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December 7, 2001

VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

Re: PETITION FOR STAY OF AGENCY ACTION

Dear Madam or Sir:

On behalf of our client, Pharmacia Corporation and its affiliate G.D. Searle ("Pharmacia"), and pursuant to 21 C.F.R. § 10.35, we request that the Commissioner of the Food and Drug Administration ("the Commissioner") (1) stay the effective date of pending, tentative, or final decisions to approve Abbreviated New Drug Applications ("ANDA") or section 505(b)(2) applications (hereafter "multisource applications") for Covera-HS® (verapamil hydrochloride), and (2) not accept for filing, or "receive" within the meaning of 21 C.F.R. § 314.101, nor approve pursuant to 21 U.S.C. § 355 and 21 C.F.R. § 314.105, multisource applications for Covera-HS® without first establishing their bioequivalence using appropriate measures and methods, as described herein, pursuant to the provisions of Sections 505(b)(1), (b)(2), (j)(2)(A)(iv), (j)(4)(F) of the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act"), 21 U.S.C. §§ 355(b)(1), (b)(2), (j)(2)(A)(iv), (j)(4)(F) and the Agency's regulations, 21 C.F.R. §§ 320, 314.105, 314.54.

I. Decisions Involved and Action Requested

Pharmacia requests that the Commissioner take the actions noted above.

01P-0546

II. Executive Summary

The FFDCA prohibits the FDA from approving a generic version of an approved drug in the absence of information that establishes that the generic is as safe and effective as the approved drug. In this case, the unique properties and clinical benefits of verapamil administered in a controlled-onset, extended-release chronotherapeutic regimen—Covera-HS®'s controlled-onset, extended-release ("COER") formulation of verapamil hydrochloride—necessitate the adoption of specific bioequivalence requirements for multisource versions to ensure that patients with hypertension and angina receive products that are as safe and effective as Covera-HS®. Pharmacia respectfully requests FDA to mandate such requirements and stay the effective date of any pending, tentative or final decisions regarding Covera-HS®-based multisource applications until such requirements are met.

- **The Benefits of Covera-HS®'s Chronotherapeutic Design Must be Preserved in Multisource Products.**

Covera-HS® is a COER formulation of verapamil hydrochloride (a calcium antagonist) that was approved for marketing in 1996 for the management of both hypertension and chronic stable angina. Covera-HS®'s unique drug delivery system was designed using chronotherapeutic principles, i.e., drug blood levels are purposefully modulated in synchrony with biological need and/or biological tolerability over a 24-hour period to optimize treatment outcome and to minimize adverse effects. Because close adherence to these principles may impact clinical outcomes, they must be preserved in multisource products.

Chronotherapeutic principles are important in the treatment of hypertension and angina because these conditions exhibit distinct circadian (i.e., biological rhythms with a cycle of about 24 hours) patterns, and modulation of verapamil levels consistent with these patterns over 24 hours may optimize treatment outcome and minimize adverse effects. In diurnally active (i.e., active during the daytime rather than at night) normotensive individuals, blood pressure is lowest during nighttime sleep, rises sharply with the commencement of diurnal activity, and reaches an absolute peak in the late afternoon or early evening. Heart rate follows a similar circadian pattern. Similar, although exaggerated, circadian patterns in blood pressure are exhibited by patients with uncomplicated essential hypertension. It is believed that a rapid morning rise in blood pressure increases the risk of cardiovascular events (e.g., myocardial infarction and stroke) in hypertensive patients by suddenly increasing cardiac workload and causing injury to unstable coronary plaque.

Covera-HS® is administered at bedtime and incorporates a four- to five-hour delay in drug delivery, to synchronize drug delivery with the circadian patterns of blood pressure and heart rate. Maximum plasma levels of verapamil are therefore achieved in the morning hours, approximately 11 hours post-dosing, when blood pressure is rising sharply, followed by a slow decline. Covera-HS®'s four- to five-hour lag time results in minimal drug

concentrations during sleep, when blood pressure is at its lowest. The result is safe and effective control of hypertension for the entire 24 hours with little risk of hypotension during the night. The COER design of Covera-HS® also effectively controls angina, especially during the morning hours when the risk of myocardial ischemia is greatest. In total, Covera-HS® is specifically formulated to release verapamil in concert with normal circadian rhythms associated with the cardiovascular system, to achieve the optimal pharmacodynamics and safety of verapamil and its active metabolites.

- **Specific Bioequivalence Testing is Necessary to Assure Multisource Products Provide Comparable Clinical Benefits to Covera-HS®.**

The complex and unique pharmacologic properties and clinical benefits of Covera-HS®'s chronotherapeutic regimen necessitates that FDA consider these characteristics in assessing the bioequivalence of multisource products. Specifically, bioequivalence studies should include a single-dose, replicate design, fasting study, and a food-effect non-replicate design study, of the highest strength product using nighttime dosing in subjects who follow a consistent routine of diurnal activity alternating with nocturnal sleep. Bioequivalence should be determined on the basis of area-under-the-concentration-time curve from time zero to infinity ("$AUC_{0-\infty}$"), the maximum serum drug concentration ("C_{max}"), and partial AUC (from dosing to T_{max}). Partial AUC_{0-Tmax} will assure equivalence of initial exposure and delayed delivery, which are crucial to the safety and efficacy of multisource versions. Moreover, if data from the aforementioned studies indicate that a multisource product has a different input rate than Covera-HS®, equivalence of the parameters listed above 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. The sum of this testing will ensure that patients with hypertension and angina are not exposed to less safe or effective multisource versions of Covera-HS®.

III. Statement of Grounds

A. Covera-HS® Offers Important Chronotherapeutic-Based Clinical and Safety Benefits for Patients with Hypertension and Angina

Verapamil [2,8-bis- (3,4-dimethoxyphenyl)-6-methyl-2-isopropyl-6-azaoctanitrile], the active ingredient in Covera-HS®, has repeatedly been demonstrated to be a safe and effective treatment for hypertension and angina pectoris, and has been used safely for decades.[1] Covera-HS® (verapamil hydrochloride) was approved for marketing on February 26, 1996 (NDA #20552) for the management of hypertension and angina—it is available in doses of 240 mg and 180 mg. FDA approved this drug delivery system for verapamil as a new drug based on its innovative release pattern, separating Covera-HS® from the traditional sustained-release verapamil products. As reflected in the product labeling, Covera-HS® has a unique delivery system, designed for bedtime dosing, incorporating a four to five-hour delay in drug delivery.[2] Consequently, maximum plasma concentrations of verapamil are reached in the morning hours, approximately 11 hours post dosing, when they are most necessary, after which they slowly decline.[3] Comparable doses of conventional sustained-release products, on the other hand, reach higher peak plasma concentrations approximately three to four hours post dosing, and then rapidly decline over the next four hours.[4] These basic differences in pharmacokinetics highlight the dose-controlled management of Covera-HS® as a once-daily administered anti-hypertensive and anti-anginal agent. Covera-HS® also offers safety benefits that result from its chronotherapeutic design, including lower rates of heart block and hypotension compared to other verapamil formulations, and a reduced risk of hypertensive target organ damage and adverse cardiovascular events for primary hypertensives that are "non-dippers" (i.e., primary hypertensives that lack the typical 10 to 20 percent decrease in blood pressure during sleep or exhibit a blunted dip in blood pressure).

1. The Chronotherapeutic Design of Covera-HS® Provides Critical Clinical Benefits

The science of chronobiology has demonstrated that the biology of human beings is not constant but, rather, is characterized by an inherited time structure defined by rhythms of specific periods that range from as short as a tenth of a second to as long as one year. Circadian (about 24-hour) rhythms are important to medicine, affecting the findings of certain diagnostic tests, occurrence and severity of medical conditions, and even the pharmacokinetics—absorption, distribution, metabolism, and elimination—and effects of

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1 See Declaration of William B. White, M.D., F.A.C.P. ¶¶ 4-6 (Oct. 25, 2001). (See Attachment A).

2 See id. at 1.

3 See id.

4 See Declaration of William B. White, M.D., F.A.C.P. ¶ 7 (Oct. 25, 2001). (See Attachment A).

various classes of medications.[5] Knowledge of circadian patterns in medical conditions and disease as well as side effects of certain medications has stimulated interest in chronotherapeutics—the purposeful modulation of drug level in synchrony with biological need or tolerance over 24 hours to optimize treatment outcome and to minimize adverse effects.[6,7]

Blood pressure and heart rate display significant circadian rhythmicity. As shown in Figure 1, blood pressure is lowest during sleep, rises sharply (systolic blood pressure by 20 to 25 mmHg and diastolic blood pressure by 10-15 mmHg) with the commencement of daytime activity, and reaches an absolute peak generally late in the afternoon or early evening.[8] The blood pressure and heart rate circadian rhythm is a result of circadian rhythms of the autonomic nervous system, hormones like catecholamines, renin, angiotensin, aldosterone and vasopressin, and day-night differences in mental stress, activity and posture.[9]

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5 See Smolensky MH, Lamberg L. Body Clock Guide to Better Health. NY. H. Holt, 2000; Smolensky MH, Haus E. Circadian Rhythms in Clinical Medicine with Special Reference to Hypertension. Am. J. Hypertens. 2001;14;(9 part 2):280S-290S. (See Attachment 1).

6 See Lemmer B. (ed). Chronopharmacology: Cellular And Biochemical Interactions. New York, Marcel Dekker, Inc., 1989; Redfern P, Lemmer B (eds). Physiology and Pharmacology of Biological Rhythms. Heidelberg. Springer Verlag, 1997.

7 Dosing based on chronobiology is an established, longstanding approach to drug therapy. For example, the package insert for Medrol® (methylprednisolone), a drug approved in the 1960s, describes "ADT®" (Alternate Day Therapy), which optimizes the therapeutic effect of this corticosteriod while minimizing disturbance of the diurnal cycle of the hypothalamic-pituitary-adrenal system. See Pharmacia & Upjohn, Medrol® US Approved Prescribing Information (revised Apr. 2000), at http://www.pharmacia.com/products/pharm.asp#M.pdf. (See Attachment 2).

8 See Baumgart P. Circadian Rhythm of Blood Pressure: Internal and External Time Triggers. Chronobiol. Int. 1991;8:444-450. (See Attachment 3).

9 See Portaluppi F, Smolensky MH. Circadian Rhythm and Environmental Determinants of Blood Pressure Regulation in Normal and Hypertensive Conditions. White WB (ed). Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics. Humana Press Inc. Totowa, NJ, 2001 pp.79-138; Portaluppi F, Smolensky MH. Time-Dependent Structure and Control of Arterial Blood Pressure. Ann. N.Y. Acad. Sci.. 1996;783pp; Pickering T.G. Ambulatory Monitoring and Blood Pressure Variability. London, Science, Press, 1991.

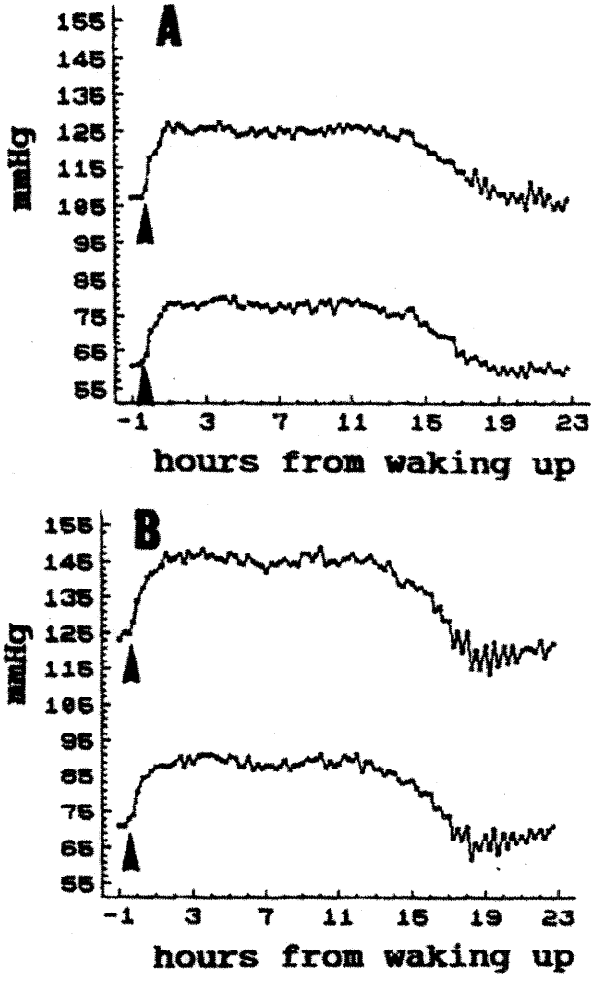

Figure 1. Systolic and diastolic 24-hr blood pressure profiles at intervals of 15 minutes after synchronization by the time of awakening (arrow). **A**: Normotensives (n=11); **B**: Essential hypertensives (n=109). Reprinted from Chronobiology International 1991; 8(6):444-50, p. 448 by courtesy of Marcel Dekker, Inc.

Cardiovascular events display prominent 24-hour patterns. Myocardial ischemia is as much as tenfold more frequent between 8:00 and 11:00 a.m. than between midnight and 5:00 a.m.[10] (see Figure 2); myocardial infarction is roughly 60 percent more frequent between 6:00 a.m.

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[10] See Rocco MB, Barry J, Campbell S, et al. Circadian Variation of Transient Myocardial Ischemia in Patients with Coronary Artery Disease. Circulation. 1987;75:395-400 (See Attachment 4); Mulcahy D, Cunningham D, Crean P, et al. Circadian Variation of Total Ischemic Burden and Its Alteration with Anti-Anginal Agents. Lancet. 1998;ii:755-759. (See Attachment 5).

and noon than midnight and 6:00 a.m.;[11] cardiac arrest is nearly threefold more common during the first half of the daily activity span than during sleep;[12] and sudden cardiac death is almost twice as frequent between 6:00 a.m. and noon compared to between midnight and 6:00 a.m.[13] Experts believe the rapid acceleration of blood pressure in the morning plays an important role in increasing the potential for cardiovascular events by suddenly increasing cardiac workload and causing injury to unstable coronary plaque as a result of the aforementioned changes. Environmental triggers, such as mental stress, anger and activity are also contributory to cardiovascular events at this time of day.[14]

Hemorrhagic and ischemic stroke also are two-to-three-fold more frequent between 6:00 and 9:00 a.m. than between midnight and 3:00 a.m. or 3:00 a.m. and 6:00 a.m.—Experts believe the increase in strokes in the morning is due in part to the circadian rhythm in blood pressure, particularly its sharp rise in the morning.[15]

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11 See Cohen MC, Rohtla KM, Lavery CE, et al. Meta-Analysis of the Morning Excess of Acute Myocardial Infarction and Sudden Cardiac Death. Am. J. Cardiol. 1997;79:1512-1516. (See Attachment 6).

12 See Levine RL, Pepe PE, Fromm RE, Curka PA, Clark PA. Prospective Evidence of Circadian Rhythm for Out-of-Hospital Cardiac Arrests. JAMA. 1992;267:2935-2937. (See Attachment 7).

13 See Cohen et al., 1997, supra note 11. The increased occurrence of these events in the morning is theorized to result from circadian rhythms in catecholamines, increased coronary vascular tone and left ventricular stroke work, increased myocardial oxygen demand, increased platelet aggregation with enhanced coagulation, and decreased fibrinolysis.

14 See Chasen C, Muller JE. Cardiovascular Triggers and Morning Events. Blood Press. Monit. 1998;3:35-42 (See Attachment 8); Portaluppi F, Manfredini R, Fersini C. From a Static to a Dynamic Concept of Risk: The Circadian Epidemiology of Cardiovascular Events. Chronobiol. Int. 1999;16:33-49. (See Attachment 9).

15 See Elliott WJ. Circadian Variation in the Timing of Stroke Onset: A Meta-Analysis. Stroke. 1998;29:992-996. (See Attachment 10).

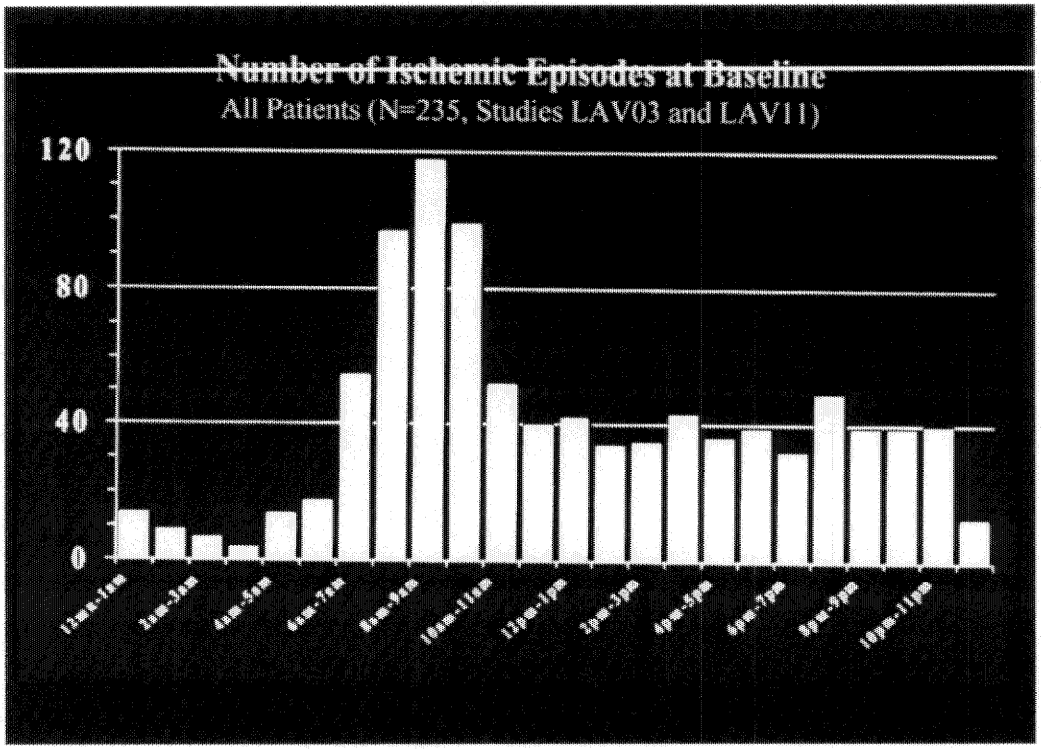

Figure 2. Incidence of myocardial ischemia over a 24-hour period. Provided courtesy of Michael H. Smolensky, Ph.D., Professor of Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston.

The early morning rise in blood pressure, therefore, is a physiologically relevant target for pharmacotherapies aimed to reduce cardiovascular events.

To address these circadian features, Covera-HS® is designed to attain C_{max} (maximal plasma concentration) of verapamil during the morning hours from approximately 5:00 a.m. to 11:00 a.m. The COER delivery system, unique to Covera-HS® (Figure 3), incorporates a four- to five-hour delay in delivery of the drug, so that drug will not be excessively delivered during the nighttime when blood pressure is at its lowest in patients with essential hypertension. This delay is achieved by the introduction of a special layer between the drug and the outer semipermeable membrane (Figure 3). Only when this layer is solubilized can verapamil hydrochloride leave the tablet at a controlled rate with approximately zero-order kinetics. Thus, when Covera-HS® is administered at bedtime, the COER delivery system synchronizes delivery of the drug with the early morning rise in blood pressure, ensuring not

only a convenient dosing schedule, but also maximum therapeutic results and an improved safety profile. The lag time also prevents hypotensive crises during the nighttime.[16]

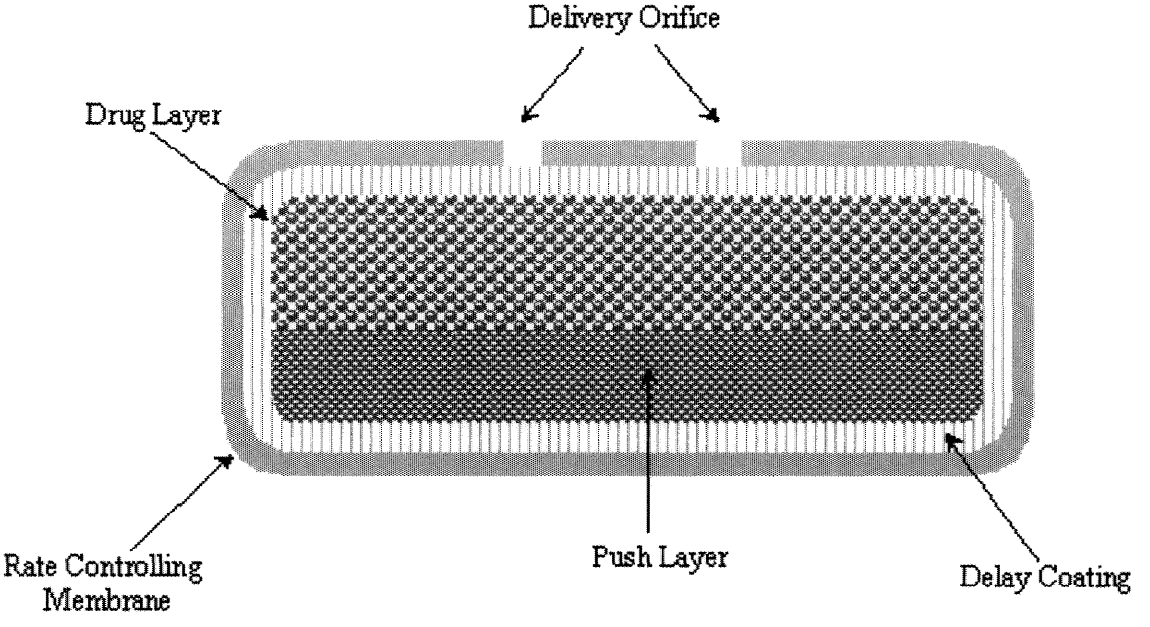

Figure 3. Delayed Onset Formulation Design of Covera-HS®. Pharmacia Corporation.

Covera-HS® is unique among sustained-release verapamil products because it is also indicated for chronic stable angina.[17] Importantly, Holter monitoring data suggests Covera-HS® is effective in decreasing myocardial ischemia during the crucial early morning hours.[18]

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16 See White WB, Mehrotra DV, Black HR, Fakouhi TD, COER-Verapamil Study Group. Effects of Controlled-Onset Extended-Release Verapamil on Nocturnal Blood Pressure (Dippers versus Nondippers). Am. J. Cardiol. 1997;80:469-474 (See Attachment 11); Hayreh SS, Zimmerman MB, Podhajsky P, Alward WLM. Nocturnal Arterial Hypotension and Its Role in Optic Nerve Head and Ocular Ischemic Disorders. Am. J. Ophthalmol. 1994;117:603-624. (See Attachment 12).

17 In two clinical studies of patients with chronic stable angina, Covera-HS® was demonstrated to be more effective than placebo in the improvement of exercise tolerance, with significant increases in exercise times for symptom limited duration, time to angina, and time to ST segment change in the electrocardiogram. See Covera-HS® Extended-Release Tablets Controlled-Onset (Prescribing Information) (May 1, 1997), at http://www.searlehealthnet.com/pdf/covera_v5197.pdf [hereinafter Prescribing Information for Covera-HS®]. (See Attachment 13). Additional data from outpatient diaries indicate decreased incidence of angina attacks with reduced sub-lingual nitroglycerin use during the fourth week of treatment with 360 mg and 540 mg doses of Covera-HS®, compared to placebo. See Cutler NR, Anders RJ, Jhee SS, Sramek JJ, Awan NA, Bultas J, Lahiri A, Woroszylska

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The clinical advantages of the Covera-HS® delivery system are evident from comparisons between Covera-HS® and traditional antihypertensives.[19] Although all treatments decrease 24-hour and early-morning blood pressure, only the Covera-HS® delivery system significantly reduces early morning heart rate, heart rate-systolic blood pressure product ("double product"), and the rate of early morning rise of blood pressure and heart rate.[20,21] The decreased rate of rise of blood pressure and heart rate and the decreased double product reduce the risk of myocardial ischemia, illustrating that the unique timing of administration of Covera-HS®-delivered verapamil yields significant clinical benefits.[22]

M. Placebo-Controlled Evaluation of Three Doses of a Controlled-Onset, Extended-Release Formulation of Verapamil in the Treatment of Stable Angina Pectoris. Am. J. Cardiol. 1995;75:1102-1106. (See Attachment 14).

18 See id.; Frishman WH, Glasser S, Stone P, Deedwania PC, Johnson M, Fakouhi TD. Comparison of Controlled-Onset, Extended-Release Verapamil with Amlodipine and Amlodipine Plus Atenolol on Exercise Performance and Ambulatory Ischemia in Patients with Chronic Stable Angina Pectoris. Am. J. Cardiol. 1999;83:507-514. (See Attachment 15).

19 The clinical effects of Covera-HS® have been compared to those of the calcium antagonist nifedipine, the ACE-inhibitor enalapril, and the angiotensin-receptor antagonist losartan. See White WB, Black HR, Weber MA, Elliott WJ, Bryzinsku B, Fakouhi TD. Comparison of Effects of Controlled-Onset, Extended-Release Verapamil at Bedtime and Nifedipine Gastrointestinal Therapeutic System on Arising on Early Morning Blood Pressure, Heart Rate, and the Heart Rate-Blood Pressure Product. Am. J. Cardiol. 1998;81:424-431 (See Attachment 16); Bakris G, Sica D, Ram V, Fagan T, Vaitkus P, Anders RJ. A Comparative Trial of Controlled-Onset, Extended-Release Verapamil, Enalapril, and Losartan on Blood-Pressure and Heart-Rate Changes. In Press. (See Attachment 17). Covera-HS® is more effective than both enalapril and losartan in reducing early morning systolic and diastolic blood pressure, and, therefore, produces changes in blood pressure that more closely match normal circadian hemodynamic rhythms than these alternative therapies. See id.

Similarly, Covera-HS® was demonstrated to be superior to amlodipine and comparable to amlodipine plus atenolol in treating chronic stable angina. Covera-HS® significantly decreased heart rate and ambulatory myocardial ischemia, especially during the hours of 6:00 a.m. to 12:00 noon. See Frishman et al., 1999, supra note 18.

20 See id. The double product is a surrogate measure of myocardial oxygen demand and cardiac workload. It displays a marked day-night rhythmicity—it is lowest during nighttime sleep and greatest in the late afternoon. See Hermida RC, Fernández JR, Ayala DE, Mojón A, Alonso I, Smolensky M. Circadian Rhythm of the Double (Rate-Pressure) Product in Healthy Normotensive Young Subjects. Chronobiol. Int. 2001;18:475-489. (See Attachment 18).

21 The double product displays a similar circadian rhythm in angina pectoris patients. In this regard, Deedwania and colleagues demonstrated a close link between surges in the double product, particularly in the morning, and ST segment depression and angina pectoris pain in patients with coronary artery disease. See Deedwania PC, Nelson J. Pathophysiology of Silent Myocardial Ischemia During Daily Life. Circulation. 1990;82:1296-1304. (See Attachment 19).

22 See id. Although designed for maximal chronotherapeutic efficacy, the COER delivery system of Covera-HS® possesses many non-chronobiological advantages. For example, the nighttime dosing of Covera-HS® is particularly advantageous in women with angina and/or hypertension who are also

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2. The Chronotherapeutic Design of Covera-HS® Also Provides Other Important Safety Advantages

Covera-HS'® chronotherapeutic design provides important safety benefits. In particular, Covera-HS® is associated with less heart block and hypotension than other verapamil formulations (see Table 1). Heart block is a known risk for patients taking verapamil because of its effects on cardiac conduction,[23] and this risk may be even higher in elderly patients.[24]

No episodes of high-grade (i.e., second degree or higher) heart block were observed in 1,999 patients with hypertension or chronic stable angina who received 180 to 240 mg Covera-HS® in seven double-blind, multicenter randomized trials.[25]

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being treated for osteoporosis (i.e., with Fosamax®). The prescribing information for Fosamax®, for example, indicates that this medication must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only. Waiting less than 30 minutes, or taking Fosamax® with food, beverages (other than plain water), or other medications will lessen the effect of Fosamax® by decreasing its absorption into the body. Moreover, Fosamax® should not be taken at bedtime or before arising for the day because of the risk for esophageal irritation. See FOSAMAX® (Prescribing Information) (Jan. 2001), at http://www.merck.com/product/usa/fosamax/shared/product_info/pi/7957019.pdf. (See Attachment 20). Women who are taking Fosamax®, for example, should not take an antihypertensive and/or anti-anginal medication that must be administered in the morning—Covera-HS® is particularly well-suited to their needs.

23 See Kawai C, Konishi T, Matsuyama E, Okazaki H. Comparative Effects of Three Calcium Antagonists, Diltiazem, Verapamil and Nifedipine, on the Sinoatrial and Atrioventricular Nodes: Experimental and Clinical Studies. Circulation. 1981;63:1035-42. (See Attachment 21).

24 See Schwartz JB. Calcium Antagonists in the Elderly: A Risk Benefit Analysis. Drugs & Aging. 1996;9:24-36. (See Attachment 22).

25 See White, WB, Johnson MF, Anders RJ, Elliot WJ, Black HR. Safety of Controlled-Onset Extended-Release Verapamil in Middle-Aged and Older Patients with Hypertension and Coronary Artery Disease. Am. Heart J. 2001;142:1010-5. (See Attachment 23).

Table 1

Summary of Adverse Reactions[26]

Adverse Reaction	Placebo (n=261) %	Covera-HS® (all doses studied) n=572 %	Other Verapamil Formulations (n=4,954) %
Constipation	2.7	11.7*	7.3
Headache	7.3	6.6	2.2
Upper Respiratory Infection	4.6	5.4	—
Dizziness	2.7	4.7	3.3
Fatigue	3.8	4.5	1.7
Edema	3.1	3.0	1.9
Nausea	1.9	2.1	2.7
AV Block (first degree)	0.0	1.7	1.2 (includes secondary and tertiary)
AV Block (second and third degree)	0.0	0.0	0.8
Elevated Liver Enzymes	0.8	1.4	—
Bradycardia	0.4	1.4	1.4
Paresthesia	0.0	1.0	—
Flushing	0.3	0.8	0.6
Hypotension	0.0	0.7	2.5
Postural Hypotension	0.3	0.4	—
CHF/Pulmonary Edema	—	—	1.8
Dyspnea	—	—	1.4
Rash	—	—	0.6

* Constipation was typically mild, easily manageable, and the incidence usually diminished within about one week. At a typical once-daily dose of 240 mg, the observed incidence was 7.2 percent.

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[26] Prescribing Information for Covera-HS®, supra note 17. The Covera-HS® doses in Table 1 include administration of a 540 mg formulation that is not clinically available, and data from trials of both hypertension and angina. No statistical comparisons were made for these data.

Moreover, the attenuated nighttime reduction in blood pressure seen with Covera-HS® protects against possible drug-induced hypotensive events that could occur with conventional sustained-release verapamil formulations.[27] This is particularly important in elderly patients and patients with small vessel disease because excessive lowering of blood pressure during the night may increase the risk for ischemic stroke and ischemia-induced neuropathy of the anterior optic nerve.[28]

Covera-HS® also offers important protections for certain types of hypertensives. The full clinical efficacy of verapamil depends on its timed release during the entire 24-hour period, because different forms of hypertension differentially affect the circadian patterns of cardiovascular hemodynamics.[29] Normotensives and most primary hypertensives show a 10 percent to 20 percent decrease in blood pressure during sleep, and consequently, are often referred to as "dippers." However, approximately 25 percent of primary hypertensives lack this nighttime dip or exhibit a blunted dip in blood pressure, and are referred to as "non-dippers."[30] If blood pressure deviates from normal circadian rhythms (i.e., dip of 10–20% at night), there is an increased risk of developing hypertensive target organ damage, as well as adverse cardiovascular events.[31] Consistent with its chronotherapeutic design, Covera-HS® delivers proper plasma concentrations of verapamil during the nighttime trough period and decreases the nocturnal blood pressure of non-dippers to a greater extent than dippers, thereby restoring the normal circadian profile.[32]

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27 See White WB, Anders RJ, MacIntyre JM, Black HR, Sica DA, Verapamil Study Group. Nocturnal Dosing of a Novel Delivery System of Verapamil for Systemic Hypertension. Am. J. Cardiol. 1995;76:375-380. (See Attachment 24).

28 See Kario K, Matsuo T, Kobayashi H, et al. Nocturnal Fall of Blood Pressure and Silent Cerebrovascular Damage in Elderly Patients: Advanced Silent Cerebrovascular Damage in Extreme Dippers. Hypertens. 1996;27:130-135 (See Attachment 25); Watanabe N, Imai Y, Nagai K, et al. Nocturnal Blood Pressure and Silent Cerebrovascular Lesions in Elderly Japanese. Stroke. 1996;27:1319-1327 (See Attachment 26); White WB, Mansoor GA, Tendler BE, Anwar YA. Nocturnal Blood Pressure: Epidemiology, Determinants, and Effects of Antihypertensive Therapy. Blood Press. Monit. 1998;3:43-51 (See Attachment 27); Hayreh et al., 1994, supra note 16; Verdecchia P, Schillaci G. Prognostic Value of Ambulatory Blood Pressure Monitoring. In: White W.B. (ed). Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics. Humana Press Inc. Totowa, NJ, 2001, pp191-218.

29 See Portaluppi F, Vergnani L, Manfredini R, et al. Time-Dependent Effect of Isradipine on the Nocturnal Hypertension of Chronic Renal Failure. Am. J. Hypertens. 1995;8:719-726. (See Attachment 28).

30 See White et al., 1997, supra note 16; Noel HC, Saunders E, Smolensky MH. Hypertension Chronotherapy, and Patient Management. Nurse Practitioner. 2000;Mar;25(3 Suppl):2-10, available at http://www.springnet.com/ce/j003b.htm. (See Attachment 29).

31 See Hayreh et al., 1994, supra note 16; Kario et al., 1996, supra note 28.

32 See White et al., 1997, supra note 16.

3. Generic Formulations Deviating From the Covera-HS® Drug Delivery Profile Will Not Provide These Critical Chronotherapeutic Benefits and Will Present Additional Safety Risks

Covera-HS® represents a significant advancement in antihypertensive therapy because it specifically addresses the morning surge in blood pressure and provides for nighttime dosing.[33] The clinical consequences of using a multisource product that releases verapamil at a rate or extent inconsistent with Covera-HS'® chronotherapeutic principles may include an increased risk of myocardial infarction, sudden cardiac death, thrombotic stroke, and myocardial ischemia.[34] Moreover, hypertensive or angina patients who have been stabilized on Covera-HS® could be placed at undue risk of loss of effectiveness and/or increased risk of new side effects if switched to a multisource product with a distinctly different pharmacokinetic profile.[35] Trough plasma concentrations should be sufficient enough to reduce significantly nighttime blood pressure, but should not be so high as to make the patient hypotensive, which would increase the risk for ischemic events.[36]

Generic formulations that deviate from the drug delivery profile of Covera-HS®, will not only compromise drug safety and effectiveness, but may also present additional dangers to patients. Excessive systolic blood pressure reduction during nighttime sleep—a time when blood pressure typically declines to its lowest level—has been shown to increase the risk of ischemic damage to the retina, nocturnal hypotension with heightened risk of falls in the

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33 Conventional sustained-release calcium antagonists were not designed to address the early morning rise in blood pressure. Their peak activities, two to eight hours post dosing, do not allow for proper control of the sharp increase in blood pressure, unless the drugs are taken during the middle of the night. When administered daily at 0800, conventional sustained-release nifedipine, diltiazem, and verapamil failed to adequately control the early morning rise in blood pressure. See Carter, BL. Optimizing Delivery Systems to Tailor Pharmacotherapy to Cardiovascular Circadian Events. Am. J. Hosp-Syst. Pharm. 1998;55(Suppl 3):S17-S23. (See Attachment 30). Other agents considered to be long-acting, including atenolol, enalapril, nitrendipine and propranolol, have also been shown to inadequately control early morning blood pressure. See id.

34 See Declaration of William B. White, M.D., F.A.C.P. ¶ 10 (Oct. 25, 2001). (See Attachment A).

35 See Declaration of William B. White, M.D., F.A.C.P. ¶ 10 (Oct. 25, 2001); see also Citizen Petition of Andrx Pharmaceuticals, Inc. 8-9 (Feb. 26, 1998) (Docket No. 98P-1045) [hereinafter Andrx Pharmaceuticals' Citizen Petition] (quoting Bertram Pitt, M.D. as stating that the introduction of a new formulation with different hemodynamic properties could result in "an increased incidence of [untoward] drug interactions and potentially deleterious episodes of hypotension and myocardial ischemia with resultant myocardial infarction, stroke, and possibly death").

36 See Declaration of Michael H. Smolensky, Ph.D. ¶ 16 (Nov. 26, 2001). (See Attachment B).

elderly when awakening at night to use the toilet, and even cardiovascular events such as ischemic stroke.[37]

The delayed release of the COER delivery system protects against these administration problems. Several different clinical trials have shown that Covera-HS®, administered before bedtime, effectively controls blood pressure over the entire 24-hour dosage period.[38] Covera-HS® reaches peak efficacy in patients with uncomplicated essential hypertension during the early morning blood pressure rise, the time when blood pressure control is most crucial, and reaches its trough between midnight and 4:00 a.m., the time when blood pressure naturally drops.[39] Thus, Covera-HS®'s maximal blood pressure reduction occurs in the early morning, while a smaller, yet significant reduction occurs at night.[40]

The Agency has recognized the unique considerations inherent in testing chronotherapeutic drugs. In a 1997 FDA article, Gerald Sokol, M.D., of the Agency's Center for Drug Evaluation and Research, stated that chronotherapeutic clinical trials need to consider additional efficacy parameters not usually required of other clinical trials.[41,42] These considerations should also be applied to the assessment of multisource chronotherapeutic drugs in determining their bioequivalency with pioneer formulations.

B. Bioequivalence Requirements for Multisource Versions of Covera-HS® Must Incorporate Methods and Measures That Take Into Account Covera-HS®' Chronotherapeutic Design and Related Clinical and Safety Benefits

FDA must mandate pharmacodynamic and pharmacokinetic bioequivalence requirements that assure multisource products are clinically equivalent. In the case of Covera-HS®, bioequivalence requirements must assure that multisource products are equivalent with

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37 See Kario et al., 1996, supra note 28; Watanabe et al., 1996, supra note 28; White, Mansoor et al., 1998, supra note 28; Hayreh et al., 1994, supra note 16; Verdecchia & Schillaci, 2001, supra note 28.

38 See Nguyen BN, Parker RB, Noujedehi M, Sullivan JM, and Johnson JA. Effects of COER-Verapamil on Circadian Pattern of Forearm Vascular Resistance and Blood Pressure. J. Clin. Pharmacol. 2000;40(12 pt 2):1480-1487 (See Attachment 31); White et al., 1995, supra note 27; Neutel JM, Alderman M, Anders RJ, Weber MA. Novel Delivery System for Verapamil Designed To Achieve Maximal Blood Pressure Control During the Early Morning. Am. Heart J. 1996;132:1202-1206. (See Attachment 32).

39 See White et al., 1995, supra note 27.

40 See Neutel et al., 1996, supra note 38.

41 Stehlin I. 1997. A Time to Heal: Chronotherapy Tunes In to Body's Rhythms. FDA Consumer Mag., available at http://www.fda.gov/fdac/features/1997/397_chrono.html. (See Attachment 33).

42 Additional factors that must be considered include: (1) time of day a drug is administered; (2) time-related biological factors, such as seasonal disorders (e.g., seasonal affective disorder); and (3) patients' normal routines (e.g., eating times and sleep patterns). See id.

respect to their ability to control elevated arterial pressure and angina pectoris, the two major indication's for the life-threatening diseases for which it is prescribed (i.e., hypertension and angina pectoris). Specifically, multisource products must not only precisely mimic the lag time and the initial release during the peak morning hours, but also the trough concentrations during the night.[43]

A drug shall be considered to be bioequivalent to a listed drug if—when administered at the same molar dose of therapeutic moiety under similar conditions—the rate and extent to which its active ingredient or active moiety becomes available at the site of drug action is not significantly different than that of the listed drug.[44] FDA must use reasonable and scientifically supported criteria to make a finding of bioequivalence, and must impose a specific bioequivalence requirement on all generic drugs.[45] The Agency, in turn, has delineated specific in vivo and in vitro approaches in its regulations as acceptable for determining bioavailability or bioequivalence.[46] A primary objective of establishing bioequivalence is to assure interchangeability between pioneer and generic formulations. With respect to establishing the bioequivalence of extended-release dosage forms, FDA has stated that:

> Although bioavailability studies have been conducted on these dosage forms, they may be subject to bioavailability differences, primarily because firms developing extended-release products for the same active ingredient rarely employ the same formulation approach. FDA, therefore, does not consider different extended-release dosage forms containing the same active ingredient in equal strength to be

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43 See Declarations of William B. White, M.D., F.A.C.P. ¶ 11 (Oct. 25, 2001) (See Attachment A); Michael H. Smolensky, Ph.D. ¶¶ 12-13 (Nov. 26, 2001) (See Attachment B); see also Andrx Pharmaceuticals' Citizen Petition, supra note 35 ("With respect to cardiovascular drugs, [Andrx] believes that potential hemodynamic and electrophysiologic effects, as well as possible adverse drug-drug interactions require a particularly stringent regulatory assessment of the adequacy of standard pharmacokinetic parameters to describe meaningful profile (i.e., "shape-of-the-curve" comparisons between generic and reference drug products.").

44 See 21 C.F.R. § 320.1(e) (2001); see also 21 U.S.C. § 355(j)(8)(B)(i) (1994 & Supp. V 1999). "The in vivo bioavailability of a drug product is demonstrated if the product's rate and extent of absorption, as determined by comparison of measured parameters (e.g., concentration of active ingredient in the blood, urinary excretion rates or pharmacological effects), do not indicate a significant difference from the reference material's rate and extent of absorption." 21 C.F.R. § 320.23(a)(1) (2001). FDA's proposed revisions to the regulations concerning bioequivalence propose that this definition should be the basis for demonstrating bioequivalence. See Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Proposed Revisions, 63 Fed. Reg. 64,222 (proposed Nov. 19, 1998) (to be codified at 21 C.F.R. pts. 314 and 320).

45 See Bristol-Meyers Squibb Co. v. Shalala, 923 F. Supp. 212, 218 (D.D.C. 1996).

46 See 21 C.F.R. § 320.24 (2001) (setting forth pharmacokinetic and pharmacodynamic bioequivalence testing approaches).

> therapeutically equivalent unless equivalence between individual products in both rate and extent has been specifically demonstrated through appropriate bioequivalence studies.[47]

The chronotherapeutic design and clinical and safety benefits of Covera-HS® necessitate the adoption of bioequivalence requirements that address these characteristics.[48] The Agency's regulations require it to consider specific factors in identifying multisource drugs that are not bioequivalent to their reference listed drugs.[49] One such factor is a competent medical determination that a lack of bioequivalence would have a serious adverse effect in the treatment of a serious disease or condition.[50] The Agency has stated that:

> Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption [1] are intentional and are reflected in the labeling, [2] are not essential to the attainment of effective body drug concentrations on chronic use, and [3] are considered medically insignificant for the particular drug studied.[51]

FDA also has stated that this definition of bioequivalence is specifically applicable in considering whether two controlled-release products are bioequivalent,[52] but has consistently emphasized that drugs with intentional differences in rates of absorption will not be considered bioequivalent if "the difference in rate of absorption is medically significant" when considered on a "case-by-case basis."[53]

As noted above, scientific evidence and clinical experts have indicated that a lack of bioequivalence of multisource Covera-HS® formulations may have serious consequences—

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47 Division of Data Management and Services, FDA, Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), at Preface (2001) (emphasis added), available at http://www.fda.gov/cber/ob/docs/preface/ecpreface.htm.

48 See FDA Response to Andrx Pharmaceuticals' Citizen Petition 6 (Oct. 22, 1999) (Docket No. 98P-1045) [hereinafter FDA Response to Andrx Pharmaceuticals' Citizen Petition] ("If the Agency determines that the reference listed drug's safety and/or efficacy is affected by a distinct and consistently reproducible [pattern] in the plasma profile, and that this [pattern] therefore is medically significant, an ANDA applicant will be required to match the plasma profile of the reference listed drug prior to approval of the generic drug product.").

49 See 21 C.F.R. § 320.33 (2001).

50 See id. § 320.33(d).

51 Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,940 (proposed July 10, 1989) (to be codified at 21 C.F.R. § 320.23(b)) (emphasis added).

52 See id.

53 Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,974 (Apr. 28, 1992).

an increased risk of myocardial infarction, sudden cardiac death, thrombotic stroke, and myocardial ischemia.[54] Relatedly, precise bioequivalence of multisource formulations is essential to attain effective and comparable (i.e., not statistically significantly different) body-drug concentrations during chronic use for hypertension and angina. Thus, bioequivalence must be established with a high level of certainty and precision. An appropriate study design and parameters for determining the bioequivalence of a multisource form of Covera-HS® must, therefore, include the characteristics discussed below.

1. Early Morning Plasma Concentrations Must be Closely Assessed

As discussed in Section III, Covera-HS® has been specifically designed to provide a delayed-onset of drug release to coincide with the early-morning rise in blood pressure and heart rate. As depicted in Figure 4, after administration of 240 mg of Covera-HS® at bedtime, systemic concentrations of the primary active enantiomer, S-verapamil, remains low for four to five hours, followed by higher exposure between 5:00 a.m. and 11:00 a.m. when there is an increased risk of serious cardiovascular disease sequelae. Covera-HS® is, therefore, specifically formulated to release verapamil in concert with normal circadian rhythms associated with the cardiovascular system, to achieve the optimal pharmacodynamics of verapamil and its active metabolites.

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[54] See Declaration of William B. White, M.D., F.A.C.P. ¶ 10 (Oct. 25, 2001). (See Attachment A).

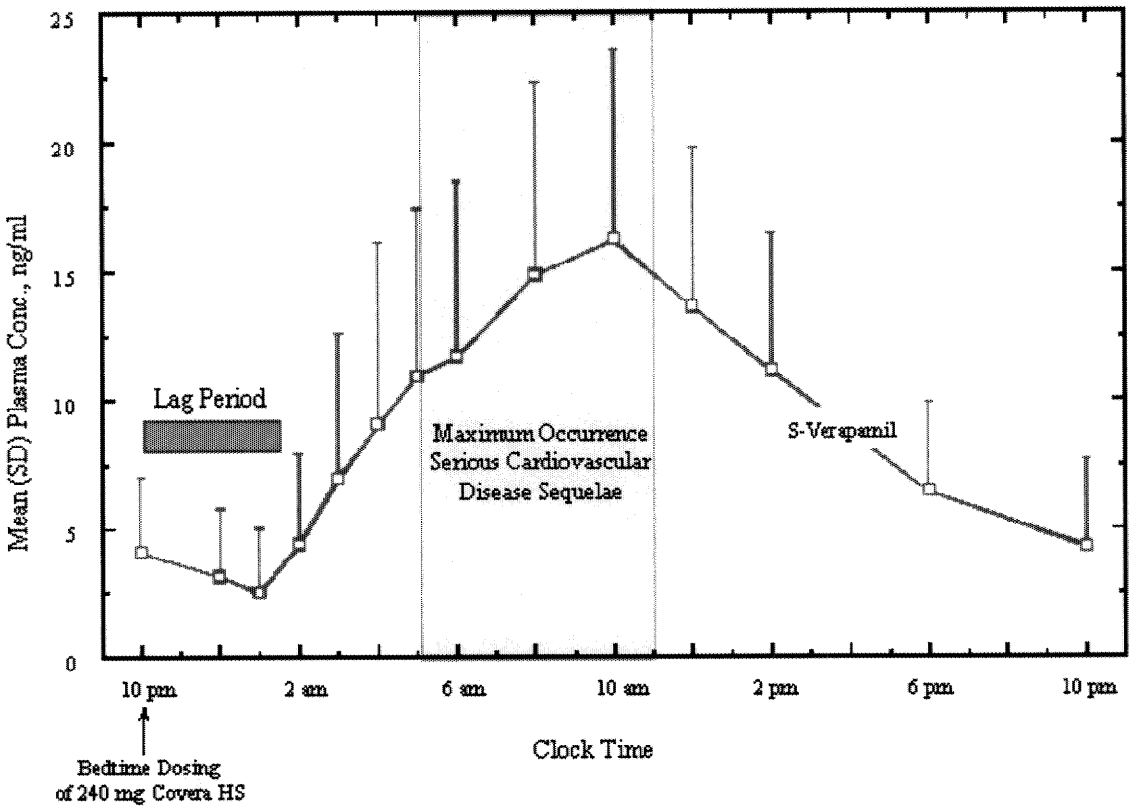

Figure 4. Steady state plasma concentration-time curves of S-verapamil following 240 mg once-a-day administration of racemic verapamil given for five days to 49 healthy subjects. Pharmacia Corporation.

Importantly, the drug release profile of Covera-HS® is also designed to minimize the risk of hypotensive events during the normal sleep cycle when blood pressure is typically lowest. Release of the pharmacologically primary active verapamil species (S-verapamil and S-norverapamil) is timed to coincide with the morning rise in blood pressure during the hours immediately before and following the patient's awakening. The initial morning rise in verapamil concentration is precisely timed to avoid premature vasodilatory responses, and to reach peak values during the narrow morning period of peak blood pressure, heart rate, and increased risk of cardiovascular events. Thereafter, release of the active parent drug is designed to be continuous and controlled for the remainder of the 24-hour dosing period.

a. ***Assessment of Partial AUC Will Assure Multisource Products Have Covera-HS®'s Nighttime and Early Morning Drug Release Profile***

Based on Covera-HS®'s precise and deliberately designed drug release profile, FDA should require that applicants submitting multisource applications demonstrate bioequivalence based

on initial exposure (partial AUC, area under the concentration-time curve from time zero to T_{max}), in addition to $AUC_{0-\infty}$ (area under the concentration-time curve from time zero to infinity), and C_{max} (maximum serum drug concentration).

The importance of determining bioequivalence for multisource formulations based on initial exposure is underscored by the scenario depicted in Figure 5. This figure illustrates how two extended-release formulations of verapamil, one with Covera-HS®'s lag period (i.e., from approximately 10:00 p.m. to 2:00 a.m.) and one without a lag period, could be deemed bioequivalent in terms of C_{max} and AUC—and even T_{max} (time of maximum serum drug concentration)—and yet have different initial input rates of the drug.[55] It is for this reason that assessment of initial exposure is essential to determining the bioequivalence of multisource versions of Covera-HS® where the delay in drug delivery is an important feature of the formulation design. Partial AUC has been demonstrated to be a more accurate and clinically relevant parameter in assessing early exposure—particularly for drugs with complex absorption kinetics[56]—and may be more sensitive than C_{max} for detection of input rate differences between formulations.[57] As a result, in a recent scientific article FDA Office of Pharmaceutical Science and United States Pharmacopoeia officials have proposed that "bioequivalence metrics for drugs that achieve their therapeutic effects after entry into the systemic circulation are best expressed in terms of early (partial AUC), peak (C_{max}) and total (AUC) exposure measures."[58]

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55 See Karim A. Enantioselective Assays in Comparative Bioavailability Studies of Racemic Drug Formulations: Nice to Know or Need to Know? J. Clin. Pharmacol. 1996;36:490-499. (See Attachment 34).

56 See Niazi SK, Alam SM, and Ahmad SI. Partial-Area Method in Bioequivalence Assessment: Naproxen. Biopharmaceutics & Drug Disposition. 1997; 18(2):103-116. (See Attachment 35); Chen ML, Lesko L, Williams RL. Measures of Exposure Versus Measures of Rate and Extent of Absorption. Clin. Pharmacokinet. 2001;40:565-572. (See Attachment 36).

57 See Chen et al., 2001, supra note 56, at 569 ("[C]onsideration of early exposure may be useful when a rapid … or slow (e.g., an antihypertensive effect) input is important to achieve an optimal safety or efficacy profile. In these settings, C_{max} alone may be insufficient as a measure to assure equivalence in performance, and the comparison of early exposure may be essential. Early exposure may be the partial area with a cutoff at the t_{max} of the drug").

58 See id. at 570.

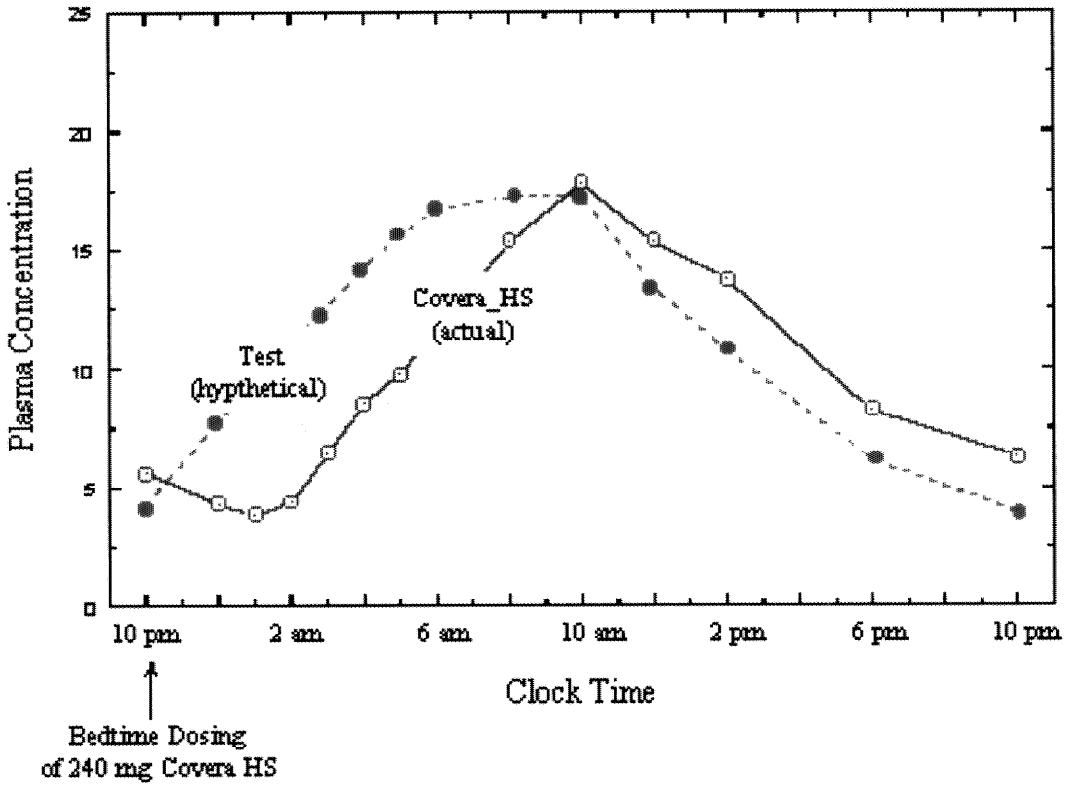

Figure 5. Steady state plasma concentrations of S-verapamil following dosing with Covera-HS® and a hypothetical test extended-release formulation of racemic verapamil. Pharmacia Corporation.

FDA's bioequivalence requirements for controlled-release formulations state that in vivo bioavailability studies for such drugs should assure that the drug "meets the controlled release claims made for it."[59] Moreover, FDA's regulations concerning single-dose in vivo bioavailability studies state that when comparison of multisource and pioneer products is to be based on blood concentration time curves, the frequency of the collection of blood samples should generally permit an estimate of C_{max} and AUC, as well as other approaches if there are valid scientific reasons for doing so.[60] In the case of a single-dose in vivo bioavailability study for a multisource formulation of Covera-HS®, there are strong scientific

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59 21 C.F.R. § 320.25(f)(i) (2001).

60 See 21 C.F.R. § 320.26(c) (2001). FDA's proposed revisions to the regulations concerning bioequivalence suggest that these requirements are also applicable to in vivo bioequivalency studies. See Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Proposed Revisions, 63 Fed. Reg. 64,222 (proposed Nov. 19, 1998) (to be codified at 21 C.F.R. pts. 314 and 320).

reasons for determining bioequivalence based on partial AUC to assure that such formulations closely match the drug release profile of Covera-HS®.[61]

FDA's most recent guidance concerning bioavailability and bioequivalence studies for orally administered drug products supports an assessment of partial AUC for multisource versions of Covera-HS®.[62] The guidance recommends a change in focus from direct or indirect measures of absorption rate to measures of systemic exposure—systemic exposure rates are defined relative to early, peak, and total proportions of the plasma, serum, or blood-concentration time curve.[63] Regarding measurement of early exposure the guidance states:

> 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.[64]

A failure to match Covera-HS®'s drug release profile through the period of low nighttime blood pressure and heart rate could present safety risks for patients if there is premature onset of significant exposure to verapamil (e.g., hypotensive events during sleep). In vivo bioequivalence studies for multisource versions, therefore, must be designed to assure that they closely match the in vivo drug release profile of Covera-HS® during the night.

Moreover, because FDA recommends single-dose studies even for drugs, such as Covera-HS®—which have non-linear kinetics and for which there is significant subject-to-subject

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61 See Declarations of Reza Mehvar, Pharm.D., Ph.D. ¶¶ 4.2-4.3 (Nov. 16, 2001) (See Attachment C); Kamal K. Midha, C.M., Ph.D., D.Sc. ¶ 10 (Nov. 27, 2001) (See Attachment D); Grant R. Wilkinson, Ph.D., ¶ 5 (Nov. 16, 2001) (See Attachment E); Michael H. Smolensky, Ph.D. ¶ 13 (Nov. 26, 2001) (See Attachment B); and William B. White, M.D., F.A.C.P. ¶ 11 (Oct. 25, 2001) (See Attachment A). Unlike the situation with Cardizem CD, where FDA determined that Hoechst Marion Roussel, Inc. did not consider a specific pharmacokinetic feature in the development and testing of the product, the precise drug release profile of Covera-HS® is intentional and clinically important to achieve the desired in vivo performance. See FDA Response to Andrx Pharmaceuticals' Citizen Petition, supra note 48.

62 See Center for Drug Evaluation and Research, FDA, Guidance for Industry: Bioavailability and Bioequivalence for Orally Administered Drug Products—General Considerations 9 (2000) [hereinafter FDA-General Considerations].

63 See id.

64 Id. (emphasis added).

variability in bioavailability[65]—demonstrating equivalence of partial AUC is essential to assuring the equivalence of T_{max} and the timing of the lag period.

b. Multisource Applicants Must Collect an Adequate Number of Samples to Perform a Proper Assessment of Partial AUC

Given the importance of the shape of the time-concentration curve from initial onset to C_{max}, Pharmacia believes it is important that a sufficient number of quantifiable samples (e.g., eight to ten samples) be collected before C_{max} to estimate the partial AUC. Pharmacia collected 18 samples over 36 hours, with half of these measurements before C_{max}, for its bioequivalence studies comparing the clinical and commercial versions of Covera-HS®.[66] This sampling pattern is consistent with that used in studies FDA has required to support the approval of multisource versions of other verapamil hydrochloride extended-release tablet products,[67] and should be required for assessing multisource versions of Covera-HS®.

2. Multisource Products With Different Input Rates Than Covera-HS® Must Be Bioequivalent With Respect to the Verapamil Enantiomers

Verapamil is almost completely absorbed from the intestinal tract when given orally as a racemate, but has only about 25 percent systemic availability because of extensive and saturable enantioselective first-pass metabolism. Verapamil hydrochloride is a racemic mixture consisting of equal parts R(d, +) and S(l, -) enantiomers.

S-verapamil, however, has approximately 10 times the dromotropic activity (i.e., its effect on the conductivity of cardiac muscle fibers) of R-verapamil, and is more extensively metabolized.[68,69] The preferentially greater plasma protein binding of R-verapamil results in

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65 See, e.g., Harder S, Thürmann 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. (See Attachment 37).

66 See Bioequivalence Summary: Bioequivalence of Clinical and Commercial Lots of Verapamil GITS 180mg and 240mg Following Multiple Dosing in Healthy Subjects. (See Attachment 38).

67 See FDA, Summary Basis of Approval for Mylan's Verapamil Hydrochloride Extended Release Tablets, Review of Bioequivalence Studies and Dissolution Data, Moheb H. Makary (Oct. 7, 1996) (ANDA #074587) [hereinafter SBOA for Mylan's Verapamil]. For the single-dose, two-way crossover, fasting bioequivalence studies required for approval, Mylan was required to collect ten mL (10) blood samples at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, and 48 hours after dosing. FDA has, therefore, required 15 samples to be drawn in the first 12 hours of dosing.

68 See Vogelgesang B, Echizen H, Schmidt E, Eichelbaum M. Stereoselective First-Pass Metabolism of Highly Cleared drugs: Studies of the Bioavailability of L- and D-Verapamil Examined with a Stable Isotope Technique. Br. J. Clin. Pharmacol. 1984;18:733-740. (See Attachment 39).

greater availability of the S-enantiomer, further increasing its relative activity. Due to the enantioselective metabolism of the racemate, however, S-verapamil is also the minor enantiomer.[70] Thus, the primary efficacy/safety of verapamil resides with the minor enantiomer S-verapamil. The major metabolite of verapamil in the plasma, norverapamil, has approximately 20 percent of the activity of the parent drug.[71]

The systemic concentrations of R and S enantiomers, as well as overall bioavailability, are dependent upon the route of administration and on the rate and extent of release from a given dosage form. The pharmacokinetic profiles of the S- and R-enantiomers differ significantly, such that the pharmacokinetic profile of racemic verapamil does not accurately predict or reflect the profile of the active S-enantiomer. Upon oral administration, there is rapid stereoselective biotransformation during the first pass of verapamil through the portal circulation[72]—S-verapamil is metabolized substantially more upon first-pass than R-verapamil.[73]

Thus, the relative proportions of each verapamil enantiomer present in vivo depends on the input rate of a drug. FDA has previously concluded that "[a]s long as the rates of input of the reference listed drug and generic drug products are similar, FDA expects that there will not be a different pattern of absorption of isomers of the two drugs prior to first-pass extraction."[74] If, however, the input rates of the verapamil enantiomers in a multisource

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69 See Kroemer HK, Echizen H, Heidemann H, Eichelbaum M. Predictability of the In Vivo Metabolism of Verapamil from In Vitro Data: Contribution of Individual Metabolic Pathways and Stereoselective Aspects. J. Pharmacol. Exp. Ther. 1992;260:1052-1057. (See Attachment 40).

70 See Mehvar R, Jamali F. Bioequivalence of Chiral Drugs: Stereospecific Versus Non-Stereospecific Methods. Clin. Pharmacokinet. 1997;33:122-141. (See Attachment 41).

71 See Prescribing Information for Covera-HS®, supra note 17, at 4.

72 See Prescribing Information for Covera-HS®, supra note 17. In a study in five subjects with oral immediate-release verapamil, the systemic bioavailability was from 33 percent to 65 percent for the R enantiomer and from 13 percent to 34 percent for the S enantiomer.

73 See Vogelgesang et al., 1984, supra note 68; Kroemer et al., 1992, supra note 69. If the input rates of multisource products differ from that of Covera-HS®, therefore, the concentration-related, saturable hepatic first-pass metabolism of S-verapamil should be considered in assessing bioequivalence. Furthermore, after oral administration, S-verapamil exhibits less plasma protein binding than R-verapamil. See Gross AS, Heuer B, Eichelbaum M. Stereoselective Protein Binding of Verapamil Enantiomers. Biochem. Pharmacol. 1988;37:4623-4627. (See Attachment 42). Because the altered blood concentration ratios of the enantiomers have potential consequences on cardiovascular function (e.g., heart rate), assessing the bioequivalence of the verapamil enantiomers would assure the safety and efficacy of multisource products.

74 Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, to Robert Bogomolny, Vice President and General Counsel, G.D. Searle & Co. (Mar. 6, 1996) (responding to Searle Petition for Stay of Action, 89P-0220/PSA1, 89P-0430/PSA1, 89P-0141/CP2, and 89P-0141/PRC1).

racemic mixture differ from that of Covera-HS®—resulting in a change in the systemic enantiomer ratio—the products potentially could have clinically significant differences in effect, because the R and S enantiomers have different levels of pharmacologic activity.[75] S-verapamil has approximately 10 times the dromotropic activity of R-verapamil,[76,77,78] i.e., the S-enantiomer is approximately 10 times more potent at slowing the conduction through the AV node, thereby slowing heart rate and reducing myocardial oxygen consumption. Verapamil is effective in the treatment of angina because it decreases oxygen demand and increases oxygen supply through vasodilation.[79]

A series of experiments seeking to establish plasma concentration-response curves (for PR interval prolongation) of racemic verapamil (administered orally and intravenously to healthy young men) have demonstrated the clinical significance of a change in input rates that, in turn, impact the enantiomer ratio. These studies showed a wide disparity between oral and intravenous EC_{50}[80] values,[81,82,83] and a significant difference in EC_{50} values between

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75 See Prescribing Information for Covera-HS®, supra note 17. In studies in animals and humans the S enantiomer has 8 to 20 times the activity of the R enantiomer in slowing AV conduction. In animal studies, the S enantiomer has 15 and 50 times the activity of the R enantiomer in reducing myocardial contractility in isolated blood-perfused dog papillary muscle and isolated rabbit papillary muscle, respectively, and twice the effect in reducing peripheral resistance. In isolated septal strip preparations from five patients, the S enantiomer was eight times more potent than the R in reducing myocardial contractility. Dose escalation study data indicate that verapamil concentrations increase disproportionally to dose as measured by relative C_{max} plasma concentrations or areas under the plasma concentration versus time curves. See Declarations of Reza Mehvar, Pharm.D., Ph.D. ¶¶ 3.4-3.5 (Nov. 16, 2001) (See Attachment C) and Kamal K. Midha, C.M., Ph.D., D.Sc. ¶ 13 (Nov. 27, 2001) (See Attachment D).

76 See Echizen H, Brecht T, Niedergesäss S, Vogelgesang B, Eichelbaum M. The Effects of Dextro-, Levo-, and Racemic Verapamil on Atrioventricular Conduction in Humans. Am. Heart J. 1985;109:210-217. (See Attachment 43).

77 See Echizen H, Manz M, Eichelbaum M. Electrophysiologic Effects of Dextro- and Levo-Verapamil on Sinus Node and AV Node Function in Humans. J. Cardiovasc. Pharmacol. 1988;12:543-546. (See Attachment 44).

78 See Echizen H, Vogelgesang B, Eichelbaum M. Effects of d,l-Verapamil on the Atrioventricular Conduction in Relation to Its Stereoselective First-Pass Metabolism. Clin. Pharmacol. Ther. 1985;38:71-76. (See Attachment 45).

79 See Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lyttle BW, O'Rourke RA, Schafer WP, Williams SV. ACC/AHA/ACP-ASIM Guidelines for the Management of Patients with Chronic Stable Angina: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). J. Am. Coll. Cardiol. 1999;33:2092-2197. (See Attachment 46).

80 The EC_{50} is the effective concentration of the drug that causes 50 percent of the maximum response.

81 See Harder et al., 1991, supra note 65.

immediate-release and conventional sustained-release oral administration of verapamil.[84] Taken together, these findings indicate that input rates significantly affect the enantiospecific first-pass metabolism of verapamil, thereby altering the proportion of R- and S-verapamil in plasma. Indeed, the R/S ratios of verapamil and norverapamil differ depending on the input rates of oral administration.[85] Thus, although equal doses of verapamil contain equal proportions of each enantiomer (R/S = 1), a difference in input rate can result in significantly different proportions of these enantiomers in vivo. For example, a computer simulation was performed to determine whether identical products with different input rates would yield bioequivalency for both the racemate and enantiomers of verapamil. Based on published kinetic parameters for verapamil, Mehvar and Jamali generated AUC, C_{max}, and T_{max} data for a reference and test drug with dissolution rates of 0.5 and 1.0 h^{-1}, respectively. The reference and test drugs would be considered bioequivalent in terms of AUC for total drug (<15% difference), but they would not be considered bioequivalent in terms of AUC for the S-enantiomer (<30%) difference.[86]

A small, yet significant difference in the input rate and, in turn, the R/S ratio between similar products may, therefore, have important clinical consequences. Analyzing only plasma concentration-time data in terms of the racemate (pooled R- and S-verapamil) may obscure possible clinical consequences. Sahajwalla et al. determined that when one alters the

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82 See Eichelbaum M, Mikus G, Vogelgesang B. Pharmacokinetics of (+)-, (-)-, and (+/-)-Verapamil After Intravenous Administration. Br. J. Clin. Pharmacol. 1984;17:453-458. (See Attachment 47).

83 See Reiter MJ, Shand DG, Pritchett ELC. Comparison of Intravenous and Oral Verapamil Dosing. Clin. Pharmacol. Ther. 1982;32:711-720. (See Attachment 48).

84 See Harder et al., 1991, supra note 65.

85 Karim and Piergies determined that input rates vary widely between immediate- and conventional sustained-release formulations of equal doses of verapamil (immediate-release C_{max} (racemate) = 327 (44% coefficient of variation ng/ml at 1.71 (36%) hours; sustained release C_{max} (racemate) = 73.5 (58% coefficient of variation) at 10.8 (62%) hours). Karim A, Piergies A. Verapamil Stereoisomerism: Enantiomeric Ratios in Plasma Dependent on Peak Concentrations, Oral Input Rate, or Both. Clin. Pharmacol. Ther. 1995;58:174-184 (See Attachment 49). The R/S ratios at these C_{max} (racemate) values were significantly lower, however, for the immediate-release than the sustained-release verapamil (4.52 (13%) versus. 5.83 (18%); $p<0.01$). The time course of R/S ratios varied significantly, as well. Similarly, Bhatti and colleagues compared the pharmacokinetics of immediate and controlled-release formulations of verapamil and found different bioavailability of enantiomers in the plasma for different drug formulations. See Bhatti MM, Lewanczuk RZ, Pasutto FM, Foster RT. 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. (See Attachment 50). In vitro studies in verapamil-infused isolated rat livers provide further evidence for input rate-dependent stereoselective pharmacokinetics. See Mehvar R, Reynolds J. Input Rate-Dependent Stereoselective Pharmacokinetics: Experimental Evidence in Verapamil-Infused Isolated Rat Livers. Drug Metab. Dispos. 1995;23:637-641. (See Attachment 51).

86 See Mehvar & Jamali, 1997, supra note 70.

concentration of S-verapamil in a racemate by 30 percent, there is only a seven percent difference in total drug (R- plus S-verapamil) plasma concentrations.[87] The bioequivalence of the verapamil enantiomers, therefore, properly should be demonstrated for multisource products that have potentially different input rates to assure their safety and efficacy.

More specifically, if bioequivalence metrics (such as AUC and C_{max} values) for multisource products fall well within the accepted 90 percent confidence interval range (e.g., 80-125% for $AUC_{0-\infty}$ and C_{max}), FDA can be assured that the input rates are equivalent. If, however, bioequivalence measures are close to the extremes of the 90 percent confidence interval range (e.g., 80-85% or 120-125% for $AUC_{0-\infty}$ or C_{max}), FDA properly cannot establish that the input rates are equivalent and should require a showing of bioequivalence on the basis of the verapamil enantiomers to ensure that the bioequivalence of the minor verapamil enantiomer does not fall outside of the acceptable 90 percent confidence interval range.[88]

FDA guidance supports this recommendation. In its recent guidance concerning bioavailability and bioequivalence studies for orally administered drug products, the Agency acknowledges the potential clinical significance of changes in enantiomer ratios in multisource racemic mixtures, and recommends the measurement of individual enantiomers in bioequivalence studies if a drug exhibits the following four attributes:

(1) the enantiomers exhibit different pharmacodynamic characteristics;

(2) the enantiomers exhibit different pharmacokinetic characteristics;

(3) primary efficacy/safety activity resides with the minor enantiomer; and

(4) non-linear first-pass metabolism is present (as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug) for at least one of the enantiomers.[89]

As discussed above, the S- and R-enantiomers of verapamil meet these conditions, and therefore should be measured under relevant conditions.

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87 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. (See Attachment 52).

88 See Declarations of Reza Mehvar, Pharm.D., Ph.D. ¶ 3.5 (Nov. 16, 2001) (See Attachment C) and Kamal K. Midha, C.M., Ph.D., D.Sc. ¶ 14 (Nov. 27, 2001) (See Attachment D). Understanding the importance of this assessment, Pharmacia demonstrated the bioequivalence of the clinical and commercial versions of Covera-HS® not only with respect to S- and R-verapamil, but also with respect to S- and R-norverapamil. See Bioequivalence Summary: Bioequivalence of Clinical and Commercial Lots of Verapamil GITS 180mg and 240mg Following Multiple Dosing in Healthy Subjects. (See Attachment 38).

89 FDA-General Considerations, supra note 62, at 19.

3. The Active Metabolite of Verapamil Should be Measured

FDA guidance states that "if the metabolite contributes meaningfully to safety and/or efficacy, the metabolite and the parent drug should be measured."[90] Norverapamil possesses approximately 20 percent of the activity of verapamil, and norverapamil enantiomers can reach steady-state plasma concentrations equal to those of the parent drug.[91] FDA, therefore, properly should require that multisource sponsors demonstrate bioequivalence for norverapamil. Importantly, the Agency has required this of other sponsors of multisource versions of extended-release verapamil tablets.[92]

C. Appropriate Study Protocols Should Be Adopted for Assessing the Bioequivalence of Multisource Versions of Covera-HS®

Consistent with current FDA guidance, in addition to the requirements identified in the preceding sections, the bioequivalence of multisource versions should be determined on the basis of the following:

- **Single-dose, replicate design, fasting study of the highest strength product.**

  FDA recommends that extended-release products submitted as ANDAs be required to demonstrate bioequivalence on the basis of a single-dose, replicate design, fasting study comparing the highest strength of the test and reference listed product.93 FDA recommends replicate design studies for highly variable drug/products (within-subject coefficient of variation $\geq$ 30%) and for extended-release dosage forms. Replicate designed studies are a powerful method for assessing bioequivalency, and offer several advantages compared to nonreplicate study designs.[94]

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90 FDA-General Considerations, supra note 62.

91 See Prescribing Information for Covera-HS®, supra note 17.

92 See SBOA for Mylan's Verapamil, supra note 67.

93 See FDA-General Considerations, supra note 62, at 7, 16.

94 The advantages of replicate studies include: (1) they permit comparison of within-subject variances for the test and reference products; (2) they indicate whether a test product exhibits higher or lower within-subject variability in the bioavailability measures when compared to the reference product; (3) they suggest whether a subject-by-formulation (S*F) interaction may be present; (4) they provide more information about factors underlying formulation performance; and (5) they reduce the number of subjects needed in the bioequivalence study.

As Covera-HS® is both an extended-release dosage form and it contains a drug molecule that is a highly variable drug,[95] any ANDA for a multisource version should only be determined bioequivalent on the basis of a replicate design study.

In particular, FDA recommends a "four-period, two-sequence, two-formulation design" for replicated bioequivalence studies.[96] In the context of this study, the within and between subject variability in the peak and total exposure of verapamil from the multisource formulation should not exceed that from Covera-HS®. Moreover, the study should include a number of subjects sufficient to provide adequate power (>80%) at α of 0.05 in pharmacokinetic parameters.

- **Food-effect, non-replicate design study of the highest strength product.**

FDA also recommends that extended-release products submitted as ANDAs be required to conduct a single-dose, two-period, two-treatment, two-sequence crossover food-effect study comparing the highest strength of the test and reference product.[97] Food does not alter the pharmacokinetic or hemodynamic effects of verapamil or norverapamil.[98] In turn, there are no specific instructions in the Covera-HS® labeling with respect to administration with or without food because its drug delivery profile is not significantly influenced by food. Consistent with its new draft guidance on food-effect bioavailability and fed bioequivalence studies, FDA should, therefore, require that multisource applicants assess the effect of food on their versions of Covera-HS® to confirm that their pharmacokinetics also are not affected by food.[99]

- **Nighttime Dosing.**

Previous studies have demonstrated that the rate of verapamil absorption is affected by time of dosing by approximately 20 to 30 percent, with nighttime dosing resulting in a longer lag until peak blood levels are achieved.[100] Thus, dosing time is a critical factor in the safe and effective use of Covera-HS®. For the above studies, subjects should,

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95 See supra note 85.

96 Center for Drug Evaluation and Research, FDA, Guidance for Industry: Statistical Approaches to Establishing Bioequivalence 7 (2001).

97 See FDA-General Considerations, supra note 62, at 16, 18; see also Center for Drug Evaluation and Research, FDA, Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling 5 (Draft, 2001) [hereinafter FDA Food-Effect].

98 See Gupta SK, Yih BM, Atkinson L, Longstreth J. The Effect of Food, Time of Dosing, and Body Position on the Pharmacokinetics and Pharmacodynamics of Verapamil and Norverapamil. J. Clin. Pharmacol. 1995;35(11):1083-1093. (See Attachment 53).

99 See FDA Food-Effect, supra note 97, at 5.

100 See, e.g., Gupta et al., 1995, supra note 98.

therefore, be administered the test and reference products in a manner consistent with the Covera-HS® label with respect to time of dosing. Specifically, subjects should be administered the test and reference products starting at approximately 10:00 p.m., and vital signs (heart rate and blood pressure) should be monitored throughout the complete dosing interval to ensure the safety of the subjects.[101] Of consequence, Pharmacia's bioequivalence studies involving the clinical and commercial versions of Covera-HS® were conducted consistent with these principles.[102] The fundamental concept behind Covera-HS®'s release profile is to address important variations in blood pressure and heart rate that follow circadian rhythm. Unless a multisource product can be demonstrated bioequivalent over this specific time, it cannot be assured to provide the clinical benefits and safety profile of Covera-HS® and may increase risk of cardiovascular events. Thus, bioequivalence testing should ensure the delivery of verapamil to coincide with the early morning increases in heart rate, blood pressure, adrenergic tone, and plasma viscosity. Furthermore, the rate of absorption of verapamil differs with time of dosing, as the mean C_{max} and T_{max} values of S- and R-verapamil obtained after nighttime dosing are approximately 19-29 percent higher than those obtained after morning dosing.[103] The circadian factors that govern hemodynamics and absorption therefore necessitate that a multisource version of Covera-HS® be tested according to its labeling and indication. As noted above, it is important that quantifiable samples (e.g., eight to ten samples) be collected before C_{max}, at approximately 10:00 a.m., to estimate partial AUC (initial exposure).

- **Subject Selection.**

As the staging (i.e., timing of the peak and trough) of circadian rhythms, including that of blood pressure in essential hypertension, is determined by the sleep-wake routine, inclusion criteria for subject selection for bioequivalence studies must be specific for persons for whom the medication is primarily intended, i.e., those who follow a fairly consistent routine of diurnal activity alternating with nocturnal sleep (rise at approximately 6:00 a.m. ± 1 hour and go to sleep at approximately 11:00 p.m. ± 1 hour). Exclusion criteria thus should not include persons who have a recent (i.e., within one week) or current history of night or shiftwork, irregular sleep-wake routine due to university study or work requirements, and sleep disorders.[104]

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101 See Declarations of Michael H. Smolensky, Ph.D. ¶ 15 (Nov. 26, 2001) (See Attachment B) and Grant R. Wilkinson, Ph.D., ¶¶ 6,7 (Nov. 16, 2001) (See Attachment E).

102 See Bioequivalence Summary: Bioequivalence of Clinical and Commercial Lots of Verapamil GITS 180mg and 240mg Following Multiple Dosing in Healthy Subjects. (See Attachment 38).

103 See Gupta et al., 1995, supra note 98.

104 See Declaration of Michael H. Smolensky, Ph.D. ¶ 17 (Nov. 26, 2001) (See Attachment B).

IV. Summary

The complex and unique pharmacologic properties and clinical benefits of verapamil administered in a delayed-onset, extended-release chronotherapeutic regimen, demand that FDA require applicants of multisource versions of Covera-HS® meet the bioequivalence standards set forth herein. Specifically, these products should be demonstrated to be bioequivalent to Covera-HS® based on the following:

- Single-dose, replicate design, fasting study of the highest strength product (four-period, two-sequence, two-formulation design) and a food-effect, non-replicate design study of the highest strength product, both with nighttime dosing with subjects who follow a consistent routine of diurnal activity alternating with nocturnal sleep; and

- Equivalence of the racemic verapamil and norverapamil in terms of $AUC_{0-\infty}$ (area under the concentration-time curve from time zero to infinity), C_{max} (maximum serum drug concentration), and partial AUC (from dosing to T_{max}), and, if data indicate that a multisource product potentially has a different input rate than Covera-HS®, equivalence of the foregoing parameters for the individual verapamil enantiomers.

This testing will assure that patients with hypertension and angina are not exposed to less safe or effective multisource versions of Covera-HS®.

V. Sound Public Policy Grounds Relating to Patient Safety Support The Stay

There are sound public policy concerns for FDA to grant the stay that Pharmacia requests in this Petition. FDA's approval of multisource formulations of Covera-HS® that are not determined to be bioequivalent pursuant to the requirements set forth in this Petition, would pose a significant adverse safety risk to patients with cardiovascular disease, whose risk of a cardiovascular event are heightened in the morning hours. More specifically, significant adverse health consequences of using a multisource product that releases verapamil at a rate or extent inconsistent with Covera-HS'® chronotherapeutic principles may include an increased risk of myocardial infarction, sudden cardiac death, thrombotic stroke, and myocardial ischemia. Hypertensive or angina patients who have been stabilized on Covera-HS® could be placed at undue risk of loss of effectiveness and/or increased risk of new side effects if switched to a multisource product with a distinctly different pharmacokinetic profile. Moreover, excessive systolic blood pressure reduction during nighttime sleep—a time when blood pressure typically declines to its lowest level—could increase a patient's risk of ischemic damage to the retina, nocturnal hypotension resulting in a heightened risk of falls, especially in the elderly, when awakening at night to use the toilet, and cardiovascular events such as ischemic stroke.

FDA, therefore, should only approve an ANDA or 505(b)(2) application for a multisource version Covera-HS® that meets these requirements. The exclusion of products that do not meet these requirements from the U.S. market falls directly within, and is required under, the Agency's mission and public health authority, and can only benefit the public health. Thus, public policy grounds strongly support grant of the stay requested in this Petition.

VI. The Delay Resulting From The Stay Would Not Be Outweighed By Public Health Or Other Public Policy Interests

As the reference listed drug product, Covera-HS® establishes the standard for safe and effective chronotherapeutic treatment for hypertension and angina. A stay would not deprive cardiovascular patients with the unique and meaningful clinical benefits of this therapeutic option, and will not conflict with the public health interest in the availability of useful medical products.

To the contrary, FDA's grant of a stay will promote an important public interest by assuring the proper application of statutes and regulations currently in effect that are intended to protect U.S. consumers from unsafe products.

Accordingly, the delay in approval of a new product resulting from the stay will serve, rather than contravene, FDA's goals and important public interests by ensuring that any multisource formulations follow chronotherapeutic principles for the treatment of both hypertension and angina, and will be equally effective and as safe as the pioneer product.

VII. Pharmacia Will Suffer Irreparable Injury If The Stay Is Not Granted

The FDA's denial of the stay requested in this Petition would result in irreparable injury to Pharmacia Corporation and, potentially, harm to patients with hypertension and angina who rely on the unique safety and efficacy characteristics of Covera-HS®. Multisource versions must not only be demonstrated bioequivalent in terms of their pharmacodynamic and pharmacokinetic properties, they must, in fact, be equivalent with respect to their ability to control elevated arterial pressure and angina pectoris, the two major indications for the life-threatening diseases for which Covera-HS® is prescribed (i.e., hypertension and angina pectoris). The Agency's denial would likely cause damage to the reputation of Covera-HS® as a safe and effective treatment for hypertension and angina, resulting in diminished goodwill toward the product and Pharmacia. If less safe or effective versions are available, patients would likely associate any product failure with the pioneer product, Covera-HS®, because they are unlikely to be informed about the existence of generic formulations. Further, the medical community may also associate reports of additional failures with the pioneer product, if such reports are not properly investigated.

If FDA denies this Petition, it is possible that multisource formulations of Covera-HS® that do not provide a proper delayed-onset of drug release to coincide with the early-morning rise

in blood pressure and heart rate will be introduced into the U.S. market. Mandated substitution of interchangeable products by state Medicaid programs, managed care organizations, and other state and federal government entities, and the imposition of additional fees for choosing pioneer formulations, would likely result in widespread use of such products. The fact that patients would, in general, be unaware if they received a generic formulation of Covera-HS®, would exacerbate the impact of such unreliable generic products. Patients and health care professionals are likely to attribute any reduced efficacy and safety of multisource formulations of Covera-HS® to the pioneer formulation. Therefore, Pharmacia's reputation, and the goodwill associated with Covera-HS®, will be irreparably injured, despite Pharmacia's efforts to develop and provide a highly effective and safe product, and its notification to FDA of appropriate steps the Agency can take to assure multisource formulations exhibit a safety and effectiveness profile comparable to that of the pioneer formulation.

In addition, if the stay is not granted, Pharmacia can be expected to suffer an improper reduction in use of this product by medical professionals, and a resultant irreparable loss of sales. If a multisource formulation of Covera-HS® is approved that has lower efficacy and/or safety as compared to the pioneer formulation, it can be expected that health care professionals will reduce their use of Covera-HS® in the mistaken belief that increased adverse events or cardiovascular mortality or morbidity attributable to such a formulation would also occur with Covera-HS®. The denial of a stay by FDA would, therefore, irreparably harm Pharmacia.

VIII. Pharmacia's Case Is Not Frivolous and is Being Pursued in Good Faith

Pharmacia has extensively assessed the bioavailability of Covera-HS®, and the complex stereoselective pharmacokinetics of the highly variable verapamil molecule. This ongoing research, combined with the Company's extensive understanding of the challenges commensurate with developing a safe and effective chronotherapeutic therapy for hypertension and angina, has led Pharmacia to conclude that there are credible scientific grounds for requiring the types of studies described in this Petition to be conducted by sponsors of generic formulations of Covera-HS®.

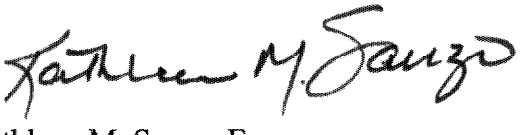
The available science provides a sound basis for public concern, and for Pharmacia to intercede on its own and the public's behalf, with respect to the potential availability of multisource formulations of Covera-HS® that do not exhibit a safety and/or effectiveness profile comparable to the pioneer formulation. The Company seeks to cooperate with the Agency by sharing its significant experience concerning Covera-HS®, and by illuminating the potential for multisource formulations to have reduced efficacy and safety if their bioequivalency is not demonstrated consistent with the principles articulated herein. Consequently, Pharmacia's case is not frivolous.

CONCLUSION

Pharmacia requests that the FDA promptly (1) stay the effective date of pending, tentative, or final decisions to approve ANDAs or section 505(b)(2) applications for multisource versions of Covera-HS®, and (2) not accept for filing, or "receive" within the meaning of 21 C.F.R. § 314.101, nor approve pursuant to 21 U.S.C. § 355 and 21 C.F.R. § 314.105, multisource formulations of Covera-HS® without first establishing bioequivalence using appropriate measures and methods, as described herein, pursuant to the provisions of Sections 505(b)(1), (b)(2), (j)(2)(A)(iv), (j)(4)(F) of the FFDCA, 21 U.S.C. §§ 355(b)(1), (b)(2), (j)(2)(A)(iv), (j)(4)(F) and the Agency's regulations, 21 C.F.R. §§ 320, 314.105, 314.54.

In order for FDA's response to this Petition to be prompt, as required under 21 C.F.R. § 10.35(e), and not impose any undue burden on petitioner, FDA must respond to this Petition before any approval of an ANDA or 505(b)(2) application for a multisource formulation of Covera-HS®.

Respectfully Submitted,



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Attachments