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March 21, 2005

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

Re: Comments on Draft Guidance for Industry: ANDAs –  
Pharmaceutical Solid Polymorphism. Chemistry,  
Manufacturing and Controls;  
**FDA Docket No. 2004D-0524**

Dear Sir or Madam:

Greenblum & Bernstein, P.L.C. respectfully submits these comments on the above-referenced Draft Guidance relating to polymorphism in ANDAs.

As an initial matter, Greenblum & Bernstein is a general patent law firm having substantial experience with issues surrounding approval of generic drugs. While we count a number of generic and branded drug companies among our clients, the enclosed comments were prepared in the public interest, and not with any particular client in mind. That is, these comments were not requested or paid for by any client, and should not be taken as espousing the views or furthering interests of any particular company.

Because the comment period is scheduled to expire on March 21, 2005, these comments are timely submitted. The undersigned respectfully asks FDA to consider these comments when deciding whether to issue final Guidance, and, if issued, what form the Guidance should take.

Our comments follow:

*The FDA Polymorph Guidance is Unnecessary  
Because ANDA Applicants Already Must Meet BA/BE and Stability Requirements*

The draft Guidance is intended to assist ANDA applicants when a drug substance exists in polymorphic forms and to provide recommendations as to “sameness” and recommendations

for monitoring and controlling polymorphs in drug substances and products.

The Guidance clearly suggests that ANDA applicants must be familiar with polymorphism of their drug substance, including the potential affect of polymorphism on BA/BE and screening methods to identify problematic polymorphs. Today's sophisticated generic drug manufacturer is probably already aware of these issues discussed in the Guidance.

In most cases, we do not believe that further characterization of polymorphs by ANDA applicants is necessary for the applicants to meet their 505(j) requirements for providing the FDA with adequate data showing BA/BE.

Even if a polymorph in an applicant's drug product is of low solubility, the applicants must still submit the required evidence of BA/BE and stability in their ANDA. If either blood levels or stability are not acceptable, then the ANDA should be either not submitted or not approved, and polymorphism is only one possible culprit out of many. There is no requirement in the statute or regulations for a separate polymorph specification to support such evidence.

FDA should not require additional characterization of a polymorph specification if applicants meet their statutory and regulatory requirements as currently required. FDA's current requirements of safety and efficacy in an ANDA, which include (among other requirements) BA/BE and stability, have proven adequate. By addressing polymorphism, FDA points to an issue, but has not indicated how and if this issue has been a problem a problem in the past. The fact that FDA intends to apply the Guidance only to the generic industry further suggests that the investigations are not considered generally necessary.

*The FDA Guidance is in Effect Mandatory, and Seeks to Accomplish What FDA Declines to do by Formal Notice and Comment Rule-Making*

The proposed FDA Guidance recommendations only apply to ANDA applicants, and their submission for approval of chemistry, manufacturing, and controls (CMC) information in the ANDA. By making the Guidance only applicable to ANDAs, and not to NDAs, FDA seems to be implying that ANDAs are somehow especially vulnerable to issues of polymorphism. Yet FDA does not point to any evidence of this. FDA, however, does parenthetically note that the Guidance also may be relevant for new drug applications (NDA) including the submission of patent information for polymeric forms of the active ingredient pursuant to 21 CFR 314.53(b).<sup>1</sup> While perhaps being relevant to NDAs, the Guidance recommendations do not apply to NDA applicants.

According to the document itself, the draft Guidance would not be mandatory if finally adopted. Nevertheless, the detailed "suggestions" in the Guidance may be perceived by the generic

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<sup>1</sup> Draft Guidance, footnote 2.

industry as necessary in order to secure ANDA approval. That is, a generic company may, understandably, be under the impression FDA will look rather negatively on an ANDA if a reviewer learns that the “voluntary” Guidance was not followed. Accordingly, a generic company might be under the impression that to maintain a favorable standing before the FDA reviewer then the generic company should do everything possible to show that they have followed FDA Guidance. In this sense, the Guidance will be viewed in effect to be mandatory.

If the Guidance is thus effectively mandatory in the eyes of the good-faith ANDA applicant, then the Guidance would achieve the same effect as FDA regulations which would normally require statutory formal notice and comment rulemaking.

The Food Drug and Cosmetics Act prohibits FDA from requiring any information in an ANDA in addition to that required by the statute.<sup>2</sup> In 1992, FDA specifically rejected the view that “sameness” required identical physical and chemical properties. The draft Guidance explicitly states that polymorphism falls under this rubric, and that “differences in drug substance polymorphic forms do not render drug substances different active ingredients for purposes of ANDA approvals . . . .”<sup>3</sup> Thus, the FDA Guidance may be attempting to accomplish by “voluntary” guidance what it appears to acknowledge it cannot do by formal rulemaking.

To the extent that FDA implements the voluntary Guidance, It is respectfully requested that FDA explicitly make clear, in view of the voluntary nature of the Guidance, that:

- a) FDA will draw no negative inference if an ANDA applicant does not perform, or does not submit, polymorphism information propounded in the Guidance; and
- b) No FDA reviewer will make lack of compliance with the Guidance any part of any deficiency letter.

It is respectfully submitted that if FDA declines to make such statements, then this indicates that FDA actually considers the Guidance mandatory, not voluntary. As FDA is aware, any “mandatory Guidance” should be characterized as such during a formal Notice and Comment rulemaking procedure.

*The FDA Guidance Creates an Experimental Record Discoverable in Patent Litigation,  
Even Over Patents Not Listed in the Orange Book*

An increasing number of patents directed toward polymorphs, including commercially unimportant or undesirable polymorphs, are being filed by the brand manufacturers. Many, if not

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<sup>2</sup> See FDCA § 505 (j)(2)(A) (21 U.S.C. § 355 (j)(2)(A)).

<sup>3</sup> Draft Guidance, lines 184-192.

most, of these forms will never be listed in the Orange Book. Establishing guidelines for ANDA applicants to make note of, and in some cases further characterize, any such polymorphs would appear to be overly burdensome on the applicant for an ANDA. In particular, by following such recommendations the applicants for the generic would be creating a written record that might be discoverable in later litigation.

If a generic company decides to follow the draft Guidance (whether through sense of compulsion or for any other reason), then this will result in creation of a written record of such Guidance-directed investigations. Such investigational work resulting from the Guidance might have to be turned over to the NDA holder and patent owner pursuant to discovery during litigation. This would be true regardless of whether or not the patent being litigated is listed in the Orange Book, and whether or not the litigation is pursuant to a Paragraph IV certification before the FDA.

Therefore, an unintended consequence of the FDA Guidance could be to create numerous new confidentiality issues with regard to internal business practices of generic companies even on products that will never be litigated pursuant to a Paragraph IV certification.

*If FDA Believes Polymorphism is a BA/BE or Stability Issue  
Then it is also a General QA/QC Issue that Should Apply to Both NDA and ANDA Applicants.*

To the extent that the FDA truly believes that polymorphism is a true BA/BE or stability issue, then polymorphism is also a general QA/QC issue for NDA applicants as well as ANDA applicants. Making the Guidance apply only to ANDA applicants places a disproportionate and unfair burden on only a select group of applicants for drug approval. Also, the fact that FDA only makes the Guidance applicable to ANDAs weakens the FDA's argument that polymorphism is, in general, an important property to be considered in a drug application.

*Conclusion: The FDA Should Withdraw the Guidance,  
or Expressly Apply it to Both NDA and ANDA Applicants*

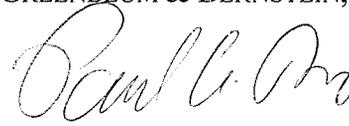
For the above reasons, the proposed FDA guidance is not necessary for facilitating the ANDA application process, and the Guidance should not be issued in final form.

In the alternative, if FDA decides to issue the Guidance, then FDA should revise the Guidance as appropriate to have it apply to both NDA and ANDA applicants. Moreover, because FDA states that the Guidance is voluntary, then upon issuance, FDA should explicitly state that a) FDA will draw no negative inference if an ANDA applicant does not perform, or does not submit, polymorphism information propounded in the Guidance; and b) no FDA reviewer will make lack of compliance with the Guidance any part of any deficiency letter.

March 21, 2005

Thank you for the opportunity to comment on the above-referenced draft Guidance.

Sincerely,  
GREENBLUM & BERNSTEIN, P.L.C.

A handwritten signature in cursive script, appearing to read "Paul A. Braier".

Paul A. Braier, Ph.D., Esq.

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