasonably be inferred from the face of section 505(b)(2).

With that in mind, and putting aside the statutory issues raised above, were FDA to expand the TE system to 505(b)(2) applications, it would need to proceed through notice and comment rulemaking. Fundamental principles of administrative law require that the agency use notice and comment rulemaking in make binding changes to an existing standard. *See Shell Offshore Inc. v. Babbitt,* 238 F.3d 622 (5th Cir. 2001); *Alaska Hunters*, 177 F. 3d at 1035.

For example, in the *Draft Guidance*, FDA announced that it would use section 505(b)(2) to approve drug products that contain active ingredients derived

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7/ TE ratings do not meet the criteria for a non-substantive rule that is exempt from notice and comment rulemaking procedures under 5 USC 553(b)(3)(A). TE ratings are not "interpretive rules" designed to "explain ambiguous terms in legislative enactments." *See American Hosp. Ass'n v. Bowen*, 834 F.2d 1037, 1045 (D.C. Cir. 1987). They are not "general statements of policy" announcing "tentative intentions for the future." *Id.* at 1046. Finally, they are not "rules of agency organization, practice or procedure" relating to the "internal operations" of FDA. *Id.* at 1047; *see Paralyzed Veterans of America v. D.C. Arena*, 117 F.3d 579, 587 (D.C. Cir. 1997), *cert. denied* 523 U.S. 1003 (1998).

from natural sources, or that rely on recombinant manufacturing technology. *Draft Guidance* at 5. According to FDA, a 505(b)(2) application could include clinical investigations needed to show that the active ingredient is the same as that of an previously approved drug product. Such investigations could not be submitted under section 505(j). Nevertheless, at the end of the process, the 505(b)(2) applicant would be eligible to receive an A-rating, just as if the applicant had submitted an ANDA under section 505(j). *See* Joint Petition at 25 (noting statements by agency officials regarding the use of A-ratings for 505(b)(2) products).8/

This use of A-ratings, particularly for products that *ab initio* could not meet the standard for approval under section 505(j), is a departure from settled practice that is beyond FDA's authority or, at a minimum, requires rulemaking. Moreover, the determination that a 505(b)(2) product may be regarded as interchangeable with another product triggers obligations under state and federal law (*see* section I.B, above) which, in turn, raise serious issues as to whether the determination itself is a rule. *See Tozzi*, 271 F.3d at 312 (Silberman, J. concurring) (noting that DHHS's listing of chemicals as carcinogens "certainly has more bite than the typical policy statement" and raises interesting APA questions).

In short, by failing to bind itself to any fixed standard, the agency cannot now expand the TE system in a manner that both exceeds its authority and uses a procedurally deficient process. This type of haphazard regulatory approach is simply impermissible. *See, e.g., Sugar Cane Growers Cooperative of Florida v. Veneman*, 289 F.3d 89 (D.C. Cir. 2002) (holding that the Department of Agriculture could not implement a new payment-in-kind program applicable to all applicants under the Food Security Act of 1985 through a notice in the federal register, a press release, and a question-and-answer document).

III. CONCLUSION

The TE system as applied to generic drug products approved under section 505(j) of the FDCA has been fully integrated into state, federal, and private health care systems. Abbott believes that the TE system is legally sustainable in its

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8/ There are numerous legal issues associated with the proposed use of section 505(b)(2), including the "phantom ANDA" concept (*see* April 10, 1987, letter from Paul Parkman, Acting Director, Center for Drug Evaluation and Research, to all NDA and ANDA holders), to approve complex and recombinant drug products. Abbott supports, in general, arguments that have been raised questioning the agency's proposed approach presented in the *Draft Guidance*.

current form only when used to memorialize the findings that FDA is required to make under section 505(j) of the FDCA. Any other use of the system, including the assignment of A-ratings to 505(b)(2) products, raises statutory and procedural issues that have yet to be resolved.

For these reasons, and as requested in the Joint Petition, the agency must refrain from assigning TE ratings to any 505(b)(2) product until it has adequately resolved these issues and articulated its reasoning.

Sincerely,

David M. Fox

Enclosure

cc: Neal B. Parker, Counsel
Abbott Laboratories