



March 6, 2000

1782 '00 APR 14 10:13

Mr. Dennis Baker
Associate Commissioner for Regulatory
Affairs
Food and Drug Administration
Rockville, MD 20857

Re: Docket No. 98P-0145/PRC 1

Dear Mr. Baker:

This is in response to your letter of February 29, 2000, which responded to the Petition for Reconsideration (PRC) we filed on November 5, 1999 in connection with the referenced Citizen's Petition. We filed that PRC for many reasons, including our belief that it was in substantial part based, mistakenly, on data from our ANDA submission for Dilacor XR® (ANDA 74-852), instead of our ANDA submission for a bioequivalent version of Cardizem® CD (ANDA 74-752). While your letter acknowledges that error, the Agency now concludes that an analysis of the correct product would have yielded a similar result because "Cardizem CD's pharmacokinetic profile is highly variable, ... does not always exhibit two peaks, and when a second peak is present it occurs at variable times" (p. 2).

We continue to disagree with many of the Agency's observations and conclusions concerning Cardizem CD's pharmacokinetic profile. According to your letter, those observations and conclusions were not obtained from any ANDA, but rather from the new drug application for Cardizem CD and from additional data from lots of Cardizem CD submitted to support various postapproval supplemental applications. (p.2). Particular emphasis was placed on an analysis the Agency conducted on a study submitted by HMR for the approval of a new dosage strength of, and manufacturing site for, its Cardizem CD product. (p.4). Once again, it appears that the Agency has made a critical mistake and has based its determinations on an analysis of the wrong product.

As noted by your letter, "the formulation of Cardizem CD combines fast- and slow-dissolving beads, resulting in a two-peak pharmacokinetic profile in the majority of the subjects receiving the drug product." (p. 2). The recently approved new 360 mg. strength of Cardizem CD does not fit this criterion, and is a very different product. This new Cardizem CD dosage form employs a different drug delivery technology, licensed from Ethypharm, which does not combine fast- and slow-dissolving beads. Unlike the previously approved dosage forms of Cardizem CD, which employ a patented drug delivery system owned by Carderm

98P-0145

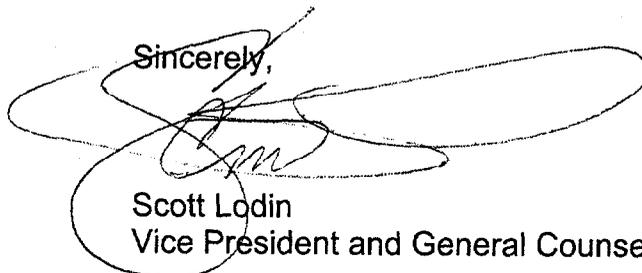
C19

Capital LP, this new product is not designed to result in the two-peak pharmacokinetic profile. See, February 22, 2000 press release attached hereto.

Similar to Biovail's ANDA, HMR filed this new product as a supplemental line extension of its Cardizem CD NDA in order to take advantage of the standard criteria of Cmax and AUC used by the Agency for determining bioequivalence. Our Citizen Petition recognized that these standard criteria were inappropriate for the 120, 180, 240 and 300 mg strengths products such as Cardizem CD, for they exhibit a distinct and measurable two-peak pharmacokinetic profile and, for patients' safety, requested that the Agency pharmacodynamically relevant standards to those products.

We believe there were a significant number of additional material errors in your letter as well and bring this matter to your attention so that the Agency can better monitor this situation and thereby protect American consumers whose safety we believe may be at risk, for all of the reasons cited in our Citizen Petition and the comments thereon.

Sincerely,

A handwritten signature in black ink, appearing to read "S. Lodin", is written over a large, loopy scribble. The signature is positioned above the printed name and title.

Scott Lodin
Vice President and General Counsel