DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Re: Dockets Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1

Dear Petitioners:

This letter is a consolidated response to the citizen petitions in the dockets referred to above and comments submitted on the petitions.[1] Although each of these petitions has a slightly different focus and concerns different drug products or classes of products, each is, in essence, a challenge to the Food and Drug Administration's (FDA's) interpretation of section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the FDCA or the Act)(21 U.S.C. 355(b)(2)). For the reasons

[1] 2001P-0323/CP1 submitted by Morgan, Lewis & Bockius, LLP, on behalf of Pfizer Inc. and Pharmacia Corporation (2001 Pfizer petition); 2001CP-0323/C5 submitted by the Biotechnology Industry Organization (BIO) (BIO petition); 2002P-0447/CP1 submitted by Morgan, Lewis & Bockius, LLP on behalf of Pfizer Inc. (2002 Pfizer petition); 2003P-0408/CP1, submitted by Lord, Bissell & Brook LLP on behalf of TorPharm (TorPharm petition). The BIO petition contains regulatory and legal arguments challenging FDA's implementation of section 505(b)(2) of the FDCA, as well as scientific and technical arguments as to why biologically derived products, in particular, are not suited for approval under section 505(b)(2). This response addresses the legal and regulatory issues; the unique scientific issues associated with biologically derived products present a separate set of challenges that will be addressed in a response to be issued later. The BIO petition, although designated a citizen petition by BIO, was docketed as a comment. FDA is responding to the document as a petition. The 2002 Pfizer petition contains scientific arguments specific to a pending application. Because this application is not approved, FDA cannot comment on the scientific issues raised in this petition. (See 21 CFR 314.430.)

described below, FDA declines to alter its current interpretation of section 505(b)(2). Accordingly, those portions of the petitions seeking such a change are denied.[2] However, the Agency also grants certain specific portions of the petitions as described below (section IV.M) related to therapeutic equivalence ratings for 505(b)(2) drug products.

I. INTRODUCTION

Section 505(b)(2) of the Act was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments). Section 505(b)(2) provides:

> An application [may be] submitted under [section 505(b)(1)] for which the [safety and effectiveness] investigations . . . relied upon by the applicant [to support] approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted [and] shall also include [patent certifications for patents on the drug for which investigations were conducted or a method of use statement].

The Hatch-Waxman Amendments reflect Congress's attempt to balance the need to encourage innovation with the desire to speed the availability of lower cost alternatives to approved drugs. (*See Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990); and *Bristol-Myers Squibb Company v. Royce Laboratories, Inc.*, 69 F.3d 1130, 1132, 1133-34 (Fed. Cir. 1995).) With passage of the Hatch-Waxman Amendments, the Act describes different routes for obtaining approval of two broad categories of drug applications: new drug applications (NDAs), for which the requirements are set out in section 505(b) and (c) of the Act, and abbreviated new drug applications (ANDAs), for which the requirements are set out in section 505(j). These categories can be further subdivided into the following:

- an application that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference (section 505(b)(1)) (a stand alone NDA);
- an application that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)) (a 505(b)(2) application);
- an application for a *duplicate*[3] of a previously approved drug that contains information to show that the proposed product is identical in active ingredient(s), dosage form, strength, route of administration, labeling, quality, performance

[2] As discussed in greater detail in section IV.N below, FDA is considering whether to commence a public process to examine the narrow question of whether to change our interpretation of section 505(b)(2) as it applies to applications for which the only change from the listed drug is a change in active ingredient.

[3] The informal term *duplicate* is used in this response to refer to an application under section 505(j) describing a product that is the same as the listed drug with respect to active ingredient, dosage form, route of administration, strength, and conditions of use, among other characteristics.

characteristics, and intended use, among other things, to a previously approved product, and for which clinical studies are not necessary to show safety and effectiveness (section 505(j))(an ANDA); and

- an application for a drug that differs from a previously approved drug product in dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient), for which FDA has determined, in response to a "suitability petition" submitted under section 505(j)(2)(C), that clinical studies are not necessary to show safety and effectiveness (section 505(j))(a petitioned ANDA).

Each type of application may rely on different sources and types of information to support the safety and effectiveness of the drug product. The statute also provides for drug development incentives in the form of marketing protections and patent extensions. The marketing protections available will depend on the type of application submitted. Similarly, some applications will be subject to the marketing protections and patent rights of other applications.

A 505(b)(2) application shares characteristics of both ANDAs and stand alone NDAs. Like a stand alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) and approved under section 505(c). As such, it must satisfy the requirements for safety and effectiveness information. A 505(b)(2) application is similar to an ANDA as well because it may rely on the FDA finding that the listed drug it references is safe and effective as evidence in support of its own safety and effectiveness. However, although an ANDA is generally required to duplicate the innovator product (with a few limited exceptions) — and an ANDA therefore may not include new clinical safety or effectiveness information to support approval — a 505(b)(2) application often describes a drug with substantial differences from the listed drug it references. Accordingly, it must support those differences with appropriate safety and effectiveness information. For example, a 505(b)(2) application may seek approval for a new dosage form, indication, or new formulation of a previously approved drug. In such cases, the 505(b)(2) application can rely on the finding of safety and effectiveness of the listed drug only to the extent the product seeking approval and the listed drug are the same. To the extent the products are different, the 505(b)(2) application, like a stand alone NDA, must include sufficient data to demonstrate that the product with those different aspects meets the statutory approval standard for safety and effectiveness.

FDA's longstanding interpretation of section 505(b)(2) is intended to permit the pharmaceutical industry to rely to the greatest extent possible under the law on what is already known about a drug. The Agency's approach is to use the 505(b)(2) drug approval pathway to avoid requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval with no corresponding benefit to the public health.

In addition, the conduct of duplicative studies raises ethical concerns because it could subject human beings and animals to medically or scientifically unjustified testing.[4] The 505(b)(2) pathway permits sponsors and FDA to determine what studies are necessary to support the approval of the new aspect of a drug. It then allows sponsors to target drug development resources to studies needed to support the proposed difference or innovation.

FDA's interpretation of section 505(b)(2) is supported by the plain language of that provision, as well as the overall structure and purpose of the Act and, in particular, the Hatch-Waxman Amendments. As discussed below in section III.B, since passage of the Hatch-Waxman Amendments, FDA has approved more than 80 section 505(b)(2) applications for drugs for indications ranging from cancer pain to attention deficit disorder. Many of these drugs would never have reached the market, or would have been significantly delayed, without the 505(b)(2) pathway.

II. LEGAL AND REGULATORY BACKGROUND

A. Background on NDAs and ANDAs

The petitions challenge FDA's interpretation of section 505(b)(2), not the statutory provisions related to stand alone NDAs, ANDAs for duplicate drugs, or petitioned ANDAs. To understand how the 505(b)(2) application fits into the drug approval landscape, however, it is important to fully appreciate the characteristics of NDAs, ANDAs, and petitioned ANDAs. A 505(b)(2) application is a subset or variation on an NDA, and it is subject to the NDA approval requirements set out in section 505(b) and (c) of the Act. A 505(b)(2) application also shares certain features with an ANDA. As such, it is subject to the patent certification requirements and many of the exclusivity delays that apply to ANDAs.

1. NDAs

Section 505(b)(1) requires that an applicant submit in an NDA: evidence that the drug is safe and effective; a list of the components of the drug; a statement of the drug's composition; a description of the manufacturing, processing, and packaging of the drug; samples of the drug as necessary; and proposed labeling for the drug. Because 505(b)(2) applications, like stand alone NDAs, are submitted under section 505(b)(1) and approved under section 505(c), 505(b)(2) applications must also satisfy these NDA requirements. FDA's regulations in 21 CFR part 314 describe the NDA approval requirements in detail at § 314.50. Section 314.54 specifically describes how 505(b)(2) applications must satisfy these requirements.

In 1984, with the Hatch-Waxman Amendments, section 505 was amended to require that an NDA applicant (including a 505(b)(2) applicant) submit to FDA information about any patent that (1) claims the drug, or a method of using the drug, for which the applicant submitted the

[4] The ethics of duplicative studies was one of the concerns leading to passage of Hatch-Waxman. See House Report 98-857, part 1, 98th Congress 2d. Sess. June 21, 1984 (House Report) at 16: "[S]uch retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective."

application and (2) with respect to which a claim for patent infringement could reasonably be asserted if a person not licensed by the patent owner were to engage in the manufacture, sale, or use of the drug (section 505(b)(1) and (c)(2)). Patents that must be submitted include patents on the drug's active ingredient (drug substance), the drug product (formulation or composition), and the use of the drug.[5] Once the drug product has been approved, FDA must publish the patent information in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). Approved drug products listed in the Orange Book with their relevant patent information are referred to in the statute and regulations as *listed drugs* (section 505(j)(2)(A)(i)). As explained in more detail below, the statute requires that 505(b)(2) and ANDA applicants certify whether their proposed products may infringe the patents on the listed drugs they reference in their applications.

The Hatch-Waxman Amendments also provided different marketing exclusivity periods for drugs approved in NDAs (including drugs approved in 505(b)(2) applications), based on the level of innovation represented by the drug product. While these five- and three-year *exclusivity* periods are in effect, FDA may not accept or approve certain applications that rely on the protected product for approval (section 505(c)(3)(D)(ii)-(iv) and (j)(5)(D)(ii)-(iv)).[6]

Five-year exclusivity is granted to a drug that contains no active ingredient (including any ester or salt of the active ingredient) previously approved under section 505(b) (section 505(c)(3)(D)(ii) and (j)(5)(D)(ii); § 314.108). During this five-year period that begins with approval, FDA may not receive for review any 505(b)(2) or 505(j) application referring to the listed drug with this protection. However, if the NDA holder for the listed drug with five-year exclusivity has submitted a patent for the drug pursuant to section 505(b)(1) or (c)(2), a 505(b)(2) or ANDA applicant wishing to challenge that patent may submit an application referencing the listed drug at the end of four years (section 505(c)(3)(D)(ii) and (j)(5)(D)(ii); § 314.108).

Three-year exclusivity is granted to a drug for which approval of an NDA or NDA supplement requires FDA to review new clinical studies conducted or sponsored by the applicant that are essential to the approval. This exclusivity bars FDA from approving for three years a 505(b)(2) application or ANDA referencing the listed drug (or the change to the listed drug) for which the

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[5] FDA has recently issued new regulations governing patent submissions, the provision of notice of paragraph IV certifications, and the availability of 30-month multiple stays on ANDA and 505(b)(2) approvals (68 FR 36676, June 18, 2003). These regulations apply to patent submissions made on or after August 18, 2003, and to patent certifications to those patents. The matters addressed by the new regulations are not at issue in these citizen petitions. However, the interpretation of section 505(b)(2) discussed in this response is consistent with both the old and the new regulations.

[6] Title II of the Hatch-Waxman Amendments also establishes a process for the extension of the terms of certain patents for approved innovator drug products. Specifically, subject to certain caps, sponsors can seek a patent extension equal to one-half the drug development time plus the length of time the product was under FDA review. This is to compensate for marketing time lost to the sponsor while the drug product was under development and being reviewed by FDA. The patent term extension provisions are codified in the Patent Code at Title 35, sections 156 and 271.

new studies were submitted (section 505(c)(3)(D)(iii) and (iv); 505(j)(5)(D)(iii) and (iv); § 314.108).

As explained further below, 505(b)(2) applications are hybrid applications that receive the benefits of patent listing and marketing exclusivity available to NDAs. They are also subject to the burden of patent certifications and delays in approval to which ANDAs are subject, resulting from the patents and marketing exclusivity protecting the listed drugs they reference.

2. ANDAs

Before the Hatch-Waxman Amendments were passed, there was no explicit abbreviated statutory pathway to approve duplicates of post-1962 drugs. In 1962, Congress added an effectiveness requirement as a condition of drug approval. After this change, under the Drug Efficacy Study Implementation (DESI) program, the Agency undertook to review all drugs that had been approved based on safety alone (before the 1962 effectiveness requirement was added) to determine whether there was sufficient evidence of effectiveness to warrant their continued approval. To ensure that the largest number of drugs possible came under the Agency's approval provisions, unapproved *generic* versions of pre-1962 drugs were permitted to obtain approval under DESI without showing independent evidence of safety or effectiveness if they were duplicates of drugs that the Agency determined had sufficient evidence of effectiveness to warrant continued approval (as memorialized by a *Federal Register* notice) and contained all other information required in a new drug application (34 FR 2673, February 27, 1969; 35 FR 6574, April 24, 1970). The preamble to FDA's proposed rule implementing the Hatch-Waxman Amendments briefly describes the DESI program (54 FR 28872 at 28872 and 28873, July 10, 1989).

The DESI program and abbreviated route of approval for duplicates did not apply to drugs approved after 1962. For post-1962 duplicates, FDA initially concluded that the statute did not provide an abbreviated pathway for approval. Accordingly, for duplicates of post-1962 drugs, the Agency created the "paper NDA" policy. That policy applied narrowly to permit an applicant to rely on evidence from published scientific literature to satisfy the approval requirements for full reports of safety and effectiveness. (See "Publication of 'Paper NDA' Memorandum," 46 FR 27396, May 19, 1981.) The application of this policy to literature-based duplicates was upheld in *Burroughs Wellcome Co. v. Schweiker*, 649 F.2d 221 (4th Cir. 1981). Because so few post-1962 drugs had an adequate quantity of published literature to support the full reports requirement for approval, in 1982 FDA announced that it was reconsidering its initial assessment of the scope of its authority and was contemplating changing its regulations to create an abbreviated pathway for post-1962 drugs similar to the DESI process for pre-1962 drugs (47 FR 1765 at 1767 January 13, 1982). However, the need for such a change was obviated when, in 1984, the Hatch-Waxman Amendments were passed.

Among other things, the Hatch-Waxman Amendments established an abbreviated process to approve duplicates of post-1962 drug products. They also integrated into the drug approval process recognition of the listed drug's patent protections and provided patent extensions, as well as additional periods of market exclusivity, to encourage development of innovative drug

products. In creating an explicit regulatory pathway to approve duplicates of post-1962 drugs, the Hatch-Waxman provisions eliminated the need to approve duplicates of post-1962 drugs via the paper NDA route. Specifically, the Hatch-Waxman Amendments established a process, under section 505(j) of the FDCA, to approve duplicates of listed drugs on the basis of chemistry, manufacturing, and bioequivalence[7] data without evidence from literature or clinical data to establish effectiveness and safety. Under these provisions, if an ANDA applicant establishes that its proposed drug product has the same active ingredient, strength, dosage form, route of administration, labeling, and conditions of use as a listed drug, and that it is bioequivalent to that drug, the applicant can rely on the fact that the FDA has previously found the listed drug to be safe and effective. FDA is not permitted to require safety or effectiveness trials to support 505(j) approval (section 505(j)(2)(A)).

The legislation also permitted ANDA applicants to petition for permission to submit ANDAs for products that differ from the listed drug in any of four specified ways — dosage form, route of administration, strength, or active ingredient[8] — where such changes do not require review of clinical data (section 505(j)(2)(C)). If such a petition is granted, the applicant may seek approval for the altered drug product in a petitioned ANDA.[9]

Under section 505(j), the approval of both ANDAs and petitioned ANDAs depends upon the ANDA applicant demonstrating that the proposed product is sufficiently similar to the approved product for which safety and effectiveness have already been established so that no additional evidence of safety and effectiveness need be submitted for review.

Section 505(j) also contains procedures whereby the patents and marketing exclusivity protecting the listed drug are considered by FDA during the approval process for ANDAs, including petitioned ANDAs. The proposed drug described in the ANDA may not be finally approved until the patents and marketing exclusivity have expired or until the NDA holder and patent owners for patents on the listed drug have had an opportunity to defend their patent rights in court. These procedures and requirements to protect the patents and market exclusivity rights of listed drugs are duplicated with respect to approval of 505(b)(2) applications.

With respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA, petitioned ANDA, or 505(b)(2) applicant must submit to FDA a certification under section 505(j)(2)(A)(vii) or 505(b)(2)(A) stating:

> (I) that such patent information has not been filed,
> (II) that such patent has expired,

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[7] Two drugs are considered bioequivalent if, in general, the rate and extent of absorption of the proposed drug do not show a significant difference from the rate and extent of absorption of the listed drug (section 505(j)(8)(B)).

[8] Under FDA regulations, a change in active ingredient is permitted only where "one active ingredient is substituted in for one of the active ingredients in a listed combination drug" (§ 314.93(b)). The petitioned ANDA route is not available for a change in active ingredient in a single active ingredient product.

[9] If such a petition is denied because clinical studies are necessary to demonstrate that the altered drug product is safe and effective, an applicant may submit a 505(b)(2) application.

> (III) the date on which such patent will expire, or
> (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.

If an ANDA, petitioned ANDA, or 505(b)(2) applicant does not challenge the listed patents, the application will not be approved until all the listed patents claiming the listed drug have expired. If an applicant wishes to challenge the validity of the patent, or to claim that the patent would not be infringed by the product proposed in the ANDA, petitioned ANDA, or 505(b)(2) application, the applicant must submit a paragraph IV certification to FDA. The applicant must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed[10] (section 505(b)(2)(B); 505(j)(2)(B)). Once the NDA holder and patent owner have received the ANDA, petitioned ANDA, or 505(b)(2) applicant's notice and explanation as to why the listed patent is invalid or will not be infringed by the proposed drug, they have 45 days within which to sue the applicant for patent infringement and thus trigger a 30-month stay of FDA approval of the proposed drug (section 505(c)(3)(C); 505(j)(5)(B)). FDA will approve the proposed drug before the 30-month period expires only if a court finds the patent invalid or not infringed or the court shortens the period because the parties fail to cooperate in expediting the litigation (section 505(c)(3)(C); 505(j)(5)(B)).

An ANDA, petitioned ANDA, or 505(b)(2) application will not be approved until all applicable listed drug product exclusivity has expired and the listed patents have expired, have been successfully challenged by an applicant, or any applicable 30-month stay has expired (§ 314.107). ANDAs with paragraph IV certifications to a listed patent may also be subject to 180-day exclusivity held by the first ANDA with a paragraph IV certification to that patent; this exclusivity does not apply to petitioned ANDAs[11] or 505(b)(2) applications.

B. Background on 505(b)(2) Applications

In addition to creating the ANDA approval process, the Hatch-Waxman Amendments also created a new subset of NDA. Section 505(b)(2) of the FDCA permits the filing of an NDA where the sponsor does not have a right of reference to all of the studies supporting approval, as follows:

> An application submitted under [section 505(b)(1)] for a drug for which the investigations described in [section 505(b)(1)(A)] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include —

[10] See footnote 5.

[11] Because petitioned ANDAs are for a different drug product (different strength, active ingredient, route of administration, dosage form), they become a separate listed drug and are not subject to the 180-day exclusivity of the first ANDA applicant for the listed drug.

> (A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section —
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> (i) that such patent information has not been filed,
> (ii) that such patent has expired,
> (iii) of the date on which such patent will expire, or
> (iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and
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> (B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

Thus, this section states that an applicant may rely for approval on investigations *not conducted by or for* the applicant and for which the applicant *has not obtained a right of reference*[12] (emphasis added). It also anticipates that the studies on which a 505(b)(2) applicant can rely may be studies on an approved drug product. This is the case because patent certifications apply only to patents on approved drug products listed in the Orange Book. The statute also was amended throughout, as described above, to ensure that the patent and exclusivity bars to approval that apply to ANDAs apply as well to the approval of 505(b)(2) applications. (See, e.g., section 505(c)(3).)

Section 505(b)(2) permits FDA to review applications that are not reviewable under section 505(j) either as duplicates or minor variations of a listed drug and that do not require a full stand alone NDA supported by new scientific studies. Without the 505(b)(2) approval pathway, the available approval routes would be limited to: (1) new studies on all aspects of a drug's safety and efficacy (stand alone NDA) or (2) almost complete reliance on established findings of safety and efficacy (ANDA). For example, a modification to a listed drug (e.g., a novel dosage form) that could not be approved in a petitioned ANDA under section 505(j) because review of new clinical data would be necessary for approval could only be reviewed in a complete new stand alone NDA. This approach is not necessary. Instead, FDA believes that it is reasonable to interpret the statute so that: (1) if a proposed modification may be approved without additional studies, the drug may be reviewed in a 505(j) application that relies *entirely* on the Agency's finding of safety and effectiveness for the listed drug; and (2) if the proposed modification will require additional data for approval, the drug may be reviewed in a 505(b)(2) application that relies *in part* on the Agency's finding of safety and effectiveness for the listed drug.

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[12] *Right of reference or use* is defined in § 314.3(b) as "the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary."

After passage of Hatch-Waxman, FDA explained its interpretation of the new 505(b)(2) provision in a series of public statements, including an open letter to the drug industry in 1987 written by Dr. Paul D. Parkman (the 1987 Parkman letter) (enclosed with this response),[13] the 1989-1994 Hatch-Waxman rulemaking process, and a 1999 draft guidance. In addition, the Agency has responded to many inquiries from industry regarding whether specific drug products could be approved through the 505(b)(2) route.

1. The 1987 Parkman Letter

The first detailed statement by the Agency explaining the scope of section 505(b)(2) was in the April 10, 1987, letter to industry from Dr. Paul D. Parkman, then Acting Director of the Center for Drugs and Biologics. The 1987 Parkman letter addressed the statutory route by which an applicant "may make modifications in approved drugs when such modifications require submission of clinical data" (1987 Parkman letter at 1). In assessing the various regulatory options, the Agency rejected the idea of requiring a full NDA for such modifications, which would require duplication of the basic safety and effectiveness research. This course, the letter stated, would be inconsistent with the Hatch-Waxman Amendments in that it "would be a disincentive to innovation and require needless duplication of research." The Agency also rejected the option of requiring the submission and approval of an ANDA, followed by a supplement to that ANDA containing the data necessary to support the change. The Agency noted that to generate all of the stability and other data required for ANDA approval, the sponsor would have to take steps to manufacture a product that it had no intention to market. The Agency concluded that the better course was to permit submission of an application under section 505(b)(2) for a change to an already approved drug product *without* requiring that the applicant first obtain approval of an ANDA (the phantom ANDA). The 1987 Parkman letter stated that such changes could include changes in dosage form, strength, route of administration, and active ingredients (for which clinical studies are necessary) as well as new. As described in the 1987 Parkman letter, such applications would rely on the approval of the listed drug together with the clinical data to support the change. The 505(b)(2) applicant "will thus be relying on the approval of the listed drug only to the extent that such reliance would be allowed under section 505(j) to establish the safety and effectiveness of the underlying drug."[14] The letter further noted

[13] Much of the initial implementation of the Hatch-Waxman Amendments was explained to the public in a series of letters to industry, which were issued between 1984 and 1988 and were mailed to all known NDA and ANDA applicants and holders. These letters described the Agency's initial views, as it regulated directly from the statute before completion of the rulemaking process.

[14] When FDA approves a stand alone NDA submitted under section 505(b), the approval is based on the data and information submitted in the application. Later approvals under section 505(j) of duplicates or minor modifications to this listed drug will rely on the Agency's conclusions that a drug with those specific characteristics (e.g., active ingredient, strength, dosage form, conditions of use) was previously found to be safe and effective. Similarly, when reviewing a 505(b)(2) application that relies in part on the earlier approval of a listed drug, FDA may rely on its earlier conclusions regarding safety and effectiveness to whatever extent the conclusions are appropriate for the drug under review in the 505(b)(2) application. Although reliance on an FDA finding of safety and effectiveness for an NDA is certainly indirect reliance on the data submitted in the original NDA, reliance on the conclusions supported by that data is not the same as manipulating those data to reach new conclusions not evident from the existing approval. For example, if the NDA for the listed drug contained studies indicating that the drug may be effective for indications X and Y, but the listed drug is not approved for use Y, a 505(b)(2) applicant could not rely on those

that the patent certification and exclusivity bars applicable to ANDA approvals would also apply to 505(b)(2) applications.

2. The 1989 Proposed Rule

In 1989, FDA proposed regulations to implement the Hatch-Waxman Amendments, including section 505(b)(2). (*See* "Abbreviated New Drug Application Regulations; Proposed Rule," 54 FR 28872, July 10, 1989.) In proposed § 314.54, FDA laid out the requirements for submission of an application under section 505(b)(2) (54 FR 28919). In the preamble to the proposed regulations, FDA acknowledged that the legislative history referred to "paper NDAs." The paper NDA policy permitted an applicant to rely on evidence derived primarily from scientific literature to demonstrate the safety and effectiveness of duplicates. As noted above, before the enactment of Hatch-Waxman, FDA had used the paper NDA policy to approve literature-based duplicates of certain post-1962 pioneer drug products. FDA noted that despite the reference to paper NDAs in the legislative history, the text of section 505(b)(2) and 505(c)(3)(D) is considerably broader. It does not limit 505(b)(2) applications to applications for literature-supported duplicates of already approved products (54 FR 28890). FDA further explained in the preamble that 505(b)(2) applies to any application that relies on investigations the applicant has not conducted or to which it has not obtained a right of reference "regardless of the similarity or dissimilarity of the drug product to the previously approved drug product" (54 FR 28890). Such applications may be "for variations of approved drug products" or for new chemical entities.

FDA explained that 505(b)(2) applications should be used for never-before-approved changes in approved drug products and that it was "proposing to treat as a 505(b)(2) application *an application for a change in an already approved drug supported by a combination of literature or new clinical investigations and the Agency's finding that a previously approved drug is safe and effective*" (54 FR 28891) (emphasis added). FDA noted, however, that certain applications that were previously approvable under the paper NDA policy would no longer be approvable under section 505(b)(2). Specifically, FDA stated that it would not approve 505(b)(2) applications for literature-based duplicates because it would be inconsistent with Hatch-Waxman purposes to undertake duplicative review of safety and effectiveness data when the abbreviated approval route under section 505(j) is available (54 FR 28890 and 28891). FDA also discussed the patent certification and exclusivity bars for 505(b)(2) applications, emphasizing that they are the same as those that apply to ANDAs (54 FR 28892).

3. The 1992 Final Rule

The regulation proposed in 1989 is, in all relevant respects, the same as the current regulation at § 314.54, which was finalized in 1992.[15] There were two comments on the proposed provisions

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studies to get approval for indication Y; it could only rely on the fact that the Agency found the drug to be effective for use X.

[15] Section 314.54 *Procedure for submission of an application requiring investigations for approval of a new indication for, or other change from, a listed drug* provides:

regarding 505(b)(2) applications, neither of which addressed FDA's fundamental interpretation of section 505(b)(2). These comments were addressed in the preamble of the final rule that established the regulation at § 314.54 governing the types of applications that could be submitted under section 505(b)(2) (57 FR 17950 at 17954, April 28, 1992).

FDA's regulation at § 314.54 makes clear that FDA interprets section 505(b)(2) to permit approval of an application that relies on the finding of safety and effectiveness of a listed drug to the extent such reliance is scientifically justified. Specifically, it provides that "[a]ny person seeking approval of a drug product that represents a modification of a listed drug . . . and for which investigations other than bioavailability or bioequivalence studies are essential to approval of the changes may . . . submit a 505(b)(2) application. This application need contain only that information needed to support the modification of the listed drug" (§ 314.54(a)). It further requires applicants seeking approval under 505(b)(2) to "[identify] the listed drug for which FDA

(a) The act does not permit approval of an abbreviated new drug application for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change. Any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application. This application need contain only that information needed to support the modification(s) of the listed drug [including]

> (iii) Identification of the listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product by established name, if any, proprietary name, dosage form, strength, route of administration, name of listed drug's application holder, and listed drug's approved application number.
>
> (iv) If the applicant is seeking approval only for a new indication and not for the indications approved for the listed drug on which the applicant relies, a certification so stating.
>
> (v) Any patent information required under section 505(b)(1) of the act with respect to any patent which claims the drug for which approval is sought or a method of using such drug and to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.
>
> (vi) Any patent certification or statement required under section 505(b)(2) of the act with respect to any relevant patents that claim the listed drug or that claim any other drugs on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug.
>
> (vii) If the applicant believes the change for which it is seeking approval is entitled to a period of exclusivity, the information required under § 314.50 (j).

(b) An application may not be submitted under this section for a drug product whose only difference from the reference listed drug is that: (1) The extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug; or (2) The rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is unintentionally less than that of the reference listed drug.

has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product" (§ 314.54(a)(1)(iii)).

4. The 1994 Final Rule

In 1994, FDA issued regulations governing the patent certification and exclusivity aspects of 505(b)(2) applications ("Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule" (59 FR 50338, October 3, 1994)). Because 505(b)(2) applications are NDAs submitted under section 505(b) and approved under section 505(c), they are eligible for the same three-year new clinical study exclusivity and five-year new molecular exclusivity as are other NDAs (§ 314.108). The sponsors of 505(b)(2) applications also must submit the same required information regarding patents that claim the drug, or the use of the drug, described and approved in the 505(b)(2) application (§ 314.53). The regulations also addressed the fact that approval of a 505(b)(2) application is, as with ANDAs, subject to the listed patents, as well as the three- and five-year exclusivity protecting the listed drug. A 505(b)(2) application will not be approved until all applicable listed drug product exclusivity has expired, and the listed patents have expired, have been successfully challenged by an applicant, or any applicable 30-month stay has expired. (*See* §§ 314.50, 314.107, and 314.108.)

5. The 1999 Draft Guidance

In response to many requests from industry and based upon accumulated agency experience in applying section 505(b)(2), FDA drafted and published in October 1999 a draft guidance for industry entitled *Applications Covered by Section 505(b)(2)* (1999 draft guidance). The 1999 draft guidance describes existing practice as well as certain possible uses within the scope of section 505(b)(2) that had not yet been employed by industry. It notes that "[s]ection 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" (1999 draft guidance, p. 2). The 1999 draft guidance contains information for industry regarding the type of information an applicant could rely on for approval under section 505(b)(2) as well as the types of changes approvable under that section. The 1999 draft guidance states that an applicant seeking approval under section 505(b)(2) can rely on a combination of published literature, its own clinical studies, and/or the agency's finding of safety and effectiveness for a listed drug (1999 draft guidance, p. 3). The guidance also notes that a 505(b)(2) application can be submitted for different types of applications, including for a new chemical entity, or for a change to a previously approved drug such as a new dosage form, strength, route of administration, substitution of an active ingredient in a combination product, new formulation, new dosing regimen, new active ingredient, new combination product, a new indication, or for a naturally derived or recombinant active ingredient.

FDA received a number of comments on the 1999 draft guidance. Some of the comments stated that the approach described in the guidance would result in improper use of data in innovator NDAs. Other comments supported the guidance as describing an appropriate use of section 505(b)(2) to permit approval of innovative drug products without requiring unnecessary

duplication of research, including clinical research. The guidance has not been published in final form.

III. ANALYSIS

FDA's long-standing interpretation of section 505(b)(2) permits the Agency to approve drug applications that rely on studies not conducted by or for the applicant and which the applicant has not received permission to use from the sponsor, so long as the 505(b)(2) applicant complies with the applicable statutory requirements regarding patent protection and new drug exclusivity. The 505(b)(2) process permits an applicant seeking approval for a drug product that differs from the approved drug product to obtain approval without conducting new studies to demonstrate to the Agency what has already been demonstrated. This approach is based on the broad statutory language, its historical context, and its place within the Hatch-Waxman statutory scheme, as well as relevant policy and public health considerations.

The linchpin of FDA's interpretation of 505(b)(2) is that a 505(b)(2) applicant may rely on the FDA's finding of safety and effectiveness for a listed drug only to the same extent an ANDA applicant may rely on such a finding under section 505(j). (See 54 FR 28872 at 28892: "The [505(b)(2)] applicant will thus be relying on the approval of the listed drug only to the extent such reliance would be allowed under 505(j) of the act.") In the 505(j) approval process, the ANDA applicant seeking approval of either a duplicate to the listed drug, or a petitioned modification, relies solely on the previous finding of safety and effectiveness for the listed drug; the ANDA must be approvable without additional clinical or preclinical evidence of safety or effectiveness. In the 505(b)(2) process, the applicant also relies on the previous finding of safety and effectiveness for the listed drug. But such reliance will be appropriate only to the extent that the proposed product in the 505(b)(2) application shares characteristics (active ingredient, dosage form, strength, route of administration, indications, and conditions of use) in common with the listed drug. The safety and effectiveness of any differences between the listed drug and the drug proposed in the 505(b)(2) application must be supported by additional data, including clinical or animal data, as appropriate (§ 314.54).

Since the Agency began implementing section 505(b)(2) with the 1987 Parkman letter, FDA's approach to 505(b)(2) applications has been governed by consistent scientific principles. In enacting the Hatch-Waxman Amendments, Congress authorized FDA to rely on information about the safe and effective use of an approved drug product to approve another drug with similar characteristics, because duplicative clinical testing to reestablish what has already been shown is wasteful, unnecessary, and may raise ethical issues. In the 505(b)(2) context, the applicant can rely on established conclusions about the approved drug to the extent these conclusions are applicable to the proposed product. However, the applicant must supply data to support any differences between the two products.

Precisely what additional data will be necessary for approval of a drug will vary from case to case and is generally the subject of discussion between the sponsor and FDA during the drug development process. For example, a 505(b)(2) application for a new dosage form (such as a transdermal patch or a novel drug delivery mechanism) that cannot be approved as a petitioned

ANDA — because clinical studies are necessary to demonstrate safety and/or effectiveness — must contain whatever data are necessary to demonstrate that the new dosage form is safe and effective to treat the indications approved for the listed drug. Similarly, approval of a drug product for a new indication with the same strength and dosing regimen as a previously approved drug product will require evidence establishing that the drug is effective for the new indication. But new safety information may not be necessary because the underlying drug has already been shown to be safe at the approved dosing level. Thus, the nature and extent of the reliance on the agency's conclusion of safety and effectiveness for a listed drug are the same for applicants under section 505(b)(2) and 505(j); it is only the amount of *additional* data necessary to support the approval of the proposed drug product that may differ.

Reliance on FDA's conclusion that an approved drug is safe and effective does not involve disclosure to the ANDA or 505(b)(2) applicant — or to the public — of the data in the listed drug's NDA. Instead, it permits the ANDA or 505(b)(2) applicant to rely on the fact that FDA found a drug product with certain characteristics to be safe and effective and, in the case of a 505(b)(2) applicant, to target its studies to prove how changes from this previously approved drug product also meet the FDA's safety and effectiveness standards.

FDA's interpretation is supported by the text of section 505(b)(2), the structure of the Hatch-Waxman Amendments, and the purposes of that legislation. The interpretation is also supported by policy considerations. By permitting appropriate reliance on what is already known about a drug, thereby saving time and resources in the drug development and approval process, FDA's interpretation allows the pharmaceutical industry to target investment on innovative drug development. It avoids the ethical concerns associated with unnecessary duplicative testing that could deny effective treatment to sick patients taking placebos or ineffective dosages. And it allows improved products to reach the market that may not otherwise have been developed, such as modifications to products needed for a small patient population. Thus, FDA's current interpretation is in the interest of the public health.

A. Statute and Legislative History

1. The Language and Legislative History of Section 505(b)(2)

FDA's interpretation is based on and supported by the plain language of the statute. Section 505(b)(2) permits applicants to rely on studies which "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use." This provision does not limit the sources of the studies on which 505(b)(2) applicants may rely. The statutory language does not suggest Congress intended to codify the paper NDA policy in effect before the statute's passage or to limit 505(b)(2) approvals to literature-based duplicates or changes that could be approved under an ANDA followed by a supplement. Thus, on its face, the statute goes beyond the old paper NDA policy. Even if the statute were considered ambiguous, however, FDA has reasonably construed the broad language of section 505(b)(2).

The legislative history of the 505(b)(2) provision does not require a contrary interpretation. The House Report defines *paper NDA* as "any application submitted under section 505(b) of the

FDCA in which the investigations relied upon by the applicant to show safety and effectiveness were not conducted by or for the applicant and the applicant has not obtained a right of reference or use from the person who conducted the studies or for whom the studies were conducted" (House Report at 32). Notably, this definition makes no mention of either literature or duplicate products, the two hallmarks of the paper NDA under the paper NDA policy in effect when Hatch-Waxman was passed. (See "Publication of 'Paper NDA' Memorandum" (46 FR 27396).) Had Congress intended to use section 505(b)(2) to codify the paper NDA policy then in existence, it presumably would not have defined a 505(b)(2) application or paper NDA in a way that was considerably broader than its preexisting definition. Rather, given that the broad definition of paper NDA in the House Report mirrors the broad statutory language, it is reasonable to presume that Congress intended that section 505(b)(2) extend beyond the literature-based duplicates permissible under the paper NDA policy.[16] This seems especially likely given that when Hatch-Waxman was passed, it was widely recognized that few, if any, additional applications could be approved based on published literature alone, given the state of such literature (House Report at 16: "[Paper NDA policy] is inadequate, however, because FDA estimates that satisfactory reports are not available for 85% of all post-1962 drugs").

In assessing the role of section 505(b)(2) in the drug approval process, it is important to bear in mind that, in the Hatch-Waxman Amendments, Congress created a specific, detailed abbreviated route for approval of duplicates through section 505(j), which permits reliance on the previous finding of safety and effectiveness for a listed drug. Thus, codification of the inadequate and ineffective paper NDA process for literature-based duplicates would have been unnecessary and superfluous. In addition, section 505(b)(2) would have been unnecessary as an approval route for changes to drug products for which a petition can be filed seeking approval as a petitioned ANDA under section 505(j) because no additional safety or effectiveness data are necessary to the approval in that case. Thus, Congress created a new type of application, a 505(b)(2) application, to fill specific gaps left by the other approval pathways: a 505(b)(2) application can be used for approval of those changes that are not so significant that they require a stand alone NDA, but that are significant enough that they may require additional safety or effectiveness data (and, therefore, are not eligible for approval under section 505(j)).

As described in the 1987 Parkman letter, an applicant wishing to make a change to an approved drug could submit an ANDA for a duplicate of the listed drug (or a petitioned ANDA for a petitioned change to that drug). Once the ANDA applicant received approval of the ANDA, that ANDA holder could submit a supplemental application under 505(b) to make a change to the approved drug, and include in that supplement whatever information and studies are needed to approve the change.[17] Although there is no statutory barrier to permitting an ANDA holder to

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[16] Because Congress specifically defined *paper NDA* in the legislative history in a way that was broader than the definition that FDA had used previously, the presumption that Congress gave the term the same meaning as the Agency had previously does not apply.

[17] FDA has long interpreted the term *application* as used in section 505 to include new NDAs, amendments, and supplements (§§ 314.3(b), 314.50). Thus, for example, when the holder of an approved application seeks approval for a supplement to change that drug, it must submit a supplement that meets the relevant application requirements in § 314.50 (§ 314.71(b)).

request approval under section 505(b) for a supplement to that ANDA, as described in the 1987 Parkman letter, the Agency decided that it is not necessary to require that an applicant obtain approval of a phantom ANDA when the applicant seeks to make a change to a listed drug. In this situation, the section 505(b)(2) mechanism provides an appropriate regulatory pathway that also ensures adequate marketing protections for the listed drug.

The language of the statute does not limit 505(b)(2) approvals to those changes that could be proposed in a supplement to an approved ANDA under section 505(j). The changes (such as a new indication, new dosage form, new strength or new formulation) that may be submitted in a supplement rather than requiring a separate application (i.e., what products may be bundled) are a matter of FDA administrative policy and practice, not a function of statutory requirements.

Nor does the language of section 505(b)(2) necessarily prohibit approval of a 505(b)(2) application before an ANDA for the listed drug has been or could be approved. If a 505(b)(2) application could only be approved after an ANDA referencing the listed drug had been approved, or after all patent and exclusivity rights have expired (as some have contended), the independent patent certification obligations that apply under section 505(b)(2) (and the opportunity to challenge a listed patent and obtain approval upon a finding of noninfringement or upon expiration of the 30-month stay) would be superfluous. (See *Gustafson v. Alloyd Co.*, 115 S. Ct. 1061, 1069 (1995) (courts should avoid interpretations that render some words of statute redundant).) Similarly, if Congress had wanted to impose such a limitation on 505(b)(2) approvals, it likely would have placed the relevant provision in section 505(j) rather than in section 505(b) of the statute or would have otherwise signaled that only this limited subset of applications could be submitted and approved under section 505(b)(2).

2. Differences Between Section 505(b)(2) and 505(j)

The differences between section 505(b)(2) and 505(j) of the statute (and the references to one or the other type of application in other parts of the statute) further support FDA's interpretation. These differences include differences in disclosure and withdrawal provisions, among others, and reflect the fact that drugs approved under 505(b)(2) applications, unlike those approved under 505(j) applications, are not required to be duplicates of listed drugs. [18]

The disclosure provisions of section 505(l) are a case in point. Under section 505(l)(5), absent extraordinary circumstances, all safety and effectiveness data in an NDA shall be disclosed to the public upon request when an ANDA has been or could have been approved. There is no comparable provision requiring disclosure, absent extraordinary circumstances, when a 505(b)(2) application is approved. This difference reflects Congress's understanding that 505(b)(2) applications, in contrast to ANDAs, may rely on some aspects of a listed drug's approval (such as the toxicology profile) but not on others. Given the possibility that the product under a 505(b)(2) application could have significant differences from the listed drug referenced, approval of a 505(b)(2) application based, in part, on a previous approval of an NDA would not give rise to a

[18] In fact, FDA regulations state that section 505(b)(2) is not an appropriate approval pathway for an application for a duplicate eligible for approval under section 505(j). See §§ 314.54(b), 314.101(d)(9).

presumption that all of the NDA data cease to retain their value and should be available for public disclosure. In contrast, because an ANDA is for a duplicate of an approved drug, it is logical to presume that once a 505(j) application has been approved, the information in the original application ceases to retain much of its value and thus may be available for public disclosure. This difference explains why section 505(l)(5) uses ANDA approvals as a disclosure trigger, but has no comparable trigger based on 505(b)(2) approval.

Similarly, there are no analogues in section 505(b)(2) to the provisions in section 505(j) requiring that the product under the 505(j) application be bioequivalent to, have the same conditions of use as, and use the same labeling as the listed drug referenced. These differences do not suggest that 505(b)(2) applications cannot rely, in part, on FDA's conclusion that a listed drug is safe and effective. Rather, they support FDA's longstanding interpretation that the products under 505(b)(2) applications, unlike those under ANDAs, need not be duplicates of the listed drugs referenced. If 505(b)(2) applications were limited to literature-based duplicates, surely Congress would have required that, like those approved in ANDAs, products approved in 505(b)(2) applications be bioequivalent to, have the same conditions of use as, and the same labeling as the listed drugs referenced. No such sameness requirement was included, however, because section 505(b)(2) was never intended to be limited to literature-based duplicates.

Furthermore, differences in withdrawal provisions reflect the differences in the two types of applications. Because ANDAs are, by definition, for duplicates (or minor variations) of a reference listed drug, drug products approved in ANDAs are expected to have the same safety and effectiveness profile as the listed drugs they reference. Thus, it is not surprising that ANDAs must be withdrawn when the listed drug is withdrawn for safety or effectiveness reasons (section 505(j)(6)). In contrast, because the product under a 505(b)(2) application can differ significantly from the listed drug referenced, there is no comparable withdrawal requirement when the listed drug is withdrawn for safety or effectiveness reasons.

B. Drug Approvals Under Section 505(b)(2)

Since 1984, 505(b)(2) applications have been used by a wide range of sponsors in the pharmaceutical industry (including petitioner Pfizer and members of petitioner BIO) to obtain approval of more than 80 drug products. Over 30 additional 505(b)(2) applications are currently under review by the Agency. Most of these applications have not been solely literature-based 505(b)(2) applications.

The 505(b)(2) approval pathway has been particularly important in certain areas of drug development where a limited or uncertain market warrants maximum leveraging of current knowledge about a drug. The Agency has approved 505(b)(2) applications for drugs for treatment of exposure to radiation and chemical warfare, drugs targeted to pediatric populations, novel dosage forms, and new formulations for antibiotics and cancer drugs, among others. In many of these areas, drug development resources are scarce. Creating an abbreviated pathway that allows sponsors to focus these limited resources to develop data on the innovation has led to the creation of new therapeutic options that otherwise might not have been available. For example, certain patient groups, such as children, may have trouble swallowing capsules or

tablets. But the size of that patient population may not support the expense of a stand alone NDA to seek approval for a pediatric-friendly dosage form. Section 505(b)(2) provides a more efficient and cost-effective pathway to bring such innovations to market.

The following noncomprehensive list provides some examples of 505(b)(2) applications that the Agency has approved:

1. *Treatments for Exposure to Radiological or Chemical Terrorism or Warfare*

- The U.S. Army's 505(b)(2) application for pyridostigmine bromide was approved in 2003 as a pretreatment to increase survival after exposure to the nerve agent Soman. This application relied on animal efficacy data to support the effectiveness of pyridostigmine bromide to treat exposure to nerve gas; it relied for safety on the fact that pyridostigmine bromide had been approved and used for many years as Mestinon at a higher dose to treat myesthenia gravis.

- The U.S. Army's 505(b)(2) application for atropine/pralidoxime autoinjectors was approved in 2002 for treatment of poisoning by nerve agents and relied on the previous approvals of atropine and pralidoxime products. Before approval of this 505(b)(2) application, there had been two approved NDAs for the separate autoinjectors, and military personnel were required to carry separate injectors for atropine and pralidoxime. This 505(b)(2) application approved one autoinjector that administers both drugs in a single injection.

- The U.S. Army's 505(b)(2) application for a diazepam autoinjector was approved as an anticonvulsant in December 1990. When the Army entered into discussions with the Agency about approval of an autoinjectable anticonvulsant, the Agency concluded that, because of necessary variations from innovator labeling, such an application would not be appropriate for an ANDA through the suitability petition process. Section 505(b)(2) provided for a prompt approval to meet an immediate need.

- Heyl's 505(b)(2) application for Radiogardase (prussian blue) was approved in 2003 for use in patients with known or suspected exposure to thallium or radioactive cesium, an orphan indication. Prussian blue was approved as new chemical entity (a drug in which no active moiety has been previously approved).

2. *Pediatrics*

- Mallinckrodt's 505(b)(2) applications for chewable tablet and oral solution forms of methylphenidate were approved in 2002 and 2003, respectively, to treat attention deficit disorder.

- Ascent's 505(b)(2) application for trimethoprim hydrochloride in oral solution was approved in 1995 for treatment of urinary tract infections.

- Wyeth Consumer Healthcare's 505(b)(2) application for Children's Advil Cold Suspension (ibuprofen and pseudoephedrine) was approved in 2002 for the temporary relief of cold, sinus, and flu symptoms.

3. New Drugs, Alternative Dosage Forms and New Formulations for Antibiotics and Cancer Drugs

- Bryan Corporation's 505(b)(2) application for Sclerosol (sterile talc powder) was approved in 1997 to treat malignant pleural effusion. Sclerosol was approved as a new chemical entity (a drug in which no active moiety has been previously approved).

- Elan's 505(b)(2) application for Duraclin (clonidine HCl) was approved in 1996 for epidural administration to treat cancer pain.

The 505(b)(2) approach also has been used to approve less toxic formulations of cancer drugs, for example, a chemotherapy agent that is made without a toxic excipient. Use of the 505(b)(2) pathway has allowed some sponsors to avoid using scarce cancer research resources to conduct unnecessary trials to re-demonstrate efficacy for such a product.

4. Other Examples of Section 505(b)(2) Applications

- Pfizer's 505(b)(2) application for Zyrtec D (certirizine and pseudoephedrine) was approved in 2001 as a new combination for the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis.

- Pfizer's 505(b)(2) application for Rid Mousse (piperonyl butoxide and pyrethins) was approved in 2000 for the treatment of head, pubic, and body lice.

- Andrx's 505(b)(2) application for Altocor (lovastatin) was approved in 2002 as an extended release formulation for lowering cholesterol levels.

- Galderma's 505(b)(2) application for clindamycin phosphate was approved in November 2000 as a once daily gel (others are twice daily) for the treatment of acne.

- Orion Pharma's 505(b)(2) application for Stalevo (carbidopa, levodopa, and entacapone) was approved in 2003 as a new combination product for treatment of Parkinson's disease.

- Novartis Consumer's 505(b)(2) application for Tavist, a new combination of acetaminophen, clemastine, and pseudoephedrine, was approved in 2001 for the temporary relief of symptoms associated with hay fever, allergic rhinitis, and the common cold.

- Dey Labs' 505(b)(2) application for Duoneb (albuterol sulfate and ipratropium) was approved in 2001 for the treatment of bronchospasms associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator.

- Duramed's Cenestin (synthetic conjugated estrogens) was approved in 1999 for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and the treatment of vulvar and vaginal atrophy.

- Celegene's Thalomid (thalidomide) was approved 1998 to treat erythema nodosum leprosum (leprosy) (an orphan indication).

- OPR's Cafcit (caffeine citrate) was approved in 1999 for treatment of apnea of prematurity (an orphan indication).

The pharmaceutical industry continues to rely on the 505(b)(2) pathway for drug development and innovation. FDA has identified more than 30 pending 505(b)(2) applications, and the Agency is currently in discussions with many additional sponsors about their development and research plans for 505(b)(2) applications.

IV. FDA'S RESPONSE TO ARGUMENTS IN THE PFIZER, BIO, AND TORPHARM CITIZEN PETITIONS

A. The Language of Section 505(b)(2)

Petitioners argue that FDA's interpretation of section 505(b)(2) is inconsistent with the statutory language. They argue that section 505(b)(2) simply permits a sponsor to rely on studies in the published literature to support approval, or that such approval is limited to duplicate products. They assert that section 505(b)(2) does not permit a sponsor to rely on FDA findings that an approved drug is safe and effective when those findings are based on the listed drug's nonpublic studies (2001 Pfizer petition at 3, TorPharm petition at 8).

FDA Response: As explained above, the plain language of 505(b)(2) does not support petitioners' narrow construction. Section 505(b)(2) permits applicants to rely on studies which "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use." The statute does not limit the sources of the studies on which 505(b)(2) applicants may rely to published literature or other publicly available studies — even though Congress could easily have added such a limitation. Indeed, petitioner Pfizer appears to concede in its April 28, 2003, submission that the broad language of section 505(b)(2) permits more than approval of literature-based duplicates. Specifically, Pfizer acknowledges that the principle expressed in the 1987 Parkman letter is a permissible interpretation of the statute (April 2003 comment at 2).[19]

[19] In the 1987 Parkman letter, the Agency explained that section 505(b)(2) allowed submission of an application for a change in an already approved drug product, without requiring that the applicant first obtain approval of an ANDA and then supplement that approval with a 505(b) supplement for the change. However, Pfizer construes the 1987

B. The Legislative History of Section 505(b)(2)

Petitioners cite to legislative history in which a 505(b)(2) application is referred to as a *paper NDA* to support their argument that the statute codified — rather than expanded on or replaced — the paper NDA policy in effect before the passage of the Hatch-Waxman Amendments. Petitioners TorPharm and BIO assert that section 505(b)(2), like the paper NDA policy, is intended to permit approval of NDAs for duplicates of approved drugs that are fully supported by published literature. In petitioners' views, no reliance on previous approvals or previous findings of safety and effectiveness is contemplated under section 505(b)(2) (TorPharm petition at 9-10; BIO petition at 17). Petitioner BIO notes that court decisions examining FDA's paper NDA policy before the passage of section 505(b)(2) found that FDA could not approve an application in which one manufacturer relied on another's proprietary information. BIO contends that it is "improbable that Congress would have changed the law in this field without an explicit statement in the statute, or, at the very least, the legislative history" (BIO petition at 17).

FDA Response: As explained above, petitioners selectively excerpt from the legislative history. Although the House Report uses the phrase *paper NDA* to describe a 505(b)(2) application, the House Report defines paper NDA far more expansively than the then-existing paper NDA policy. Specifically, the House Report defined paper NDA as "any application submitted under section 505(b) of the FDCA in which the investigations relied upon by the applicant to show safety and effectiveness were not conducted by or for the applicant and the applicant has not obtained a right of reference or use from the person who conducted the studies or for whom the studies were conducted" (House Report at 32). This definition does not mention either literature or duplicates, just as the language of section 505(b)(2) does not mention either limitation. Thus, contrary to BIO's contention, the statute and the legislative history indicate a change from existing policy by describing a 505(b)(2) application and defining a paper NDA, respectively, more broadly than the preexisting definition of a paper NDA.

C. Limitations on Section 505(b)(2) from Statute as a Whole

Petitioner Pfizer argues that, reading the statute as a whole, there are two important limitations on the subset of approvals that constitute permissible changes to listed drugs under section 505(b)(2). First, according to Pfizer, the opportunity to use section 505(b)(2) to seek approval for a change to a listed drug is only available at or after the time an ANDA for that listed drug has been or could be approved. In Pfizer's view, the Agency may not approve any 505(b)(2) application that relies on the finding of safety and effectiveness for an approved drug before a 505(j) application referencing that drug has been or could be approved (April 2003 comment at 13). Second, Pfizer suggests that, regardless of the timing of approval, a 505(b)(2) application cannot be used for a change to a listed drug that could not be made through submission of an

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Parkman letter narrowly to sanction use of the 505(b)(2) pathway to approve only limited types of changes and then argues that only this limited use is a permissible statutory interpretation. Thus, in Pfizer's view, changes that would require submission of a separate application under FDA's current bundling policy are not within section 505(b)(2)'s scope and FDA exceeds the authority granted under the statute when it uses section 505(b)(2) as a pathway for approval of such changes.

ANDA followed by a supplement to that ANDA (April 2003 comment at 13). In this view, the Agency may only rely on the finding of safety or effectiveness for a given drug if the change proposed is one that could be made in a supplement to an ANDA rather than requiring an entirely separate application. In the limited circumstances where an applicant can obtain approval of an ANDA and file a supplement for a change to that ANDA, the applicant may collapse the process and file a single application under section 505(b)(2) (April 2003 comment at 3).

FDA Response: There is no temporal language in the statute limiting 505(b)(2) approvals to those occurring after an ANDA has been approved; nor is there any sequential language in the statute that limits changes to those that could be approved under section 505(j) followed by a supplement. As explained above, if a 505(b)(2) application could only be approved after an ANDA referencing the listed drug had been approved, or after all patent and exclusivity rights have expired, the independent patent certification obligations that attach under section 505(b)(2) (and the related opportunity to challenge a listed patent with a paragraph IV certification and obtain approval upon a finding of noninfringement or invalidity, or upon expiration of the 30-month stay) would be superfluous. Similarly, if Congress had wanted to impose either proposed limitation on 505(b)(2) approvals, it likely would have placed the relevant provision in section 505(j), rather than in section 505(b) of the statute, or would have otherwise signaled that only this limited subset of applications could be submitted and approved under section 505(b)(2). Instead, as discussed above, the plain language of section 505(b)(2) is broad, strongly suggesting that Congress intended to create two different pathways for approval, rather than to have section 505(b)(2) function simply as an offshoot of section 505(j).

D. Differences Between Section 505(b)(2) and 505(j)

In support of their statutory interpretation arguments that section 505(b)(2) only contemplates reliance on the finding of safety and effectiveness for an approved drug, if at all, in limited circumstances, petitioners cite differences between provisions in section 505(j) and 505(b)(2) and in references to the two sections in other provisions of the statute. Both Pfizer and TorPharm emphasize the differences between section 505(b)(2) and 505(j) to argue that FDA's interpretation of section 505(b)(2) to allow reliance on the finding of safety or effectiveness of a listed drug is unreasonable. TorPharm argues that the language in section 505(j)(2)(A)(i) that requires an ANDA to contain "information to show the conditions of use prescribed, recommended, or suggested in the labeling have been previously approved for a listed drug" permits FDA to rely on a previous finding of safety and effectiveness to approve a 505(j) application. Because section 505(b)(2) contains no comparable provision, TorPharm argues that no such reliance is permitted in the 505(b)(2) context (TorPharm petition at 13). Similarly, Pfizer notes that section 505(j)(6) requires approval of an ANDA to be withdrawn if the listed drug is withdrawn for safety or effectiveness reasons. Pfizer argues that section 505(b)(2) does not contain an analogous withdrawal provision because Congress never intended for 505(b)(2) applicants to rely in whole or part on the finding of safety or effectiveness of a listed drug. Accordingly, a 505(b)(2) application would not be expected to face withdrawal when a listed drug is withdrawn (2001 Pfizer petition at 8).

FDA Response: As discussed above, the differences in section 505(b)(2) and 505(j) (or in references to one or the other type of application in other parts of the statute) do not indicate that Congress precluded sponsors from relying on the finding of safety or effectiveness of an approved drug in support of a 505(b)(2) approval. These differences merely reflect that 505(b)(2) applications, unlike 505(j) applications, are not required to be duplicates of listed drugs. For example, in response to TorPharm's argument that there is no 505(b)(2) analogue to the provision in section 505(j) requiring that the applicant seek approval for the *same conditions of use* as the listed drug, the difference reflects that 505(b)(2) applications, unlike ANDAs, may seek approval for different conditions of use than the listed drugs they reference. Thus, the 505(b)(2) application may not need information on the same conditions of use; however, FDA may require that other appropriate information be submitted. The differences noted by petitioners do not establish that 505(b)(2) applications may not rely on the finding of safety or effectiveness for a listed drug.

Similarly, the differences in withdrawal provisions noted by Pfizer reflect the differences in the two types of applications. Because ANDAs are, by definition, for duplicates or minor variations of a reference listed drug and are, by definition, approved without submission of clinical or preclinical studies to establish safety or effectiveness, they are statutorily presumed to have the same safety and effectiveness profile as the listed drug they reference. Thus, it is not surprising that an ANDA must be withdrawn when the listed drug it references is withdrawn for safety or effectiveness reasons (section 505(j)(6)). In contrast, because the drug described in a 505(b)(2) application can differ significantly from the listed drug it references, withdrawal of the latter for safety or effectiveness reasons does not necessarily require automatic withdrawal of the former. Under these circumstances, it is appropriate to approach withdrawal of a 505(b)(2) application on a case-by-case basis, even in the face of the withdrawal of the listed drug it references.

E. Section 505(l)

Pfizer contends that the disclosure provision at section 505(l)(5) establishes that ANDA approval (or the expiration of all patents on the listed drug) is a prerequisite to approval of a 505(b)(2) application. Pfizer notes that section 505(l)(5) provides that, absent extraordinary circumstances, safety and effectiveness data in an NDA are available for public disclosure at the time an ANDA has been, or could be approved. Based on this provision, Pfizer contends that it is only after an ANDA has been, or could be, approved that the data in NDA are available for any purpose, including support for a 505(b)(2) approval. Pfizer thus argues that, to give meaning to section 505(l)(5), if no ANDA for a listed drug has been approved (because, for example, the sponsor of the listed drug has a patent on some aspect of the drug that has not been challenged by an ANDA applicant), then no 505(b)(2) application is eligible for approval (2001 Pfizer petition at 9).

Pfizer argues that this interpretation of section 505(l)(5) is consistent with the approval scheme under section 505(j) because section 505(j) "authorizes reliance on data in an innovator company's NDA once other patent and exclusivity rights have expired" to support approval of an ANDA. Pfizer argues that it logically follows that an approval under section 505(j) triggers release of those data under section 505(l). Pfizer opines that there is no comparable disclosure provision that triggers broader disclosure of data in the NDA of a listed drug when a 505(b)(2)

application is approved because section 505(b)(2), itself, does not authorize reliance on the proprietary data in another company's NDA to support a 505(b)(2) approval. Pfizer contends that FDA's interpretation of section 505(b)(2) — permitting reliance on the finding of safety and effectiveness for an approved NDA before the raw data in the NDA are fully disclosable under section 505(l) — renders section 505(l) meaningless, upsets the settled expectations of NDA holders, and is inconsistent with Congress's intent (2001 Pfizer petition at 9).

FDA Response: As noted, section 505(l)(5) is silent as to the effect of 505(b)(2) approval on disclosure of innovator data because applications approved under section 505(b)(2), in contrast to those approved under section 505(j), need not be duplicates. Given that a drug approved under section 505(b)(2) can differ significantly from the listed drug it references, an approval of a 505(b)(2) application does not — and logically cannot — give rise to the presumption that the data in the listed drug's NDA cease to retain commercial value.

Moreover, Pfizer's contention is not supported either by the language of section 505(l) or by its place in the statutory scheme. Section 505(l) provides in relevant part:

> Safety and effectiveness data and information which has been submitted in an application under [section 505](b) for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown . . . (5) upon the effective date of the approval of the first application under [section 505](j) which refers to such drug or upon the date upon which the approval of an application under [section 505](j) which refers to such drug could be made effective if such an application had been submitted.

This provision is exactly what it appears to be — a public disclosure provision stating the outer limits after which public disclosure of safety and effectiveness data must occur absent extraordinary circumstances. It does not provide that FDA may not rely on the finding of safety and effectiveness for an approved drug before this outer limit — in this case 505(j) approval — is reached. Moreover, section 505(l) deals with public disclosure of raw safety and effectiveness data in an application, not with its use by the Agency to support approval of another application. The Agency need not disclose proprietary data for an applicant or FDA to rely on the fact that a particular drug with particular characteristics has been found safe and effective. In fact, FDA routinely approves ANDAs by relying on the safety and effectiveness of a listed drug without triggering full disclosure of raw data under section 505(l)(5).

Pfizer's premise that its reading of section 505(l) makes sense because ANDAs cannot be approved until all patents and exclusivities have expired is also faulty. Approval is possible under section 505(j) even when patent rights are still in force. If, for example, an ANDA applicant were to file a patent challenge, be sued within 45 days, and the patent litigation were ongoing, approval would be possible during the pendency of the litigation if the 30-month stay were to expire. Similarly, an ANDA is eligible for approval during the pendency of patent litigation over a listed patent if that litigation was not commenced within the 45-day period that the statute provides. Furthermore, a patent on a dosage form that prevents approval of a

duplicate under section 505(j) will not bar approval of a petitioned ANDA for a different, noninfringing dosage form.

In each of these cases, approval under section 505(b)(2) is not correlated with expiration of the innovator's patent rights. Thus, Hatch-Waxman contemplates that some applications referencing a listed drug could be approved while a patent on the listed drug is in force. Like 505(j) applicants, 505(b)(2) applicants are subject to patent certification requirements and patent and exclusivity bars to approval. These are the requirements that protect the listed drug's intellectual property rights, and bar approvals of competitor products, until certain conditions are met.

Section 505(l) cannot bear the weight that Pfizer ascribes to it. Under Pfizer's interpretation, approval of a 505(b)(2) application would be blocked before ANDA approval (or expiration of all patent and exclusivity rights) even if the 505(b)(2) applicant were to describe a drug product that differs significantly from the listed drug, and the 505(b)(2) applicant were to certify to the listed patents as required by the statute and succeed in avoiding a lawsuit or in proving noninfringement. To interpret section 505(l) as placing this additional implicit barrier to 505(b)(2) approval, even after all of the patent and exclusivity bars to 505(b)(2) approval that are explicit in the statute have expired, would unduly stretch the language and structure of the Hatch-Waxman Amendments. Section 505(l) is exactly what it appears to be on its face — a statutory provision governing disclosure of raw safety and effectiveness data in an NDA. It does not create an additional barrier to 505(b)(2) approval.

F. Pfizer's Suitability Petition Argument

Petitioners TorPharm and Pfizer each raise distinct and incompatible challenges to FDA's interpretation of section 505(b)(2) based on the relationship of section 505(b)(2) to the suitability petition process described in section 505(j)(2)(c). Pfizer argues that it would be illogical to use section 505(b)(2) as a pathway to approve changes that could not be approved under a suitability petition because the changes raise potential safety or effectiveness issues that require further exploration. Pfizer asserts that the suitability petition process is a public process because Congress recognized the importance of changes that can be approved under a petition and wanted to give the public the opportunity to weigh in before FDA could conclude that those changes are permitted without requiring a full stand alone NDA. Pfizer notes that certain changes, such as a change to a new salt of the approved active ingredient, is not a petitionable change because the particular salt used can have relatively significant effects on the safety or effectiveness of a new product. Pfizer contends it would render the suitability petition process meaningless if FDA were to require a public process for relatively minor changes approvable through a petition, while allowing more significant changes, such as a change to a new salt, to be made through the 505(b)(2) route without the benefit of any formal or public process (2002 Pfizer petition at 6-7).

FDA Response: FDA's interpretation of section 505(b)(2) does not undermine and render meaningless the suitability petition process. The suitability petition process described in section 505(j)(2)(C) specifically determines whether a particular change to a listed drug is suitable for approval under section 505(j) *without submission* of any additional studies outside of section

505(j)'s scope. If FDA approves a suitability petition, it has concluded that the proposed ANDA can be submitted and approved under section 505(j) without further review of clinical or preclinical studies (other than bioavailability studies). However, because a 505(b)(2) application is a type of NDA, under section 505(b)(1), FDA has the authority to request any and all clinical and nonclinical studies it deems necessary to support approval. Given that the 505(b)(2) pathway gives FDA the flexibility to specify the types and numbers of clinical and preclinical studies necessary to support approval, no public process to determine suitability for approval without additional studies is required. Similarly, no public process is required to determine suitability for approval of a stand alone NDA submitted under section 505(b)(1) because FDA has the opportunity to specify what studies are required for approval and to refuse to approve if those studies do not adequately demonstrate safety and effectiveness.

FDA's interpretation of section 505(b)(2) complements, rather than supplants, the suitability petition process. For example, if a suitability petition for a new dosage form of a previously approved product were denied because FDA believes bioequivalence alone is insufficient to support safety and effectiveness, section 505(b)(2) provides a route for FDA to determine what additional studies may be required for approval.

G. TorPharm's Suitability Petition Argument

TorPharm argues that FDA's interpretation of section 505(b)(2) renders the suitability petition process meaningless for entirely different reasons. TorPharm suggests that because a change to a new salt is a change in active ingredient, the suitability petition process established in section 505(j)(2)(C) provides the proper abbreviated pathway for approval of a new salt. According to TorPharm, interpreting section 505(b)(2) to permit approval of a new salt (or other change to an active ingredient in a single ingredient product) renders the petition process superfluous (TorPharm petition at 12).

FDA Response: Although TorPharm suggests that a change to a new salt should be reviewed, if at all, in an ANDA submitted through the petition process, FDA does not interpret the statute to permit an applicant to change the active ingredient in a single active ingredient product by this route. Section 505(j)(2)(C) describes in general terms the submission of a petition to change an active ingredient. However, section 505(j)(2)(A)(ii)(I) states that if the listed drug referenced in an ANDA has only one active ingredient, the ANDA must contain information "to show that the active ingredient of the new drug is the same as that of the listed drug." It is only in the provision related to submission of ANDAs referencing a listed drug with "more than one active ingredient" that the ability to use the petitions process in section 505(j)(2)(C) for a change in an active ingredient is referenced (section 505(j)(2)(A)(ii)(III)). The preamble to FDA's proposed rule implementing the Hatch-Waxman Amendments contains a lengthy discussion of FDA's interpretation of these provisions. (*See* 54 FR 28872 at 28878 and 28879, 28881, July 10, 1989.) FDA's regulations implement the statute by permitting the use of a suitability petition for a change in active ingredient only where "one active ingredient is substituted for one of the active ingredients in a listed combination drug" (§ 314.93(b). Thus, a change to a new salt is not a petitionable change unless it is substituted in a combination product where the remaining ingredients remain the same. Because section 505(b)(2) is the only abbreviated route available

for approval of such a change in a single ingredient product, it is essential rather than superfluous.

H. Exclusivity

TorPharm contends that use of the 505(b)(2) process to approve a drug product whose only change from the listed drug is the substitution of a different salt of the approved active ingredient undercuts the right to 180-day exclusivity under section 505(j)(5)(B)(iv) awarded to the first ANDA applicant to challenge a listed patent, because 180-day exclusivity does not block approval of 505(b)(2) applications. TorPharm argues that Congress did not intend that the 505(b)(2) approval process could be used to obtain approval of a bioequivalent drug product when the 180-day exclusivity would block approval of a 505(j) application for a duplicate (TorPharm petition at 3).

FDA Response: FDA's interpretation of section 505(b)(2) does not undercut the 180-day exclusivity incentive. The 180-day exclusivity awarded to the first generic applicant to challenge a patent on a listed drug is not a monopoly that prevents FDA from approving any similar or potentially competing drug product. The provision has been consistently interpreted to prevent approval only of another application submitted under section 505(j) for a pharmaceutical equivalent that relies on the finding of safety and effectiveness for the listed drug and includes a paragraph IV certification to the listed patent. Put another way, 180-day exclusivity blocks approval of later-submitted ANDAs for duplicate drug products. An ANDA's 180-day exclusivity would not block approval of a stand alone NDA for a duplicate of the listed drug. Nor would it block approval of a pharmaceutical alternative (such as a different dosage form) approved under a petitioned ANDA, even though these products might be marketplace competitors to the ANDA with exclusivity. Thus, like these types of applications, a 505(b)(2) application for a bioequivalent and potentially competing drug product can be approved without undermining the 180-day exclusivity incentive in ways that Congress did not intend.

In fact, the limitation of 505(b)(2) approvals to literature-based duplicates that petitioners BIO and TorPharm advocate would undercut 180-day exclusivity significantly more than the interpretation FDA has adopted. To ensure that section 505(b)(2) is not used to circumvent 180-day exclusivity, FDA regulations provide in two separate places that section 505(b)(2) may not be used for duplicates. (See §§ 314.54(b) and 314.101(d)(9).) If section 505(b)(2) were available for approval of duplicates, including literature-based duplicates, applicants could circumvent 180-day exclusivity by filing for the approval of a duplicate under section 505(b)(2); such an application, even if a true duplicate, would not be blocked from approval under the 180-day exclusivity provisions in section 505(j)(5)(b)(iv).

I. Section 314.54 and the 1999 Draft Guidance

Petitioner BIO argues that the 1999 draft guidance improperly created new law. BIO argues on Administrative Procedure Act grounds that FDA can only adopt a broad interpretation of section 505(b)(2) (such as that spelled out in the 1999 draft guidance), if at all, through notice-and-comment rulemaking. BIO argues that FDA regulations at § 314.54 do not adequately advise

industry that FDA would interpret section 505(b)(2) to permit 505(b)(2) applicants to rely on the finding of safety and effectiveness for an approved application. Specifically, BIO suggests that the broad language of § 314.54, coupled with the 1989 preamble statement that section 505(b)(2) permits FDA to approve an 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," did not adequately signal to industry that FDA intended to interpret section 505(b)(2) to extend beyond the paper NDA policy as well as the narrow principle that 505(b)(2) applications can be used to approve modifications to a listed drug that could otherwise be made through submission of an ANDA followed by a supplement. Given this alleged ambiguity in the regulations, BIO argues that the 1999 draft guidance created new law when it made explicit the uses to which section 505(b)(2) had been and could be put. BIO further argues that because it made new law, the 1999 draft guidance should have been promulgated as a regulation and subjected to notice and comment before implementation. In support of its arguments that the regulations at § 314.54 did not inform industry of FDA's broad interpretation of section 505(b)(2), BIO notes that FDA received only two comments after publication of the proposed regulations, neither of which addressed issues as to the provision's scope (BIO petition at 26-39).

FDA Response: As discussed above, the 1999 draft guidance is not the first time FDA announced its intention to interpret section 505(b)(2) broadly to extend beyond the paper NDA policy. FDA announced its interpretation of section 505(b)(2) in the 1987 Parkman letter and the 1989 proposed and 1992 final regulations. Although BIO argues that the scope of § 314.54 is unclear and that industry did not understand that section 505(b)(2) would be used in ways that extend beyond literature-based duplicates, industry's extensive use of this provision over time (including use by members of BIO and by Pfizer) belies BIO's assertion. Moreover, the implementing regulations at § 314.54 and their preamble make clear that FDA has long interpreted section 505(b)(2) to permit approval of NDAs that rely on the finding of safety or effectiveness of an approved drug to the extent such reliance is scientifically justified. As discussed above, the regulations provide that, where an application seeks approval under section 505(b)(2) of a "drug product that represents a modification of a listed drug," . . . the "application need contain only that information needed to support the modification(s) of the listed drug" (§ 314.54). Indeed, FDA's preamble to the 1989 proposed rule explicitly revokes the paper NDA policy and states that "section 505(b)(2) has broader applicability [than the paper NDA policy]" (54 FR 28872 at 28875, July 10, 1989). FDA explained in the 1989 preamble that FDA intended to use section 505(b)(2) to approve modifications to listed drugs if they were adequately supported by appropriate data. FDA further stated in the preamble that applications for literature-based duplicates (which would previously have been approved under paper NDAs) should be approved under section 505(j), not section 505(b)(2) (54 FR 28890). Thus, FDA has never relied on the 1999 draft guidance as law; the guidance merely seeks to make explicit and transparent the ways in which FDA has interpreted the law set out in the statute and regulation. The public had the opportunity to comment on the proposed regulations when they were issued and declined to do so; BIO cannot reasonably argue that additional public process is required before this regulation is implemented.

J. Section 314.54(a)(1)(i)

TorPharm cites FDA's regulation at § 314.54(a)(1)(i) in support of its argument that section 505(b)(2) does not automatically authorize an applicant to rely on proprietary data from another applicant's NDA. TorPharm notes that § 314.54(a)(1)(i) states that 505(b)(2) applications must comply with § 314.50(g). Because § 314.50(g) states that a reference to information submitted by a person other than the applicant must contain a written and signed statement of authorization by the submitter, TorPharm argues that an applicant submitting an application under section 505(b)(2) cannot reference a listed drug's application (or the finding of safety and effectiveness for a listed drug) without permission of the NDA holder (TorPharm petition at 9).

FDA Response: TorPharm's reliance on the language in § 314.54 referencing § 314.50(g) is misplaced. Under § 314.50(g), "[a] reference to information submitted to the agency by a person other than the applicant is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information." This provision was not intended to refer to situations where a sponsor identified a listed drug and sought to rely on FDA's finding of safety or effectiveness of the listed drug. If the applicant were required to and succeeded in obtaining a right of reference to the application on which it relied to support approval, the application would be a stand alone NDA, not a 505(b)(2) application. Thus, TorPharm's reading of this provision would write section 505(b)(2) out of existence. Instead, the regulation is intended to address the circumstance where certain information about the proposed drug that is needed for FDA to review and approve the specific 505(b)(2) application (e.g., information about the chemistry of the bulk drug substance that the applicant plans to use in manufacturing its drug product) is contained in a place separate from the application (e.g., in a drug master file owned by the supplier of the bulk drug substance). In this case, for FDA to consider this information in approving the application, a right of reference to that external source is required. In other circumstances, when one applicant has received permission from the sponsor of another application for FDA to rely on information (including the raw data) in the applicant's NDA, the regulation describes that such a right of reference must be in writing and signed. (See footnote 12.) As noted above, if such a right of reference is given, the application is a stand alone NDA and none of the patent certification requirements or exclusivity bars will apply.

K. Takings

Petitioners Pfizer and BIO suggest that the statutory language, legislative history, and implementing regulations gave them a reasonable investment-backed expectation that data in an approved NDA would not be used to support approval of a 505(b)(2) application for a change that could not be made through an ANDA and supplemented (and would not be used for any purpose before an ANDA had been or could be approved). Petitioners contend that nothing in the 1987 Parkman letter or in the regulations implementing section 505(b)(2) signaled that FDA would permit 505(b)(2) applicants to rely on a pioneer's NDA data before an ANDA approval or to approve modifications that could not be approved in an ANDA followed by a supplement. Petitioners claim that FDA's suggestion in the 1999 draft guidance that section 505(b)(2) is an appropriate approval route for a new salt or for a follow-on to a biological product submitted

under section 505(b)(1) was a radical departure from past practice and was directly contrary to the industry's understanding of section 505(b)(2) and congressional intent when enacting that provision. Accordingly, petitioners contend that the policy announced in FDA's 1999 draft guidance (and FDA's approval of a new salt of paroxetine under section 505(b)(2)) amounts to an unconstitutional taking of petitioners' property without adequate compensation (BIO petition at 37; 2001 Pfizer petition at 17).

FDA Response: The Supreme Court has established three significant factors as a guide to determining whether a taking has occurred: (1) the character of the Government action; (2) the extent to which it has interfered with reasonable investment-backed expectations; and (3) its economic impact (*Concrete Pipe and Prods. of Calif., Inc. v. Constr. Laborers Pension Trust*, 508 U.S. 602, 643-46 (1993)). With regard to the second factor, to be reasonable, expectations must take into account the power of the state to regulate in the public interest (*Pace Resources, Inc. v. Shrewsbury Township*, 808 F.2d 1023, 1033 (3d Cir.), *cert. denied*, 482 U.S. 906 (1987)). Reasonable expectations must also take into account the regulatory environment, including the foreseeability of changes in the regulatory scheme. "In an industry that long has been the focus of great public concern and significant government regulation" (*Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1008 (1984)), the possibility is substantial that there will be modifications of the regulatory requirements. "Those who do business in the regulated field cannot object if the legislative scheme is buttressed by subsequent amendments to achieve the legislative end" (*Connolly v. Pension Benefit Guar. Corp.*, 475 U.S. 211, 227 (1986) (citation omitted); *Branch v. United States*, 69 F.3d 1571, 1579 (Fed. Cir. 1995) (same), *cert. denied*, 519 U.S. 810 (1996); *cf. Lucas v. South Carolina Coastal Council*, 505 U.S. 1003, 1027-28 (1992) ("[I]n the case of personal property, by reason of the State's traditionally high degree of control over commercial dealings, [the property owner] ought to be aware of the possibility that new regulation might even render his property economically worthless . . . .")). Participants in a highly regulated industry are "on notice that [they] might be subjected to different regulatory burdens over time" (*California Housing Secs., Inc. v. United States*, 959 F.2d 955, 959 (Fed. Cir. 1992), *cert. denied*, 506 U.S. 916 (1992)).

Petitioners should have been well aware that the Agency would permit a 505(b)(2) applicant to rely on the finding of safety and effectiveness for an approved NDA, based not only on the broad statutory language first enacted in 1984, but also on the Agency's subsequent publicly announced interpretation and application of section 505(b)(2). FDA's written pronouncements on the statute's scope embodied, among other places, in proposed and final regulations have further provided public notice of that broad scope. Consequently, any purported expectation that the Agency would not permit a 505(b)(2) applicant to rely on the finding of safety and effectiveness for an approved NDA is unreasonable and cannot provide the basis for a takings claim.

L. New Salts

Pfizer contends that new salts are traditionally and statutorily beyond the reach of section 505(b)(2). Pfizer relies largely on the 1987 Parkman letter to argue that the 1999 draft guidance went further than ever before in stating that new salts may be appropriate for approval under section 505(b)(2). Pfizer asserts that the 1987 Parkman letter, which discussed section 505(b)(2)

as a way to shortcut the ANDA approval and supplementation process, represents the outer limits of 505(b)(2) approvals. Given that a drug product containing a new salt cannot be approved through an ANDA and supplement (because an ANDA is required to have the same active ingredient as the listed drug and, under FDA's bundling policy, a change to a different active ingredient requires a separate application), Pfizer argues that the 505(b)(2) route is also unavailable for such a change (April 2003 comment at 14).

FDA Response: Pfizer's argument lacks support in the statute, regulations, or FDA's history of implementation. Although Pfizer is correct that the 1987 Parkman letter discussed the specific inefficiency associated with requiring an applicant to obtain approval for an ANDA before seeking a change to a listed drug, and changes to an active ingredient are not changes permitted in a supplement to an ANDA, the 1987 Parkman letter specifically mentioned section 505(b)(2) as an approval route for changes in active ingredients. When read in its entirety, the 1987 Parkman letter stands more generally for the proposition that an applicant seeking any change to a listed drug can rely on the listed drug's approval to establish the safety and effectiveness of the listed drug and need only provide data to support those aspects of the proposed drug that differ from the listed drug. The policy expressed in that letter — to eliminate unnecessary and potentially unethical duplication of research — applies equally to changes that can be approved through an ANDA and a postapproval supplement, as well as to those changes (such as changes to new salts) that have generally been considered to fall outside of the type of changes that may be approved in a supplement.

In addition, in section 735(1)(B)(i) of the statute, as part of the statutory provisions regarding user fees adopted in the Prescription Drug User Fee Act enacted in 1992, Congress explicitly included as examples of the type of applications that could be approved under section 505(b)(2), applications for new active ingredients. Section 735(1)(B)(i) states "the term 'human drug application' means an application for . . . approval of a new drug submitted under section 505(b)(2) after September 30, 1992, which requests approval of a molecular entity which is an active ingredient (including any salt or ester of an active ingredient)... that had not been approved under an application submitted under section 505(b)."

M. Therapeutic Equivalence

Pfizer contends that FDA may not assign an "A" therapeutic equivalence code rating to a drug product that — because it differs in salt — is a pharmaceutical alternative to, not a therapeutic equivalent of, the reference listed drug (2001 Pfizer petition at 25).

FDA Response: FDA agrees. Because it contains a different salt, Synthon's paroxetine mesylate product will not be "A" rated with respect to either GlaxoSmithKline's Paxil (paroxetine hydrochloride) or to any paroxetine hydrochloride product that is "A" rated to Paxil, including TorPharm's paroxetine hydrochloride product.

Where there is more than one approved application for a particular active ingredient and a particular dosage form, FDA provides therapeutic equivalence evaluations in the Orange Book. Single source products do not receive a therapeutic equivalence code. To obtain an "A"

therapeutic equivalence rating from FDA, a sponsor must show that its drug is pharmaceutically equivalent and bioequivalent to a listed drug and that it is expected to have the same clinical safety and effectiveness profile when administered under the conditions of use described in the labeling (Orange Book at viii).

FDA has defined pharmaceutically equivalent drug products as drug products that contain the same amount of the same active ingredient (i.e., the same salt or ester of the same therapeutic moiety) in identical dosage form, but not necessarily containing the same inactive ingredients, and that meet the compendial standards for identity, strength, quality, purity, and potency, and where applicable, content uniformity, disintegration times, and/or dissolution rates. Drug products denoted as pharmaceutical equivalents must be adequately labeled and manufactured under current good manufacturing practice. Different salts of the same active moiety are considered different active ingredients, so that drug products containing different salts are not pharmaceutical equivalents. (See 44 FR 2932 at 2937 and 2938, January 12,1979; § 320.1(c).)

Drug products are considered to be pharmaceutical alternatives if they contain the same therapeutic moiety (or its precursor) but not necessarily in the same amount or dosage form or as the same salt or ester where each drug product individually meets either the same or its own respective compendial or other applicable standard of identity, strength, quality, purity, and potency, and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (See 44 FR 2932 at 2938; § 320.1(d).) Pharmaceutical alternatives are not considered to be therapeutic equivalents even where they have demonstrated bioequivalence (44 FR 2938).

Because Paxil and TorPharm's products both contain the hydrochloride salt of paroxetine and are bioequivalent, they are considered pharmaceutical equivalents and therapeutic equivalents. However, because Synthon's product contains the mesylate salt of paroxetine, it is considered a pharmaceutical alternative, not a pharmaceutical equivalent, to Paxil. As such, Synthon's product is not eligible to obtain an "A" therapeutic equivalence rating to Paxil or to the products to which Paxil is "A" rated.

N. Marketplace Confusion and Incentives for Development

Both Pfizer and TorPharm raise challenges to the 505(b)(2) policy in the context of approval of drug products that differ from the innovator product only in active ingredient. Such approvals also raise concerns about inappropriate marketplace substitution of these products for the innovator drug when the drugs have not been rated as therapeutically equivalent by FDA. TorPharm is also concerned that approval of Synthon's paroxetine product will undermine the 180-day generic drug exclusivity TorPharm has earned pursuant to section 505(j)(5)(B)(iv) by virtue of having been one of the first applicants to challenge patents listed for Paxil (TorPharm petition at 5). Finally, this type of application raises questions about whether permitting approval of pharmaceutical alternatives before therapeutically equivalent drugs are approved by FDA will discourage investment in innovative new drug products.

FDA Response: The application of section 505(b)(2) to products that differ from the innovator product only in the active ingredient has been very limited. FDA believes that its decisions to

date on these applications have been justified by the language of the statute, the legislative history, and the purposes of the Hatch-Waxman Amendments. However, the Agency may wish to consider further whether there is some narrow subset of applications that should be exempted from the scope of section 505(b)(2) in the future.

FDA is particularly interested in examining the use of 505(b)(2) applications to obtain approval of drug products for which the *only* difference from the listed drug is in the form of the active ingredient, such as a change in salt. These are products that have the same dosage form, route of administration, strength, conditions of use, and labeling as the listed drug. The only reason these products may not be reviewed and approved in ANDAs submitted under section 505(j) is that they contain a different active ingredient from the listed drug.

This use of section 505(b)(2) does not result in the approval of an innovative drug product that offers a new therapeutic benefit or alternative, such as a new indication, novel dosage form, or improving administration for a new patient population. Nor do such changes in the active ingredient generally represent an improvement in terms of safety or effectiveness.

FDA is concerned that, in addition to not representing innovative drug development, this use of 505(b)(2) applications may have undesirable policy and public health consequences:

1. It may undermine current incentives for development of promising new active moieties that Congress included in the Hatch-Waxman Amendments.

2. It may lead to proliferation of pharmaceutical alternative drug products, with resulting confusion in the marketplace.

3. It may divert resources, otherwise available for innovative drug research, to the development and patenting of alternative active ingredients, where such patents are used solely either to establish a barrier to competition or to preempt the holder of the listed drug from establishing such a barrier.

Accordingly, FDA is reserving for further review the issues raised by this narrow use of section 505(b)(2), and is considering whether to begin a public process to seek input from interested parties, including the pharmaceutical and health care industries, as well as consumer groups.

V. CONCLUSION

FDA's consistent and long-standing interpretation is that section 505(b)(2) permits an applicant to rely on literature and/or the Agency's finding of safety and effectiveness to support approval of a new drug product. FDA's approach is consistent with the text of section 505(b)(2) and the structure of the statute, as well as with the policy balance struck in Hatch-Waxman between protecting innovator pharmaceutical investment and promptly approving ANDAs and 505(b)(2) applications once those protections are no longer barriers. The 1987 Parkman letter, the regulatory preambles, and FDA's regulation at § 314.54 described the types of changes to approved drug products for which approval may be sought under section 505(b)(2). In addition,

in 1999, FDA published its draft guidance, which consolidated and made public detailed information on the types of applications that had been or could be reviewed under section 505(b)(2). As demonstrated by the number and variety of 505(b)(2) approvals over the 19 years since the Hatch-Waxman Amendments were passed, the pharmaceutical industry has been well aware of the scope of section 505(b)(2). Moreover, as is clear from the partial list of drug products approved under section 505(b)(2) included in this petition, the Agency's scientific considerations, and the policy implications for the current and future use of section 505(b)(2), there are substantial public health benefits to the Agency's approach, as it allows for leveraging past research and targeting new research investment on innovative drug products, while at the same time protecting innovator patent rights and marketing exclusivity.

Sincerely yours,

FOR Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Enclosure: April 10, 1987, letter from Dr. Paul D. Parkman, then Acting Director, Center for Drugs and Biologics, to NDA and ANDA holders and applicants.

ENCLOSURE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

To all NDA and ANDA holders and applicants

APR 10 1987

Dear Sir or Madam:

This is another in a series of letters intended to provide informal notice to all affected parties of developments in policy and interpretation of the Drug Price Competition and Patent Term Restoration Act of 1984. This letter deals with an issue about which a number of questions have arisen, namely the statutory mechanism by which ANDA applicants may make modifications in approved drugs if the modifications require the submission of clinical data. For example, an applicant may wish to obtain approval of a new indication for a listed drug that is only approved for other indications. If the applicant has an approved ANDA for the approved indications, agency policy permits the applicant to submit a supplemental application that contains reports of clinical investigations needed to support approval of the new indication. (Because such a supplement would require the review of clinical data, FDA would process it as a submission under section 505(b) of the Federal Food, Drug and Cosmetic Act.)

A similar case may arise where an applicant wishes to seek approval of a modification of an approved product but has no interest in marketing the drug in its originally approved form. Assuming that clinical data were required for approval, the statute could be interpreted to require such an applicant to first manufacture, and obtain approval of an ANDA for, the listed drug's approved form and then file a 505(b) supplement to the approved ANDA containing the clinical data to obtain approval of the modification. If the applicant did not first obtain an ANDA for the approved form, the applicant could be required to submit a full NDA for modification and duplicate the basic safety and effectiveness studies conducted on the listed drug.

FDA has concluded that such an interpretation is inconsistent with the legislative purposes of the Drug Price Competition and Patent Term Restoration Act of 1984 (the 1984 Amendments), because it would serve as a disincentive to innovation and would require needless duplication of research.

FDA believes that a more consistent and less burdensome interpretation of the 1984 Amendments is to allow a generic applicant to submit a 505(b) "supplement" (a form of NDA) for a change in an already approved drug that requires the submission of clinical data, without first obtaining approval of an ANDA for a duplicate of the listed drug. This submission would include data only for those aspects of the proposed drug that differ from the listed drug. Changes in already approved drugs for which such applications will be accepted include changes in dosage form, strength, route of administration, and active ingredients for which ANDA suitability petitions cannot be approved because studies are necessary for approval as well as new indications. Like similar supplements to approved ANDAs, these applications will rely on the approval of the listed drug together with the clinical data needed to support the change. The applicant will thus be relying on the approval of the listed drug only to the extent that such reliance would be allowed under section 505(j): to establish the safety and effectiveness of the underlying drug.

FDA believes that it would be inconsistent with the policies of the 1984 Amendments to allow these applications to rely on the approval of a listed drug without due regard for the listed drug's patent rights and exclusivity. Therefore, an application that relies in part on the approval of a listed drug and in part on new clinical data will, for this purpose, be considered an application described in section 505(b)(2) and must contain a certification as to any relevant patents that claim the listed drug. In addition, the date of submission and effective approval of these applications may, under section 505(c)(3), be delayed to give effect to any patent or period of exclusivity accorded the listed drug.

Because these submissions will be reviewed as applications under section 505(b), they will be subject to the statutory and regulatory requirements applicable to such applications, including the patent filing requirements of sections 505(b) and (c). These submissions also may be eligible for three years of exclusivity under sections 505(c)(3)(D)(iii) and (iv) and 505(j)(4)(D)(iii) and (iv). These applications should be submitted to the appropriate review division in ODRR/OBRR for review and final action.

Sincerely yours,

Paul D. Parkman, M.D.
Acting Director
Center for Drugs and Biologics