



Corporate Headquarters:  
TEVA PHARMACEUTICALS USA  
1090 Horsham Road, PO Box 1090  
North Wales, PA 19454-1090

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Deborah A. Jaskot, M.S., RAC  
Executive Director, Regulatory Affairs

Phone: (215) 591 3000  
FAX: (215) 591 8600

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Dockets Management Branch (HFA-305)  
United States Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, Maryland 20852

**Re: Docket No. 99D-4809**  
**Draft Guidance For Industry Applications Covered By Section 505(b)(2)**

Teva Pharmaceuticals USA, Inc. ("Teva"), a world leader in the manufacture and marketing of high quality generic pharmaceuticals, respectfully submits these comments regarding FDA's December 8, 1999 Draft Guidance on New Drug Applications covered by 21 U.S.C. § 355(b)(2) ("505(b)(2) Applications"). These comments also respond to the April 3, 2000 submission by the trade association Pharmaceutical Research and Manufacturers of America ("PhRMA"). As discussed herein, Teva supports the approach outlined in FDA's Draft Guidance and the agency's effort to facilitate the use of this underutilized statutory approval mechanism. Teva believes, however, that even more can and should be done to encourage companies to take advantage of section 505(b)(2) in order to spur more research and innovation involving existing drug products. Finally, Teva urges FDA to reject PhRMA's self-serving request to rescind the draft Guidance, as well as PhRMA's baseless arguments in support of that request.

In discussing the implementation of section 505(b)(2), it is important to start with a clear grasp of the actual statutory language. Under the plain language of the statute, two things are indisputable: first, Congress intended to permit an applicant to seek approval of a drug based on another company's safety and efficacy data, whether or not those data are published, without the other company's permission; and second, in exchange for this right, Congress provided strong intellectual property protections to companies whose data are used by 505(b)(2) applicants.

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## **THE STATUTORY PROVISIONS CLEARLY SUPPORT FDA’S GUIDANCE**

In light of section 505(b)(2)’s clear expression of Congressional intent, it is not surprising that nowhere in its comments does PhRMA ever quote, or even discuss, the actual statutory language. Indeed, PhRMA’s position is directly contradicted by the statutory language as shown below:

<b>PhRMA’s Position</b>	<b>The Statute</b>
<p>“FDA is incorrect in interpreting section 505(b)(2) as authorizing the agency to approve a new drug by reference to a prior finding of safety and efficacy based on another company’s proprietary data.”</p> <p>PhRMA comments at 3-4,</p>	<p>“(2) An application [may be] submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph<sup>1</sup> and relied upon by the applicant for approval of the application <u>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. . . .</u>”</p> <p>21 U.S.C. § 355(b)(2) (emphasis added).</p>

Thus, FDA’s position that 505(b)(2) applications may be approved based on the agency’s prior findings of safety and/or efficacy for a drug, Guidance at 2, is squarely supported by the plain language of the statute.

The legislative history further supports FDA’s interpretation of the type of applications eligible for approval under section 505(b)(2). Although, as PhRMA points out, the House Report used the term “Paper NDA” as a shorthand reference to 505(b)(2) applications, the Report also clearly reflects Congress’ intent to define such applications more broadly than was true under the old paper NDA policy:

Paper NDAs are defined as any application submitted under section 505(b)(2) 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.

H.Rep. 98-857 at 32, reprinted at 1984 U.S.C.A.A.N. 2665 (emphasis added). If Congress had meant to limit paper NDAs solely to those NDAs that relied on published

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<sup>1</sup> “Clause (A)” of section 505(b)(1) requires an NDA sponsor to submit “full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use.” 21 U.S.C. § 355(b)(1)(A).

articles to support findings of safety and/or effectiveness, it could easily have stated its intention.

FDA's draft Guidance does not represent any great change in policy, but rather reflects the agency's consistent interpretation of section 505(b)(2) for nearly a decade. As FDA explained in the preamble to the 1992 final rule implementing Hatch-Waxman's generic drug approval provisions,

The 1984 amendments also amended section 505(b) of the act (21 U.S.C. § 355(b)) to create another type of application. These applications, known as 505(b)(2) applications, are similar to applications under the agency's "paper NDA" policy. Unlike the paper NDA policy, however, section 505(b)(2) of the act applies to applications that contain investigations relied upon by the applicant to provide full reports of safety and effectiveness where the investigations 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 investigations. (See 21 U.S.C. § 355(j)(2)). Thus, section 505(b)(2) of the act is not restricted to literature-supported NDA's for duplicates of approved drugs; it covers all NDA's for drug products that rely on studies not conducted by or for the applicant or for which the applicant does not have a right of reference.

57 Fed. Reg. 17950, 17952 (April 28, 1992) (emphasis added).

Permitting 505(b)(2) applications to be approved based on FDA's prior safety and efficacy determinations also reflects sound public policy. As Congress has long affirmed, a requirement to conduct duplicative testing in the drug approval process is unwarranted. Once it is established that a drug is safe and effective for a particular use, conducting additional tests in animals and in humans is scientifically unnecessary. See, e.g., H.Rep. 98-857 at 16, reprinted at 1984 U.S.C.C.A.N. 2649 ("FDA considers retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective."). Congress also recognized that subjecting sick patients to placebo-controlled experiments, thereby depriving some of much-needed medication, is unethical when such tests are scientifically unnecessary. See H.Rep. 98-857 at 16, reprinted at 1984 U.S.C.C.A.N. 2649 ("such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective."). Eliminating duplicative testing requirements also lowers drug development costs and should result in lower-priced drugs to the consumer. Thus, as a matter of public health policy, FDA should do everything within its authority to encourage the widest possible use of 505(b)(2) applications.

For the reasons discussed above, the draft Guidance simply and reasonably embodies the plain statutory language of section 505(b)(2), the Congressional intent and understanding of that provision at the time it was enacted, FDA’s consistent long-term statutory interpretation, and sound public health policy. PhRMA’s pecuniary displeasure with this simple truth in no way justifies its request to rescind the Guidance and FDA’s implementing regulations (21 C.F.R. § 314.54) and to initiate new rulemaking to adopt regulations that would further restrict consumer access to affordable drugs.

**THE STATUTE PROVIDES SUFFICIENT INTELLECTUAL PROPERTY PROTECTION FOR PATENT HOLDERS AND NDA SPONSORS**

One of PhRMA’s chief complaints is that FDA’s Guidance will somehow abrogate the intellectual property rights of patent holders and NDA sponsors. PhRMA comments at 2-3, 7-8. This concern is wholly unfounded. The intellectual property protections Congress provided in exchange for the right to rely on safety and efficacy data are similar to, but stronger than, the patent certification and notification requirements imposed upon ANDA applicants who seek approval of a generic version of an approved drug prior to expiration of a listed patent for that drug.<sup>2</sup> See 21 U.S.C. § 355(j)(2)(A)(vii). Whereas ANDA applicants need only certify to patents covering the listed drug (or a use thereof) for which the applicant seeks ANDA approval, 505(b)(2) applicants must certify to all patents relating either to the drug involved in the investigations the applicant seeks to rely upon, or to the drug for which the 505(b)(2) applicant seeks approval:

<b>505(b)(2) Patent Certification Requirement</b>	<b>ANDA Patent Certification Requirement</b>
<p>(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which <u>claims the drug for which such investigations were conducted</u> <u>or</u> which <u>claims a use for such drug for which the applicant is seeking approval</u> under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section –</p> <p>21 U.S.C. § 355(b)(2)(A) (emphasis added).</p>	<p>(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which <u>claims the listed drug referred to in clause (i) or which claims a use for such listed drug</u> for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) –</p> <p>21 U.S.C. § 355(j)(2)(A)(vii)(emphasis added).</p>

<sup>2</sup> For both ANDAs and 505(b)(2) applications, there are four basic patent certifications: “(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.” 21 U.S.C. § 355(b)(2)(A); 21 U.S.C. § 355(j)(a)(A)(vii).

This difference in certification requirements between ANDAs and 505(b)(2) applications exposes the fallacy of PhRMA's complaint that FDA's implementation of section 505(b)(2) "might not provide meaningful patent and data exclusivity protection(s) to the pioneer."<sup>3</sup> PhRMA comments at 8. Indeed, if the 505(b)(2) applicant makes a Paragraph IV certification (claiming that the relevant patent is invalid or will not be infringed by the sale of the applicant's drug), section 505(b)(3) requires the applicant to so notify all patent holders and holders of approved NDAs covered by the patents for which a certification is required. 21 U.S.C. § 355(b)(3). In response to such a Paragraph (iv) notification, the patent holder may bring a patent infringement action which, if filed within 45 days of the notification, automatically delays the approval of the 505(b)(2) application for 30 months while the case is litigated. 21 U.S.C. § 355(c)(3)(C). If the patent holder prevails, its intellectual property right will be vindicated.

Moreover, PhRMA's complaint that safety and efficacy data protection would be destroyed (or in Pfizer's view, subject to an "unconstitutional taking," Pfizer Comments at 3) under FDA's application of section 505(b)(2) fails to take into account the statutory provisions by which such data must be released to the public. Specifically, section 505(l)(5) requires FDA to publicly release "safety and effectiveness data and information which has been submitted in an [NDA]. . . (5) upon the effective date of the approval of the first application under subsection (j) [i.e., an ANDA] which refers to such drug or upon the date upon which the approval of an application under subsection (j) which refers to such drug could be made effective if such an application had been submitted." 21 U.S.C. § 355(l)(5) (emphasis added).<sup>4</sup> Because any patent that would be subject to potential certification under the ANDA procedures would also be subject to certification under the 505(b)(2) procedures – and the result of any judicial challenge would be the same – the period of confidentiality of NDA-based safety and effectiveness data is not shortened by FDA's interpretation of section 505(b)(2).

### **DRUGS APPROVED UNDER SECTION 505(b)(2) ARE ELIGIBLE FOR "AB" RATING IN THE ORANGE BOOK**

After many years of denial and fruitless challenges, PhRMA appears to have finally conceded the legitimacy and necessity of FDA assigning "AB" ratings in the Orange Book for therapeutically equivalent and bioequivalent versions of reference listed drugs approved through the ANDA process. See PhRMA Comments at 5. Having

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<sup>3</sup> This key statutory distinction also clearly reflects Congress' understanding that it was enacting a law that allows approval of a drug that differs from the drug upon which the safety and efficacy studies relied upon were performed.

<sup>4</sup> See also H.R. Rep. 98-857 PT 2 at 20 ("Section 104 of the bill adds [21 U.S.C. § 355(l)]. . . which makes hitherto undisclosed safety and effectiveness information that has been submitted in an NDA available to the public upon request. Absent extraordinary circumstances, safety and effectiveness information and data shall be disclosed in the following circumstances: . . . (5) upon the effective date of approval of the first ANDA which refers to the drug or upon the date which an ANDA could have been approved if an application had been submitted.").

retreated from that fight, PhRMA has now sought to draw a new line in the sand by arguing that drugs approved via section 505(b)(2) should not be eligible for “A” or “AB” ratings in the Orange Book. As its sole support for this argument, PhRMA claims that “The pharmaceutical industry has long held the view that A ratings are reserved for generic copies approved through the ANDA process and simply are not available to modified drugs approved by 505(b)(2). PhRMA believes that the notion that modified drugs will be deemed substitutable is not what Congress intended when it enacted 505(b)(2).” *Id.* Again, PhRMA is wrong, and its position would constitute bad public policy, enriching its member companies at the expense of poor and underinsured Americans.

PhRMA’s self-serving assertion that the pharmaceutical industry has “long held the view” that only ANDA-approved drugs may receive “A” ratings could only be true for members of the industry who have never actually read the Orange Book. As defined in the Orange Book, “A” ratings are available for any

“Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which:

(1) there are no known or suspected bioequivalence problems...; or

(2) actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence.”

Orange Book, 20<sup>th</sup> Ed. at xiii. There is no restriction in this definition that would limit “A” ratings to ANDA-approved products, nor is there any reason to rationally believe that Congress did not intend to allow such ratings where warranted by the medical facts. Like so many of PhRMA’s anti-consumer, anti-competitive positions, its position in this regard is plainly wrong and should be rejected by FDA.

### **INDIVIDUALIZED FDA REVIEW AND APPROVAL OF 505(B)(2) APPLICATIONS IS REQUIRED UNDER THE FDCA**

PhRMA also requests that FDA establish detailed substantive guidance on the approval criteria for 505(b)(2) applications that would include specific study requirements to support specific types of changes that may be submitted under a 505(b)(2) application, complaining that data requirements would otherwise be determined on an ad hoc basis by FDA staff. PhRMA comments at 4-7. Needless to say, it is impossible even to attempt to establish such guidelines in the abstract. It is also unnecessary because individualized FDA evaluation of whether particular drugs meet the requisite approval requirements is mandated by the statute itself. See 21 U.S.C. § 355(d). Further underscoring the importance and legitimacy of individualized drug reviews – and

the fatuousness of PhRMA's complaint that "the clinical studies and other data needed to support the 505(b)(2) application will be determined in large part by direction from FDA staff to individual applicants," PhRMA Comments at 7 – the FDA Modernization Act of 1997 ("FDAMA") specifically requires FDA to meet with sponsors (including 505(b)(2) sponsors) "for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim." 21 U.S.C. § 355(b)(4)(B). Thus, Congress has specifically required FDA to do what PhRMA now asks FDA not to do.

In any event, case-by-case scientific determinations of whether a sponsor has demonstrated that its drug meets the statutory safety and efficacy requirements is FDA's core historical function, which cannot be altered at the whim of one element of the regulated industry. PhRMA's request that the agency anticipate every scenario and establish data requirements in advance is a feeble and transparent attempt to delay implementation of a final 505(b)(2) guidance and should be rejected.

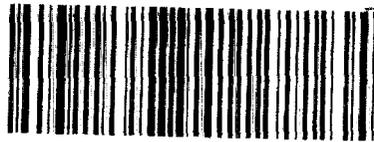
## **CONCLUSION**

For the reasons stated above, Teva strongly supports the draft Guidance and urges the agency to reject the anti-consumer positions advocated by PhRMA and its members in opposition to the fullest possible use of the 505(b)(2) approval mechanism.

Respectfully submitted,

  
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Teva Pharmaceuticals, USA, Inc.

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