DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 21 2003

8835 '03 DEC -9 P1:38

Kathleen M. Sanzo, Esq.
Lawrence S. Ganslaw, Esq.
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, NW
Washington, D.C. 20004

Re: Docket No. 01P-0546/PSA1 & SUP1

Dear Ms. Sanzo and Mr. Ganslaw:

This responds to your citizen petition (Petition), dated December 7, 2001, filed on behalf of Pharmacia Corporation and its affiliate G.D. Searle. You request that the Food and Drug Administration (FDA) stay the effective date of pending, tentative, or final decisions to approve (1) abbreviated new drug applications (ANDAs) or (2) applications for Covera-HS (verapamil hydrochloride (HCl)) that are filed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(b)(2)). You also request that we not accept for filing or receive within the meaning of § 314.101 (21 CFR 314.101), nor approve under section 505 of the Act and under § 314.105, applications for Covera-HS without first establishing their bioequivalence using appropriate measures and methods as follows:

1. Conduct study protocols that include a single-dose, replicate design, fasting study and a food-effect, nonreplicate design study, both using the highest strength product and nighttime dosing in subjects who follow a consistent routine of diurnal activity alternating with nocturnal sleep (Petition at 3).

2. Determine bioequivalence on the basis of area-under-the-concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum serum drug concentration (C_{max}), and partial AUC (from dosing to T_{max}) (Petition at 3). If data indicate that a generic drug product has a different input rate from Covera-HS, equivalence of these parameters should be demonstrated for the individual R- and S-enantiomers of verapamil, which are known to undergo different first-pass metabolism and to elicit different pharmacodynamic effects.

In reaching its decision, the FDA has considered all of the information in the Petition, including the supplemental declaration of Edward D. Frohlich, M.D., M.A.C.P., F.A.C.C., dated February 26, 2002, and other information available to the Agency. For the reasons set forth below, your request that we not accept for filing or receive applications without first establishing bioequivalence is denied. In addition, your request

01P-0546 PDN1

for a stay of the effective date of pending, tentative, or final decisions to approve ANDAs or 505(b)(2) applications for Covera-HS is denied in part and granted in part.

Section 314.101(d) and (e) lists the reasons that FDA will refuse to receive an ANDA. Under § 314.101(a)(2), the Agency will receive the application if FDA finds that none of the reasons in § 314.101(d) and (e) for refusing to receive an application apply. You assert in your petition that before an ANDA is accepted for filing, it must demonstrate bioequivalence. This statement is incorrect for several reasons. Section 314.101(d)(3) states that an application may be refused for filing if, on its face, the application does not contain the required information. This section does not require FDA to make a determination about bioequivalence or about the approvability or likely approvability of an ANDA before accepting the ANDA for review. To make such a determination, the FDA would need to conduct a thorough review of the information contained in an ANDA, which would in effect condition the acceptance of an ANDA on its approvability. This is clearly not the purpose of accepting an application under § 314.101. As stated in the regulations, the purpose is to make a threshold determination that the ANDA is sufficiently complete to permit a substantive review (21 CFR 314.101(b)(1)). Thus, your request is denied insofar as it would require a substantive FDA review of the information in an ANDA to determine whether the ANDA is approvable or likely to be approvable prior to its acceptance. This request is denied on the grounds that such a review is not required or contemplated by FDA regulations. FDA has concluded that the arguments in your petition are unpersuasive. As such, we will not refuse to receive or otherwise delay the review of an ANDA that meets applicable requirements for receipt of an ANDA, as provided under § 314.101.

I. Verapamil HCl

Verapamil HCl is a cardiovascular drug belonging to the calcium channel blocker class of drugs. Verapamil has antiarrhythmic, antianginal, and antihypertensive properties. Covera-HS is a controlled-onset, extended-release tablet formulation of verapamil HCl indicated for the management of hypertension and angina. Its formulation consists of an osmotically controlled, oral drug delivery system that contains a core composed of a drug (verapamil HCl) layer and an osmotic push layer. The FDA approved Covera-HS on February 26, 1996. It is marketed in strengths of 180 and 240 milligrams (mg). The Agency-approved labeling states that Covera-HS should be administered once daily at bedtime.

II. Statutory and Regulatory Basis for the Approval of ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the current ANDA approval process. An ANDA applicant does not have to submit evidence on the safety and effectiveness of the drug product because an ANDA relies on FDA's previous finding that the reference listed drug is safe and effective. Instead, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the reference listed drug as required by section 505(j)(2)(A)(iv) of the Act.[1] The scientific premise underlying the Hatch-Waxman Amendments is that, in most circumstances, bioequivalent drug products may be substituted for each other. A generic drug is bioequivalent to the listed drug if:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . .[2]

III. Bioequivalence Testing

Marketing approval of a generic verapamil extended-release tablet formulation is based in part on an acceptable in vivo bioequivalence study comparing the generic with the brand formulation. Statistical evaluation of most in vivo bioequivalence studies is based on analysis of drug concentrations in blood or plasma. The area under the plasma concentration versus time curve (AUC) is used as an index of the extent of drug absorption. Generally, both AUC determined until the last blood sampling time ($AUC_{0\text{-}t}$) and AUC extrapolated to infinity (AUC_{∞}) are evaluated.[3] Drug peak plasma concentration (C_{max}) is used as an index of the rate of drug absorption.[4]

The Agency specifies that the rate and extent of bioavailability of the generic formulation relative to the reference listed drug should be equivalent. For this purpose, equivalence is defined as the 90 percent confidence interval of the test to reference ratio (log transformed data) falling completely within 0.80 to 1.25 (80 to 125%). The analysis of variance (ANOVA) is applied to bioequivalence study data to determine the 90 percent confidence interval limits. The ANOVA is performed on log-transformed AUC (extent) and C_{max} (rate) data. The pharmacokinetic parameter T_{max} is defined as the time to reach peak plasma drug concentration following dosing. T_{max} is also a rough indicator of the rate of drug absorption and serves as supportive data in demonstrating bioequivalence between products.

FDA has discretion with respect to what constitutes sufficient information to show that a verapamil extended-release product is bioequivalent to Covera-HS. As noted by the Third Circuit, "[a]lthough the Act mandated a showing of bioequivalence for approval, there is no evidence that Congress intended to limit the discretion of the FDA in

---

[1] A generic drug that establishes bioequivalence as well as pharmaceutical equivalence is rated as therapeutically equivalent to the reference drug in FDA's *Approved Products With Therapeutic Equivalence Evaluations*, commonly referred to as the *Orange Book*.
[2] 21 U.S.C. 355(j)(8)(B)(i)); *see also* 21 CFR 320.1(e) and 320.23(b).
[3] AUC means *area under the curve*, which in this context refers to a measurement of the extent of absorption of a drug in the body as expressed in the resulting area under the plasma concentration-time curve (*Orange Book* at ix-x). The *0-t* subscript refers to calculation of the last measured concentration (e.g., 0-8 would be after 8 hours).
[4] C_{max} means *maximum concentration,* which in this context refers to the maximum or peak concentration of a drug in the body (*Orange Book* at x).

determining when drugs were bioequivalent for purposes of ANDA approval." *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995).

IV. Bioequivalence Requirements

A. Assessment of early morning plasma concentrations

You state that because the primary active enantiomer, S-verapamil, remains low 4 to 5 hours after dosing (lag period) and has a higher exposure between 5 a.m. and 11 a.m., it is timed to coincide with the morning rise in blood pressure (Petition at 18 and 19). In addition, this drug release profile is designed to minimize the risk of hypotensive events during a normal sleep cycle when blood pressure is lowest (Petition at 18 and 19). Accordingly, you request that FDA closely monitor early morning plasma concentrations in the pivotal fasting studies.

We agree with your request that the Agency closely assess early morning plasma concentrations in the pivotal fasting studies. We will ask applicants to develop generic verapamil HCl extended-release tablets for bedtime dosing. As a general rule, the Agency considers T_{max} to be so variable that it does not apply strict statistical criteria to this parameter in the ANDA approval process.[5]

1. Assessment of partial AUC

You claim that a failure to match Covera-HS's drug release profile, with its lag period during low nighttime blood pressure and heart rate, could compromise safety if there were a premature onset of verapamil (e.g., hypotensive events during sleep) (Petition at 22). To prevent such safety risks, you argue that the in vivo bioequivalence studies for an ANDA must be designed to assure that the in vivo drug release profile of the proposed ANDA closely matches the in vivo drug release profile of Covera-HS during the night.

You state that generic applicants should be required to demonstrate bioequivalence based on initial exposure (partial AUC, defined as the area under the concentration-time curve from time zero to T_{max}) in addition to parameters $AUC_{0-\infty}$ (area under the concentration-time curve from 0 to infinity) and C_{max} (maximum serum drug concentration) (Petition at 19 and 20). You assert that the evaluation of partial AUC will assure that generic drug products have Covera-HS's nighttime and early morning drug-release profile (Petition at 21 and 22). Because of Covera-HS's lag period, you suggest that a generic version without a lag period could have a different initial input rate but still be considered bioequivalent according to the AUC_t, AUC_∞, C_{max}, and T_{max} (Petition at 20). You cite several articles indicating that partial AUC is more accurate and clinically relevant because it would detect differences in drug input rates (Petition at 20).

[5] C_{max} for the generic version must be equivalent to the innovator drug product.

You support this request with the following language from a Center for Drug Evaluation and Research (CDER) guidance recommending the use of partial AUC as an early exposure measure under certain circumstances:

> An early exposure measure may be indicated on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this setting, the guidance recommends use of partial AUC as an early exposure measure. The partial area should be truncated at the population median of T_{max} values for the reference formulation.[6]

However, you have omitted the sentence that precedes your quotation from the guidance. That sentence states: "For orally administered *immediate-release* drug products, BE may generally be demonstrated by measurements of peak and total exposure" (BA/BE guidance at 8, emphasis added). The guidance discussion of a possible use for partial AUC in certain circumstances does not apply to extended-release products such as Covera-HS. Partial AUC is not an acceptable parameter for extended-release drug products. These products are too complex for the data derived from partial AUC to be meaningful.

The BA/BE guidance states that the partial area should be truncated at the population median of T_{max} values for the reference formulation (AUCpR). The guidance suggestions for the use of partial AUC were based on findings from studies using simulated data.[7] However, several recent studies using actual bioequivalence data have shown that the high variability of AUCpR raises questions regarding its usefulness in bioequivalence evaluation. Noonan and Davenport recently evaluated data from two such studies, one using an immediate-release (IR) product and the other using a modified-release (MR) product. They compared how AUCpR, C_{max}, and AUC met the Agency's 90 percent confidence interval criteria.[8] Using AUC and C_{max}, the two studies passed the limits of 80 to 125 percent with intrasubject variability ranging from 17 to 28 percent. Nonetheless, both studies failed the same criteria using AUCpR, and the intrasubject variability was 2- to 4-fold greater than for AUC and C_{max}. Noonan and Davenport concluded that using AUCpR appropriately to evaluate bioequivalence would require

[6] Guidance for Industry on: *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (hereinafter, BA/BE guidance) (October 2000). This guidance was revised in March 2003 and the language quoted from the Petition differs slightly from the language in the March 2003 guidance. The March 2003 guidance is available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

[7] Endrenyi L et al., "The Duration of Measuring Partial AUCs for the Assessment of Bioequivalence," *Pharmaceutical Research,* 1998; 15:399-404; Endrenyi L et al., "Metrics Comparing Simulated Early Concentration Profiles for the Determination of Bioequivalence," *Pharmaceutical Research,* 1998; 15:1292-1299.

[8] Noonan PK and Davenport JM, "Early Exposure and Other Metrics in BA/BE Studies," *AAPSPharmSci,* 2001; 3.

significantly increasing the number of subjects in bioequivalence studies. They suggested that additional metrics rely on actual rather than simulated bioequivalence data. Two studies conducted by FDA staff produced similar findings.[9]

Based on the information above, we believe that partial AUC truncated at the median T_{max} of the reference drug is a highly variable metric and of questionable usefulness in most bioequivalence studies. In addition, Covera-HS is an extended-release drug product that is not covered by the statement in the BA/BE guidance. Consequently, your request that applicants conduct studies to demonstrate bioequivalence based on initial exposure is denied.

The FDA regularly evaluates new approaches and methodologies to improve its assessment of drug applications in an effort to assure high quality drug products. FDA's discussion of a partial AUC approach was intended as this type of effort. At this time, however, it is neither reasonable nor in the interest of the public to impose such testing standards on generic applicants because (1) the approach has not been fully developed and (2) the current methods are effective in establishing bioequivalence between drug products.

2. Adequate number of samples to assess partial AUC

In the Petition, you ask that a sufficient number of quantifiable samples (8 to 10) be collected before C_{max} to estimate the partial AUC (Petition at 23). As stated above, we are rejecting your request to determine bioequivalence based on partial AUC. Nevertheless, we will recommend that a sufficient number of quantifiable samples be collected before C_{max} to verify that the T_{max} of the generic product is comparable to that of Covera-HS.

B. Bioequivalence with respect to the verapamil enantiomers

You maintain that for generic drug products with input rates different from Covera-HS to identically affect blood pressure, their verapamil enantiomers must be bioequivalent. In the Petition, you describe verapamil HCl as a racemic mixture consisting of equal parts of R(d, +) and S(1, -) enantiomers (Petition at 23). You also describe S-verapamil, the minor enantiomer, as having 10 times the dromotropic activity of R-verapamil and as being more extensively metabolized (Petition at 23). As such, the efficacy/safety of

[9] Wahba Z et al., "Feasibility of Application of Early Exposure Measures in Bioequivalence Studies of Immediate Release Oral Formulations," *AAPSPharmSci*, 2000; 2; Gokhale M et al., "Feasibility of Application of Early Exposure Measures in Bioequivalence Studies of Extended Release Oral Formulations," *AAPSPharmSci*, 2000; 2. These studies explored the use of AUCpR in the bioequivalence evaluation of 12 generic IR and 8 generic MR formulations. Drugs were from a wide variety of classes, and all products had passed the 90 percent confidence interval criteria for AUC and C_{max}. Using AUCpR, 75 percent of the IR products and 58 percent of the MR products failed the 90 percent confidence interval criteria. In general, the intrasubject variability in AUCpR was high (> 30%). The authors concluded that further research was needed to assess the feasibility of using AUCpR and that it may not be the most appropriate metric for early exposure assessment because of high variability.

verapamil resides with S-verapamil. Norverapamil, the major metabolite of verapamil in the plasma, has approximately 20 percent of the activity of the parent drug (Petition at 24).

You assert that a series of studies show that the input rate significantly affects the enantiospecific first-pass metabolism of verapamil, thereby altering the proportions of R- and S-verapamil in plasma (Petition at 25).[10] As a result, you conclude that the total plasma verapamil concentrations differ depending on the input rates of verapamil enantiomers (Petition at 26). Therefore, if the bioequivalence metrics fall within but close to the extremes of the 90 percent confidence interval range (e.g., 80 to 85% or 120 to 125% for AUC_∞ or C_{max}), you suggest that FDA should require a showing of bioequivalence on the basis of the individual verapamil enantiomers (Petition at 27). You assert that the S- and R-enantiomers of verapamil meet all four of the following conditions in the BA/BE guidance:

(1) the enantiomers exhibit different pharmacodynamic characteristics,
(2) the enantiomers exhibit different pharmacokinetic characteristics,
(3) primary efficacy and safety activity resides with the minor enantiomer, and
(4) nonlinear absorption is present . . . for at least one of the enantiomers.[11]

Based upon the examination of the documents submitted in the Petition and the Agency's information, we conclude that bioequivalence determinations need not include measurements of the S- and R-enantiomers individually. We agree that whenever the pharmacokinetics of one enantiomer is nonlinear, then the relative proportion of the two enantiomers will vary, depending on the drug input rate. However, FDA has determined that the published studies cited in the Petition do not establish nonlinear absorption of at least one of the enantiomers. Rather, we believe that the available scientific evidence supports the conclusion that the absorption of both enantiomers is linear. This evidence and conclusion mean that the plasma concentrations of each enantiomer will vary only in direct proportion to the dose of verapamil. Therefore, the relative proportions of the S- and R-enantiomers will be constant despite any variations in the verapamil input rate. The basis for our determination is described below.

- In the Karim and Piergies study, the ratios of the R- and S-enantiomers to each other (R/S ratios) differed significantly both in immediate release (IR) and sustained-release (SR) formulations when 240 mg oral doses of verapamil were administered.[12] However, fasted subjects received the IR formulation, whereas fed subjects received the SR formulation. Because food changes both AUC and C_{max} for some marketed

[10] The studies cited in the Petition showed a wide disparity between oral and intravenous verapamil EC_{50} values and a significant difference in EC_{50} values between immediate- and sustained-release verapamil formulations.
[11] BA/BE guidance, *supra* note 6, at 19.
[12] Karim A and Piergies A, "Verapamil Stereoisomerism: Enantiomeric Ratios in Plasma Dependent on Peak Concentrations, Oral Input Rate, or Both," *Clin. Pharmacol. Ther.* 1995; 58:174-184.

formulations of verapamil,[13] it is not clear whether a food effect on the formulation, the drug substance, or both caused the differences in R/S ratios of pharmacokinetic parameters.

- In the Bhatti et al. study, subjects received either an 80-mg IR formulation or a 240-mg SR formulation.[14] By the authors' own admission, findings from this study only suggested a trend of different R/S concentration ratios. A statistical comparison of the AUC and C_{max} R/S verapamil ratios revealed no significant difference between the two formulations. R/S plasma concentration ratios may have varied somewhat in the early parts of the pharmacokinetic profiles in this study. However, because drug absorption rates differ within individual subjects, plasma concentrations tend to be highly variable at early sampling times and do not necessarily reflect peak or total drug exposure. For that reason, the determination of AUC, which incorporates all plasma concentrations over the sampling interval, is viewed as an accurate index of drug exposure.

- The Mehvar and Reynolds experiment was an in vitro study using isolated rat livers perfused with verapamil.[15] The investigators varied the input rate of infused verapamil solution by two-fold and observed a significant decrease in the S/R ratio in liver tissue. Such a major change in input rate renders this study irrelevant to considering whether measuring S- and R-verapamil separately will determine bioequivalence of two products. A bioequivalence study based on the verapamil racemate in which the 90 percent confidence intervals for log-transformed C_{max} ratios were contained entirely within the bounds of 0.80 to 1.25 would detect a two-fold difference in verapamil absorption.

- The Sahajwalla CG et al. abstract summarizes a study in which subjects received either 240-mg controlled-release formulations or an 80-mg IR formulation.[16] ANOVA comparisons of AUC and C_{max} derived from R- or S-verapamil revealed no statistical differences related to formulation.

- In Sahajwalla et al., the authors simulated pharmacokinetic data and concluded that perturbation of S-verapamil data by 30 percent and 50 percent only changed total R and S concentrations by 7 percent and 12 percent, respectively.[17] It is hard to evaluate these findings because the abstract does not provide the conditions of the

---

[13] *Physician's Desk Reference*, 2002.

[14] Bhatti MM, Lewanczuk RZ, Pasutto FM, Foster FT, "Pharmacokinetics of Verapamil and Norverapamil Enantiomers After Administration of Immediate and Controlled-Release Formulations to Humans: Evidence Suggesting Input-Rate Determined Stereoselectivity," *J. Clin. Pharmacol.* 1995; 35-1076-1082.

[15] Mehvar R and Reynolds J, "Input-Rate Dependent Stereoselective Pharmacokinetics: Experimental Evidence in Verapamil-Infused Isolated Rat Livers," *Drug. Metab. Dispos.* 195; 23:637-641.

[16] Sahajwalla CG, Longstreth J, Karim A, El-Shourbagy T, Vetticaden SJ, Purich ED, Malone D, Cabana BE, "Bioavailability-Bioequivalence of Calan SR, Verapamil CR and Calan-IR Based on R-, S-, and R,S-Verapamil," *J. Clin. Pharmacol.* 1992; 32:961.

[17] Sahajwalla CG, Longstreth J, Karim A, Purich ED, Cabana BE, "Consequences in Pooling R- + S-Verapamil in Bioequivalence Assessment (abstract)," *J. Clin. Pharmacol.* 1992; 32:961.

simulations. Simulations of pharmacokinetic data require the reader to make assumptions about the experimental conditions and the pharmacokinetic parameters of the drug under investigation. For a drug with complex pharmacokinetics, such as verapamil, many parameters and assumptions should be considered in setting up the simulations to accurately reflect the drug's pharmacokinetic properties. Moreover, a simulation should be validated against in vivo data to verify that it is robust and predictive of outcome in human subjects. Without information about how the simulations were developed or whether the modeled pharmacokinetic data were validated, we cannot draw any conclusions from the authors' findings.

- The Harder et al. study investigated electrocardiograms, specifically P-R interval prolongation, in subjects given single doses of a 5-mg intravenous formulation, an 80-mg IR formulation, or a 240-mg extended-release formulation.[18] The investigators modeled the pharmacodynamic response and found that the EC_{50} (plasma concentration associated with half-maximal response in P-R interval prolongation) was significantly different for each formulation. Because a different dose of each formulation was administered, it cannot be determined whether the differences in responses were due to formulation or to dose.

In addition to the deficiencies of the studies mentioned above, a bioequivalence study sponsored by the FDA and conducted at Georgetown University showed that dose or input rate made no difference in R/S ratio in human subjects. The study enrolled 21 subjects and employed a crossover design. Subjects received single doses of 40-mg, 80-mg, or 160-mg IR formulations, and a 240-mg dose of the SR formulation. All subjects were fasted prior to dosing. The mean R/S ratios for AUC and C_{max} were as follows:

R/S ratios for AUC & C_{max} in 21 subjects given different doses, formulations				
Treatment	40-mg IR	80-mg IR	160-mg IR	240-mg SR
AUC_{0-t}	2.03	2.96	3.68	3.86
C_{max}	3.93	4.37	4.00	4.1

The ANOVA revealed no significant differences between the R/S ratios in response to the various formulations and doses. The FDA investigators concluded that the study failed to show that input rate affected R- and S-verapamil peak plasma exposure and total plasma exposure to different degrees.

In conclusion, there is no convincing evidence that the relative proportions of each verapamil enantiomer present in vivo (PK/PD profile) depend on drug input rate. Therefore, FDA will not require applicants to conduct testing specific for the R- and S-isomers of verapamil. Bioequivalence of a generic verapamil extended-release tablet formulation to Covera-HS can be established by measuring plasma concentrations of the racemate.

---

[18] Harder S, Thurmann P, Siewert M, Blume H, Huber T, Rietbrock N, "Pharmacodynamic Profile of Verapamil in Relation to Absolute Bioavailability: Investigations with a Conventional and a Controlled-Release Formulation," *J. Cardiovasc. Pharmacol.* 1991; 17:207-212.

Please note that this is the same position that the FDA put forward regarding the measurement of verapamil enantiomers in the petition response to G.D. Searle & Co. (See 89P-0220/PSA1, 89P-0430/PSA1, 89P-0141/CP2 and 89P-0141/PRC1) dated March 6, 1996, and the petition response to Knoll Pharmaceuticals (89P-0141/CP1 & AMD2) dated March 6, 1996.

C. The active metabolite of verapamil should be measured

The BA/BE guidance states that if a metabolite is formed as a result of a presystemic metabolism and contributes meaningfully to safety and efficacy, then the metabolite and the parent drug should be measured when making a bioequivalence determination.[19] Since norverapamil contributes approximately 20 percent of the activity of verapamil, you contend that it meets the criteria. Therefore, you ask FDA to require applicants to demonstrate bioequivalence for norverapamil as well as for the parent drug. (Petition at 28).

The FDA agrees that norverapamil contributes to the safety and efficacy of verapamil and therefore should be assayed in bioequivalence studies of generic verapamil HCl extended-release tablets. However, although norverapamil should be measured, in this case only the parent drug that is measured in these bioequivalence studies is analyzed using the confidence interval approach, because the parent drug is the most sensitive measure of bioequivalence. The plasma concentration data from the metabolite is more a reflection of the rate of formation of the metabolite in the body than a reflection of the bioavailability from the dosage form. Accordingly, metabolite data is used to provide supportive evidence of comparable therapeutic outcome. In accordance with the BA/BE guidance, we ask that only individual and summary statistical data be presented for the metabolite in these cases. Therefore, the Agency grants your request to the extent that we will require norverapamil to be assayed, but denies your request to the extent that full bioequivalence of the metabolite must be shown using the confidence interval approach.

V. Study Protocols

You request that the bioequivalence of generic versions of Covera-HS be determined on the basis of the following:

1. A single-dose, replicate-design, fasting study of the highest product strength, with nighttime dosing in subjects who follow a consistent routine of diurnal activity alternating with nocturnal sleep.
2. A food-effect, nonreplicate design study of the highest product strength, with nighttime dosing in subjects who follow a consistent routine of diurnal activity alternating with nocturnal sleep.
3. Nighttime dosing starting at approximately 10 p.m. with vital signs (heart rate and blood pressure) being monitored throughout the complete dosing interval.

---

[19] BA/BE guidance, *supra* note 6, at 19.

4. Subjects who follow a fairly consistent routine of diurnal activity alternating with nocturnal sleep (i.e., go to sleep at approximately 11 p.m. ± 1 hour and wake up at approximately 6 a.m. ± 1 hour). Individuals with a recent history of shift work, irregular sleeping habits, or sleep disorders should be excluded from the studies (Petition at 28 to 30).

FDA requests that applicants conduct a single-dose, replicate or nonreplicate design study on the 240- and 180-mg strengths, using a dose administered at bedtime. Vital signs should be monitored at appropriate intervals to assure the safety of the study subjects. The FDA also asks applicants to conduct a single-dose, two-way crossover, fed bioequivalence study. This study should be conducted in the morning hours. Study subjects should receive the verapamil dose after consuming a standard high-fat breakfast. We concur that subjects should have stabilized sleep patterns before enrollment in the bioequivalence studies.

VI. Conclusion

For the reasons discussed above, your Petition is denied in part and granted in part. The FDA denies your requests that the Agency (1) assess bioequivalence based on partial AUC and (2) measure the individual S- and R-enantiomers. In addition, we deny your request that the FDA not accept for filing or receive ANDAs that do not assess bioequivalence based on partial AUC and measure the individual S- and R-enantiomers. We agree to assess closely the initial lag time and early morning plasma concentrations in the pivotal fasting studies. Applicants for generic versions of Covera-HS will need to provide the Agency with the norverapamil metabolite data and develop generic verapamil HCl extended-release tablets for bedtime dosing. We also agree that study subjects should have stable sleep patterns, i.e., follow a consistent routine of diurnal activity alternating with nocturnal sleep.

To support marketing approval of generic versions of Covera-HS, verapamil and norverapamil should be measured in the bioequivalence studies. Only the racemate of verapamil and the racemate of norverapamil should be measured in nonstereospecific assays. The parameters AUC and C_{max} for only the verapamil racemate need pass the 90 percent confidence interval criteria. In addition, the verapamil T_{max} observed after a single dose of the generic drug product should be comparable to that occurring after a single dose of Covera-HS.

Sincerely yours,

William K. Hubbard
Associate Commissioner
for Policy and Planning