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

Re: Draft Guidance for Industry on Applications Covered by Section 505(b)(2)
Docket No. 99D-4809
64 Fed. Reg. 68697 (December 8, 1999)

SmithKline Beecham Corporation ("SB") submits these comments in response to FDA's request for public comment on the Draft Guidance for Industry on Applications Covered by Section 505(b)(2) (the "Draft Guidance"). SB is a global research-based pharmaceutical company that discovers, develops, and markets pharmaceutical and other healthcare products. The largest segment of SB's business consists of pharmaceutical products, including antibiotics, antidepressants, vaccines and chemotherapy drugs. SB employs scientists and support specialists worldwide to research and develop pharmaceutical products.

SB applauds FDA's efforts to clarify the procedural aspects of the 505(b)(2) application process and to solicit public comment thereon. SB is concerned, however, that FDA has taken a step to clarify procedural aspects of 505(b)(2) applications without taking necessary corresponding steps to establish clear standards for the data needed to support 505(b)(2) applications.[1] As a result, we believe the policy set forth in the Draft Guidance threatens to increase confusion about the approval process for these applications, as well as about the safety and efficacy of modified drugs approved this way. These comments identify certain issues we see in the proposed policy and make recommendations for changes to address those issues.

[1] Although not addressed in these comments, we note for the record that there are serious questions as to whether or not the FDA's interpretation of Section 505(b)(2), as reflected by recent FDA decisions and by the Draft Guidance, are correct as a matter of law. Specifically, for example, it is not clear that the law (or the US Constitution) permits 505(b) applicants to rely on the proprietary data of NDA holders without authorization, nor is it clear that Congress intended 505(b)(2) to be used for modified drugs as broadly defined by FDA.

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1. Issues Raised by the Draft Guidance

a. A Liberal Approach to 505(b)(2) Applications Raises Significant Safety and Efficacy Concerns

We recognize FDA's concern that the 505(b)(2) process has not been fully used in the past and support the agency's desire to facilitate appropriate use of these applications. Nevertheless, we note that a 505(b)(2) application is a form of a new drug application ("NDA"). As such, it must contain all information necessary to establish that the subject drug is safe and effective. And, while a 505(b)(2) applicant should not be required to "reinvent the wheel", it must be able to demonstrate that the modified product, not just the change, meets the same rigorous safety and effectiveness standards as the original product. [2]

The Draft Guidance, coupled with FDA's recent activities, signals a shift in the Agency's approach to 505(b)(2) applications. Specifically, it appears that the Agency is taking a more liberal approach towards use of 505(b)(2). Indeed, the Agency is blurring the dividing line between abbreviated new drug applications ("ANDA") and 505(b)(2) applications, especially with respect to modifications of approved drugs, by permitting modified drugs that are reviewable under 505(j) but that are bio-inequivalent to be reviewed under 505(b)(2).

The problem with the more liberal approach expressed in the Draft Guidance is that it encourages use of 505(b)(2) in the absence of articulated standards for the acceptance and review of such applications. Instead, the Draft Guidance indicates that the substantive standards will be determined on an *ad hoc* basis between FDA and each applicant. We are concerned that the absence of specific standards governing the data necessary to support each type of modification will lead to inconsistencies in the type, quality, and quantity of data relied upon by 505(b)(2) applicants, thereby enhancing the risk that review of modified drugs will be variable and in some cases not as meticulous as is appropriate for NDAs.

Modifications of drugs of the types outlined in the Draft Guidance can result in significant differences in absorption, pharmacokinetics, metabolism, stability, toxicity, drug interactions, *etc.* Even seemingly minor changes can have dramatic effects. While certain of these differences will be picked up by BE studies, others will not. Furthermore, the effects of some of the differences may manifest themselves only under certain conditions or after prolonged use. Unless there is clarity and consistency about the type, quality, and quantity of

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[2] We note that neither ANDAs nor section 505(b)(2) applications can be used for biologics regulated pursuant to section 351 of the Public Health Service Act.

data, beyond BE data, that will be required, especially but not only for modified drugs that are bio-inequivalent, there will be significant confusion and concern among prescribers and patients about the true safety and efficacy of modified drugs approved under 505(b)(2).

We are also concerned about the fact that the *ad hoc* decision making will be handled privately and therefore will exclude members of the public who may wish to comment on the standards that FDA sets for review of 505(b)(2) applications. The FDA should employ a public process to help it to specify the data that will be required for modified drugs to be reviewed and approved under 505(b)(2), just as it is seeking public input into the Draft Guidance.

We also note that the absence of clear substantive standards for approval could encourage improper end-runs around both the ANDA and NDA procedures.[3] The manufacturer of the modified drug could attempt to escape *both* (1) the ANDA requirement that it prove its product is "identical" to a listed drug and otherwise meets the requirements for approval under 505(j), and (2) the NDA requirement that all necessary studies be conducted to show that its new drug is safe and effective. Although we doubt FDA intends these results, the Draft Guidance, without modification to specify the substantive standards for approval (and without clearly articulating that drugs that are reviewable under 505(j) with or without a suitability petition cannot be approved under 505(b)) would permit them.

b. Pioneer Companies Should Be Consulted on Particular Modifications by Other Parties

The Draft Guidance does not indicate that FDA will consult with the pioneer regarding substantive aspects of 505(b)(2) applications by another entity that relies on the pioneer's studies and FDA submissions. We recognize that confidentiality concerns limit FDA's ability to disclose the identity of the applicant and specific information contained in the application. Still, we are concerned that lack of <u>any</u> consultation with the pioneer, when combined with the lack of clear guidance as to the data needed to support 505(b)(2) applications, could result in decisions being taken without the fullest information available.

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3 *Generic Recombinant Protein "Paper" NDA Approval Process Outlined by FDA*, THE PINK SHEET, at 32 (April 5, 1999) (Noting that "[a] 505(b)(2) NDA application was used for the March 24 approval of Duramed's Cenestin, a complex mixture of conjugated estrogens that was originally submitted as an ANDA referencing Wyeth-Ayerst's Premarin").

The pioneer will, in most if not all cases, possess the most comprehensive knowledge about the approved product, and the potential safety and efficacy consequences any modifications of that product might have. The pioneer typically has a great deal of data and other information that may be important for evaluating the significance of changes to the drugs or their uses and the kind of testing needed to determine whether the proposed modified drug is safe and effective.

Neither FDA nor the 505(b)(2) applicant can be expected to have as complete knowledge of the approved product simply because neither will have spent the resources studying it that the pioneer has. While the NDA, supplemental applications and post-marketing reports give FDA a detailed understanding, they still only capture a portion of the information that may be relevant to review of the modified drug, as they will not include information that is peripheral, and therefore not relevant, to the approved drug. Moreover, the studies needed to support a change sought through the full or supplemental NDA process by the pioneer will not necessarily be the same as those applicable to a change made through the section 505(b)(2) process by a company that was not involved in the development and approval of the original compound.

As mentioned above, we recognize the 505(b)(2) applicant has a legitimate need for its identity and the contents of its application to be kept confidential; we do not suggest FDA ignore the applicant's rights in this regard. Rather, we merely point out that FDA also has a countervailing public safety duty to ensure it reviews all information that could be relevant to its determination of safety and efficacy of the modified product. Therefore, we suggest FDA devise procedures to solicit information from the pioneer, on an anonomyzed basis, to assist FDA in its consideration of specific changes to specific approved drugs.

c. Modified Drugs Approved Under 505(b)(2) Are Pharmaceutical Alternatives and Cannot Be Assigned an "A" Rating in the *Orange Book*

Although not addressed in the Draft Guidance, the vagueness of the Guidance, coupled with statements attributed to FDA, cause some concern about the equivalence rating that will be accorded modified drugs approved under 505(b)(2). FDA Office of Pharmaceutical Science Director Roger Williams reportedly stated, "[w]e are postulating a path for the recombinant molecule that gets an AB rating in the Orange Book, that does not come in under the [ANDA] route, it comes in under the (b)(2) route."[4] He went on to state that to get this rating

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4 *FDA Generic Recombinant Protein Approval Process Will Use "Paper" NDAs*, HEALTH NEWS DAILY, at 1 (March 30, 1999).

the generic company would "show that the molecules are pharmaceutically equivalent. But not identical."

These statements appear to ignore FDA's longstanding test for therapeutic equivalence that was proposed and implemented through the public notice and comment process. *See Therapeutically Equivalent Drugs*, 44 F. Reg. 2,932, 41 (Jan. 12, 1979) (proposed rule), 45 F. Reg. 72,582 (final rule). The two lynchpins of this five-part test are the regulatory notions of (1) pharmaceutical equivalence; and (2) bioequivalence. *See* 21 C.F.R. 320.1(c) & (e) (1999). Indeed, the AB rating mentioned by Dr. Williams specifically contemplates that any bioequivalence problems have been resolved through adequate *in vivo* and/or *in vitro* testing. FDA, *Approved Drug Products With Therapeutic Equivalence Evaluations* 26 (1999). (*"Orange Book"*). Dr. Williams' informal public statements propose a fundamental departure from FDA's longstanding policy on therapeutic equivalence. The Draft Guidance, although silent on the issue of ratings, would appear to signal possible further departures of this sort.

We do not believe either the Draft Guidance or informal statements of agency officials should serve as the basis for modifying such a carefully deliberated policy, particularly when FDA established these criteria to protect the public health. Therefore, we strongly urge FDA not to depart from its established position on therapeutic equivalence. Modified drugs that do not have the same active ingredient, route of administration, dosage form, or strength as the original drug are Pharmaceutical Alternatives (21 C.F.R. 320 (d) (1999), *Orange Book*, at pp. 7-9), and therefore cannot be assigned an "A" rating.

2. Proposals to Address the Issues Identified

Notwithstanding these issues, we laud the FDA for attempting to clarify its policy regarding 505(b)(2) applications. Nevertheless, without addressing these critical issues, FDA could do more harm than good to its current policies and the delicate balance struck by Hatch-Waxman. Therefore, we strongly urge FDA to make the following modifications to the Draft Guidance before implementing this shift in policy.

a. *Revise the Draft Guidance to articulate clearly the substantive standards FDA will use to approve 505(b)(2) applications.* For example, the Draft Guidance should clearly articulate when BE data will suffice and what additional data will generally be required when it won't. By doing this, FDA can ensure that all drugs approved under Section 505(b), whether they be new or modified, receive proper scrutiny by the agency. Further, it will close the current hole in the Draft Guidance that may permit the

505(b)(2) process to be used as a vehicle to effect an end-run around the rigorous requirements of the NDA process.

b. *Create a presumption that preclinical toxicology and clinical safety/efficacy studies will be required as part of a 505(b)(2) application as if the application were submitted under 505(b)(1) (unless different specific requirements were established for specific modified drugs).* This presumption could be rebutted if the applicant offers a reasoned and properly supported explanation why such studies should not be required in a particular case. By applying this more structured methodology to the application process, FDA will be treating these applications as the special NDAs they truly are, rather than as an extension of the ANDA process.

c. *Develop an anonomyzed process for requesting data and other information from the pioneer concerning the approval of modified forms of its drugs.* This will need to be done carefully to protect the confidentiality rights of the 505(b)(2) applicant. Still, such a process would help ensure that FDA is making its determinations on the basis of the fullest available information so it can make the most informed decision on the safety and efficacy of the proposed modification to an approved product and on what should be required for approval.

By incorporating these recommendations, we believe the Draft Guidance will articulate a policy that both encourages greater use of 505(b)(2) applications and ensures the safety and efficacy or the products approved under the process are properly investigated.

Very truly yours,

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