



Food and Drug Administration
Rockville MD 20857

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Scott Lodin, Esq.
Vice President and General Counsel
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

Re: Docket No. 98P-0145/PRC1

Dear Mr. Lodin:

This responds to your petition for reconsideration and stay of action, as well as your petition to modify the decision, dated November 5, 1999, requesting that the Food and Drug Administration (FDA) act as follows:

1. Reverse the determination that the Agency will not revise its bioequivalence guidance to require plasma profile matches for drug products with multiple-peak plasma profiles, unless the abbreviated new drug application (ANDA) applicant can establish (in addition to other circumstances) that any profile differences are medically insignificant.
2. Reverse the determination that FDA will not refrain from approving any ANDA for a controlled release drug product that fails to match the innovator's multiple-peak plasma profile.
3. Reverse the determination that FDA will not refrain from approving any ANDA for Cardizem CD unless the applicant matches the innovator's two-peak plasma profile.
4. Reopen its review of the original Andrx citizen petition, consider new information submitted by Andrx along with information previously submitted, and modify the Agency's October 22, 1999, response to the original petition to grant the relief it requested.

We have considered the information in the petitions described above as well as the information in the original citizen petition, dated February 26, 1998, the supplement, dated September 9, 1998, and comments 1 through 18 to the original citizen petition.

98P-0145

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This response incorporates by reference our previous response to the original citizen petition (CP Response), dated October 22, 1999, with the exception of the discussion on pages 8-9 of that response related to ANDA 74-852 as explained below in section I.B. We deny your petition for reconsideration and stay of action, and your petition to modify the decision, for the reasons set forth below. In brief, we have concluded that Cardizem CD's pharmacokinetic profile is highly variable. The profile does not always exhibit two peaks, and when a second peak is present it occurs at variable times. The nominal two-peak profile is therefore not an aspect of the product's pharmacokinetics against which bioequivalence of another product should be judged. We also have determined that the Biovail ANDA 75-116 for Diltiazem Hydrochloride Extended-Release Capsules is bioequivalent to Cardizem CD applying our standard criteria, C_{max} and AUC.

I. Cardizem CD's Pharmacokinetic Profile

A. Cardizem CD

As described more thoroughly in the CP Response, Cardizem CD is an extended release diltiazem hydrochloride drug product manufactured by Hoechst Marion Roussel, Inc. (HMR). Cardizem CD capsules are administered once a day for the treatment of hypertension and the management of chronic stable angina and angina due to coronary artery spasm. 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.

B. Basis for Determination Related to Cardizem CD's Pharmacokinetic Profile

You assert in your petition for reconsideration (PRC) that we erroneously reached the conclusion in our response to your previous citizen petition, supplement, and comments (CP Response) that Cardizem CD does not possess an intentional, distinct, consistent and reproducible two-peak pharmacokinetic profile (PRC at 3). You state that "[i]t appears that all of the conclusions of the Response are based on this critical assumption" and that reliance on this assumption is faulty because we relied on data from the wrong ANDA – Andrx's ANDA using Dilacor XR as the reference listed drug (RLD), rather than its ANDA using Cardizem CD as the RLD.

We did not rely on the data from any ANDA to make a determination with respect to the intentional or reproducible nature of Cardizem CD's pharmacokinetic profile. To the contrary, we relied on data obtained directly from the new drug application (NDA) for Cardizem CD. Initially, we reviewed data from lots of Cardizem CD that the sponsor, HMR, submitted to support its NDA. We have now reviewed additional data from lots of Cardizem CD submitted since 1991 to support various postapproval supplemental applications.

As you note in the PRC, we erred when we evaluated data from Andrx's ANDA 74-852 referencing Dilacor XR. However, analysis of the data from Andrx's ANDA 74-752 referencing

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Cardizem CD leads to the same conclusion reached in the CP response. The data in that ANDA submission yield similar results with respect to the pharmacokinetic profiles of the test and reference products. See discussion in section I.D.1. below. Moreover, as described below, Cardizem CD's pharmacokinetic profile is variable, precluding the precise matching by generic drug products that Andrx would have us require.

C. Variability and Nature of Cardizem CD's Pharmacokinetic Profile

We continue to find that while Cardizem CD indisputably chose a two bead formulation to ensure blood pressure control for an entire 24 hour period, Cardizem CD's precise pharmacokinetic profile is not intentional, distinct, consistent, and reproducible. Since we issued our CP response on October 22, 1999, we have reviewed additional data that further support this determination.

1. Timing of Second Peak of Cardizem CD is Unpredictable

The second peak of Cardizem CD is altogether absent in many subjects in the studies submitted by HMR. This absence of a second peak was mentioned in our previous CP Response and was found again in review of the additional data. In single-dose studies submitted by HMR to support a manufacturing site change and higher dosage strength, between 4 and 18 percent of subjects did not exhibit a two-peak pharmacokinetic profile. In multiple-dose studies, between 19 and 27 percent of subjects did not exhibit a two-peak pharmacokinetic profile.¹ In those subjects who showed a second peak, the second peak occurred at markedly different time intervals between subjects, ranging from 12 to 21 hours postdose.

The studies submitted by Andrx in support of its ANDA confirm this observation. Using somewhat more stringent criteria, e.g. a rise of more than 30 ng/ml from the trough to represent a peak, 13 out of 21² subjects on the Cardizem CD product in the Andrx ANDA multiple-dose study had no second peak. Indeed, the Cardizem CD product might better be described as having two troughs, the nominal second peak reflecting a rise from a previous fall in blood levels. Although this late increase in blood levels preserves the 24-hour blood pressure effect of the Cardizem CD product, it is highly variable in size and timing and therefore difficult to consider it planned. These factors contributed to our determination that Cardizem CD's pharmacokinetic profile is not consistent.

¹ We applied the most lenient criteria in making this determination. We considered as a second peak any increase, however slight, in plasma concentration occurring after the initial decline in plasma concentration following the first peak.

² We excluded 3 subjects from the study in this analysis (study 95118) because they did not exhibit a second peak of any magnitude in the plasma profile.

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2. Second Peaks of Different Lots of Cardizem CD Are Not Bioequivalent

We found that if we applied bioequivalence standards to the second peak in the plasma profile of subjects administered Cardizem CD as the argument in your petition suggests (PRC, Attachment (Att.) C at 24), HMR would not be able to establish the bioequivalence of different lots of Cardizem CD. This finding is based upon an analysis we conducted on a study submitted by HMR for the approval of a new dosage strength of Cardizem CD. The new dosage strength was approved based on the sponsor's demonstration of bioequivalence between two different lots of 360-mg capsules and one lot of 180-mg capsules. The sponsor compared one 360-mg capsule of one lot to one 360-mg capsule of the different 360-mg lot and to two 180-mg capsules of the 180-mg lot. Based on our bioequivalence criteria of AUC and C_{max} , HMR was able to establish that each lot of 360-mg capsules was bioequivalent to two 180-mg capsules.

We recently analyzed these same data to determine whether the sponsor could establish bioequivalence between the different lots of the 360-mg capsules if the same testing criterion for rate, C_{max} was applied separately to the second peak in the plasma profiles of the subjects tested. When we compared the second peak in the plasma profiles of both the single- and multiple-dose study arms of those different lots of Cardizem CD, the second peaks did not pass the bioequivalence criterion.³ This analysis demonstrates that even the sponsor of Cardizem CD is unable to pass this bioequivalence criterion with respect to its own lots of the drug product. Given this fact, we cannot require a generic drug product to demonstrate a level of bioequivalence to Cardizem CD that Cardizem CD cannot demonstrate to itself.

It is interesting to note that the failure of the single-dose and multiple-dose study arms of HMR's study to meet the bioequivalence criterion when applied to the second peak occurred at opposite ends of the confidence interval (CI) spectrum.⁴ When the 90 percent CI is applied to the second peak in HMR's single-dose study arm, the point estimate of the ratio comparing C_{max2} is 0.923 with a 90 percent CI of 0.78-1.08. This lot failed the bioequivalence testing on the low end of the CI range. When the 90 percent CI is applied in a similar manner in HMR's multiple-dose study arm, the point estimate is 1.10 with a 90 percent CI of 0.96-1.26, showing that this lot failed on the high end of the CI range. This again demonstrates the highly variable nature of the second peak in the pharmacokinetic profile of Cardizem CD and further supports the conclusion that the sponsor did not formulate the drug product to have an intentional, consistent second peak.

³ We calculated the ratio of C_{max2}/C_{max2} for each lot and applied the 90 percent confidence interval analysis as described below in footnote 4. We conducted this analysis based in part on your claim in the PRC that each peak reflects a separate rate of absorption (PRC, Attachment C at 24).

⁴ The 90 percent confidence interval for the ratio of the test product means (AUC and C_{max}) to those of the innovator must lie within the interval 0.80 to 1.25 on log-transformed data.

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Moreover, these lots failed the bioequivalence analysis described above despite the fact that the analysis was weighted in favor of the sponsor. Specifically, the analysis comparing different lots of Cardizem CD to each other looked only at the subjects that exhibited two peaks in both lots. As described above in section I.C.1., many subjects in both the single- and multiple-dose arms of the HMR study were excluded because they did not have two peaks in their plasma profiles. Had we included these subjects⁵ in this lot to lot comparison, the CIs would have been much wider.

D. Inability of Andrx Product to Match Cardizem CD's Pharmacokinetic Profile

1. Percentage of Two Peaks in Pharmacokinetic Profile

We agree with your claim that in ANDA 74-752 both the Andrx ANDA drug product and Cardizem CD show the presence of a two-peak pharmacokinetic profile to varying degrees. We do not take issue with your assertion that in the single-dose study both the Andrx product and Cardizem CD exhibit two-peak pharmacokinetic profiles somewhere in the range of 90 percent - 100 percent of test subjects (PRC, Att. C at 7-8). We do not agree, however, that in the multiple-dose study two-peak plasma profiles are present in 92 percent of subjects administered the ANDA drug product and 100 percent of those subjects administered the Cardizem CD drug product. Using the same analysis that we applied to the data in ANDA 74-852, we found that for the multiple-dose study in ANDA 74-752 two-peak plasma profiles were present in 83 percent of the subjects administered the Andrx generic formulation of diltiazem HCl. The data further show two peaks in the plasma profiles in 79 percent of the test subjects receiving Cardizem CD in the multiple-dose study. These data demonstrate that a consistent, reproducible two-peak plasma profile is not present in all subjects who receive the Andrx generic diltiazem HCl or Cardizem CD under steady state conditions.

2. Relevance of Bioinequivalence of Second Peaks in Cardizem CD's Pharmacokinetic Profile

As previously discussed, we found that different lots of Cardizem CD were not able to pass the bioequivalence criterion, C_{max} , when applied to the second peak of Cardizem CD's plasma profile. This is likely related to Cardizem CD's formulation, described in detail in the CP Response, which uses a combination of fast and slow dissolving beads. The ratio of fast- to slow-dissolving beads may vary from lot to lot of Cardizem CD, resulting in a variable two-peak pharmacokinetic profile. As explained in section I.C.2., even the sponsor of Cardizem CD was unable to pass the bioequivalence criterion with respect to two of its own lots of the drug product. Given these facts, an ANDA drug product referencing Cardizem CD cannot be expected to match Cardizem

⁵ We excluded 7 out of 24 subjects in the single-dose study arm and 8 out of 24 subjects in the multiple-dose study arm of the HMR studies conducted for approval of a new dosage strength of Cardizem CD.

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CD's pharmacokinetic profile. If the second peak is too variable for the innovator to match itself in different lots of the drug products, we cannot expect an ANDA applicant to do so.⁶

II. Medical Insignificance of Second Peak in Cardizem CD's Pharmacokinetic Profile

A. Variable Nature of Second Peak

As demonstrated above, the second peak in the plasma profile of subjects administered Cardizem CD may be absent or may occur at widely varying time intervals. This variable nature of the plasma profile contributes to our conclusion that the second peak in the plasma profile is medically insignificant. It is also, on average, quite small. For example, in the multiple-dose study of the Andrx ANDA, study 95118, the average second peak for the reference product (Cardizem CD) is less than 30 ng/ml greater than the preceding trough.⁷

B. Literature Studies Do Not Establish Medical Significance of Second Peak

In the PRC you assert that we overlooked a body of evidence establishing the medical significance of the second peak in Cardizem CD's pharmacokinetic profile. You describe the importance of that evidence and supplement your arguments with evidence provided in the petition to modify the decision.

1. *American Journal of Hypertension* Article

You first describe a study comparing the pharmacokinetic and pharmacodynamic differences between Tiazac, manufactured by Biovail Laboratories, Inc. (Biovail)⁸ and distributed by Forest Laboratories, Inc., and Cardizem CD. An analysis of this study was published in the October 1999 issue of the *American Journal of Hypertension* (AJH). The authors conclude that Tiazac, which has a single microbead system, produced higher plasma concentrations, resulting in more

⁶ We question whether Andrx even intended to match the second peak of the plasma profile in the ANDA 74-752 drug product, and its purported pharmacodynamic effects, with that of Cardizem CD. We note that Andrx did not measure blood pressure of the subjects after 12 hours during the single- and multiple-dose studies. When a second peak was exhibited in these subjects, it always occurred after 12 hours postdose. Consequently, the data presented to us do not support claims of reduced blood pressure associated with a two-peak plasma profile.

⁷ In the single-dose study, 95068, the average second peak for the reference product was less than 55 ng/ml greater than the preceding trough.

⁸ Biovail is the sponsor of Tiazac, NDA 20-401, a once-a-day diltiazem HCl drug product. Biovail is also the sponsor of ANDA 75-116 which uses Cardizem CD as the RLD. Tiazac is an NDA product that is not bioequivalent to Cardizem CD. Biovail's ANDA drug product at issue in the PRC is bioequivalent to Cardizem CD.

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pronounced blood pressure lowering effects, than Cardizem CD, which has a dual microbead system. The differences in blood pressure lowering effects were of the order of 2-2.5 mm Hg for systolic blood pressure (SBP) and 1-2 mm Hg for diastolic blood pressure (DBP). This response, however, is easily explained by the increased bioavailability of Tiazac compared to Cardizem CD, rather than by any particular shape of the plasma profile. It has no implications for ANDA 75-116, which, unlike Tiazac, is bioequivalent to Cardizem CD.

Tiazac and Cardizem CD are not bioequivalent drug products according to the testing criteria, AUC and C_{max} . The AJH article thus does not provide evidence that pharmacodynamic differences will exist between single and double microbead drug products that are bioequivalent under our standards. It shows only that bioinequivalent products are not interchangeable. Interestingly, the AJH paper documents an important element of our position, namely, that the putative two-peak profile of Cardizem CD has no meaningful clinical impact on antihypertensive response. Specifically, the blood pressure reduction associated with both Tiazac and Cardizem CD, as shown in Figure 2 of the article, shows a consistent, sustained response over a 24-hour period. As an additional matter, we note that data in this article indicate no overall second peak in plasma concentration of study subjects administered the dual bead drug product, Cardizem CD.

2. *International Journal of Clinical Pharmacology and Therapeutics* Article

In a further effort to establish the clinical importance of the two-peak pharmacokinetic profile of Cardizem CD, you include at Attachment M an article from the *International Journal of Clinical Pharmacology and Therapeutics* (vol. 35, pp. 369-73, 1997). The authors compare the bioavailability of three once-a-day diltiazem HCl formulations that are not bioequivalent applying the criteria AUC and C_{max} .

Because no pharmacodynamic data were presented, the article does not provide any information to support your assertion that the second peak of Cardizem CD's pharmacokinetic profile is clinically important. The authors of the study acknowledge that "the study was not designed to evaluate differences in hemodynamics between the drug products." They further state that "[t]he relationship between plasma diltiazem levels and pharmacodynamic effects are better investigated in a controlled clinical trial using hypertensive patients" (p. 373). For these reasons, we conclude that this article does not provide any evidence of the clinical significance of the difference in plasma concentrations between two-peak and single-peak diltiazem drug products.

C. Submissions from Medical Professionals are Not Persuasive

In attachments to your petition to modify the decision, you cite letters from several medical professionals to support your belief that the two-peak pharmacokinetic profile of Cardizem CD is medically important. You thoroughly address the substance of these professional opinions expressed in those letters in Attachment C to the PRC.

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In one letter, Dr. Lawrence Solomon cites case histories purporting to establish the medical importance of a varying pharmacokinetic profile for patients administered diltiazem HCl (PRC, Exhibit I). However, in the case histories that Dr. Solomon presents, none of the patients was maintained on Cardizem CD therapy. Therefore, the case histories do not contain any data or evidence showing the medical significance of the presence or absence of a second peak in the plasma profile of Cardizem CD.

You also discuss letters from Dr. Bertram Pitt, Dr. William Jusko, and Dr. Robert Piepho. Drs. Pitt, Jusko, and Piepho also fail to provide factual data and clinical evidence to show that switching a patient from a dual microbead diltiazem formulation to a bioequivalent single microbead diltiazem system would result in clinically meaningful differences in blood pressure lowering effects. In the absence of objective data, these letters represent only the opinions of their authors and cannot be used as evidence to support any change in our position with regard to this matter. Also, these testimonials appear to be based on incorrect assumptions about the consistency of the putative two-peak profile of Cardizem CD.

Finally, the letters describe a preference for maintaining the intra-day variations in blood pressure that patients experience when administered Cardizem CD. For example, Dr. Solomon's letter expresses his belief that patients should be maintained on drug products that have the same pharmacokinetic profiles because altering the blood pressure fluctuations could harm patients. He states that patients could experience a fall because of blood pressure fluctuations, or could require hospitalization to stabilize their blood pressure.

As we discuss throughout this response and particularly in section II.D. below, we do not believe that any blood pressure fluctuations corresponding to a second plasma profile peak are medically significant. Moreover, as described in section I.C., if such fluctuations were truly medically significant, patients would be at risk each time they were administered a different lot of Cardizem CD.

D. Cardizem CD's Shallow Dose/Response Relationship Indicates Medical Insignificance of Two-Peak Versus One-Peak Formulations

Diltiazem HCl is known to have a shallow dose/response relationship. This characteristic means that one would need to increase the dose over a wide range (logarithmic scale) to obtain only modest changes in blood pressure. For example, an increase in diltiazem dose from 100 mg to 500 mg would be required to decrease DBP by 6 mm Hg. This shallow dose/response relationship means that, for the same dose of diltiazem, the increase in plasma concentration associated with a second peak will result in minimal, if any, change in blood pressure.

Using data obtained from the clinical trial conducted in support of the Biovail diltiazem NDA, we established a pharmacokinetic/pharmacodynamic (PK/PD) model correlating the plasma levels of

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diltiazem with the lowering of the DBP and SBP. The model confirms the shallow relationship between the diltiazem plasma concentration and its blood pressure lowering effects. The relationship between the diltiazem plasma concentration and blood pressure lowering effect was linear in nature with a baseline of 95 mm Hg DBP (or 153 mm Hg SBP) and slope of -0.0207 DBP (or -0.0262 SBP). According to the model, a diltiazem concentration of 100 ng/ml would lower the DBP by 2.07 mm Hg.

Application of this model to the data in the Andrx ANDA 74-752 multiple-dose study, 95118, clearly demonstrates the insignificance of the second peak/trough in plasma concentration of subjects. As noted previously, when a second peak was present in the subjects administered Cardizem CD, it was on average less than 30 ng/ml greater than the preceding trough. These data, when inserted into the PK/PD model, establish that any resulting blood pressure fluctuation associated with the second peak in the plasma concentration would be minimal, somewhere in the order of 0.6 mm Hg DBP and 0.7 mm Hg SBP.⁹ The PK/PD model, therefore, provides further evidence to support our conclusion that the differences in blood pressure lowering effect between two bioequivalent modified release diltiazem HCl products will not be clinically significant.

III. Absorption Rate of Cardizem CD

You express in the PRC your belief that the absorption rate of a diltiazem HCl drug product with a two-peak pharmacokinetic profile must differ from a diltiazem HCl drug product with a one-peak pharmacokinetic profile (PRC at 3). From that proposition, you conclude that the second sentence in § 320.23(b) is the relevant part of the bioequivalence regulations governing the assessment of bioequivalence between two diltiazem HCl drug products with such variations in pharmacokinetic profile. We disagree with this fundamental proposition.

Section 320.23(b) states that “[t]wo drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.” See also section 505(j)(8)(B)(i) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)(8)(B)(i)). Despite the presence or absence of multiple-peak pharmacokinetic profiles, if an ANDA establishes that its drug product meets the standard bioequivalence testing measures, we will in most cases determine that the product is bioequivalent to the RLD. (See section IV below for discussion of cases in which we may require additional information to make a bioequivalence determination.) Those standard testing measures are, as stated in our CP Response, the

⁹ For subjects administered Cardizem CD in the Andrx ANDA single-dose study, 95068, the model predicts that blood pressure fluctuations resulting from the second peak would be approximately 1 mm Hg DBP and 1.4 mm Hg SBP.

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equivalence of plasma concentrations expressed as AUC and C_{max} . This is especially true for controlled release products, which are designed to have broad, flat pharmacokinetic profiles, such that "peak" values may differ little from nearby time points. Thus, if an ANDA demonstrates equivalence in C_{max} between its drug product and the RLD, we determine that it has an equivalent rate of absorption to that of the RLD,¹⁰ unless there are differences of clear clinical impact, such as very low levels at the end of a dose-interval.

IV. Burden of Establishing Medical Significance of a Variation in Pharmacokinetic Profile

You state that we erred by failing to impose upon an ANDA applicant with a different rate of absorption from the reference product, Cardizem CD, the burden of establishing that its proposed product is bioequivalent under the second definition in § 320.23(b). You would have us require such an ANDA applicant to establish that the different rate is (1) intentional and reflected in the labeling, (2) not essential to the attainment of effective body drug concentrations on chronic use, and (3) considered medically insignificant for the particular drug studied (PRC, Att. C at 4). You also state that, in our CP Response, we incorrectly focused on the medical significance of the second peak in Cardizem CD's pharmacokinetic profile. You assert that the proper focus "is whether the ANDA product's failure to have an equivalent rate of release is intentional, reflected in the labeling of such ANDA product, and medically insignificant" (PRC, Att. C at 5).

The burden issue you raise is only relevant, however, when the rate of absorption of the ANDA drug product differs from that of Cardizem CD. You are correct in noting that we did not address that issue in our CP Response. We did not engage in that analysis because the Biovail product is equivalent to Cardizem CD using the standard bioequivalence criteria, AUC and C_{max} . What we addressed instead is the significance of a two-peak pharmacokinetic profile in the RLD when an ANDA drug product matches the RLD's AUC and C_{max} , but exhibits a different pharmacokinetic profile.

¹⁰ As a general matter, absorption rate is a difficult pharmacokinetic parameter to measure. Analysis of a concentration time curve for any orally administered drug product (immediate release or modified) will generally yield a rate/time plot that demonstrates that rate of absorption is continually changing. This is especially true of controlled release products. To speak of a single "rate of absorption" for any controlled release drug product thus has little meaning. For this reason, we have always accepted, and continue to accept, the systemic exposure measure C_{max} as indicating comparability in "rate" of absorption for controlled release products. This point was recently discussed at an American Academy of Pharmaceutical Sciences symposium in New Orleans in November 1999. It is also discussed in a draft FDA guidance for industry (issued in August 1999 and currently being finalized) entitled *BA and BE Studies for Orally Administered Drug Products – General Considerations*. This topic has also been addressed in several journal articles including Bois et al., "Bioequivalence: Performance of Several Measures of Rate of Absorption," *Pharm Res*, 11:966-74, 1994.

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The regulations at § 320.24(c) permit us, under certain circumstances, to require additional data from an ANDA applicant when, although the AUC and C_{max} bioequivalence criteria are met, the ANDA drug product's pharmacokinetic profile differs from that of the RLD. We assess the clinical importance of such differences in plasma profiles when determining whether to request additional data for an ANDA drug product. Determination of clinical importance is an analysis that incorporates the concepts embodied in § 320.24(c) and is therefore the appropriate focus for our responses to your petitions. In the present case we do not believe the differences between the pharmacokinetic profiles of Cardizem CD and the Biovail ANDA 75-116 drug product suggest a clinical problem for the one-peak product.¹¹

V. Request for Stay of Approval of ANDA

You have specifically requested that we “stay the tentative approval (and any contemplated final approval) of the ANDA submitted by Biovail Corporation International for a generic version of Cardizem CD” (PRC at 2). You assert that “Biovail . . . filed an ANDA for a product having a different rate of absorption than Cardizem CD” (PRC, Att. C at 4).

We will approve an ANDA referencing Cardizem CD if the drug product is bioequivalent to Cardizem CD using the criteria AUC and C_{max} . As previously stated, we have determined that the distinction between a one-peak and two-peak pharmacokinetic profile is not clinically important. Because of this determination, we do not need additional evidence from an ANDA applicant to establish bioequivalence of its drug product, nor will we request additional information. See § 314.127(a)(6)(i) and discussion above in section IV.

Because the ANDA for diltiazem HCl filed by Biovail met the bioequivalence criteria, AUC and C_{max} , we did not stay its approval. Biovail's ANDA 75-116 for Diltiazem Hydrochloride Extended-Release Capsules meets the current bioequivalence criteria for AUC and C_{max} as outlined in an FDA guidance entitled *Oral Extended (Controlled) Release Dosage Forms In Vivo Bioequivalence and In Vitro Dissolution Testing* (September 1993). For these reasons, we have determined that the Biovail product is pharmaceutically equivalent and bioequivalent and, therefore, therapeutically equivalent to Cardizem CD.

¹¹ We further find that even if the second definition of bioequivalence under 21 CFR 320.23(b) were deemed applicable because the difference in pharmacokinetic profile were interpreted to indicate a different rate of absorption, we could still conclude that the two products are bioequivalent. Given the general desirability of a smooth pharmacokinetic profile it is reasonable to conclude that Biovail's smooth profile is intentional. In addition, it does not interfere with attainment of effective plasma concentrations, and is medically insignificant.

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VI. Preference of Consistent Release of Drug Product over Dosing Interval

In two respects, you take issue with our previous statement that “it is usually preferable for a product to provide consistent release over dosing interval” (CP Response at 5, n. 9). First, you assert that we believe we can overlook significant differences between diltiazem HCl products with one or two peaks because consistent release over the dosing interval is preferable. This belief, you state, “is wholly contrary to the entire purpose of the bioequivalence statutes and regulations” and “is irrelevant to the issue of whether the products are bioequivalent” (PRC at 5). Second, you claim that while it generally may be correct that a consistent release is preferable, this is not true for diltiazem HCl because of its first-pass metabolism and resultant nonlinear pharmacokinetics. You state that this effect, in combination with the fact that “hypertensive and angina patients have, as individuals, their own patterns of blood pressure fluctuation and angina on an intra-day basis,” renders inapplicable the usual preference for consistent dosing (PRC, Att. C at 8).

With respect to your first point, as previously stated, we do not agree that significant blood pressure effect differences exist between one- and two-peak diltiazem HCl products. Consequently, we are not “overlooking” significant differences because of a preference for a particular type of release profile. We do agree, however, that a preference for a particular type of release mechanism is irrelevant to the bioequivalence determination of drug products. Therefore, you mistakenly interpreted our comment to indicate that such a preference affected bioequivalence determinations related to diltiazem HCl products referencing Cardizem CD. We are fully aware of our responsibility under the statute and regulations to approve ANDAs only if they meet bioequivalence requirements; we would not approve an ANDA that did not meet bioequivalence requirements even if we considered it a superior drug product. Your second claim, that a consistent release profile is not preferable when evaluating diltiazem HCl, is similarly not pertinent because, contrary to your reading of the CP Response, we do not consider preference in profiles when making bioequivalence determinations.

The footnote to which you refer merely notes our belief that Cardizem CD at times shows a pattern suggestive of a problematic formulation. It hardly makes sense, nor should it be construed to be intentional, for a modified release product to achieve an initial peak that falls by 50 percent or more before rising again. The clinical argument for such a product would necessarily be based somehow on a conclusion that reduced blood pressure control (yielding increases in blood pressure) between the timing of the first and second diltiazem peaks is clinically important and desirable. No such argument has been advanced by the sponsor or in your petitions.

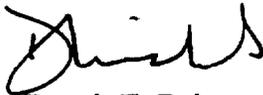
VII. Conclusion

We deny your request to reverse the determination that we will not revise our bioequivalence guidance to require plasma profile matches for drug products with multiple-peak plasma profiles

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unless the ANDA applicant can establish (in addition to other circumstances) that any profile differences are medically insignificant. We also deny your request to reverse the determination that we will not refrain from approving any ANDA for a controlled release drug product that fails to match the innovator's multiple-peak plasma profile. We further deny your request to reverse the determination that we will not refrain from approving any ANDA for Cardizem CD unless the applicant matches the innovator's two-peak plasma profile. We grant your request to reopen our review of the original Andrx citizen petition and consider new information submitted by Andrx along with information previously submitted. We deny your request to modify our October 22, 1999, response to the original petition to grant the relief it requested. We modify the October 22, 1999, response to the limited degree necessary to address the error in citation of ANDA 74-852 as discussed in section I.B. above.

Sincerely yours,


for **Dennis E. Baker**
Associate Commissioner
for Regulatory Affairs