MAYER·BROWN

Mayer Brown LLP
1999 K Street, N.W.
Washington, D.C. 20006-1101

Main Tel +1 202 263 3000
Main Fax +1 202 263 3300
www.mayerbrown.com

Dan Himmelfarb
Direct Tel +1 202 263 3035
Direct Fax +1 202 762 4267
dhimmelfarb@mayerbrown.com

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Commissioner of Food and Drugs
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

On behalf of Abbott Laboratories ("Abbott"), the undersigned submits this petition under §§ 505(b) and 701(a) of the Food, Drug, and Cosmetic Act ("FDCA" or "the Act"), 21 U.S.C. §§ 355(b), 371(a), among other provisions of law. Abbott requests that the Food and Drug Administration ("FDA" or "the Agency") refrain from granting a therapeutic equivalence ("TE") rating to any new drug submitted for approval under § 505(b)(2) of the FDCA that references Abbott's product AndroGel (testosterone gel) until FDA has conducted a rulemaking under the Administrative Procedure Act ("APA"), *see* 5 U.S.C. § 553(b), (c), to modify the procedures that apply to such ratings. That rulemaking should establish procedures for (1) FDA's assignment of TE ratings to drugs that are the subject of New Drug Applications ("NDAs") submitted under FDCA § 505(b)(2) ("§ 505(b)(2) drugs") and (2) FDA's public listing of such ratings in its publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* (31st ed. 2011) (the "Orange Book"). More specifically, the new regulations should, at minimum, characterize FDA's assignment and listing of TE ratings for § 505(b)(2) drugs as either orders or substantive rules for purposes of the APA, describe what legal process is available to interested parties for commenting on or challenging a proposed listing, and establish a coherent set of standards governing such a listing.

I. INTRODUCTION

In a 1980 administrative proceeding, FDA concluded that its making and listing of TE evaluations (hereinafter referred to as FDA's TE "listing process") was "nonregulatory," and therefore not an order or a rule. At the time, the Agency added a short provision to the Code of Federal Regulations ("CFR") that simply announced that FDA would publish a list of TE evaluations. The CFR provision did not prescribe standards or a process for making such evaluations or listings; nor did it afford any procedural rights to those with an interest in the listings. *See* 45 Fed. Reg. 72582, 72584, 72587 (1980) (adding 21 C.F.R. § 20.117(a)(3)).

FDA reasoned that the listing process was nonregulatory, and therefore not an order or rule, because such listings (1) were solely advisory and (2) entailed merely the application of FDA's TE criteria to information that was already "contained in FDA files" based on findings the Agency was statutorily authorized to make in the course of the drug approval process. 45

Fed. Reg. at 72584, 72587. Even if this reasoning was correct at the time, it is no longer correct, at least as applied to § 505(b)(2) drugs, for two main reasons.

First, TE listings are now far more than advisory. They have been expressly incorporated into state pharmacy practice statutes that control which drug products pharmacists may dispense and, therefore, which drug products patients receive when filling prescriptions at the pharmacy. TE listings also directly affect federal, state, and private insurance reimbursement schemes, and are expressly relied upon in Medicare Part B, among other federal laws. These listings materially impact the economic rights of competing drug sponsors. Thus, TE listings have automatic and significant binding legal consequences under state and federal law.

Second, TE listings for § 505(b)(2) drugs can in no way be characterized as merely the product of information already "contained in FDA files" that is based upon findings made in the course of the § 505(b)(2) approval process. The Agency can perhaps make a plausible case for characterizing TE listings for duplicate drugs approved under abbreviated new drug applications, or "ANDAs," as merely a summary of the statutory findings that FDA makes in approving such drugs under § 505(j)(1) of the FDCA. But even if so, FDA cannot make the same case for § 505(b)(2) drugs because the elements of a TE evaluation cannot be found in § 505(b)(2) (or any other statutory provision applicable to § 505(b)(2) drugs).

Thus, the reasoning that FDA advanced in 1980 for declining to treat a TE listing as either a rule or an order fails today on its own terms as applied to § 505(b)(2) drugs. This makes the 1980 proceeding infirm and inadequate as a matter of law. FDA must remedy this legal infirmity by treating the TE listing process for § 505(b)(2) drugs as either a substantive rulemaking or an informal adjudication. FDA's existing legal authorities do not provide an "adequate legislative basis" for the listings, *Am. Mining Congress v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1112 (D.C. Cir. 1993), which have the "force of law," *Pac. Gas & Elec. Co. v. Fed. Power Comm.*, 506 F.2d 33, 38 (D.C. Cir. 1974), and also have significant "practical effect[s]" or "impact[s]" on the interests of numerous parties, *Chamber of Commerce v. DOL*, 174 F.3d 206, 209, 212 (D.C. Cir. 1999). An agency can undertake action of this type only through substantive rulemaking or informal adjudication.

Before FDA issues a TE listing for any drug approved under § 505(b)(2) that references AndroGel, it must first complete a notice-and-comment rulemaking process to establish a procedure governing these evaluations that complies with the APA. Such a rulemaking is necessary in light of the existence of the 1980 rulemaking, its reliance on reasoning that is incorrect as applied to § 505(b)(2) drugs, and the existence of 21 C.F.R. § 20.117(a)(3), which does not provide for any procedural protections in connection with listing decisions. The rulemaking should resolve such fundamental issues as whether FDA will make listing decisions by notice-and-comment rulemaking or by individual adjudication and how it will involve interested persons in the decision-making process. It also should establish a coherent set of standards to govern such listings.

II. ACTION REQUESTED

Abbott requests that FDA refrain from listing a TE rating for any drug approved under § 505(b)(2) that references AndroGel unless and until it has conducted a notice-and-comment rulemaking. That rulemaking should, at minimum, characterize the listing of TE ratings for § 505(b)(2) drugs as either orders or substantive rules, establish the procedures available to interested parties in connection with the listings, and establish a coherent set of standards governing such listings.[1]

III. STATUTORY AND REGULATORY BACKGROUND

A. Drug Approval Pathways

1. Section 505 of the FDCA establishes three pathways for the approval of NDAs: (1) the full NDA process (set forth in FDCA § 505(b)(1)); (2) the "§ 505(b)(2)" process; and (3) the ANDA process (set forth in FDCA § 505(j)).

Under § 505(b)(l), an applicant must provide "full reports of investigations" showing that the drug is safe and effective. 21 U.S.C. § 355(b)(l)(A); *see also id.* § 355(c), (d). The applicant also must have full rights to all of the investigations submitted to the Agency. That is, the applicant either must have conducted the investigations itself or obtained permission to use the investigations from the person who conducted them. The "full NDA" process established by § 505(b)(1) is intended for original products, not "equivalents" to approved products.

A § 505(b)(2) application—like a full NDA—must contain full reports of investigations of safety and effectiveness. *See* 21 U.S.C. § 355(b)(2), (c), (d). But unlike a full NDA, such an application may rely on information that (1) comes from studies not conducted by or for the applicants and (2) is not subject to a right of reference obtained by the applicants. Like § 505(b)(1), § 505(b)(2) is not intended for equivalents or duplicates of previously approved drug products. As FDA has explained, § 505(b)(2) "permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product." *Guidance for Industry: Applications Covered by Section 505(b)(2),* at 2 (Oct. 1999) ("505(b)(2) Draft Guidance") . Indeed, FDA has provided specific guidance, further codified in a regulation, that "section 505(b)(2) applications should not be submitted for duplicates of approved products that

[1] Abbott is not submitting this petition pursuant to FDCA § 505(q), which, if it were to apply, would impose certain requirements on both Abbott and FDA. FDA "interpret[s] section 505(q) to apply only to petitions that request an action that could delay approval of a pending ANDA or 505(b)(2) application." *Guidance for Industry: Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*, at 7 (June 2011). Abbott has received notice that FDA has filed one § 505(b)(2) NDA for a testosterone gel product that relies on AndroGel as the reference listed drug, but Abbott is not asking that FDA take any action that could delay *approval* of such a product. Rather, Abbott is asking only that FDA refrain from listing a TE rating for such a product if, and when, FDA decides that the product's approval is warranted.

are eligible for approval under 505(j)." *Id.* at 3-4; *see* 21 C.F.R. § 314.101(d)(9) ("FDA may refuse to file an application or may not consider an abbreviated new drug application to be received if . . . [t]he application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act.").

Applications for "duplicates of approved drugs" may be submitted for approval under § 505(j)(1) based on a showing of "sameness" to an approved reference drug. Applicants under § 505(j)(1) do not develop any original data to support the approval of their drug products. Rather, they rely for approval on demonstrating that their proposed products contain the same basic elements as an already approved drug, based on the following comparisons: (1) same active ingredient, (2) same dosage form, (3) same route of administration, (4) same strength, and (5) bioequivalence (*i.e.*, same rate and extent of absorption in the body). *See* 21 U.S.C. § 355(j)(2)(A), (8)(B). An applicant that establishes the first four of these elements also has demonstrated that the proposed product is "pharmaceutically equivalent" to the listed product. *See* Orange Book at vi-vii ("Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration"). If an applicant under § 505(j)(1) can establish all five elements, and otherwise can demonstrate that its product is of a suitable quality, the Agency must approve the product. Products submitted for approval under § 505(j)(1) also must carry the same labeling as the reference drug. *See* 21 U.S.C. § 355(j)(2)(A)(v).

2. Section 505(b)(1) of the FDCA, in its present form, dates back to 1962. Sections 505(b)(2) and (j) were added to the FDCA in 1984 by the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments").

Prior to 1984, FDA had established by regulation a process for the approval of ANDAs for generic versions of drugs that FDA had approved before 1962 and that it had subsequently deemed to be effective under a process referred to as the Drug Efficacy Study Implementation program. *See* 35 Fed. Reg. 6574 (1970). "The [pre-1984] ANDA was required to contain critical information showing that the generic copy will have the same therapeutic effect as the pioneer drug product" and that the generic is bioequivalent to that product. Ellen J. Flannery & Peter Barton Hutt, *Balancing Competition and Patent Protection in the Drug Industry: The Drug Price Competition and Patent Term Restoration Act of 1984*, 40 Food Drug Cosm. L.J. 269, 274, 277 (1985); *see also* 21 C.F.R. pt. 320 (1983); *United States v. Premo Pharm. Labs., Inc.*, 511 F. Supp. 958, 962 (D.N.J. 1981) ("FDA will approve an ANDA only where the 'me-too' product is shown to be the therapeutic equivalent of the pioneer[.]"). The ANDA approval pathway codified in § 505(j) for drugs submitted under § 505(j)(1) is very similar to the pre-1984 ANDA process that it replaced; in particular, both require a showing that the proposed drug and the pioneer drug are bioequivalent and pharmaceutically equivalent and that they are intended for the same conditions of use based on the same labeling.

The pre-1984 ANDA policy was not available for duplicates of those pioneer drugs that had received their first approval after 1962. In 1981, however, FDA issued policy guidance

establishing the "paper NDA process," which permitted an applicant "to rely on studies published in the scientific literature to demonstrate the safety and effectiveness of duplicates of certain post-1962 pioneer drug products." 505(b)(2) Draft Guidance at 1 (citing 46 Fed. Reg. 27396 (1981)). Section 505(b)(2) essentially codifies the pre-1984 paper NDA process, but with a significant difference: "section 505(b)(2) . . . is not restricted to literature-supported NDA's for duplicates of approved drugs"; rather, "it covers all NDA's for drug products that rely on studies not conducted by or for the applicant or for which the applicant does not have a right of reference." 57 Fed. Reg. 17950, 17952 (1992); *see also* 54 Fed. Reg. 28872, 28890 (1989) ("sections 505(b)(2) and 505(c)(3)(D) of the [A]ct, by their terms, apply to any application that relies on investigations which the applicant has not conducted, sponsored, or obtained a right of reference to, regardless of the similarity or dissimilarity of the drug product to an already approved drug product"). Indeed, FDA has made clear that duplicates of listed drugs that would have qualified for approval under the paper NDA process prior to 1984 should be submitted for approval under § 505(j), not § 505(b)(2). *See* 505(b)(2) Draft Guidance at 1-2 ("Enactment of the generic drug approval provision of the Hatch-Waxman Amendments ended the need for approvals of duplicate drugs through the paper NDA process by permitting approval under 505(j) of duplicates of approved drugs (listed drugs).").

B. Therapeutic Equivalence Evaluations

The Hatch-Waxman Amendments also added a statutory requirement, codified at FDCA § 505(j)(7)(A)(i), for the Secretary of HHS to "publish and make available to the public":

> (I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness [pursuant to a full NDA or a § 505(b)(2) application] before September 24, 1984;
>
> (II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and
>
> (III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

21 U.S.C. § 355(j)(7)(A)(i). Section 505(j)(7)(A)(ii) further provides that "[e]very thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness [pursuant to a full NDA or § 505(b)(2) application] or approved under [§ 505(j)] during the thirty-day period."

FDA has taken the position that the Orange Book and its monthly cumulative supplements "satisfy this requirement." Orange Book at v. The Orange Book "identifies drug products approved" by the FDA "on the basis of safety and effectiveness." *Id.* at iv.

It also "contains therapeutic equivalence evaluations for approved multisource prescription drug products." Orange Book at iv. Such evaluations can result in one of two ratings (further subdivided into various sub-codes). FDA considers a drug given an "A" rating to be "therapeutically equivalent to other pharmaceutically equivalent products." *Id.* at xiii. FDA gives a "B" rating to drugs that it "considers not to be therapeutically equivalent to other pharmaceutically equivalent products, *i.e.*, drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence." *Id.* "Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents 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." *Id.* at vii. To illustrate, if two generics and one name-brand product share "A" ratings, FDA's view is that there will be no difference in clinical effect or safety profile in the particular patient who receives, for example, the innovator on filling the prescription, generic "X" upon first re-fill, and generic "Z" thereafter.

FDA began publishing the Orange Book in 1980—several years before the Hatch-Waxman Amendments created the listing requirement in § 505(j)(7)(A)(ii). The key impetus for FDA's listing of TE evaluations was requests from state governments for the Agency to assist their development of prescription drug "formularies" identifying those lower-cost generic drugs that were substitutable for brand-name drugs. *See* Orange Book at iv. Physicians and pharmacists had also begun asking FDA to provide authoritative recommendations regarding substitutable generic drugs. According to FDA, the list was offered in response to these requests to prevent the "risks . . . that drug products that are not therapeutically equivalent may by mistake be substituted and dispensed with possible adverse health consequences." 44 Fed. Reg. 2932, 2933 (1979).

The Orange Book preface describes the process that led to the list's publication as follows:

> [O]n May 31, 1978, the Commissioner of the [FDA] sent a letter to officials of each state stating FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products. The List was distributed as a proposal in January 1979. It included only currently marketed prescription drug products approved by FDA through [NDAs] and [ANDAs] under the provisions of Section 505 of the Act. . . . The final rule, which includes FDA's responses to the public comments on the proposal, was published in the *Federal Register* on October 31, 1980 (45 [Fed. Reg.] 72582). The first publication, October 1980, of the final version of the List incorporated appropriate corrections and additions.

Orange Book at iv-v.

The rule issued on October 31, 1980 ("1980 Rule") added a new paragraph (a)(3) to 21 C.F.R. § 20.117. That new paragraph, which contains the only reference to the Orange Book and TE evaluations in the CFR, remains in effect and states as follows:

> (a) The following computer printouts are available for public inspection in the Food and Drug Administration's Freedom of Information Public Room:
>
> * * * *
>
> (3) A listing of new drug applications, abbreviated new drug applications, which were approved since 1938 and which are still approved, covering marketed prescription drug products except prescription drug products covered by applications deemed approved under the Drug Amendments of 1962 and not yet determined to be effective in the Drug Efficacy Study Implementation program. The listing includes the name of the active ingredient, the type of dosage form, the route of administration, the trade name of the product, the name of the application holder, and the strength or potency of the product. *The listing also includes, for each active ingredient in a particular dosage form for which there is more than one approved application, an evaluation of the therapeutic equivalence of the drug products covered by such applications.*

21 C.F.R. § 20.117(a)(3) (emphasis added).

IV. FACTUAL BACKGROUND: ANDROGEL AND TOPICAL TESTOSTERONE DRUG PRODUCTS

On February 28, 2000, FDA approved AndroGel 1% for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired). On April 29, 2011, FDA approved Abbott's NDA for AndroGel (testosterone gel) 1.62%. Like the 1% product, AndroGel 1.62% is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).

In addition to AndroGel, there are three other topical testosterone products with approved NDAs: Testim, sponsored by Auxilium Pharmaceuticals, was approved on October 31, 2002, under NDA 21-454; Fortesta, sponsored by Endo Pharmaceuticals, was approved on December 29, 2010, under NDA 21-463; and Axiron, sponsored by Eli Lilly and Co., was approved on November 23, 2010, under NDA 22-504. Like AndroGel, Testim, Fortesta, and Axiron are each approved for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired). FDA also approved

two generic versions of the 2.5 g and 5 g packet configurations of AndroGel 1% through the § 505(j) approval process: Watson Laboratories' ANDA 76-737 (approved January 27, 2006) and Par Pharmaceuticals' ANDA 76-744 (approved May 23, 2007). The Orange Book, however, currently lists these generic versions as having been discontinued from marketing.

In 2009, in response to several reports of adverse events received by FDA, the Agency took several steps to further ensure the safe use of all topical testosterone products. Although clinically therapeutic amounts of the testosterone dose applied to the skin surface from these products is absorbed into systemic circulation, varying amounts of active ingredient can be left on the skin—and thus remain available for transference from the patient's skin to that of other individuals. This poses a particular risk for women—especially pregnant women, women who are breastfeeding, and women who may become pregnant—as well as their fetuses and children. To address these risks, FDA issued a Safety Alert, convened an Advisory Committee meeting, and imposed class-wide safety-related labeling requirements that include the need for a boxed warning; in addition, the Agency requires testosterone gel products to have a Risk Evaluation and Management Strategy that includes a Medication Guide. *See, e.g.*, FDA News Release, *Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide* (May 7, 2009).

In 2009, FDA also took the position that sponsors of proposed generic topical testosterone drug products that contain new or different inactive ingredients that could affect transfer of the drug to third persons must submit skin-transfer studies, hand-washing studies, and possibly showering studies to FDA. *See* Citizen Petition Response, Docket No. FDA-2009-P-0123 (Aug. 26, 2009) ("Auxilium Petition Response"). According to FDA, the Agency needs to review such studies as part of the approval process to ensure that proposed generics do not present a different potential than the approved reference product for the transfer of testosterone to persons other than the patient, and to enable the Agency to determine whether washing affects the amount of residual drug content left on the skin.

Such clinical data cannot be included in an ANDA submitted under FDCA § 505(j). Accordingly, FDA has explained that ANDAs are not permitted for proposed drugs that seek to reference already approved topical testosterone drugs but that contain certain new or different inactive ingredients that could affect transfer of the drug to third persons. Applications for the approval of such products instead must be submitted as § 505(b)(2) NDAs.

Abbott has received notice that FDA has accepted for filing one § 505(b)(2) NDA for a testosterone gel product that relies on AndroGel as the reference listed drug. Presumably, the application for this product has been filed as a § 505(b)(2) NDA because the drug contains a formulation that differs from Androgel's formulation and therefore, as indicated in the Auxilium Petition Response, its application must contain results of skin-transfer studies, hand-washing studies, and possibly showering studies to establish the drug's safety and effectiveness.

As explained below, FDA may not list a TE rating for this follow-on drug unless the Agency first conducts a rulemaking to establish a procedural framework for TE listings for § 505(b)(2) drugs. Such a rulemaking should establish whether the Agency will proceed through notice-and-comment rulemaking or informal adjudication in making TE determinations for § 505(b)(2) drugs, and afford interested parties procedural protections that are consistent with the requirements of the APA. It also should establish a coherent set of standards to govern such listings.

V. ARGUMENT

In the 1980 Rule, FDA set forth two rationales for treating TE listings as "nonregulatory," and therefore not rules or orders: (1) that they are solely advisory and (2) that they entail merely the application of FDA's TE criteria to information that is already in FDA's files and that the Agency is statutorily authorized to gather as part of the new-drug approval process. Both rationales are invalid as applied to § 505(b)(2) drugs.

First, the listing of TE evaluations is not merely advisory. It is agency action that has binding legal effects under federal and state law and that profoundly affects the rights and interests of patients, physicians, pharmacists, payers, and competing drug companies. *Second*, neither the approval process for § 505(b)(2) drugs nor any other statutory provision applicable to such drugs provides an adequate statutory basis for TE evaluations. Although the constituent findings (bioequivalence, pharmaceutical equivalence, and adequate labeling) that are needed for a TE evaluation are necessarily entailed by the findings FDA must make when it approves a generic drug under § 505(j)(1), those findings are not statutory components of the § 505(b)(2) approval process. *See* Point A, *infra*.

As the relevant legal authorities confirm, the APA requires FDA to proceed via notice-and-comment rulemaking or informal adjudication in issuing TE listings. Whichever approach FDA chooses, it must afford interested parties more process than it does at present. *See* Point B, *infra*.

Before issuing a TE listing for any product referencing Androgel that is submitted for approval under § 505(b)(2), FDA must engage in a notice-and-comment rulemaking to characterize such listings as either substantive rulemakings or adjudications, specify what procedural protections FDA will afford interested parties in connection with the listings, and establish a coherent set of standards governing such listings. *See* Point C, *infra*.

A. The 1980 Rule's Conclusion That Therapeutic Equivalence Evaluations Are "Nonregulatory," And Therefore Not Rules Or Orders, Is Invalid As Applied to § 505(b)(2) Drugs

1. FDA set forth two rationales in the 1980 Rule for treating therapeutic equivalence evaluations as "nonregulatory" and therefore not rules or orders

In adopting the initial Orange Book list of approved drugs and TE evaluations, FDA employed the notice-and-comment procedures typically associated with rulemakings under the APA. The Agency apparently did not originally intend to afford any administrative process in formulating this rule and issuing the first Orange Book, but made the decision to follow notice-and-comment procedures after the Pharmaceutical Manufacturers Association ("PMA") brought suit challenging FDA's authority to issue the list. *See Pharm. Mfrs. Ass'n v. Kennedy* ("*PMA*"), 471 F. Supp. 1224, 1225-26 (D. Md. 1979). FDA has published subsequent versions of the Orange Book, including the TE ratings, "without consultation with manufacturers and without notice-and-comment rulemaking." Peter Barton Hutt et al., *Food and Drug Law: Cases and Materials* 757 (3d ed. 2007).

In the 1980 Rule, FDA described the legal justification for not affording any such process in connection with the formulation and publication of the Orange Book list. It specifically responded to and rejected comments contending that "each determination of therapeutic equivalence in the List, if questioned by the manufacturer, deserves an adjudicatory hearing." 45 Fed. Reg. at 72586. FDA explained that no such process was necessary because of the "nonregulatory" character of the TE listings. *See id.* at 72587. FDA specifically rejected the proposition that the list "constitute[s] an order or a rule as defined in the [APA]," explaining that

> [it] neither determines nor adjudicates the legal rights of any drug manufacturer or distributor; it does not impose any requirement or restriction upon any person; it does not interpret or apply the act in a manner that creates any obligation on any person; it makes no recommendation as to which products persons should purchase, prescribe, or dispense, or conversely, which products should be avoided.

Id.

FDA further justified its conclusion that TE listings were "nonregulatory" by emphasizing that the purpose of those listings was to provide "only public information and advice" and by stating that the evaluations were based solely on information that FDA had already gathered in making drug approval decisions:

> To the extent that the List sets forth FDA's evaluations of the therapeutic equivalence of drug products that have been approved, it contains FDA's advice to the public and to the States regarding an important public health matter. These

> evaluations do not constitute determinations that any products are in violation of the act or that any products are preferable to others. These are nonregulatory evaluations that are based on the application of certain criteria to information contained in FDA files. Most of the reasons cited by the comments for demanding an evidentiary hearing (for example, determinations of effectiveness and bioequivalence) concern determinations that were made by FDA in clearly defined proceedings when there existed the right to an evidentiary hearing. Thus, the notice and comment procedure used in adopting this List is sufficient.

45 Fed. Reg. at 72587.

Earlier in the 1980 Rule, FDA had described in greater detail the connection between TE evaluations and the statutory drug approval process, explaining how, in its view, "[t]he new drug approval process is an important part of FDA's program for determining the therapeutic equivalence of drug products," 45 Fed. Reg. at 72585:

> FDA evaluates as therapeutically equivalent approved drug products that meet the following general criteria: (1) They are pharmaceutical equivalents in that (a) they contain identical amounts of the same active drug ingredient in the same dosage form; and (b) they meet compendial or other applicable standards of identity, strength, quality, and purity; (2) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem; or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (3) they are adequately labeled; and (4) they are manufactured in compliance with current good manufacturing practice. These four criteria are applied to information already contained in FDA files regarding the safety, effectiveness, and quality of approved prescription drug products to make a nonregulatory evaluation of therapeutic equivalence. The four criteria are regulatory determinations which FDA is statutorily authorized to make. FDA's authority to require that drug products meet compendial standards is based on section 501(b) of the act; to require that certain drug products meet bioequivalency requirements on sections 201(p), 502, 505, and 701(a) of the act; to require adequate labeling on sections 502, 505, and 507 of the act, and 21 CFR 201.100; and to require compliance with current good manufacturing practice regulations on sections 501(a)(2)(B) and 701(a) of the act.

Id. at 72584.

The 1980 Rule thus relied on two main justifications for the Agency's conclusion that its listing of TE evaluations was "nonregulatory" and therefore not an order or rule for purposes of the APA. The first justification was that those listings were merely informational and advisory, and based on information that the Agency was otherwise authorized to release to the public. *See* 45 Fed. Reg. at 72587; *see also* 44 Fed. Reg. at 2937. The second was that Congress had

statutorily authorized FDA to collect the information "regarding the safety, effectiveness, and quality of approved prescription drug products" to which it applied the four criteria it had developed for making TE evaluations. 45 Fed. Reg. at 72584. Although FDA implicitly conceded the lack of express statutory authority for the development and application of the four criteria to make such evaluations, in the Agency's view the statutory authority to collect the underlying information in making approval decisions rendered the criteria themselves "regulatory determinations which FDA is statutorily authorized to make." *Id.*

A 1979 decision by the U.S. District Court for the District of Maryland, which dismissed PMA's challenge to the TE listings on the ground that they did not constitute reviewable "agency action," 5 U.S.C. § 704, adopted at least part of FDA's rationale for deeming the listings "nonregulatory." *See PMA*, 471 F. Supp. at 1231 (concluding that FDA's "primary interest" in issuing the TE evaluations is in "public disclosure," that "no agency is ordering any PMA member to engage in or refrain from any action," and that the Agency is not "doing anything which is binding on the parties").

2. The 1980 Rule's dual rationales are invalid as applied to § 505(b)(2) drugs

Neither of the rationales that FDA advanced in the 1980 Rule for deeming TE listings "nonregulatory"—their advisory/informational character and the existence of statutory authority to collect the source information as part of the approval process—is correct as applied to § 505(b)(2) drugs. Thus, FDA's justification for failing to treat TE evaluations as rules or orders fails on its own terms.

a. The listing of therapeutic equivalence evaluations is not merely advisory but rather has a binding legal effect

When agencies make and publicize evaluations that trigger regulatory obligations under state and federal law, those actions have "binding [legal] effect" for APA purposes, *Tozzi v. U.S. Dep't of Health & Human Servs.*, 271 F.3d 301, 310 (D.C. Cir. 2001), and cannot be characterized as purely informational or advisory. FDA's listing of its TE evaluations triggers multiple regulatory obligations under state and federal law. Accordingly, FDA's reasoning that the listings are "nonregulatory" because they are purely informational and advisory is no longer valid, if it ever was. *See Bechtel v. FCC*, 957 F.2d 873, 881 (D.C. Cir. 1992) ("[i]n the rulemaking context . . . it is settled law that an agency may be forced to reexamine its approach 'if a significant factual predicate of a prior decision . . . has been removed'") (quoting *WWHT, Inc. v. FCC*, 656 F.2d 807, 819 (D.C. Cir. 1981)); *cf. Zeneca Inc. v. Shalala,* 1999 WL 728104, at *11 n.13 (D. Md. Aug. 11, 1999) ("given the increased significance attributed to an Orange Book listing over the years since this Court decided [*PMA*], it would appear that an Orange Book designation constitutes a final agency action"), *aff'd*, 213 F.3d 161 (4th Cir. 2000).

(i) In most States, an "A" rating triggers substitution of generic drugs. All 50 States and the District of Columbia have enacted laws providing for either mandatory or permissive

pharmacy substitution of a generic drug when a brand name drug has been prescribed.[2] In many States, an "A" rating from FDA is the essential factor for determining whether, and on what terms, generic substitution occurs. *See Solvay Pharms., Inc. v. Global Pharms.*, 419 F. Supp. 2d 1133, 1138 (D. Minn. 2006) ("In some states, a prescription may be automatically substituted when the substitute has been approved by the FDA and given an AB-equivalence rating, denoting that the substitute is bioequivalent to the prescribed drug."). Twenty-four States and the District of Columbia have explicitly adopted the Orange Book as authority for when drugs may, or must, be substituted for a brand name drug.[3] The Pennsylvania statute, for example, defines a "generically equivalent drug" as "a drug product that the Commissioner of Food and Drugs of the United States Food and Drug Administration has . . . determined to be therapeutically equivalent, as listed in the [Orange Book,]" and requires a pharmacist who is presented with a prescription for a brand name drug to "substitute a less expensive generically equivalent drug." 35 Pa. Stat. Ann. §§ 960.2, 960.3.[4] In addition, the generic substitution laws of another eight States incorporate FDA's TE determinations without specifically referencing the Orange Book.[5]

FDA's TE ratings also factor into state laws regarding generic substitution in the context of publicly funded healthcare programs, and most States have laws that specifically rely on FDA's "A" ratings.[6] Indeed, "[s]ince 2000, there has been a steady trend toward increased

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[2] Although some States' substitution laws are "mandatory" and others "permissive," that distinction is immaterial, as a practical matter, because of the incentives offered to pharmacies to substitute cheaper generic products for more expensive branded ones. *See* Helene L. Lipton et al., *Pharmacy Benefit Management Companies: Dimensions of Performance*, 20 Ann. Rev. Pub. Health 361 (1999). A recent study found that, as a result of these incentives, there is no significant difference in substitution rates between "permissive" and "mandatory" substitution States. *See* William H. Shrank et al., *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 Health Affairs 1383 (2010) ("Shrank").

[3] *See, e.g.,* Ariz. Rev. Stat. § 32-1963.01(K)(3); Ark. Code Ann. § 17-92-503(c), Ark. Code R. § 07-00-0006; Del. Code Ann. tit. 24, § 2502(27); D.C. Code §§ 48-803.02, 42-803.03; Haw. Rev. Stat. § 328-96(a), 328-91; Ill. Admin. Code tit. 77, § 790.40; Ky. Rev. Stat. Ann. § 217.814(7), (8), 201 Ky. Admin. Regs. 2:116; 02-392-26 Code Me. R. § 1(2); Md. Code, Health Occ. § 12-504(c); Mass. Gen. Laws. Ann. ch. 17, § 13, 105 Mass. Code Regs. 720.050; Miss. Pharm. Reg. Art. X § (7); Mo. Code Regs. Ann. tit. 20, § 2220-3.011(3); N.H. Rev. Stat. §§ 146-B:2, 318:47-d, N.H. Code Admin. R. [Ph.] 704.06; N.J. Stat. Ann. § 24:6E-6(a); N.M. Stat. Ann. § 26-3-3(B), (C); N.Y. Pub. Health Law § 206(1)(o)(2), N.Y. Comp. Codes R. & Regs. tit. 10, § 60-2.1; 35 Pa. Stat. Ann. § 960.2; S.D. Codified Laws § 36-11-2(12); Tenn. Code Ann. § 53-10-208; 22 Tex. Admin. Code § 309.7(b); Utah Code Ann. § 58-17b-102(25); Va. Code Ann. § 54.1-3401; Vt. Stat. Ann. tit. 18, § 4605(a), 18 Vt. Code § 4605; Wash. Admin Code § 246-899-030(2)(c); Wyo. Stat. Ann. § 33-24-147(a)(ii).

[4] There are exceptions if the prescription indicates that no substitution should be made, or if the patient requests otherwise. 35 Pa. Stat. Ann. § 960.3.

[5] *See* Fla. Stat. Ann. § 465.025(5), Fla. Admin. Code Ann. r. 64B16-27.520; Kan. Stat. Ann. § 65-1637(a); La. Rev. Stat. Ann. § 37:1164(16); Neb. Rev. Stat. § 71-5402(1); Nev. Rev. Stat. § 639.2597; Or. Rev. Stat. § 689.515(1)(e); R.I. Gen. Laws § 21-31-16.1(a); Wis. Stat. Ann. § 450.13(1).

[6] See, *e.g.*, Alaska Admin. Code tit. 7, § 47.271(a); Cal. Code Regs. tit. 8, § 9789.40; 10 Colo. Code Regs. § 2505-10:8.800.4; D.C. Mun. Regs. tit. 29, § 922; Iowa Admin. Code r. 191-75.18(514C)(1); Kan. Admin. Regs. § 30-5-92(d)(2)(B); 907 Ky. Admin. Regs. 1:018; 50 La. Admin. Code pt. XXIX, § 949; 10-144 Me. Code R. 10-144 Ch.

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mandatory generic substitution. In 2005, nearly all states . . . reported that they require generics to be dispensed when available." Henry J. Kaiser Family Foundation, *State Medicaid Outpatient Prescription Drug Policies: Findings from a National Survey* at 10 (Oct. 2005); *see also* Shrank, *supra* note 2, at 1384 (discussing different types of mandatory generic substitution laws affecting state Medicaid programs), 1386 Ex. 1 (table).

(ii) An "A" rating affects reimbursement levels under federal healthcare programs. FDA's "A" ratings trigger obligations under federal law as well, by affecting reimbursement levels under various federal healthcare programs. Medicare Part B is a prime example. The reimbursement rate for a drug under that program is based in part on whether the drug is a "single source" or "multiple source" product. *See* 42 U.S.C. § 1395w-3a(b). A drug qualifies as a "multiple source drug" only if "there are 2 or more drug products which . . . are rated as therapeutically equivalent (under the Food and Drug Administration's most recent publication of [the Orange Book])," *id.* § 1395w-3a(c)(6)(C); all other approved drugs are "single source" drugs, *id.* § 1395w-3a(c)(6)(D). "[S]ingle source" drugs are reimbursed based on the individual drug's reported average sales price alone, while "multiple source" drugs are reimbursed based on a weighted average of the average sales prices for that drug along with its therapeutically equivalent—*i.e.*, "A" rated—competitors. *Id.* § 1395w-3a(b)(3), (4). Thus, FDA's assignment of an "A" rating has a substantial effect on the reimbursement rates available under Medicare Part B. Similarly, FDA's TE determinations influence whether the Medicaid program establishes an upper limit on the federal payment amount for certain multiple source drugs. *See id.* § 1396r-8(e)(4) ("[T]he Secretary shall establish a Federal upper reimbursement limit for each multiple source drug for which the FDA has rated three or more products therapeutically and pharmaceutically equivalent[.]").

In addition, the Centers for Medicare and Medicaid Services ("CMS"), acting through notice-and-comment rulemaking, have incorporated FDA's TE evaluations into reimbursement determinations under those programs in multiple ways. For example, CMS regulations generally require that a Medicare Part D enrollee be informed of differences between the price of a drug and that of "the lowest priced generic version of that . . . drug that is therapeutically equivalent and bioequivalent," and define "therapeutically equivalent" as "refer[ring] to drugs that are rated as therapeutic equivalents under the Food and Drug Administration's most recent publication of [the Orange Book]." 42 C.F.R. §§ 423.132(a), 423.100.

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101, Ch. II, § 80.07-5; Md. Code Regs. 10.09.03.01; 130 Mass. Code Regs. 406.402; Miss. Code R. § 23-1-15:31.12; 471 Neb. Admin. Code § 16-005.02A; N.H. Code Admin. R. He-W 570.01(i); N.J. Admin. Code § 17:9-6.10; N.M. Code R. § 8.324.4; Ohio Admin. Code 4123-6-21(O); Okla. Admin. Code § 317:30-5-78; 72 Pa. Stat. Ann. § 3761-502; Tenn. Code Ann. § 53-10-208(a); Utah Admin. Code r. 414-10; 4-5 Vt. Code R. § 10:3(18); Va. Code Ann. § 65.2-603.1(A); Wash. Admin. Code § 388-530-4100; W.V. Code R. § 151, Series 1, Attach. B; Wis. Admin. Code DHS § 109.31; 10 Wyo. Admin. Code HLTH MDCD § 10.

(iii) *Judicial precedent establishes that therapeutic equivalence listings have a binding legal effect.* The 2001 decision of the U.S. Court of Appeals for the District of Columbia Circuit in *Tozzi v. HHS* shows that the consequences of TE listings under state and federal law necessitate the conclusion that those listings have a "binding legal effect" and cannot be characterized as merely informational or advisory.

Tozzi involved a challenge to the decision of the Secretary of Health and Human Services ("HHS") to change the carcinogenic status of the chemical dioxin in HHS's Report on Carcinogens, the Secretary's statutorily mandated biennial listing of known and suspected human carcinogens. In defending the suit, HHS argued that the dioxin classification was unreviewable because it was not "agency action," pointing out that "the Report's preamble states that it is 'for informational purposes only' and that the Secretary never published the entire report in the Federal Register." *Tozzi*, 271 F.3d at 310. The court rejected this argument, explaining that "[r]eviewability under the APA hinges upon whether the listing has 'legal effect, which in turn is a function of the agency's intention to bind either itself or regulated parties.'" *Id.* "[E]ven though the Secretary takes no action pursuant to a listing," the court said, "the contention that a listing has no 'binding effect[]' is inaccurate: Listing a substance as a human carcinogen triggers obligations under [Occupational Health and Safety Administration ("OSHA")], Department of Labor and state regulations." *Id.* (internal citation omitted); *see also id.* at 304 (noting that "OSHA's Hazard Communication Standard requires manufacturers to label as a carcinogen every substance listed in the Report" and that "[a] listing can also trigger obligations under state regulations").

Although the issue here is not whether FDA's listing of its TE evaluations constitutes final agency action, the D.C. Circuit's reasoning in *Tozzi* directly contradicts FDA's analysis in the 1980 Rule. *See Nat'l Res. Defense Council v. EPA*, 643F.3d 311, 321 (D.C. Cir. 2011) ("the inquiries into whether the agency action was final and whether the agency action was a rule [a]re essentially the same") (citing *Cement Kiln Recycling Coal. v. EPA*, 493 F.3d 207, 226 & n.14 (D.C. Cir. 2007)). As shown above, FDA's listing of TE ratings for particular drugs, like the Secretary of HHS's decision to classify substances as known or suspected carcinogens in the Report, "triggers obligations" under federal and state law. Under the reasoning of *Tozzi*, therefore, that listing has "binding [legal] effect" for APA purposes. 271 F.3d at 310.

Tozzi demonstrates that it is no longer the case, if it ever was, that FDA's listing of TE ratings can be characterized as purely informational and advisory—and thus without regulatory effect. The contrary reasoning that the *PMA* court articulated on this point—based on the status of such listings in 1979—is arguably *dicta* because the challenge was to the proposed, not the final, rule.[7] In any event, the same court has since cast doubt on the continuing validity of its

[7] The court ruled on the challenge after FDA had issued the proposed version of the 1980 Rule, but before it had issued the final rule. The court's reasoning in concluding that the TE listings were not "agency action" was not entirely clear. The court did emphasize the premature nature of the challenge to the proposed rule, however, noting that FDA had "state[d] . . . that the findings as to therapeutic equivalence evaluations are proposals only" and that (cont'd)

analysis "given the increased significance attributed to an Orange Book listing over the years since this Court decided [*PMA*]." *Zeneca Inc.*, 1999 WL 728104, at *11 n.13; *see also id.* ("it would appear that an Orange Book designation constitutes a final agency action").

b. Therapeutic equivalence evaluations are not a mere extension of the statutory NDA process for § 505(b)(2) drugs

The 1980 Rule reasoned that "[t]he four criteria" that make up a TE evaluation—pharmaceutical equivalence, bioequivalence, adequate labeling, and compliance with current good manufacturing practice regulations, *see* 45 Fed. Reg. at 72588—"are regulatory determinations which FDA is statutorily authorized to make." *Id.* at 72584. It further reasoned that the listing of TE evaluations itself is "nonregulatory" because those evaluations "are based on the application of certain criteria to information" that (1) is "contained in FDA files" and (2) was obtained through "determinations that were made by FDA in clearly defined proceedings when there existed the right to an evidentiary hearing"—*i.e.*, the drug approval process. *Id.* at 72587. The Agency emphasized that "TE evaluations are based on information already in FDA files as to safety, effectiveness, and quality of approved drug products *and as such are not new claims.*" *Id.* (emphasis added).

Whatever the accuracy of this reasoning as applied to drugs submitted for approval through the § 505(j) ANDA pathway, it is not accurate as applied to § 505(b)(2) drugs. The task of consolidating the pharmaceutical equivalence, bioequivalence, and same-labeling analyses made in the course of the ANDA approval process into a TE evaluation arguably is merely ministerial. If so, the issuance of the evaluation might be "nonregulatory" in the sense that it would have no legal effect beyond that already resulting from FDA's decision to approve the drug. The Agency's transformation of the findings made in the course of the § 505(b)(2) approval process into such an evaluation, however, constitutes a much more significant undertaking. In order to derive a TE evaluation for such a product, the Agency has to go beyond the "safe and effective" statutory finding that § 505(b)(2) directs it to make in approving the drug. It must, in addition, apply judgment and expert analysis to determine whether substitution of the § 505(b)(2) drug for a separately approved reference product at the pharmacy would have no clinical impact on the patient. In no way can that evaluation be viewed as the mere extension of the statutory approval process for § 505(b)(2) drugs.

(i) FDA implemented the pre-1984 ANDA and paper NDA processes to enable the Agency to approve duplicate drug products without the need for the applicant to submit any new

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"PMA . . . will have an opportunity to dispute any findings on equivalency both at the proposal stage and after the FDA has made its final determination." *PMA*, 471 F. Supp. at 1230-31. This analysis suggests that the court might well have decided that the listings constituted reviewable "agency action" had it been reviewing the final rather than the proposed rule.

clinical safety or effectiveness data. *See* 57 Fed. Reg. at 17950 ("FDA created the ANDA procedure for the approval of duplicate products"); *id.* at 17951 ("FDA did allow some duplicate drug products of drugs first approved after 1962 to be marketed under its 'paper NDA' policy."); 46 Fed. Reg. at 27396 (paper NDA process applies only to a drug "identical to one which is already marketed and the subject of an approved new drug application"); *see also Burroughs Wellcome Co. v. Schweiker*, 649 F.2d 221, 225 (4th Cir. 1981) (referring to paper NDA process as applying to "duplicate" drugs). In 1984, when Congress codified these pathways as § 505(j), it retained each of the basic elements of a TE evaluation. An ANDA submitted under subsection (j)(1) must demonstrate (1) pharmaceutical equivalence to a listed drug—*i.e.*, the same active ingredient, route of administration, and dosage; (2) bioequivalence to a listed drug; (3) identical (not merely adequate) labeling as a listed drug; and (4) compliance with good manufacturing practices. *See* 21 U.S.C. § 355(j)(2)(A)(ii)(II), (III); *id.* § 355(j)(2)(A)(iii) (same active ingredients), (iv) (same route of administration, dosage form, and strength), (iv) (bioequivalence), (v) (same labeling); *id.* § 355(j)(4) (adequate manufacturing); *see also* Orange Book at vi-vii (defining pharmaceutical equivalence).

Accordingly, every drug approved pursuant to the § 505(j)(1) ANDA process would appear to necessarily qualify for an "A" rating as therapeutically equivalent to a listed drug. *See* 67 Fed. Reg. 65448, 65452 (2002) ("A major premise in the ANDA approval system is that the ANDA drug is therapeutically equivalent to the brand-name or 'reference listed drug.'"); 60 Fed. Reg. 32982, 32983 (1995) ("[T]he approval of an abbreviated application is based on a showing that the generic drug is equivalent to the innovator drug on certain key chemical and pharmacologic parameters, and, thus, will be therapeutically equivalent to the innovator drug throughout the shelf life of the generic product."); *see also PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2574 (2011) ("Under [§ 505(j)(2)(A)], 'generic drugs' can gain FDA approval simply by showing equivalence to a reference listed drug that has already been approved by the FDA."). At a minimum, it is clear that all the information necessary to make the TE evaluation must be submitted as part of the ANDA process under § 505(j)(1).

(ii) FDA's reasoning in the 1980 Rule does not hold as applied to § 505(b)(2) drugs, because the statute does not direct the Agency to make findings of pharmaceutical equivalence and bioequivalence in order to approve the product as safe and effective. Nor does § 505(b)(2) direct FDA to assess whether a proposed product's labeling is "adequate" to ensure that the proposed and reference product "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." Orange Book at vii. To apply the TE concept to § 505(b)(2) drugs, the agency would have to make new findings that are not part of the statutory approval process.

A § 505(b)(2) application must contain full reports of investigations of safety and effectiveness, just like a full NDA There is no requirement that applications submitted under § 505(b)(2) contain evidence of pharmaceutical equivalence or bioequivalence—two criteria that are necessary for a finding of TE. This is sensible, as a drug need not be pharmaceutically equivalent or bioequivalent to a listed drug in order to qualify for approval under § 505(b)(2).

See 54 Fed. Reg. 28872, 28891 (1989) (noting that § 505(b)(2) applications "will generally be submitted for never before approved changes in already approved drug products" and for products that "could not be approved under section 505(j)" of the FDCA). Rather, that pathway may be used "regardless of the similarity or dissimilarity of the drug product to an already approved drug product." *Id.* at 28890.

Section 505(b)(2) likewise contains no standards or directions that would enable FDA to assess the "adequacy" of labeling for purposes of evaluating therapeutic equivalence. As noted above, FDA defines two products as therapeutically equivalent 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. For drugs approved under § 505(j)(1), the statute necessarily requires the labeling to meet the standard for an "A" rating: labeling of such a drug must be "the same" as the labeling of the reference product. But the Act supplies no like standard or direction that FDA applies to § 505(b)(2) drugs that would also establish the "adequacy" of the labeling for purposes of establishing therapeutic equivalence. Thus, the determination of whether labeling is "adequate" to support a TE rating can in no way be considered a byproduct of the § 505(b)(2) statutory approval process.

Thus, the Agency's own reasoning in the 1980 Rule for deeming TE listings "nonregulatory" fails as applied to § 505(b)(2) drugs. In making a TE evaluation for such a drug, FDA necessarily must reach new and categorically different conclusions about the drug than those involved in approving it. Determinations of pharmaceutical equivalence, bioequivalence, and whether the labeling is "adequate" to sustain a TE rating are not part of the statutory § 505(b)(2) approval process.

Accordingly, § 505(b)(2) cannot be viewed as providing a sufficient statutory basis for a determination that a follow-on drug is therapeutically equivalent to a listed drug. This conclusion holds even if there may be some circumstances in which § 505(b)(2) is the appropriate pathway for a follow-on drug that purports to be therapeutically equivalent to a listed drug—a question upon which Abbott here takes no position. Even if, in the course of approving a follow-on drug as safe and effective, FDA determines that the follow-on is bioequivalent and pharmaceutically equivalent to a listed drug and that it has "adequate" labeling, the statute itself does not make those determinations part of the approval process.[8]

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[8] The 1980 Rule identified a number of statutory provisions as supporting its claim that FDA is "statutorily authorized to make" the four TE criteria. 45 Fed. Reg. at 72584. These provisions either do not apply to § 505(b)(2) drugs or make no mention of the concepts of pharmaceutical equivalence and bioequivalence. FDCA § 505 (now § 505(b)(1)), which governed the single approval pathway that was available for new drugs in 1980, does not apply to drugs submitted for approval under § 505(b)(2). FDCA § 501(b) (21 U.S.C. § 351(b)), the only statutory provision that the 1980 Rule identified as supporting the criteria of pharmaceutical equivalence, requires merely that drugs meet certain "compendial standards" relating to strength, quality and purity; it does not mention the three elements of a pharmaceutical equivalence determination—namely, same active ingredient, route of administration, and dosage. And FDCA §§ 201(p) (21 U.S.C. § 321(p)), 502 (21 U.S.C. § 352), and 701(a) (21

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B. Therapeutic Equivalence Evaluations For § 505(b)(2) Drugs Are Rules Or Orders And The APA Requires FDA To Proceed Through Rulemaking Or Adjudication In Listing Therapeutic Equivalence Ratings For Such Drugs

"An administrative agency has available two methods for formulating policy that will have the force of law. An agency may establish binding policy through rulemaking procedures by which it promulgates substantive rules, or through adjudications which constitute binding precedents." *Pac. Gas & Elec. Co.*, 506 F.2d at 38. We have shown that FDA's listing of TE ratings has "binding legal effect" under the reasoning in *Tozzi*. We have also shown that, at least in the case of § 505(b)(2) drugs, making such an evaluation requires the Agency to consider criteria that the statute does not make part of the drug approval process and that therefore cannot be characterized as mere byproducts of that process. Accordingly, the APA requires FDA to employ either notice-and-comment rulemaking or informal adjudication in listing TE ratings for § 505(b)(2) drugs.

1. If FDA treats a therapeutic equivalence rating for a § 505(b)(2) drug as a rule, such a rule would be "substantive" and the Agency must therefore proceed by notice-and-comment rulemaking

It is clear that, were FDA to treat TE listings for § 505(b)(2) drugs as rules, the Agency would have to treat the listings as *substantive*, rather than merely "interpretive," rules—and thus, under the APA, it would have to implement formal notice-and-comment procedures. *See* 5 U.S.C. § 553. In particular, the Agency would have to give notice of its proposed rulemaking to the public, *see id.* § 553(b), and "give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments," *id.* § 553(c).

a. Substantive rules are rules that "'grant rights, impose obligations, or produce other significant effects on private interests,'" *Am. Hosp. Ass'n v. Bowen*, 834 F.2d 1037, 1045 (D.C. Cir. 1987), and do not merely "'advise the public of the agency's construction of the statutes and rules which it administers,'" *Chrysler Corp. v. Brown*, 441 U.S. 281, 302 n.31 (1979) (quoting Attorney General's Manual on the Administrative Procedure Act, at 30 n.3 (1947)). If FDA chose to treat its TE listings for § 505(b)(2) drugs as rules, those listings would qualify as substantive rules under this standard.

As we have shown, the listings trigger obligations under federal and state law, and therefore have a "binding [legal] effect" under the D.C. Circuit's reasoning in *Tozzi*. 271 F.3d at 310; *see also id.* (HHS's dioxin listing reflects "intention to bind either itself or regulated parties") (internal quotation marks omitted). It is true that FDA itself does not directly require that "A" ratings serve as the basis for generic drug substitution decisions (as they do in almost

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U.S.C. § 371(a), the statutory provisions identified as supporting bioequivalence determinations, say nothing about that concept.

two thirds of the States) or that they affect reimbursement outcomes under various federal healthcare programs. But a rule that affects parties' interests can be substantive even if it does not "formal[ly]" have the "force of law." *Chamber of Commerce*, 174 F.3d at 212.

In *Chamber of Commerce*, for example, the D.C. Circuit held that a Department of Labor "Directive" advising certain employers that the Department would inspect them unless they adopted a health and safety program designed to meet standards higher than those imposed by law was a substantive rule, even though it "operate[d] without having the force of law." 174 F.3d at 212. The court focused on the Directive's "practical effect[s]," reasoning that it was a substantive rule because it "will affect employers' interests in the same way that a plainly substantive rule mandating a comprehensive safety program would affect their rights; that it so operates without having the force of law is therefore of little, if any, significance." *Id.* at 209, 212. Here, likewise, FDA's TE listings significantly affect the interests of numerous parties—including patients, doctors, pharmacists, insurers, state agencies, and innovator and generic drug manufacturers and distributors—through the operation of the numerous state and federal laws that incorporate those listings. And those effects are the same as would result if FDA directly required the substitution of therapeutically equivalent generics for listed drugs or imposed differential reimbursement levels for multiple-source and single-source drugs.

b. TE listings for § 505(b)(2) drugs also would qualify as substantive rules under the four-part test established by the D.C. Circuit in the *American Mining Congress* case. The four criteria of this test are:

> (1) whether in the absence of the rule there would not be an adequate legislative basis for enforcement action or other agency action to confer benefits or ensure the performance of duties, (2) whether the agency has published the rule in the Code of Federal Regulations, (3) whether the agency has explicitly invoked its general legislative authority, or (4) whether the rule effectively amends a prior legislative rule.

Am. Mining Congress, 995 F.2d at 1112. If *any* of the four criteria is met, the agency action is substantive—and therefore must comply with notice-and-comment procedures under the APA. *Id.*

FDA's TE listings for § 505(b)(2) drugs qualify as substantive rules under at least the first criterion. As just described, such listings "confer benefits or ensure the performance of duties"; and there is no "adequate legislative basis" for the listings, at least in the absence of further FDA rulemaking.

The D.C. Circuit has explained that "'[t]he distinction between an interpretive rule and [a] substantive rule likely turns on how tightly the agency's interpretation is drawn linguistically from the actual language of the statute.'" *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 94 (D.C. Cir. 1997) (quoting *Paralyzed Veterans v. D.C. Arena L.P.*, 117 F.3d 579, 588 (D.C. Cir. 1997)

(alterations omitted)). As discussed above, the approval process set forth in § 505(b)(2) does not involve an assessment of either pharmaceutical equivalence or bioequivalence—two of the four criteria necessary to make a TE evaluation—and the portions of the statute governing such approvals do not mention those terms (or anything analogous). Thus, the statutory provisions governing the § 505(b)(2) approval process provide no support for FDA's additional step of granting TE ratings to drugs submitted for approval under that process. *See Syncor Int'l Corp.*, 127 F.3d at 96 ("a rule that does not purport to interpret any language in a statute or regulation" cannot "be thought an interpretive rule") (emphasis omitted); *see also Nat'l Family Planning & Reproductive Health Ass'n v. Sullivan,* 979 F.2d 227, 237 (D.C. Cir. 1992) ("[A] rule is legislative if it attempts to supplement a statute, not simply to construe it.") (internal quotation marks and alterations omitted).[9]

Nor does § 505(j)(7)(A)—which requires FDA to "publish and make available to the public" "a list . . . of the official and proprietary name of each drug which has been approved for safety and effectiveness" under § 505(b)(1), (b)(2), and (j)—provide the necessary statutory support. That provision makes no mention of TE evaluations, and such evaluations cannot be viewed as merely "clarify[ing]," "explain[ing]," or "confirm[ing]," *Nat'l Family Planning & Reproductive Health Ass'n,* 979 F.2d at 237, the names of approved drug products that the provision does require FDA to list.

Given this absence of an "adequate legislative basis" for FDA's listing of TE ratings, the Agency itself would need to supply the necessary legal basis for those listings—if it chose to treat them as rules—by making the listings through notice-and-comment rulemaking. FDA does not currently do this.

c. TE ratings for § 505(b)(2) drugs cannot be considered non-substantive rules that merely interpret § 20.117(a)(3) of Title 21 of the CFR. It is true that "an interpretative rule can construe an agency's substantive regulation as well as a statute." *Syncor Int'l Corp.*, 127 F.3d at 94. To begin with, however, FDA did not believe that "the list is . . . a rule, as defined in [the APA]," and therefore did not believe that the Agency was "required" to "adhere[]" to notice-and-comment procedures in issuing the rule. 44 Fed. Reg. at 2937. Instead, FDA took the position that notice-and-comment rulemaking procedures provided "a useful model for the agency to present a proposal and request public comments on it." *Id.* Consistent with this view, FDA described § 20.117(a)(3) itself as merely carrying into effect the Agency's desire to provide "the public" with "a point of reference reflecting the availability of th[e] [Orange Book] list." *Id.*

Further, all that § 20.117(a)(3) does (of relevance to the issues raised in this petition) is inform the public that the Orange Book listing "includes, for each active ingredient in a

[9] This may distinguish § 505(b)(2) drugs from drugs approved pursuant to an ANDA submitted under § 505(j)(1). Because all the information necessary to make a TE evaluation must be submitted as part of the statutorily authorized ANDA process, the listing of such evaluations for § 505(j)(1) drugs may have an "adequate legislative basis" even though there is none for § 505(b)(2) drugs. Abbott does not ask FDA to resolve this question.

particular dosage form for which there is more than one approved application, an evaluation of the TE of the drug products covered by such applications." The more detailed discussion of how FDA will carry out TE evaluations can be found only in less formal guidance—for example, the preamble to the 1980 Rule and the Orange Book itself. *See* 21 C.F.R. § 10.85 (preamble to a regulation is "advisory"); *see also Nat'l Res. Defense Council v. EPA*, 559 F.3d 561, 565 (D.C. Cir. 2009) ("Agency statements 'having general applicability and legal effect' are to be published in the Code of Federal Regulations."). Thus, even to the extent that § 20.117(a)(3) can be viewed as a binding source of legal authority, it does not provide a sufficient legal basis for the listing of TE evaluations without further rulemaking. "A substantive regulation must have sufficient content and definitiveness as to be a meaningful exercise in agency lawmaking. It is certainly not open to an agency to promulgate mush and then give it concrete form only through subsequent less formal 'interpretations.' That technique would circumvent section 553, the notice and comment procedures of the APA." *Paralyzed Veterans*, 117 F.3d at 584 (citation omitted). Were FDA to conclude that the TE ratings it gives § 505(b)(2) drugs merely "interpret" § 20.117(a)(3), it would run afoul of this test by attempting just such a circumvention.

Finally, FDA's listing of a TE rating for a § 505(b)(2) drug cannot qualify as an interpretive rule because that listing "modifies or adds to a legal norm"—whether § 505(b)(2) itself or 21 C.F.R. § 20.117(a)(3)—"based on [FDA's] own authority." *Syncor Int'l Corp.*, 127 F.3d at 95 (emphasis omitted). Specifically, the listing "extend[s]" FDA's "regulatory reach"—*i.e.*, its power to issue a rating that necessarily has legal consequences under state and federal law—to include a § 505(b)(2) product that was not previously subject to that reach. *Id.* The D.C. Circuit's decision in *Syncor* is almost directly on point. There, the court held that FDA's announcement that a certain type of diagnostic imaging method "'should be regulated' under the drug provisions of the [FDCA]" violated the APA because the Agency failed to proceed by notice-and-comment rulemaking in issuing the announcement. *Id.* at 92. As the court observed, the announcement was not an interpretive rule, because "[i]t does not purport to construe any language in a relevant statute or regulation; it does not interpret anything." *Id.* at 95. Here, likewise, FDA's listing of its TE ratings for § 505(b)(2) drugs does not "construe" the term "therapeutic equivalence" in § 20.117(a)(3) (or any statutory provision). Instead, those listings make a determination that is regulatory in nature about whether each of those drugs should be subject to the legal consequences that flow from a determination of therapeutic equivalence.

2. If FDA treats a therapeutic equivalence rating for a § 505(b)(2) drug as an order, the Agency must proceed by informal adjudication

FDA might have the discretion to proceed by adjudication rather than rulemaking in listing TE evaluations for § 505(b)(2) drugs. The APA defines "adjudication" as "agency process for the formulation of an order," and an order as "the whole or a part of a final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rulemaking but including licensing." 5 U.S.C. § 551(6), (7). The definition of an order overlaps significantly with the APA's definition of a rule, *see id.* § 551(4) ("'rule' means 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 or describing the organization, procedure, or practice requirements of an agency"), and many categories of agency action could qualify as either an "adjudication" or a "rulemaking," *see* 1 Richard J. Pierce, Jr., *Administrative Law Treatise* § 8.1, at 701 (5th ed. 2010). As the D.C. Circuit has observed, "[m]ost norms that emerge from a rulemaking are equally capable of emerging (legitimately) from an adjudication, . . . and accordingly agencies have 'very broad discretion whether to proceed by way of adjudication or rulemaking.'" *Qwest Servs. Corp. v. FCC*, 509 F.3d 531, 536 (D.C. Cir. 2007) (quoting *Time Warner Entm't Co. v. FCC*, 240 F.3d 1126, 1141 (D.C. Cir. 2001)).

Informal adjudications must comply with the procedures set forth in 5 U.S.C. § 555. Subsection (b) of that provision states, among other requirements, that, "[s]o far as the orderly conduct of public business permits, an interested person may appear before an agency or its responsible employees for the presentation, adjustment, or determination of an issue, request, or controversy in a proceeding, whether interlocutory, summary, or otherwise, or in connection with an agency function." 5 U.S.C. § 555(b). Section 555(b) "is universally understood to establish the right of an interested person to participate in an on-going agency proceeding." *Block v. SEC*, 50 F.3d 1078, 1085 (D.C. Cir. 1995); *see also Nichols v. Bd. of Trustees of Asbestos Workers Local 24 Pension Plan*, 835 F.2d 881, 896 & n.108 (D.C. Cir. 1987) ("a party entitled to judicial review of agency action clearly qualifies as an 'interested person' who normally may intervene in the administrative proceeding," although "[s]tanding to intervene as of right is not restricted to parties entitled to judicial review"). Further, § 555(e) provides that "[p]rompt notice shall be given of the denial in whole or in part of a written application, petition, or other request of an interested person made in connection with any agency proceeding" and that, "[e]xcept in affirming a prior denial or when the denial is self-explanatory, the notice shall be accompanied by a brief statement of the grounds for denial." An agency must "provide an explanation that will enable the [reviewing] court to evaluate the agency's rationale at the time of decision." *Pension Benefit Guar. Corp. v. LTV Corp.*, 496 U.S. 633, 654 (1990).

FDA is not presently complying with these requirements in issuing TE listings for § 505(b)(2) products. Although "[c]ourts have long accorded agencies broad discretion in fashioning rules to govern public participation" by interested persons, *Nichols*, 835 F.2d at 897, FDA has not issued any such rule. Instead, it has taken the blanket position that TE listings are not orders, and thus are not subject to the APA requirements governing informal adjudications. Before FDA could start treating its TE listings as orders, it would have to issue a rule that overrides this prior determination and specifies the procedures that will apply to its listing determinations, including the right of interested parties to intervene.

"Interested parties" in this context includes a follow-on product applicant that seeks a TE rating as well as the sponsor of the reference product that may choose to assert that its product should not be considered interchangeable with the proposed § 505(b)(2) product. If FDA decides to issue a rule characterizing TE listings as orders, it should keep in mind that "courts will not rubberstamp a challenged denial [of intervention] based merely upon an assertion of justification, especially if the agency contends simply that intervention would prove impermissibly dilatory or burdensome." *Nichols*, 835 F.2d at 897. Indeed, "[c]ourts willingly

overturn challenged denials when the responsible agency, either by failing to fashion equitable procedures or by employing its power in an unreasonably overbroad or otherwise arbitrary manner, has not acted to preserve the participation opportunities of interested persons." *Id.*

C. FDA Must Engage In Notice-And-Comment Rulemaking To Determine Whether The Listing Of Therapeutic Equivalence Ratings For § 505(b)(2) Drugs Will Be Done Through Rulemaking Or Informal Adjudication

To determine the proper characterization of TE listings as either rules or orders, and to address related issues, FDA must proceed via notice-and-comment rulemaking. That is true for two reasons.

First, "APA rulemaking is required where an interpretation 'adopt[s] a new position inconsistent with . . . existing regulations.'" *Paralyzed Veterans*, 117 F.3d at 586 (quoting *Shalala v. Guernsey Mem'l Hosp.*, 514 U.S. 87, 88 (1995)); *see also Nat'l Family Planning & Reproductive Health Ass'n*, 979 F.2d at 236 ("Obviously, HHS may for good cause, change the regulation and even its interpretation of the statute through notice and comment rulemaking, but it may not constructively rewrite the regulation, which was expressly based upon a specific interpretation of the statute, through internal memoranda or guidance directives that incorporate a totally different interpretation and effect a totally different result."). Here, FDA's initiation of rulemaking or adjudicatory proceedings in making TE evaluations would contradict the Agency's existing rules and regulations, which reject the need for either.

Second, "[i]n the rulemaking context . . . it is settled law that an agency may be forced to reexamine its approach 'if a significant factual predicate of a prior decision . . . has been removed.'" *Bechtel*, 957 F.2d at 881 (quoting *WWHT, Inc.*, 656 F.2d at 819); *see also Am. Horse Prot. Ass'n v. Lyng*, 812 F.2d 1, 5 (D.C. Cir. 1987) ("[A] refusal to initiate a rulemaking naturally sets off a special alert when a petition has sought modification of a rule on the basis of a radical change in its factual premises."). Here, the underlying facts and law have changed significantly since FDA issued the 1980 Rule. As a factual matter, many States now look to the FDA's TE listings as the essential factor for determining whether, and on what terms, generic substitution should or must occur, and Congress has expressly tied reimbursement levels under various federal healthcare programs to TE listings. As a legal matter, the Hatch-Waxman Amendments added the § 505(b)(2) approval process in 1984, and recent judicial decisions have established both that (1) agency listings that trigger obligations under state law and other federal regulatory programs have "binding [legal] effect," *Tozzi*, 271 F.3d at 310, and (2) a rule that practically affects parties' interests can be substantive even if it does not "formal[ly]" have the "force of law," *Chamber of Commerce*, 174 F.3d at 212.

The rule that FDA issues should provide robust procedural protections for parties with an interest in TE listings for § 505(b)(2) products. It also should establish the standards that will govern such listings. FDA's creation of new standards is important because, as already explained, the statutory findings that FDA is directed to make as part of the statutory process of

approving § 505(b)(2) drugs do not include findings of bioequivalence and pharmaceutical equivalence, do not assess labeling "adequacy" for purposes of supporting TE determinations, and therefore cannot readily be summarized in a TE rating. The standards should include an explanation of whether § 505(b)(2) products may still receive an "A" rating if they bear unique labeling. Likewise, formulation differences among products approved under § 505(b)(2), and even the extent of the nonclinical and clinical data submitted in support of an application for a § 505(b)(2) drug, can raise novel questions regarding how a § 505(b)(2) product compares with another previously approved drug for purposes of assigning a TE rating. All these issues need to be fully vetted through an administrative rulemaking process that fully complies with the APA.

VI. CONCLUSION

Before FDA lists a TE rating for any § 505(b)(2) drug that references Androgel, it should conduct a notice-and-comment rulemaking that supersedes the portion of the 1980 Rule describing such listings as neither rules nor orders. This rulemaking should characterize the listing of TE ratings for § 505(b)(2) drugs as either a rule or an order, specify what procedural protections FDA will afford interested parties in connection with the listings, and establish a coherent set of standards governing such listings.

VII. ENVIRONMENTAL IMPACT

The actions requested in this citizen petition are subject to categorical exclusions under 21 C.F.R. §§ 25.30 and 25.31.

VIII. ECONOMIC IMPACT

Information on the economic impact of this citizen petition will be submitted upon request of the Commissioner of Food and Drugs.

IX. CERTIFICATION[10]

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is

[10] As noted above, *see* note 1, *supra*, Abbott believes that this petition is not subject to FDCA § 505(q). Nonetheless, out of an abundance of caution and in order to avoid delay if the Agency concludes that FDCA § 505(q) is applicable, Abbott has provided the certification required by FDCA § 505(q)(1)(H), which encompasses and exceeds the certification required by 21 C.F.R. § 10.30(b).

submitted on or about the following date: March 16, 2011, when Abbott first received notice of the pending § 505(b)(2) NDA for a testosterone gel product that relies on AndroGel as the reference listed drug. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Abbott Laboratories. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Dan Himmelfarb
Mayer Brown LLP

Of Counsel:

David M. Fox
Philip Katz
Hogan Lovells

cc: Neal B. Parker, Esq., Abbott Laboratories
Perry C. Siatis, Esq., Abbott Laboratories