GlaxoWellcome

April 16, 1999

7846 '99 APR 19 A9:45

Management Dockets
Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1-23
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket Number: 99D-0121

Dear Sirs:

Please find enclosed GlaxoWellcome's comments on the draft Guidance for Industry - Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active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.

Please feel free to call me at (919) 483-6408 if you need additional information or clarification regarding the comments.

Sincerely,

Suva B. Roy

Suva B. Roy, Ph.D.
Director, Chemistry Pharmacy and Manufacturing
Regulatory Affairs and Quality Division

99D-0121

CH

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Comments from GlaxoWellcome on the Draft Guidance for Industry –

Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate Release Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on Biopharmaceutics Classification System

General

The guidance is pragmatic and a big step in the right direction. We also agree with the principles in Sections A and C on Regulatory Application of BCS.

Many older approved drugs may not have been specifically studied for solubility and permeability during their development. However, based on available in-vitro and BA/BE data, it may be possible to infer the biopharmaceutics classification of these drugs. We recommend that the guidance specifically address such situations. It will greatly simplify obtaining biowaivers for post-approval changes for these older drugs without having to undertake new in-vivo or in-vitro studies.

Certain drugs may show poor solubility at only the extremes of pHs or at only one intermediate pH while having more than adequate solubility all other pHs. Some antibiotic drugs fall under this category. By definition these drugs will be classified as low solubility and excluded from the provisions of this guidance, although they may have a high permeability. Perhaps the guidance may be expanded to include these "apparent" low solubility and high permeability drugs.

Specific

Permeability, page 3

The definition of highly permeable drugs should also include t_{max}. We suggest a $t_{max} \leq 2$ hours for these immediate release dosage forms.

Determining Solubility Class, page 4

The guidance has not specified what buffers may be used as the aqueous media for the equilibrium solubility determinations. We recommend that the guidance specify USP buffers for the purpose. This will make the guidance consistent with the dissolution class boundary test on page 3 and also the FDA's Guidance for Industry - Dissolution Testing of Immediate Release Solid Oral Dosage Forms.

The guidance recommends that octanol:water partition coefficient can be used as supportive information on permeability characteristics of the drug substance. But the guidance is silent on how the partition coefficient should be interpreted. We recommend that a partition coefficient range for high permeability drugs be included in the guidance.

Intestinal Permeability Methods, page 6

Discussion of reliability of the of permeability class states "(2) a linear relationship between doses (including the highest dose strength) of a drug and its rate and extent of absorption can be documented....". This is somewhat confusing because the extent of absorption should be independent of the dose for a passively transported drug. Perhaps "amount of drug absorbed" can be substituted for "extent" in the sentence.

Exceptions, page 8

The guidance states that a waiver would not be appropriate for dosage forms intended for retention in the oral cavity (e.g. sublingual or buccal tablets). It is however silent on chewable tablets. Perhaps this guidance should apply to chewable tablets as well. The Agency has used dissolution testing of whole chewable tablets as a way to show similarity on post-approval changes. We recognize that certain special considerations may apply to these tablets, and the guidance should include these considerations.

INDs/NDAs - Documenting Bioavailability and Bioequivalence, page 8

This discussion includes the statement "...or if problems with absorption exist, to an intravenously administered drug formulation (320.25(d)(3)". An intravenous dosing may not always be feasible or desirable for all drugs. Also, the statement may be misinterpreted to infer the need for an absolute bioavailability study without an exception. We recommend that the guidance language be clarified to ameliorate such possible misinterpretation.

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GlaxoWellcome

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