



# Bristol-Myers Squibb Company

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July 15, 2002

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

Re: Docket No. 01P-0323; Comments of Bristol-Myers Squibb Company

Dear Sir/Madam:

Bristol-Myers Squibb Company ("BMS") submits the following comments in response to the July 27, 2001 Citizen Petition filed jointly by Pharmacia Corporation and Pfizer, Inc. ("Joint Petition"). The Joint Petition dealt with the differences between Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), 21 U.S.C. §355(b)(2), which authorizes a type of New Drug Application ("NDA"), and Section 505(j) of the FDC Act, which authorizes an Abbreviated New Drug Application ("ANDA").

Overall, BMS agrees with positions set forth in the Pharmacia/Pfizer Joint Petition. We submit these comments to provide additional detail on one key point. *Section 505(b)(2) does not authorize an applicant to reference, or FDA to rely upon, the proprietary safety and effectiveness data contained in another manufacturer's NDA unless and until such data become publicly available under Section 505(l) of the FDC Act.*

Any other interpretation of Section 505(b)(2) would be contrary to both the legislative history and well-established principles of statutory construction. Consequently, the Food and Drug Administration ("FDA") should adopt an interpretation of Section 505(b)(2) that harmonizes all of the FDC Act's provisions by maintaining the confidentiality of proprietary safety and effectiveness data contained in NDA files until such data become publicly available pursuant to Section 505(l), 21 U.S.C. §355(l).

In brief, a Section 505(b)(2) application is not an ANDA. The law does not permit an applicant to "mix and match" certain features from Section 505(b)(2) and other features from Section 505(j) to achieve some sort of hybrid approval. A Section 505(b)(2) application is a type of full NDA, and a 505(b)(2) applicant may not reference or rely upon proprietary data in another applicant's NDA until that data becomes publicly available by law.

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Below is a detailed discussion of:

1. Statutory Provisions Authorizing 505(b)(2) Applications
2. The Legislative History
3. The Assertions of the Generic Pharmaceutical Association
4. Current FDA Policy
5. Recommended FDA Action

## 1. The Statutory Provisions Authorizing 505(b)(2) Applications

Section 505(b)(2) was added to the FDC Act in 1984 by the Drug Price Competition and Patent Term Restoration Act (“the 1984 Amendments”).<sup>1</sup> Section 505(b)(2) carved out a new type of New Drug Application (“NDA”), albeit one that had been recognized by FDA administratively for years as a “paper NDA.”

Under Section 505(b)(1), a “full NDA” must contain, among other things, “full reports” of investigations demonstrating that the drug product for which approval is sought is “safe and effective.” 21 U.S.C. §355(b)(1). This “full reports” requirement is one of the primary distinctions between a “full NDA” and an ANDA, which is not required to contain “full reports” demonstrating safety and effectiveness but instead must simply show that the proposed generic drug is “the same as” the pioneer drug. *Id.* §355(j).

Although a 505(b)(2) application is sometimes confused with an ANDA, it is a completely separate type of application. In fact, it is a type of “full NDA” submitted under Section 505(b)(1). Like all “full NDAs” (and unlike ANDAs), 505(b)(2) applications must contain “full reports” of investigations demonstrating that the subject drug is safe and effective for its intended use. *Id.* §355(b)(1), (2). With a 505(b)(2) application, however, some of the studies relied upon by the applicant to satisfy the “full reports” requirement “were not conducted by or for the applicant and for which the applicant has not obtained a right or reference or use . . .” *Id.* Indeed, the fact that the applicant does not have rights to all of the data in the application is the *only aspect* that differentiates a 505(b)(2) application from a 505(b)(1) application.<sup>2</sup>

It is thus very clear that the statute permits a Section 505(b)(2) applicant to obtain approval based upon safety and effectiveness data for which it has no right of reference or use. This, in fact, is the very definition of a 505(b)(2) application. Contrary to the position taken by the Generic Pharmaceutical Association, however, the statute does *not* take the further, much more significant step of authorizing 505(b)(2) applicants to appropriate and use

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<sup>1</sup> Pub. L. No. 98-417, §103, 98 Stat. 1585, 1593 (1984).

<sup>2</sup> Once an application is determined to be a 505(b)(2) application, other distinctions arise between a 505(b)(1) application and a 505(b)(2), such as the need for patent certifications. See 21 U.S.C. §355(b)(2)(A). However, these further distinctions do not arise unless the applicant does not have rights to all of the data in its application.

confidential, proprietary data contained in another company's NDA.

It is one thing to permit applicants to rely upon data they have access to but no right of reference or use – such as reports of investigations in the published literature. It is quite another thing to affirmatively authorize the use of a competitor's proprietary data submitted in confidence in an NDA. While Congress certainly authorized the former when it enacted Section 505(b)(2) in 1984, there is no evidence that it intended to authorize the latter. On the contrary, both the statutory language and the legislative history indicate that Congress intended to maintain the confidentiality of safety and effectiveness data submitted in an NDA until such time as the data are no longer valuable, i.e., until approval of an ANDA has been or could be made effective. *See* 21 U.S.C. §355(l).

## 2. The Legislative History

In order to interpret Section 505(b)(2) as authorizing applicants to reference and use other companies' proprietary safety and effectiveness data, one would have to conclude that Congress intended to radically change the laws and policies existing in 1984 that protected the confidentiality of such data. While such an argument might be made with respect to ANDAs, the plain language of Section 505(b)(2) does not demonstrate such a legislative intent with respect to NDAs to which the "full reports" requirement applies.

Prior to 1984, FDA's consistent and longstanding policy was that unpublished safety and effectiveness data submitted in an NDA was confidential commercial information and/or trade secrets that could not be disclosed to the public or used by FDA to support approval of another company's application. *See* 46 Fed. Reg. 27396 (May 19, 1981) (publication of "paper NDA" policy); 39 Fed. Reg. 44602, 44634-38 (Dec. 24, 1974); 37 Fed. Reg. 9128, 9130-31 (May 5, 1972). Under its "paper NDA" policy, FDA did permit applicants to rely upon investigations reported in the published literature even if the reported studies were not conducted by or for the applicant and the applicant did not have a right of reference or use. *See* 46 Fed. Reg. 27396. FDA, however, never extended this policy to data contained in a competitor's NDA. *Id.*

If Congress had intended to change this longstanding policy with respect to 505(b)(2) applications – a change which would have been extraordinary – it surely would have done so clearly and explicitly. The statute, however, does not clearly state anywhere (or even imply) that a 505(b)(2) applicant is permitted to reference and rely upon proprietary data in a competitor's NDA which has not and could not be made publicly available by FDA to support its application or that FDA is authorized to use such data in approving a 505(b)(2) application.

Far from radically changing the existing law, Section 505(b)(2) is more naturally and appropriately read as simply codifying a modified version of FDA's "paper NDA" policy. Under that policy, applicants could rely upon published data to support NDA approval *even if the reported studies were not conducted by or for the applicant and the applicant did not have a right of reference or use.* The reported studies could be used by the applicant,

despite the lack of any right of reference or use, because they were already in the public domain. Consequently, the phrase in Section 505(b)(2) discussing studies for which the applicant has not obtained a right of reference or use was simply meant by Congress to refer to studies already in the public domain; it was not meant to signal a fundamental shift in the existing law by authorizing the use of unpublished, proprietary safety and effectiveness data.

This interpretation of Section 505(b)(2) as merely codifying a version of FDA's "paper NDA" policy is further supported by the available legislative history. Indeed, the legislative history is replete with references to the term "paper NDA" when discussing the operation of Section 505(b)(2). For instance, the House Report contains a heading titled "Paper NDA's" which goes on to define "Paper NDA's" as

any application submitted under section 505(b) of the FFDCA 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 . . .

H. Rep. No. 98-857, Part I, 98<sup>th</sup> Cong., 2nd Session, at 32 (1984). The name "Paper NDA" was a well-known term of art referring specifically to FDA's policy permitting NDAs to be approved based upon studies reported in the published literature – but not based upon data contained in another company's NDA and protected from public disclosure. See 46 Fed. Reg. 27396 (May 19, 1981) ("Publication of 'Paper NDA' Memorandum").

The use by Congress of this well-known term in its debates and committee reports evinces a clear Congressional intent to codify FDA's existing "Paper NDA" policy and thereby permit 505(b)(2) applicants to reference and rely upon published studies to which they might not have a right of reference or use. It also strongly supports the position that Section 505(b)(2) was *not* intended to radically change the law by authorizing one company to appropriate and use proprietary data contained in another company's application.

In addition to the lack of statutory language suggesting that Congress intended to change FDA's longstanding policy regarding the confidentiality of safety and effectiveness data when it enacted Section 505(b)(2), other provisions enacted in the 1984 Amendments strongly indicate that Congress intended for FDA to maintain the confidentiality of such data until certain benchmarks had been reached.

In particular, Section 505(l), enacted in the 1984 Amendments along with Section 505(b)(2),<sup>3</sup> explicitly recognizes the proprietary nature of safety and effectiveness data. 21 U.S.C. §355(l). Section 505(l) thus provides that such information is confidential and not subject to public disclosure until, *inter alia*, the first ANDA referencing the drug product receives effective approval or, if no such ANDA has been filed, the date such an application

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<sup>3</sup> Pub. L. No. 98-417, §104, 98 Stat. 1585, 1597 (1984).

could receive effective approval if it had been filed.<sup>4</sup> *Id.* §355(l)(5). Even after this date, safety and effectiveness information cannot be made publicly available if the owner of the data can demonstrate that “extraordinary circumstances” exist that justify protecting the data. *Id.*

The legislative history provides further support that Congress did *not* intend to alter the rights to proprietary safety and effectiveness data contained in an NDA but rather intended Section 505(l) to operate to require FDA to maintain the confidentiality of such data in the same manner it had prior to 1984. The House Report explains:

The conditions under which such safety and effectiveness data shall be released upon request, unless extraordinary circumstances are shown, are merely a restatement of [FDA’s] current regulation. The Committee intends that all terms in new section 505(l) be given the same meaning that they have in the regulation. *It is not the intent of the Committee to alter the rights of the public under the Freedom of Information Act.*

H. Rep. No. 98-857, Part I, 98<sup>th</sup> Cong., 2nd Session, at 35 (1984) (emphasis added).<sup>5</sup> Accordingly, any interpretation of Section 505(b)(2) must be harmonized with Section 505(l), particularly since these two provisions were enacted at the same time. James Madison Ltd., By Hecht v. Ludwig, 82 F.3d 1085, 1093 (D.C. Cir. 1996), *cert. denied*, 519 U.S. 1077 (1997) (court has obligation to interpret statute’s provisions in harmony with each other). An interpretation that permits one applicant to reference, without permission, another applicant’s proprietary safety and effectiveness data *before* it becomes publicly available, however, effectively reads Section 505(l)(5) out of the statute. Indeed, even if the 505(b)(2) applicant never actually sees the safety and effectiveness data, the mere act of referencing that data amounts to FDA making the data “available to the public” contrary to Section 505(l)(5).

It is a well-established principle of statutory construction that a statute should be interpreted to avoid making any provision inoperable, e.g., Edison Elec. Inst. v. E.P.A., 996 F.2d 326, 335 (D.C. Cir. 1993) (a statute should not be interpreted so as to render one part inoperative). In this case, the only interpretation that makes both Section 505(b)(2) and Section 505(l)(5) fully operable is one which prohibits 505(b)(2) applicants from referencing or relying upon proprietary safety or effectiveness data contained in an innovator’s NDA until that data becomes publicly available under Section 505(l)(5).

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<sup>4</sup> The reasoning behind this provision is that once an ANDA could become effective, the need for “full reports” to obtain approval of the drug product covered by the ANDA is no longer operative and, therefore, the data (in the absence of extraordinary circumstances) are no longer considered confidential.

<sup>5</sup> The FDA regulations on which Section 505(l) was based were codified at 21 C.F.R. §314.14(f) (1983).

In most cases, safety and effectiveness data will not become publicly available until final, effective approval of an ANDA for the drug product has been or could be obtained. 21 U.S.C. §355(l)(5). In situations in which the drug product is protected by one or more patents, this typically would not occur until either the patents expire or are successfully challenged in court by a generic competitor. *Id.* §355(j)(5)(B)(iii)(I), (II).

The legislative history indicates that proprietary safety and effectiveness data should not be made publicly available upon ANDA approval if such approval is granted prior to resolution of the patent case. The House Report clarifies that Congress

does not intend that safety and effectiveness data and information be released under [Section 505(l)] if an ANDA challenging the validity of a patent is approved before there has been a court decision holding the patent invalid and if the NDA holder brings an action to restrain the disclosure.

H. Rep. No. 98-857, Part I, 98<sup>th</sup> Cong., 2nd Session, at 36 (1984). The basis for this statement apparently is that the existence of an ongoing patent case constitutes an “extraordinary circumstance” under the statute justifying non-disclosure.

Thus, during the pendency of patent litigation the NDA holder may bring suit to prevent the release or use of proprietary data in support of a 505(b)(2) application, even though an ANDA for a generic copy could be eligible for an immediately effective approval (i.e., thirty months have elapsed since the patent litigation was initiated without a final decision).

### **3. The Assertions of the Generic Pharmaceutical Association**

The Generic Pharmaceutical Association asserts that Section 505(b)(2) can be interpreted as permitting FDA to rely upon its “prior findings of safety and efficacy,” as opposed to the proprietary data contained in another company’s NDA<sup>6</sup>. Such an interpretation would contradict the plain language of the statute.

Under the statute, an ANDA is approved based upon the Agency’s prior findings of safety and effectiveness. ANDA applicants are required to identify a reference listed drug that previously received FDA approval and then demonstrate that their generic drug is “the same as” the previously approved drug. 21 U.S.C. §355(j). If the generic applicant demonstrates that its product is “the same as” the reference listed drug, the statute permits FDA to approve the generic version on the presumption that it is as safe and effective as the reference drug, i.e., on the basis of the Agency’s “prior findings” of safety and effectiveness.

A 505(b)(2) application, however, is not an ANDA – or even a type of ANDA. Unlike an

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<sup>6</sup> See Comments of Generic Pharmaceutical Association, Docket No. 01P-0323, C1, p. 2-3 (Dec. 10, 2001).

ANDA, a 505(b)(2) application cannot be approved merely by demonstrating that it is “the same as” – or even “similar to” – a reference listed drug. On the contrary, a 505(b)(2) application is a type of full NDA, and like all full NDAs, it must contain “full reports” demonstrating that the drug product is safe and effectiveness. *Id.* §355(b)(1)(A), (b)(2). The requirement for “full reports” is not waived simply because FDA has previously approved another similar drug product. Under the statute, waiver of the “full reports” requirement is appropriate only for ANDAs.

Moreover, the statutory language makes clear that 505(b)(2) applicants are not referencing or relying upon FDA’s “prior findings” of safety and effectiveness. On the contrary, they are relying upon particular “investigations” that “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 . . .” 21 U.S.C. §355(b)(2).

This language makes clear that a 505(b)(2) application cannot rely upon FDA’s “prior findings” of safety and effectiveness as if they were hybrid ANDAs. Rather, 505(b)(2) applications must satisfy the full reports requirement of Section 505(b)(1)(A) and, in satisfying that requirement, must identify and rely upon particular reports of investigations supporting the safety and effectiveness of the drug product.

In effect, the Generic Pharmaceutical Association (“GPA”) takes the position that the right of an NDA applicant to rely on published data and clinical trials under Section 505(b)(2) is *additive* to the right of a generic applicant to rely on the safety and efficacy findings of innovative company under Section 505(j). In other words, the GPA takes the view that Section 505(b) authorizes some form of “super ANDA” or hybrid not bound by the specific legislative provisions of either Section 505(j) or Section 505(b)(2). This is unsupportable.

#### 4. Current FDA Policy

FDA’s current policy expressed in regulations and guidance documents is that Section 505(b)(2) permits one company to reference, without permission, another company’s proprietary safety and effectiveness data. This policy is codified in FDA regulations at 21 C.F.R. §314.54. It has also been expressed in the preamble to those regulations, 57 Fed. Reg. 17950, 17952 (April 28, 1992), and, most recently, in FDA’s *Draft Guidance on Applications Covered By Section 505(b)(2)* (Oct. 1999) (“*Draft Guidance*”). In the *Draft Guidance*, for instance, FDA explicitly states its position that Section 505(b)(2) permits the approval of New Drug Applications (“NDAs”) based, in part, on “the Agency’s previous finding of safety and/or effectiveness for a drug.” *Draft Guidance* at 2.

The Agency never specifies, however, whether there are any limitations on this policy based upon the status of the innovator’s data as publicly available or not under Section 505(l). In the *Draft Guidance*, FDA states that its regulation at 21 C.F.R. §314.54 “permits a 505(b)(2) applicant to rely on the Agency’s finding of safety and effectiveness for an approved drug *to the extent such reliance would be permitted under the generic drug approval provisions at section 505(j).*” *Draft Guidance* at 3 (emphasis added). Unfortunately, this statement has

been interpreted as permitting 505(b)(2) applications to be submitted and at least tentatively approved *before* the innovator's proprietary data becomes publicly available, just like certain classes of ANDAs. A more appropriate interpretation of this statement would be to prohibit the submission or approval of a 505(b)(2) application unless and until approval of an ANDA could be made effective, which is one of the triggers for disclosure of the innovator's proprietary data under Section 505(l). *See* 21 U.S.C. §355(l)(5).

Only the latter interpretation is consistent with the FDC Act and FOI Act. While the FDC Act permits FDA to approve a 505(b)(2) application on the basis of data to which the applicant has no right of reference or use, the Act does *not* thereby authorize 505(b)(2) applicants or FDA to reference or use unpublished, proprietary data contained in another manufacturer's confidential NDA files. Indeed, interpreting Section 505(b)(2) in this manner not only makes a leap that goes well beyond the plain language of Section 505(b)(2), but also renders other provisions of the FDC Act – namely, Section 505(l) governing the releasability of safety and effectiveness data in an NDA – inoperable.

## 5. Recommended FDA Action

If the Agency currently interprets Section 505(b)(2) as permitting reliance on another manufacturer's proprietary data only after such data can be publicly released under Section 505(l), we hereby request that FDA clarify this intent in its regulations and guidance documents.

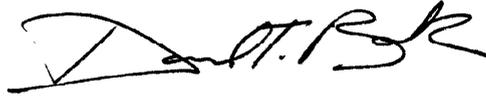
If, on the other hand, the Agency interprets Section 505(b)(2) as permitting reliance on another manufacturer's proprietary data without regard to whether such data can be publicly released under Section 505(l), we hereby request that FDA reconsider this position. As discussed above, FDA has no statutory authority to permit one manufacturer to rely, without permission, upon another manufacturer's proprietary safety and effectiveness data until such data becomes publicly available. If FDA were to accept or approve a 505(b)(2) application under these circumstances, its actions would be arbitrary and capricious, contrary to law, and in excess of FDA's statutory authority. *See* 5 U.S.C. §706(2)(A), (C).

Finally, FDA is prohibited not only from *approving* a 505(b)(2) application until the referenced safety and effectiveness data become publicly available, but also from *accepting* such an application. Since the mere act of referencing data results in a public use of that data, 505(b)(2) applicants should not be permitted to reference safety and effectiveness data contained in an NDA until such data are no longer confidential. Without the referenced data, however, the 505(b)(2) application is incomplete on its face for failing to contain the necessary "full reports" of safety and effectiveness required by Section 505(b)(1)(A). 21 U.S.C. §355(b)(1)(A), (b)(2). As such, the 505(b)(2) application should be subject to a "refuse to file" decision until it would be permissible under Section 505(l) to reference the confidential data. 21 C.F.R. §314.101(d)(3).

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For the reasons discussed above, Section 505(b)(2) does not authorize an applicant to reference, or FDA to rely upon, the proprietary safety and effectiveness data contained in another company's NDA unless and until such data become publicly available under Section 505(l). The FDA should thus grant the Joint Petition.

Sincerely,

A handwritten signature in black ink, appearing to read "D. T. Bonk". The signature is stylized with a large, sweeping initial "D" and a prominent "B".

David T. Bonk

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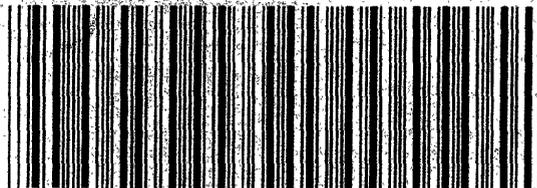
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