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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 01P-0470 -- Citizen Petition to Establish Appropriate Approval Standards for Generic Clonidine Transdermal Products

Dear Sir or Madam:

We submit this supplement to our petition on behalf of Boehringer Ingelheim Pharmaceuticals, Inc. ("Boehringer") to respond to comments filed on the petition on behalf of Mylan Technologies, Inc. ("Mylan") on April 17, 2003, and to statements made by representatives of Mylan and Elan Pharmaceutical Research Corp. ("Elan") at the scientific meeting hosted by the Food and Drug Administration ("FDA") on April 29, 2003.[1]

Elan

Elan has to date done nothing, either in a filing in the public docket or in expert statements at the scientific meeting, to address the serious issues raised by Boehringer's petition. Nor has it presented any data concerning its product for public review. Mylan, at least, had sufficient confidence in its arguments to expose them to consideration and contradiction, and we necessarily focus this submission on the weaknesses and errors we see in Mylan's position.

Our arguments, however, apply equally, or, depending on what is in Elan's data, may apply with even greater force to the Elan patch. We ask FDA to review Elan's data in light of the discussion here. If Elan is privately making additional and different arguments, we ask FDA to review those arguments with skepticism. After all, if Elan believed it had good points to make, it would not have been afraid to expose them to critical review.

[1] We understand that the transcript of that meeting will be placed in the record of this docket. The slides utilized by Boehringer for its presentation are Exhibit DD to the Petition, which is among the exhibits submitted with this document. References cited in the slides that have not been previously submitted are attached as Exhibits EE-KK.

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Mylan

Mylan's arguments contain several fatal flaws:

1. Mylan understates the safety issues presented and the role of the rate-controlling membrane in Catapres-TTS® in maintaining patient safety

A. Mylan's Arguments Ignore the Significant Safety Risks Associated with Clonidine Overdose

Mylan has suggested that, on the basis of FDA's prior approval of other transdermal products, FDA should consider the bioequivalence data submitted by Mylan to be sufficient to approve Mylan's CTS products. See Mylan Submission, pp. 3-5. Mylan cites to the following generic transdermal products that it says have been approved pursuant to an ANDA with a drug in adhesive system for support of the proposition that a generic with a differing delivery mechanism is approvable pursuant to an ANDA: nitroglycerin, estradiol, nicotine, and oxybutynin. Mylan admits that variability in skin permeability exists, but contends that since that variability is also experienced with other drugs, FDA should approve a clonidine patch without a rate-controlling membrane on the same theory as with these other products. Id. at p. 6. Unlike those other products, however, clonidine is classified by FDA as a narrow therapeutic range drug, and unintentional increases in clonidine blood levels could result in safety problems for this drug.

An unexpectedly high dose of clonidine can lead to injury resulting from hypotension (syncope and accidental injury from falling), unexpected somnolence which can lead to, inter alia, automobile accidents, and other unpleasant side effects. See Declaration of William B. White, M.D. (Exhibit OO). See also Lowenthal, D, "Clinical Pharmacokinetics of Clonidine." Clin. Pharm. 14:287-310 (1988), p. 291 (Exhibit Q) ("Clonidine overdose can produce severe cardiorespiratory dysfunction and coma."); Klein-Schwartz, W. "Trends and Toxic Effects From Pediatric Clonidine Exposures." Arch. of Pediatr. Adolesc. Med., 2002, 156:392-396 (Exhibit QQ). ("While most of the clonidine exposures resulted in minimal toxic effects, serious toxic effects and death can occur"). Mylan points to the fact that Catapres-TTS's labeling states that most side-effects are mild, but that is, we submit, precisely because the rate-limiting membrane works. If a patch without a rate-limiting membrane were to permit too high a blood level, it could lead to situations more akin to unintentional overdose than to adverse events from proper use of Catapres-TTS. The labeling for Catapres-TTS notes that overdose can lead to "[h]ypertension ... followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis" (Exhibit F).

There is in fact a wealth of literature detailing the significant risk of adverse events associated with transdermal clonidine, when a patient receives too large a dose of

the drug. See Roberge, RJ, Krenzelok, EP, and Mrvos, R, "Transdermal Drug Delivery System Exposure Outcomes." Journal of Emergency Medicine, 2000, 18(2):147-151 (Exhibit RR); Broderick-Cantwell, JJ, "Case Study: Accidental Clonidine Patch Overdose in Attention-Deficit/Hyperactivity Disorder Patients." Child and Adolescent Psychiatry, January 1999, 38(1), 95-98 (Exhibit SS); Seger, DL, "Clonidine Toxicity Revisited." Clinical Toxicology, 2002, 40(2):145-55 (Exhibit TT); Klein-Schwartz, W. "Trends and Toxic Effects From Pediatric Clonidine Exposures." Arch. Pediatr. Adolesc. Med., 2002, 156:392-396 (Exhibit QQ); Kappagoda, C. Schell, DN, Hanson, RM, and Hutchins, P, "Clonidine Overdose in Childhood: Implications of Increased Prescribing." Journal of Paediatrics and Child Health, December 1998, 34(6):508 (Exhibit UU); Gitter et al., "Clonidine Toxicity in An Adolescent Patient," Journal of the Mississippi State Medical Association, October 2000, 41(10):757-9 (Exhibit VV); Kraft, ME, "Pediatric Update: A 9-Month Old with Bradycardia and Periodic Apnea." The Journal of Emergency Nursing, October 1998, 24, 457-459 (Exhibit WW); Reed et al., "Person to Person Transfer of Transdermal Drug-Delivery Systems: A Case Report." New England Journal of Medicine, April 24, 1986, 314(17):1120-21 (Exhibit XX); Killian, CA, Roberge, RJ, Krenzelok, EP, and Stonage, CL, "'Cloniderm' Toxicity: Another Manifestation of Clonidine Overdose," Pediatric Emergency Care, 1997, 13(5):340-41 (Exhibit YY); Mrvos, R, Roberge, RJ, Killian, CA, et al., "Transdermal Clonidine Toxicity: A Serious Pediatric Hazard." Journal of Toxicology - Clinical Toxicology, 1996, 34(5):572 (Exhibit ZZ); Henretig, F, Wiley, J, and Brown, L, "Clonidine Patch Toxicity: The Proof's in the Poop!." Journal of Toxicology - Clinical Toxicology, 1995, 33(5):520-21 (Exhibit AAA).

For example, an analysis of 61 overdose exposures involving transdermal delivery systems over a five year period was conducted by Roberge, et al. in 1999. That analysis collected data through a Regional Poison Information System. See Roberge, RJ, Krenzelok, EP, and Mrvos, R, "Transdermal Drug Delivery System Exposure Outcomes." Journal of Emergency Medicine, 2000, 18(2):147-151 (Exhibit RR). The transdermal delivery systems studied involved clonidine, fentanyl, nitroglycerin, estradiol and nicotine. Id at. 148. The study concluded that "[r]elative to all exposures, clonidine was statistically associated with hospital admission" and that "ICU admission correlated significantly with clonidine exposure." Id. at 148. The study noted that among the significant adverse events reported for these clonidine exposures were coma, hypotension, somnolence, profound persistent bradycardia, miosis, and depressed respiration. Id. at 149. The study characterized these effects as a "reflection of the drug's potent pharmacologic effects...the exquisite toxic sensitivity of children to even small amounts of clonidine...and the possibility of prolonged toxicity from ongoing absorption from skin depot sites after removal of the offending [patch]." Id. at 150. The study went on to note that "[a]ny alteration of the [patch's] rate-limiting membrane can result in enhanced drug exposure and toxic effects." Id. (emphasis added).

In fact, the incidence of clonidine overdose is reported to be increasing. Seger, DL, "Clonidine Toxicity Revisited." Clinical Toxicology, 2002, 40(2):145-55 (Exhibit TT). In a recent study of symptomatic children[2] reported to poison control centers, the most common symptoms were lethargy (80%), bradycardia (17%), hypotension (15%) and respiratory depression (5%). Klein-Schwartz, W, "Trends and Toxic Effects From Pediatric Clonidine Exposures," Arch. of Pediatr. Adolesc. Med., 2002, 156:392-396 (Exhibit QQ). These exposures can result in toxic effects. Id.

Another study of overdose reported that depressed level of consciousness and bradycardia were observed in 75% and 88% of cases, respectively, and noted that "[c]lonidine overdose is a potentially serious condition, often requiring intensive care management." Kappagoda, C, Schell, DN, Hanson, RM, and Hutchins, P, "Clonidine Overdose in Childhood: Implications of Increased Prescribing." Journal of Paediatrics and Child Health, December 1998, 34(6):508 (Exhibit UU).

Another report, involving patch abuse by three adult drug addicts, concluded that: "Overdoses of clonidine can result in serious deleterious effects such as central nervous system depression, bradycardia, and hypotension." Rapko, DA, Rastegar, DA, "Intentional Clonidine Patch Ingestion By 3 Adults in a Detoxification Unit." Archives of Internal Medicine, 2003, 163(3):367-68 (Exhibit BBB).[3] See also Dy, EC, and Yates, WR, "Atypical Drug Abuse: A Case Report Involving Clonidine." American Family Physician, September 1, 1996, 54(3):1035-38 (Exhibit CCC).

"When taken in excess, [clonidine] can produce profound CNS depression, apnea, bradycardia and hypotension." Gitter et al., "Clonidine Toxicity in An Adolescent Patient," Journal of the Mississippi State Medical Association, October 2000, 41(10):757-9 (Exhibit VV). Cf. Kraft, ME, "Pediatric Update: A 9-Month Old with Bradycardia and Periodic Apnea." The Journal of Emergency Nursing, October 1998, 24, 457-459 (Exhibit WW). ("The triad for clonidine toxicity is central nervous system depression, bradycardia, and miosis....Hypotension, apnea, and hypothermia are also commonly associated with clonidine toxicity").

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[2] Doctors prescribe clonidine patches for treatment of attention deficit disorder in children, an unapproved use. As described in the references in the text, children are also affected by accidental exposure to patches used by adults.

[3] As this report notes, clonidine is sometimes used, outside its approved labeling, for relieving the symptoms associated with opiate withdrawal.

B. Safety Risks of Other Patches Can be Further Exacerbated When Heat and/or Moisture, Either through Exercise, Fever, External Application, or Ambient Temperature, Are Applied to the Skin

The literature also details many instances in which patients using other transdermal products have received an overdose of product due to the application of heat, such as from external heat sources, temperature conditions, or fever. It is significant, however, that neither the literature nor other sources show such similar problems with Catapres-TTS.

In a Japanese study of a new transdermal clonidine patch without a rate-controlling membrane, the influences of bathing and hot weather on plasma concentrations of clonidine were examined during applications of the new transdermal clonidine system, M-5041T, in eight healthy volunteers. Fujimura, A, Sasaki, M, Harada, K, et al., "Influences of Bathing and Hot Weather on the Pharmacokinetics of a New Transdermal Clonidine, M-5041T," J Clin. Pharmacol. 1996, 36:892-896 (Exhibit DDD). The authors noted that M-5041T, the new transdermal clonidine system, consists of two layers: a drug-containing adhesive layer, which is a high moisture permeable pressure-sensitive acrylicvinyl-copolymer containing clonidine in a quantity 0.4 mg/cm^2; and a backing layer which is a chemically stable, thin, and microporous polytetrafluoroethylene film with a good air and moisture permeability. Id.

Studies were completed in the winter and in the summer. The authors noted that mean temperature inside and outside the hospital and mean relative humidity outside the hospital were higher during the summer than during the winter. The study found that there was a significant increase in plasma concentrations of clonidine during the summer compared with the winter trial. The AUC value also was higher in the summer trial than in the winter trial in 7 of the 8 participants. As the values for clearance in the two trials did not differ significantly, the authors stated that they believe that the transdermal absorption of clonidine in the summer trial was enhanced compared with that in the winter trial. They stated that hydration of the stratum corneum by excessive sweating could play a major role in this phenomenon. Id.

A survey paper focusing on heat enhanced transdermal drug delivery cited the Fujimara study, noting "the significant (150% to 200%) increase in the plasma concentrations of clonidine during the summer trial when compared to the winter trial. The mechanisms cited for this result included increased blood flow through the dermal vessels and hydration of the stratum corneum, excessive sweating due to increased temperature and relative humidity during the summer trial." Hull, W, "Heat-Enhanced Transdermal Drug Delivery: A Survey Paper." Journal of Applied Research, 2002, 2(1) (Exhibit EEE).

Hull cites other studies finding that application of heat resulting in subcutaneous temperature increases caused a threefold, four to sixfold, and even a ten to twelvefold increase in skin blood flow, respectively. Id. Enhanced cutaneous blood flow during heat exposure dramatically alters the pharmacokinetics of many transdermally administered drugs. The results of these studies indicate that external heating is significant for transdermal as well as subcutaneous drug absorption, resulting in increased plasma drug concentrations. Id.

In one report involving a fentanyl patch[4], a 44-year old male with painful HIV neuropathy attended a summer family camp for HIV patients. Newshan, G, "Heat-Related Toxicity with the Fentanyl Transdermal Patch." Journal of Pain and Symptom Management, 1998, 16(5):277 (Exhibit FFF). The authors suggested "that the [patient's] increase in outdoor activities, combined with the sunny and warm environment, caused a unique situation in which fentanyl absorption increased because of a rise in body temperature," resulting in an effective overdose. Id. at 277-78.

In another report, an upper-body-warming blanket was placed on a patient who was using a transdermal fentanyl patch. Frolich, M, Giannotti, A, and Modell, JH, "Opioid Overdose in a Patient Using a Fentanyl Patch During Treatment with a Warming Blanket." Anesth. Analg. 2001, 93:647-8 (Exhibit GGG). The authors conclude that this mechanism was responsible for increased systemic fentanyl levels and the observed symptoms of opioid overdose in this patient. Id. See also Rose, PG, Macfee, MS, and Boswell, MV, "Fentanyl Transdermal System Overdose Secondary to Cutaneous Hyperthermia." Anesth. Analg. 1992, 77:390-1 (similar experience with a hospital heating pad) (Exhibit HHH).

C. Contrary to Mylan's Assertions, Both the Published Literature and Historical Patient Experience with Catapres-TTS Demonstrate that these Safety Risks are Avoided in Catapres-TTS With its Rate-Controlling Membrane

Enscore et al. have noted:

> The rate controlling membrane in the Catapres-TTS controls the rate of drug input to the blood stream, minimizing the intra- and inter-patient variability in the dose of drug received which could result if skin, with its inherent variability in permeability, were allowed to control the rate of drug input. The rate of drug

[4] The fentanyl patch contains a rate-controlling membrane, but one with different properties than that in Catapres-TTS. Also, the pharmacokinetics of the two drugs differ, and fentanyl is highly lipophilic, while clonidine is not. Heat appears to be a particular issue for the fentanyl patch, and avoidance of heat is a precaution in its labeling.

input from Catapres-TTS is directly proportional to the area of the dosage form applied to the skin.

Enscore, D. "Structure and Function of Catapres-TTS: in Weber, et al., (eds.) Low Dose Oral and Transdermal Therapy of Hypertension at 114-117, p. 117 (Exhibit S). As previously noted, once the content of the contact adhesive layer of Catapres-TTS falls below saturation, clonidine is released from the reservoir at a rate determined by the properties of the rate-controlling membrane. Enscore in fact states the authors' view that the membrane in Catapres-TTS provides 75% control over the rate of drug permeation through the skin. Id. at 116. Enscore states that the advantages conferred by this design include: "reduction of the frequency and intensity of side-effects..." Id. at 114.

In fact, Catapres-TTS, with its rate-controlling membrane, has a remarkable safety record over the many years that it has been marketed. However, in the rare instances in which the rate-controlling membrane of the patch has been compromised, so that this patch acted like a true monolith, significant toxicity has resulted. See, e.g., Broderick-Cantwell, JJ, "Case Study: Accidental Clonidine Patch Overdose in Attention-Deficit/Hyperactivity Disorder Patients." Child and Adolescent Psychiatry, January 1999, 38(1):95-98 (Exhibit SS). In the Broderick-Cantwell report, the authors considered a case in which the rate-controlling membrane was removed from Catapres-TTS inadvertently by a mother with the resultant near term delivery of an overdose of clonidine resulting in significant hypotension, bradycardia, and somnolence. The authors noted that, several hours after removal of the patch, the patient was still quite drowsy, hyposensitive, and bradycardic. Id. at 96.

Broderick-Cantwell also considered a second case in which a patient "was suffering from an unintentional overdose of clonidine caused by trauma to the [rate] control membrane, which he caused while scratching his back, and increased absorption resulting from his abraded skin." (The authors also noted the possible thinning of his skin due to application of a topical hydrocortisone product to relieve the itching.) The authors commented that "these cases illustrate that the safety and efficacy of the clonidine patch are dependent on the integrity of the transdermal system and the condition of the dermal surface to which it is applied." Id. at 96.

The authors report the most common presenting symptom of a clonidine overdose as an altered level of consciousness (86%-96%) which usually begins 30 to 60 minutes after ingesting clonidine tablets, but could take longer with the patch because of slower absorption. Id. However, they also noted other serious and high frequency side effects of an overdose: "bradycardia (29%-53%), hypotension (12%-38%), transient hypertension (4%-44%), arrhythmia (30%), respiratory depression (17%-48%), miosis (19%-56%), and hypothermia (6%-55%)." Id.

The authors go on to note that "[s]evere hypotension, respiratory depression, and coma have been reported in several young children after ingestion of only 0.2 mg of clonidine." They state that both patients discussed in the article "presented with altered levels of consciousness, hypotension, and bradycardia as a sign of their clonidine toxicity." Id. at 96-97.

It is thus apparent that clonidine at inappropriate levels can be dangerous to patients. It is also apparent that, for other potent transdermal drugs, like fentanyl, experience with heat, etc., has produced toxicity associated with overdose. Catapres-TTS, on the other hand, has had a remarkable safety record, when the patch has been used in accordance with its labeling, during the 20-year historical patient experience with the product.[5] We believe, therefore, that the rate-controlling membrane of Catapres-TTS serves the purpose of controlling the delivery of clonidine and thus avoids what could be significant safety risks with a patch that lacks the patient-protection features of Catapres-TTS. Generic versions lacking such a membrane differ significantly in their inactive ingredients, a difference that raises safety issues. As the ANDA applicants, the burden is, of course, on Mylan and Elan to demonstrate that their different release mechanisms do not in fact pose these risks. If they cannot, approval under an ANDA is prohibited.

2. Mylan seriously mischaracterizes the function of rate control

Mylan and its expert declarant, Dr. Hadgraft, have at several points misstated the function of rate control in a transdermal patch. As Boehringer's expert Dr. Hopfenberg explained at the FDA meeting, absorption is determined by resistance, and the total resistance from a transdermal patch is a function of the resistance offered by the skin combined with the resistance offered by the patch itself.[6] The equation presented by Dr. Hopfenberg[7] explains this phenomenon:

$$R_{total} = R_{skin} + R_{device}$$

[5] Boehringer recognizes that neither the absence of literature reports nor the absence of adverse event reports is definitive evidence of safety, but over the 20-year history of the product neither literature nor spontaneous data have generated a signal with respect to heat-related increases in absorption concerning Catapres-TTS. Nor has the literature we have reviewed disclosed any evidence of heat-related toxicity involving Catapres-TTS.

[6] This was what Dr. Hopfenberg said in his original declaration (Exh. T to this petition), ¶ 9: "The stratum corneum offers a significant contribution to the overall resistance controlling drug delivery, thereby serving to reduce, predictably, the overall rate of clonidine delivery."

[7] See the second declaration of Harold B. Hopfenberg, Ph.D. (hereinafter "Second Hopfenberg Declaration"), ¶ 2 (Exhibit LL to this submission), and Exhibit DD, slide 8.

This equation should be compared to the statements, made throughout the Mylan papers, that imply that the equation is:

R_{total} = the greater of R_{skin} or R_{device}

For example, in arguing that the drug delivery from the Catapres-TTS patch should be the same when applied to sites at which the skin has different permeabilities (e.g., the chest as opposed to the outer thigh), Mylan said that "Catapres TTS, with its so-called rate-controlling membrane, should have delivered clonidine at the same rate at each site." (Mylan Submission, p. 9). Since, in the cases discussed, the skin has a resistance greater than zero, the Mylan statement can only be based on adoption of the second, erroneous, equation, rather than the first. Dr. Hadgraft himself recognizes that the statements in the Mylan submission are wrong. In his declaration, addressing the same study, he says that "I would have expected Catapres TTS, with a 'rate controlling' membrane, to deliver clonidine at the same, or at least more similar, rate at each site." Hadgraft Declaration, ¶ 15 (emphasis added). Dr. Hadgraft has himself stated in a publication that, for transdermal patches, "the absorption into the systematic circulation is governed by two factors, the release from the device and the rate of transfer across the stratum corneum."[8] As Dr. Hadgraft knows, there is no reason to expect that any transdermal device would deliver clonidine at the same rate through skin with different resistance.

Instead, however, the rate-controlling membrane in the Catapres-TTS patch does control the rate. The membrane assures that the rate of drug delivery will not exceed the rate at which clonidine is released from the reservoir. Moreover, the Catapres-TTS patch is specifically designed to release the drug at a steady rate after the initial loading dose from the adhesive layer of the patch. When one applies the correct equation, it is apparent that the rate-limiting effect of Catapres-TTS (i.e., R_{device} for Catapres-TTS) does provide an effective upper limit on the rate of absorption. Thus, if R_{skin} becomes very small, R_{total} can still never be smaller than R_{device}. Thus, the rate of drug release from Catapres-TTS into the bloodstream can never be higher than the rate of release of drug from the device.

The reported experience with relatively higher absorption from areas of the skin asserted to be more permeable, such as the chest, in no situation involved anything approaching the 11.6 microgram per hour in vitro release rate for the Catapres-TTS-1

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[8] Hadgraft, J. "Review: Pharmaceutical Aspects of Transdermal Nitroglycerin." Int. J. Pharm. 135:1 (1996) (hereinafter "Hadgraft review article"), page 10 (copy submitted by Mylan on April 21, 2003).

patch.[9] Thus, the assertion by Mylan that "Clinical Testing Shows that the Membrane in Catapres TTS is Not Rate Limiting" (Mylan submission, page 7) is flatly wrong. Rather, the clinical testing shows, or at least is consistent with,[10] the fact that the membrane in Catapres-TTS is in fact rate-controlling.

3. Dr. Hadgraft's mathematical calculations are irrelevant

As a general proposition, the calculations presented by Mylan's expert Dr. Hadgraft are totally beside the point. Second Hopfenberg Declaration, ¶¶ 6, 7. The concern about a monolith is that, in patients with highly permeable skin, there could be damage from the high release of drug early in the 7-day period. It is an obvious point, but one that seems to have been ignored in the calculations presented by Dr. Hadgraft, that if one looks only at total release from a device over 7 days, a drug that released at a very high rate early and a low rate later in the week could well have a relatively low total release.

For example, a patch that released 2 mg of clonidine in the first 8 hours and did not release any more drug for the remainder of the 7 days would have a lower total release than a drug that released a steady .3 mg per day over the 7 day period. A calculation based on total release divided by total time in that circumstance would

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[9] See Toon, et al. "Rate and Extent of Absorption of Clonidine from a Transdermal Therapeutic System." J. Pharm. Pharmacol., 1989, 41: 17-21, page 19, Table 1. (Mylan Exhibit G). The 11.6 figure is from the 3.5 cm^2 patch, and is roughly consistent with Mylan's in vitro data for that size patch. (See Mylan Exhibit F). The data on permeability from different sites relied on by Mylan (Hopkins, et al. "Absorption of clonidine from a transdermal therapeutic system when applied to different body sites," (Mylan Exhibit D)) were in fact from a 3.75 sq. cm^2 patch, which can only have been the result of the investigators cutting a larger patch.

[10] One data report relied on by Mylan, relating to a single subject in the Toon study, upon close examination makes no sense. Subject 6 is reported, in figure 3 of that paper, to have received a significant percentage of his total drug input in the first 48 hours after administration of the patch. Dr. Hadgraft calculates the amount as 60% of a total absorbed dose of 1367.5 micrograms, i.e., 820.5 micrograms (.82 mg). Hadgraft Declaration, ¶14. It appears to us that the percentage is higher, more than 70%. (The raw data are not available. One can only calculate by measuring the scale on the figure presented.) Using the 70% figure, the absorption into the blood at 48 hours would equal 957.25 micrograms or .96 mg. Using either calculation, the amount reported to have been absorbed is greater than the in vitro release from the 3.5 cm^2 device during the first 48 hours, which is calculated by Mylan as .8 mg. Because all skin will have some resistance and can be expected to retain some drug, and it is not possible for more drug to go into the bloodstream than would come out of the device, the only reasonable explanation is that this report of one subject simply reflects experimental error. See Second Hopfenberg Declaration, ¶ 3.

certainly be nonsense. But what Dr. Hadgraft has done in his declaration is based on exactly that fallacy. See Hadgraft Declaration, ¶ 19, Table II. Boehringer's point is that a monolith patch could release at high levels early in the 7-day period and lower levels later in those seven days. How then can it make sense to respond to that concern with calculations of the mathematical formulae based on total absorption averaged over the 7 days?

Average absorption is, as noted, itself irrelevant to the significant safety issue raised by Boehringer it its Petition. What is relevant is the potential for delivery of increased dose at any point along the drug absorption curve, which is the precise risk that may be presented by a patch like that of Mylan or Elan that lacks a rate-controlling membrane.

Mylan's insistence that an in vivo test is unnecessary because effects on highly permeable skin can all be calculated based on mathematical formulae is, in any case, belied by the fact that Dr. Hadgraft, in three different calculations based on different data, produces 3 different factors for Catapres-TTS device control (Hadgraft Declaration, ¶ 19-.41, ¶ 21-.53, ¶ 22-.37). All of these calculations just show the obvious, that both skin resistance and device resistance contribute to total resistance, the truism discussed earlier.

Ultimately, safety issues affecting human patients cannot be resolved by mathematical calculations from in vitro data. In vitro data is no substitute for in vivo testing. A calculation of average micrograms per hour as determined by in vitro data is simply irrelevant.

4. Mylan's patch does not have substantially the same delivery mechanism as Catapres-TTS

Mylan curiously argues, throughout its paper and in the Hadgraft declaration, that "[t]he Mylan CTS and Catapres TTS products have substantially the same mechanisms for delivering steady state plasma levels of clonidine." (Mylan Submission, p. 5; ¶ 10 of the Hadgraft declaration (same sentence verbatim)). But, surely both Mylan and Dr. Hadgraft know that the mechanisms for delivering plasma levels of clonidine by the two patches are radically different. The design of the Catapres-TTS patch has been explained and should be clear – the patch has a multilayer delivery mechanism (reservoir, rate-controlling membrane, adhesive layer) that assures a steady rate of delivery of the drug into the body after the release of the initial loading dose from the adhesive. The Mylan product does not have a rate-controlling membrane. Rather, so far as Mylan has revealed, it is a monolith that simply relies on the rate at which clonidine is released from the monolith for control over absorption of the drug. At most, Mylan can argue that its data, if complete and accurate, show that its technology produces a result in vitro apparently similar to that seen with Catapres-TTS. It is misleading and inaccurate to claim substantially the same mechanism. See Second Hopfenberg Declaration, ¶ 4.

5. The Mylan patch's release rate is not controlled by the dissolution rate of undissolved clonidine

Inexplicably, Dr. Hadgraft states that: "The release rate of clonidine is controlled by the concentration of solubilized clonidine at the skin surface, which in turn is controlled by the dissolution rate of undissolved clonidine maintained in the saturated solution of clonidine within the PIB/MO matrix," (emphasis added). Hadgraft Declaration, ¶ 10. This statement is difficult to understand from an expert in this area. The dissolution rate of undissolved clonidine itself is quite fast once the solution drops below saturation. Second Hopfenberg Declaration, ¶ 5. The solution, however, drops below saturation only when clonidine leaves the patch and enters the skin. The resistance from the other components of Mylan's patch, and, of course, the resistance of the skin itself will mean that clonidine will leave solution much more slowly than the dissolution rate of undissolved clonidine. Accordingly, that dissolution rate is in no sense controlling.

6. A true monolith patch must exhibit a monolith dissolution pattern

Mylan asserts that the release from the two patches has been shown not to be materially different in an in vitro test. This is surprising if the Mylan product is truly a monolith of the type described. As Dr. Hopfenberg explained at the April 29 meeting, a true monolith, even one containing undissolved drug, would not be expected to release clonidine at a more or less constant rate. Instead, it must initially release quickly and thereafter release more slowly. See also Second Hopfenberg Declaration, ¶ 5. Indeed, the in vitro release of the lowest strength Mylan patch (Mylan CTS-1), even as reported by Mylan's figures, does show an ever decreasing rate of delivery during the 168 hours measured. The following table compares the reported amounts released between the different time points measured in the Mylan tests, expressed as a percent of the target dose of .1 mg per day (.7 mg over 168 hours)[11]:

	8	24	48	72	96	120	144	168
Mylan CTS-1	66	26	19	19	13	14	14	10
Catapres-TTS-1	51	26	37	34	32	30	26	24

[11] See Mylan Exhibit F. The amounts on the chart reflect simple subtraction of each stated result from the next stated result to determine rate of release during each interval.

The Catapres-TTS product is designed to release clonidine at a high rate initially from the adhesive layer but, even so, for the lowest dose patch, using Mylan's reported figures, the Catapres-TTS product releases during the first 24 hours less than a third of the total amount released during 7 days (77 of 260% of the target dose). In contrast, the Mylan CTS-1 patch releases during those first 24 hours roughly half of the clonidine that it will release over 7 days (92 of 181% of the target dose).

Mylan's claimed deviation from the release dynamics inherent in a monolith product for its other doses may reflect a mischaracterization by Mylan of the construction of its patch. This possibility is suggested by its insistence that the Deponit transdermal nitroglycerin patch is a monolith (see, e.g., Hadgraft Declaration, ¶ 9), when its FDA-approved labeling states that it is a "multilayered adhesive film" (Exhibit MM). If the Mylan patch is not a true monolith, it may, like Deponit, have different release characteristics than do monolith patches. Nevertheless, its release mechanism clearly differs from that of Catapres-TTS and may in fact differ from that of any other marketed patch.

If the Mylan patch is a true monolith, and if its in vitro release data as reported are complete and accurate, a partial explanation for its apparent deviation from the expected profile may be that it has a very high release rate in the first few hours that is not captured by measurement at the 8 hour time point. The adhesive layer of the Catapres-TTS patch is itself a monolith that releases very quickly to provide a loading dose to the skin. That release is roughly five times faster than is permitted through the rate-limiting barrier of Catapres-TTS, but only applies to the limited amount of clonidine contained in the adhesive layer. A question not answered by the Mylan in vitro data is whether the Mylan patch may be capable of an even faster initial release rate,[12] which then reduces so that the average over the first 8 hours appears more moderate. If so, that could produce clonidine levels in persons with highly permeable skin (and/or in situations involving exercise, sweating, fever, or increased ambient temperature) that could make the patch unsafe.

Only Elan and FDA know, at this point, whether the Elan patch is a true monolith. Certainly arguments based on Mylan in vitro data should not be used to support approval of the Elan patch if there are not similar data for it.

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[12] As the experience reported by Broderick-Cantwell (Exhibit SS) attests, blood levels may increase many fold without the protection of a rate-controlling membrane.

7. Because they release differently, the three Mylan patches should not be approved on the basis of bioequivalence testing of the highest dose

Curiously, the reported release from the Mylan CTS-2 patch during the first 8 hours is less than the reported release from the Mylan CTS-1 patch, while the amount released at that time period from the Mylan CTS-3 mg patch is similar to that from the CTS-1 patch. Thus, per square centimeter, the CTS-1 patch is releasing three times as much in the first 8 hours as the CTS-3 patch and the CTS-2 patch is releasing 1.5 times as much as the CTS-3 patch. See Mylan Exhibit F and Exhibit NN to this Petition. As Mylan has reported a bioequivalence test using the CTS-3 patch, we ask FDA to look carefully at the question of whether Mylan's other two dosage strengths should be considered dose equivalent so that bioequivalence testing of those two patches, with their higher earlier release, can be waived.

We respectfully suggest that no waiver is appropriate, as the lower dose releases at a higher rate initially and the Mylan CTS-3 product already, accepting Mylan's data reported at the April 29 meeting, produces higher blood levels than does Catapres-TTS in the Mylan bioequivalence trial. If the Elan patch has a similar problem, the same result should apply.

8. Mylan's in vitro data are inconsistent with its in vivo data, undercutting its arguments and raising a concern about protection of persons with highly permeable skin

Boehringer, of course, does not have the actual data from Mylan, either with respect to its reported in vitro study or the reported bioequivalence study. We ask that FDA look closely at the data that Mylan supplies.[13] It is extremely curious that Mylan reports, in its in vitro study, that its CTS-3 patch releases less clonidine than does the Catapres-TTS counterpart while, in its in vivo bioequivalance study, the Mylan patch's recorded parameters of absorption into the blood are noticeably higher than those recorded for Catapres-TTS (112% AUCL, 115% AUCI, and 107% CPEAK). The AUC confidence intervals are both above 100%.

Mylan's argument that FDA should reject the need for an in vivo study to address the question of skin permeability because of its in vitro data should require that, at a

[13] Mylan deviates from the FDA dissolution method by using .001M Phosphoric Acid, with a low pH (3). (Mylan Exhibit F.) Compare FDA's statement that media different from FDA's choice of water or .005M Phosphoric Acid resulted in "low release rate for clonidine, reaction with the patches, and/or patch holders, and interference in the chromatogram." (Boehringer Ex. O, page 348 (emphasis added).) FDA should inquire whether Mylan tried other media for dissolution and, if so, what results it found.

minimum, Mylan provide some explanation for why its in vitro comparison of its patch with Catapres-TTS is so clearly at odds with its in vivo comparison. Particularly important would be any evidence, in examination of the individual results in the Mylan bioequivalence study, that certain individuals had much higher absorption from the Mylan patch than from Catapres-TTS at certain time points, thus drawing up the mean. If that is in fact the case, that would support the concern that Boehringer has expressed. While in most patients the benefit of the rate-controlling function of Catapres-TTS might not show itself in a bioequivalence comparison, in some patients with higher permeability skin, that difference could be important.

9. The larger skin area per unit used by the Mylan patch raises new issues

In any clonidine transdermal patch, a significant percentage of the drug released by the device does not get to the blood. See, e.g., Toon (Mylan Exhibit G at 21) (40% of released drug unaccounted for). Some portion of that drug (Toon suggests under 10%) is held in the skin and released to the bloodstream after the patch is removed. See id.

Mylan's larger skin coverage presents a potential problem when the patch is used as directed, i.e., one patch is removed and a second is applied on a different spot on the skin. At that point, drug from the skin under the removed patch is released into the bloodstream. Because the Mylan patch covers nearly twice as much skin, nearly twice as much drug could be released from the skin after patch removal per dosage strength for the Mylan patch as for the Catapres-TTS patch. If this higher residual dose from the old patch is combined with a possibly higher initial dose from the new patch, continuous use of the Mylan patch could result in clonidine blood rates that are periodically higher than those seen with Catapres-TTS, for which residual skin release from the old patch roughly maintains steady state while the drug from the new patch is saturating the skin beneath it.

The larger Mylan patch will inevitably have different dynamics than Catapres-TTS. Because, to our knowledge, no multiple dose in vivo test has been performed, there is no way to predict with certainty what will happen with continued use of the Mylan patch. (Similar issues may, of course, be presented by the Elan patch, about which nothing has been publicly revealed.)

In addition to the drug held and later released in the skin, there is a significant amount of clonidine (30% in the Toon calculation) that appears to go into the skin and disappear, perhaps because it is metabolized in some unknown way. Mylan's product could thus, for each dosage strength, result in twice as much metabolism, with unknown effects. This underscores the risks of approving a new patch with a different release mechanism without clinical trials. When reviewed in light of the risks associated with clonidine discussed above, approval of this very different patch without a clinical trial could be a dangerous miscalculation.

10. Drug content in the patch matters for clonidine

While no information has been provided on the amount of drug in either the Mylan or the Elan patch, Mylan argues that requiring its amount to be within 10% of that in Catapres-TTS is unnecessary. The fact remains, however, that a significant number of the adverse reactions reported for Catapres-TTS are related to children chewing on patches. See, e.g. Klein-Schwartz, W. "Trends and Toxic Effects From Pediatric Clonidine Exposures." Arch. Pediatr. Adolesc. Med., 2002, 156:392-6 (Exhibit QQ), a review of 10,060 exposures to clonidine of children under 19 reported to Poison Control Centers, with 80% unrelated to treatment of the child; Henretig, F, Wiley, J, and Brown, L, "Clonidine Patch Toxicity: The Proof's in the Poop!" Journal of Toxicology - Clinical Toxicology, 195, 33(5):520-21 (Exhibit AAA) (an illustrative case). This is an issue that should not be ignored. Clonidine is a potent drug. Higher drug levels in a generic patch would make it less safe than the innovator, a result of the composition of its inactive ingredients or the way they are used that makes approval of the generic illegal.

11. Persons with highly permeable skin are at risk from a clonidine patch with insufficient rate control

While Mylan attacks the theory, its expert admits (see, e.g. Hadgraft Declaration, ¶ 20),[14] and FDA well knows, that the permeability of the skin varies markedly among individuals.[15] In addition, as noted, factors such as exercise can increase an individual's skin permeability. With a patch that has a rate-controlling membrane, it is certain that the rate will not exceed that permitted by the dynamics of the patch. Without the protection of rate control, patients with highly permeable skin will inevitably be put at risk.

As explained in his second declaration, Dr. Maibach and others have provided in vivo evidence of the significant variation in permeability between subjects. See Second Declaration of Howard I. Maibach, M.D. (hereinafter "Second Maibach Declaration") ¶ 2 (Exhibit PP); see also slide 21 of the presentation attached as Exhibit DD to the Petition and the report of Drs. Wester and Maibach, Exhibit CC to the Petition. The data show, not only a distribution in permeability, but also that one subject showed permeability greatly in excess of the others – more than three times the median value and more than ten times that of other subjects.

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[14] See also Hadgraft, J. "Pharmaceutical Aspects of Transdermal Nitroglycerin." Int. J. Pharm. 135 (1996) 1-11 (submitted by Mylan on April 21, 2003), pg. 10 "It is well documented that the permeability of skin (both inter and intra subject) is very variable."

[15] See, e.g., Enscore, D. "Structure and Function of Catapres-TTS." pg. 117 (Exhibit S) (rate control membrane in Catapres-TTS minimizes "the intra- and inter-patient variability in the dose of drug received which could result if skin, with its inherent variability in permeability, were allowed to control the rate of drug input.").

As Mylan admits, there is variation in biological systems, including permeability (Mylan Submission at 2 ("normal variability in skin permeability")). Dr. Maibach suggests that the distribution of skin permeability resembles a bell-shaped curve. Second Maibach Declaration at ¶ 2. Dr. Maibach designed his proposed study to focus on a sample taken from among those subjects who are identified in the top quartile in skin permeability of the 100 in the study.

12. Occlusion does not negate the importance of differences in skin permeability

At the April 29 meeting at FDA, Dr. Gordon Flynn argued in his presentation on behalf of Mylan that occluded skin is fully hydrated and serves to level skin permeability. The three studies he cited in his slides did not involve clonidine and do not demonstrate his assertions about occlusion, especially in the context of clonidine transdermal products.

Dr. Maibach discusses each of the studies in his Second Declaration, ¶¶ 4-6. The following are some of the points he makes: Each of the studies was too small to pick up with any certainty variation in skin permeability. The Marquardt study involved only 5 subjects, the Benowitz study involved only 11 subjects, and the Bucks study involved only 5 subjects for some measurements, 6 for others. Thus, as Dr. Maibach points out, such studies tell us little useful about effects that might be seen in, for example, 1 in 50 in the population. See Second Maibach Declaration, ¶5. The Benowitz and Bucks studies, in any case, actually did show significant variability. The Marquardt study tested fentanyl remaining in a transdermal fentanyl system after three days of use, and such tests of residue in a patch are not reliable measures of absorption on their own. Mylan, on the other hand, is using the data to show absorption, without testing other elements of a mass balance to see whether the amount that left the patch was actually absorbed.

13. The data submitted by Mylan on application site are not relevant

Mylan cited in its submission data on absorption from different anatomic sites and argued that such data show that the rate-controlling membrane is not effective and that the particular sites chosen for use of Catapres-TTS mean that the range of skin permeability is narrow. As noted above, Boehringer does not argue that the rate-controlling membrane of Catapres-TTS provides all of the resistance in the product. Rather, the skin provides some resistance, and the contribution of the skin drops in patients with high permeability skin. Thus, the Hopkins study is in no way inconsistent with the expected benefits of the rate-controlling membrane.

Mylan argued at the April 29 meeting that the placement on the chest or upper arm narrows the range of skin permeability. It provided no evidence to support that view

and, in any case, such placement does not mean (1) that there are not subjects whose permeability at those areas is substantially higher than others, or (2) that such subjects would not be protected by a rate-controlling membrane.

14. TEWL provides a way to identify subjects in which to test a transdermal product's functionality in high permeability skin patients

Mylan argued that using a TEWL method has "flaws" and does not predict permeability. As explained by Dr. Maibach, no evidence submitted by Mylan negates the utility of TEWL in the proposed study. See Second Maibach Declaration, ¶¶ 9-12.

Mylan cites three articles for its view that TEWL does not predict permeability. In so doing, Mylan ignores years of data on correlations, including those data cited in the referenced articles. The data cited by Mylan is of limited value. The Chilcott data (which is discussed in the report by Drs. Wester and Maibach previously submitted to the docket) is from in vitro studies in which the authors concluded that TEWL did not correlate for two substances that are not of relevance to clonidine. Moreover, some of the testing used pigskin. See Second Maibach Declaration, ¶ 9. The Oestman study has limitations, but even it notes at least a weak correlation. Maibach Second Declaration ¶ 19. The Tsai study involved disrupting the skin barrier with acetone, which is of questionable relevance to whether one can use TEWL measurements to stratify a population whose skin has not been so treated. Nevertheless, it shows a correlation and the authors suggest that the results imply the possibility of using TEWL to predict alterations in skin permeability. Second Maibach Declaration, ¶ 11.

15. The data cited on the range of residuals is limited

Mylan cited to a variation in amount "delivered" from the patch of from 25 to 80% and argued that evidence of such a variation suggests that the rate-controlling membrane does not provide rate control. (See Mylan Submission p. 9, Hadgraft Declaration, ¶ 16.) Mylan cited two case reports that do not have independent data, but refer back to data on residual amounts in patches after application reported in the third study cited, a 1985 study by Boehringer's Dr. Thomas MacGregor. The range in residual amount remaining simply serves to demonstrate, if anything, the range of relevant contribution made by the skin in different individuals.

Testing the residual amount in a patch alone is not, in any case, a reliable parameter because it does not consider what actually happened to the drug released from the patch. See, e.g., the statement in the Toon paper (Mylan Exhibit G), pg. 21, that 40% of clonidine released from the patch as determined by residual amount was not absorbed. On the other hand, residual amount testing is valid and useful when performed in conjunction with blood and urine measurements under a mass-balance approach. That is

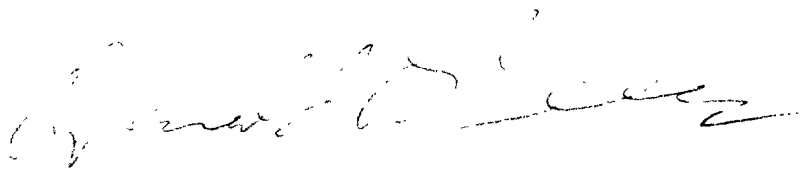
why it is included in the bioequivalence testing that is the subject of our original petition, as well as the protocol proposed by Dr. Maibach.

CONCLUSION

Boehringer is well aware that it does not have access to the data Elan and Mylan have submitted on their respective patches. It is, however, not disputed that 1) those patches lack the rate-controlling membrane found in the Catapres-TTS products, and 2) neither Mylan nor Elan have offered in vivo data to show that their alternative patch designs will protect equally well the patients with highly permeable skin that the rate-controlling membrane is designed to protect.

Boehringer has suggested an in vivo method to determine whether or not the generic products' deviation from the rate-controlling membrane design would endanger some patients. In the absence of in vivo data showing equivalent absorption in patients with highly permeable skin, Boehringer continues to believe that approval, without clinical trials, of generic versions of this potent transdermal drug that have a different drug release mechanism than Catapres-TTS is inappropriate and illegal, and more importantly, may put a significant number of patients at risk.

Respectfully submitted,



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