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Laurie Smaldone, M.D.
Senior Vice President
Worldwide Regulatory Affairs

April 19, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99D-0121; Proposed Draft Guidance, *"Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System"* (Federal Register Vol. 64, No. 31, February 17, 1999)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on the FDA draft guidance for industry, *"Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System"*.

99D-0121 C11

Bristol-Myers Squibb Company respectfully suggests that this Draft Guidance should not be finalized until several critical issues, discussed below, are addressed and adequately resolved. Implementation prior to that time could create safety and intellectual property concerns. Attempts to resolve these concerns after implementation of this Draft Guidance could result in the Agency having to divert its resources from more meaningful and productive activities.

A. The Draft Guidance exceeds FDA's authority under Hatch-Waxman.

The draft guidance expands the category of drugs for which in vivo bioequivalence tests are waived. This exceeds the FDA's authority under Hatch-Waxman and upsets the balance between innovator and generic pharmaceutical companies which was established by Congress. Although this Draft Guidance may be viewed as an attempt to clarify "how to" information for a class of compounds for which in vivo bioequivalence is self-evident, there does exist the possibility that a compound for which bioequivalence does not exist could be swept up into this class.

For example, the intestinal metabolism of several compounds can be inhibited by commonly used amounts of several GRAS (generally regarded as safe) pharmaceutical excipients. Therefore, it is conceivable that despite meeting solubility, permeability and dissolution criteria, the pharmacokinetics of the active substance from a new drug product could be affected if the excipients have different effects on drug metabolizing enzymes. The impact of such changes could vary widely. Significant changes in the pharmacokinetics of drugs that show substantial nonlinearity or time dependence in the therapeutic range could also result from slight changes in the rate of absorption produced by changes in dissolution. These effects would not be detected with a dissolution test unless a quantitative relationship between dissolution rate and bioavailability was established.

In light of this, the Draft Guidance has the potential to create a problem where one currently does not exist by mis-identifying compounds as not needing in vivo studies to establish bioequivalence, when in reality performing such studies would show the lack of bioequivalence. Therefore, the implementation of this Draft Guidance would provide an unfair advantage to certain generic manufacturers by inappropriately freeing them of the obligation imposed under Hatch-Waxman to either establish bioequivalence or to substantiate (through a waiver request) the fact that in vivo methods need not be used to show bioequivalence. Furthermore, the current system of waivers, established under 21 CFR 314.22(b)(3), has not been shown to improperly identify drugs which do not need in vivo bioequivalence studies.

B. Application of the Draft Guidance to narrow therapeutic index (NTI) drugs is unclear.

There is no currently agreed upon criteria for defining NTI drugs. Until such criteria are created and agreed upon, it is open to interpretation as to which drugs might be excluded from the application of this Guidance.

Notwithstanding the statement in the Draft Guidance to the contrary, it appears that the FDA may intend to include NTI drugs, according to Dr. Ajaz Hussain, the primary FDA contact for the Draft Guidance. On October 22, 1998 at a meeting of the FDA Pharmaceutical Science Advisory Committee, in response to a question about the basis for excluding NTI drugs from the Class I category, Dr. Hussain replied: "I think the working group debated that issue and we felt it was more prudent to take a more conservative and cautious step in this direction. I think once we ... gather more information, probably we will have to reexamine that question." This poses significant concerns as to whether FDA is embarking on a 'slippery slope' of lessening ANDA standards. Until greater clarity as to where the FDA ultimately intends to end up, the implementation of this Draft Guidance will create more issues than it resolves.

C. The FDA should either delay implementation of the Draft Guidance, or revise it, in order to promote the goal of international harmonization.

The European Agency for the Evaluation of Medicinal Products (EMEA) is in the process of developing a guidance for the investigation of bioavailability and bioequivalence. The most recent draft states that bioequivalence studies should be performed for all generic immediate release products intended for systemic action, unless the applicant can establish that in vitro data alone are sufficient to ensure bioequivalence. The draft EMEA document basically overlaps the requirements of the draft FDA Guidance, with one exception: the EMEA would require applicants to show that the drug's pharmacokinetics are characterized by a pre-systemic elimination/first pass metabolism less than seventy percent and are linear (i.e., not dose or time dependent) within the therapeutic range. Delaying the implementation of this Guidance provides further time to discuss the merits of the EMEA approach.

Alternatively, the Draft Guidance could be modified to include in Section V these two criteria. This will allow the initial standards to match those currently being considered by the EMEA in its draft. Should the EMEA choose to drop these standards from its final document, the FDA could do the same and harmonization would be achieved. If, however, the Draft Guidance were to be implemented as currently written, and the EMEA chooses to retain the above criteria, harmonization would be thwarted.

D. If the Draft Guidance is implemented there is no method for identifying incorrect assumptions of bioequivalence.

If there is the slightest possibility that a bio-inequivalent compound will be incorrectly assumed to be bioequivalent, there should be a system in place for spotting and correcting such errors of assumption. The FDA's adverse events reporting system would catch those cases where death or serious injury occur. Lesser complications arising from bio-inequivalence, however, may go unnoticed for a protracted period of time.

The FDA's inability to adequately identify problems arising from the implementation of this Draft Guidance as it applies to Class 1 compounds will be a factor in any subsequent considerations to expand the Draft Guidance to other Classes. Assuming the Draft Guidance is implemented, the FDA should perform a periodic, random verification of actual bioequivalence of compounds that take advantage of its provisions.

E. Continued Data Exclusivity as provided by Hatch-Waxman is Unclear.

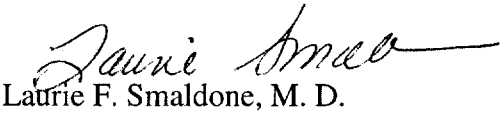
The solubility and permeability data provided in an NDA, if not otherwise publicly available, is propriety information. It is unclear from the Draft Guidance whether such data would, in certain cases, need to be relied upon to determine whether a compound has high solubility and high permeability. Since the NDA filer controls the right of reference to such information, the Draft Guidance should clarify the types of alternative information the ANDA applicant must supply in order to make the determination in such circumstances. Particular attention should be paid to the fact that literature reports would not necessarily rely on data generated from active pharmaceutical ingredients produced at facilities subject to FDA GMP inspections.

F. Dissolution fit factors should be applied to all potencies.

Finally, the draft Guidance, if it is to be implemented, should be revised in Section V.3 to make it clear that the referenced fit factors apply to all potencies of an ANDA application.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



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