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September 4, 2002

VIA FEDERAL EXPRESS

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

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

Dear Sir or Madam:

This submission responds to two comments submitted on behalf of Mylan Technologies, Inc. ("Mylan"), dated April 9, 2002, on the above-referenced citizen petition (the "Petition") and on the accompanying Petition for Stay of Action. Mylan proposes that an important safeguard that is integral to the design of the Catapres-TTS[®] clonidine transdermal system marketed by our client Boehringer Ingelheim Pharmaceuticals, Inc. ("BI") be totally disregarded. It does not base its argument on data showing that that safeguard is unnecessary. Instead, Mylan argues that FDA does not have the authority under the Federal Food, Drug, and Cosmetic Act ("FFDCA") to impose requirements to assure the safety of a generic version of the Catapres-TTS[®] system. The Mylan position — that FDA is powerless to protect the public — is utterly without merit. The comment does, however, prompt us to reiterate our request that FDA focus on the serious scientific issue presented by the Petition.

We recognize that, for FDA to grant our Petition, FDA must first be convinced of the scientific merit of the points raised by BI. In that respect, we are troubled by the suggestion that FDA should accept Mylan's characterization of our position as merely an attempt by a branded manufacturer to extend its franchise, and respond to our Petition without a careful scientific evaluation by agency scientists of the issues presented. Because the issues are, potentially, serious ones of health, BI specifically asks FDA to seek guidance on these issues from agency scientific experts is not only the Office of Generic Drugs but also the Division of Cardio-Renal Drug Products, which initially approved the Catapres-TTS system, and the Division of Dermatologic and Dental Drug

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Products, which has expertise and experience in issues of dermal absorption. We are confident that FDA experts will endorse the BI concerns. To aid in that expert analysis, we attach (as Exhibit CC) a recently completed review of available research on skin permeability. To facilitate FDA's review of these issues, we are providing copies of this submission and the February supplement to our Petition to Mr. Buehler, Dr. Throckmorton, and Dr. Wilkin.

Mylan and Elan Should Address the Evidence Submitted in BI's February 20 Supplement on the Public Record

In the original Citizen Petition filing of October 10, 2001, BI addressed the implications of not having a rate-controlling membrane in a clonidine transdermal product with respect to Elan's proposed product, and more generally. The Petition argued that: 1) a patch without a rate-controlling membrane should not be approved under an ANDA based solely on bioequivalence testing comparing it to the BI patch; and 2) no generic version should be approved without successful completion of the type of bioequivalence testing described in the Petition. Mylan's April 9 comments address aspects of this Petition, and BI responds to those comments below.

Curiously, Mylan totally ignores BI's February 20, 2002 Supplement to the Citizen Petition. In that Supplement, BI provided expert scientific support for the proposition that generic clonidine patches without a rate-controlling membrane should not be approved under an ANDA. BI also addressed specific aspects of the generic transdermal clonidine product that is being proposed by Mylan. Mylan's April 9 comment fails to address BI's February 20 Supplement altogether, and thus Mylan has not responded to the substantial scientific data and expert opinion provided by BI in the Supplement. Elan has submitted no public response at all. Because both Mylan and Elan, as the ANDA applicants, have the burden of demonstrating the approvability of their products, their failure to take any public position on the important issues raised is significant evidence of the merit of BI's concerns.¹

Monolith Clonidine Patches Should Not Be Approved Under An ANDA

¹ Perhaps their strategy is to seek to hide their arguments from public scrutiny and BI response by submitting them as part of their ANDAs. When the proponents of arguments fear subjecting them to critical analysis and response, the validity of such arguments must be considered suspect.

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Mylan argues that FDA cannot impose requirements that a generic applicant submit data beyond that listed specifically in FDCA Section 505(j)(2)(A), 21 U.S.C. § 355(j)(2)(A). Mylan has engaged in selective citation, however, as that section tells only part of the story.

As noted in the Citizen Petition, the FDCA *requires* FDA to deny approval of an ANDA if “the composition of the drug is unsafe under [the prescribed] conditions [of use] because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.” FDCA Section 505(j)(4)(H), 21 U.S.C. § 355(j)(4)(H). FDA’s regulations, 21 C.F.R. § 314.127(a)(8), implement that provision. See also 21 C.F.R. § 314.94(a)(9)(ii) (requiring that ANDA applicants provide information to show that the inactive ingredients of their products do not affect the safety of their products). Certainly, the lack of a rate-controlling membrane falls squarely within the statute’s provision, whether as the absence of an inactive ingredient (the membrane itself) or “the manner in which the [utilized] inactive ingredients are included.”

FDA’s regulations implementing the statutory mandate are straightforward and controlling here.

FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an abbreviated new drug application under paragraph (a)(8)(i) of this section if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety.

21 C.F.R. § 314.127(a)(8)(ii)(A) (emphasis added). There can be no denying that a monolith patch that uses the skin rather than an internal rate-limiting barrier as the mechanism to control clonidine delivery is “[t]he use of a delivery or a modified release mechanism never before approved for” clonidine, 21 C.F.R. § 314.127(a)(8)(ii)(A)(5), and such a use of a new mechanism is explicitly identified in the regulation as an “[e]xample[] of the changes that may raise serious questions of safety,” 21 C.F.R. §

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314.127(a)(8)(ii)(A) (emphasis added). Thus, under FDA's regulations, FDA should refuse to approve a generic application for a product with such a different mechanism.²

BI also notes that transdermal products are administered topically, although the therapeutic effect is through systemic absorption. The fact that they are administered topically should not be ignored (and, indeed, is the reason for requiring skin adhesion, sensitization, and irritation tests). FDA regulations provide:

Generally, a drug product intended for topical use shall contain the same inactive ingredients as the reference listed drug However, an applicant may seek approval of a drug product that differs from the reference listed drug provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product.

21 C.F.R. § 314.94(a)(9)(v) (emphasis added). Note that this regulation also implements FFDCa Section 505(j)(4)(H), and directly contradicts Mylan's contention that the ANDA approval provision denies FDA the ability to protect the public by requiring information demonstrating the safety of inactive ingredients.

Mylan also asserts that BI did not provide evidence that any patch actually "being considered for approval is in fact, or likely to be, unsafe," and that BI provided only "speculation," "attorney argument," and employee declarations. First, BI submits that Mylan has no standing to make such an argument. Mylan's notice of paragraph IV certification, Exhibit BB to the Petition, provided only the most minimal information about its product. Despite repeated requests from BI for additional information to permit BI to evaluate Mylan's assertion that its product would not infringe the listed patent,

² This regulation of course applies whether or not the generic and innovator would be classified as the same "dosage form." Thus, Mylan's claim that its product is the same dosage form as the Catapres-TTS system (Mylan Comment at 4, n.1) is irrelevant.

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*Mylan flatly refused to provide any additional information about its proposed product. Elan similarly refused to provide additional information.*³

Second, even the small amount of information provided by each of these companies is sufficient to demonstrate the drastically different design of both the Elan and Mylan patches from the BI patch, as BI has brought to FDA's attention in the Petition and the Supplement. As for Mylan's contention that BI submitted only declarations of BI and Alza employees, that is simply inaccurate. See the declarations of noted experts Dr. Howard Maibach and Dr. Harold Hopfenberg submitted with the Supplement.

Mylan again seriously misstates the record when it says that "The Package Insert (as well as the Citizen Petition) states that with the Catapres-TTS patch, the skin is kept saturated with clonidine, meaning that delivery to the skin is at the maximum rate for skin absorption at all times, and the rate at which the drug reaches the bloodstream is dictated by how fast it leaves the skin, not how fast it enters it. Package Insert, page 1, 'Release Rate Concept,' Citizen Petition at 4." (Mylan Comment at 6.) A review of the cited references reveals that they do not support any part of this statement. In fact, as the cited portion of the Package Insert states, flow of clonidine into the skin is "limited by the rate-controlling membrane." It is exactly our point that, in many people, in most circumstances, the skin will in fact be the rate-controlling barrier for the Catapres-TTS system. It is that fact which would allow a showing of apparent bioequivalence between a monolith generic patch and the Catapres-TTS system in persons with normal skin permeability, presumably what Mylan and Elan have done. **But persons with high skin permeability would be protected by the Catapres-TTS rate-controlling membrane,**

³ In a footnote (Mylan Comment at 4, n. 1), Mylan attempts to defend Elan's statements about how different its product is from the BI patch, claiming that those statements were just argument under the patent laws. Facts are, however, facts, no matter the context in which they may be used. We fail to understand how a product can only be "different" for patent law purposes. Elan asserted factual differences that Elan claimed demonstrated non-infringement. BI simply took those same statements at face value and, assuming they are true, applied them under the law of ANDA approvals. There is no reason that FDA should not do the same thing.

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and would be at risk for higher than intended clonidine blood levels with a generic lacking that safeguard.⁴

Mylan Does Not Show Why BI's Proposed Bioequivalence Study is Not Appropriate

BI submits that a test lacking the attributes discussed in the Petition is not adequate to show bioequivalence,⁵ especially for a product with as potent an active ingredient as clonidine, and especially in a seven-day patch. Mylan disagrees on four points:⁶

1. Measurement of Steady-State Plasma Levels at Days 4, 5, and 6

Mylan asserts that the proposed comparison of steady-state plasma levels at days 4, 5, and 6 is not helpful to determine rate. For an extended release dosage form like transdermal clonidine that releases the equivalent of 14 immediate release doses in one

⁴ In a footnote (Mylan Comment at 6, n. 4), Mylan refers to the loading dose of the Catapres-TTS system but seems to misunderstand the use of the drug. When the patch is replaced after 7 days, it is placed on a different area of the skin. The drug in the skin from the previous patch then enters the systemic circulation during the time in which the loading dose from the subsequent patch is saturating the skin under it, thus providing continuous drug delivery.

⁵ As noted, it is BI's position that any bioequivalence testing is inadequate to show safety for patches without rate-limiting barriers.

⁶ This suggests that Mylan's bioequivalence test fails to meet these standards. BI also recently received public data submitted by Elan to the formulary board in Illinois. The data demonstrate that at least Elan has not submitted data from the type of study proposed (and performed) by BI. For example, the data only contain AUC measurements in plasma, and do not contain information about total clonidine excreted in urine or the residual amount remaining in the patch after removal without such measurements. The study does not reveal how much of this potent drug may be stored in the skin after administration of the Elan patch. For the same reasons as discussed in the text, these actual data submitted by Elan are wholly inadequate to demonstrate that the Elan product is bioequivalent to the Catapres-TTS system and poses no serious safety concerns.

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week of wear, a study demonstrating steady state during a week of wear is necessary. To demonstrate steady state, three systemic assessments of plasma clonidine concentrations are needed. Days 4, 5, and 6 are logical choices for these assessments, and a single-point test of Cmax would be inadequate. With a single-point test, the amount of drug in the bloodstream after several days' administration could differ markedly between the innovator and the purported generic copy.

2. Measurement of Total Drug By Measurement of Drug Excreted in Urine

Mylan also asserts that measurement of total drug delivered by measuring excreted drug is not helpful because current standards do not include that measurement and the data are only an estimate of total drug delivered. Urine is a valuable test because it is a reliable measure and, because, as an end-product assessment, the total content would be measured rather than individual time points, thus eliminating the effect of flux.⁷

Unlike an oral tablet, the delivered dose obtained from a transdermal delivery system is unknown until empirically determined. Therefore, residual system analyses of used transdermal patches are required after a bioequivalence study to determine the dose released from an applied patch for each test subject. Since the test and reference systems have different inert ingredients, urine analysis is also needed to determine if the systemic *in vivo* dose was the same. Differences in absorption rate and inert ingredients have an effect on the metabolic potential of the skin prior to systemic absorption. Thus, without urine testing, one would know how much clonidine left the patch (through residual system analysis) but one would not know what portion of that clonidine entered the systemic circulation and what portion was, instead, metabolized in the skin. A difference in metabolism can produce inequivalent plasma clonidine concentrations after chronic multiple dosing.

3. Statistical Analysis

Mylan asserts that BI has not established that the proposed statistical analysis is necessary to prove bioequivalence. Mylan misrepresents (and perhaps has misunderstood) what BI has argued. The statistical tests requested in the Petition are consistent with FDA confidence interval requirements of 80-125% on a log-transformed

⁷ Urine sampling has, in fact, long been the gold standard in forensics, due to its superior reliability and imperviousness to the inconsistency of blood level testing.

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scale. It is logical that the point estimate be within 10% of the innovator in order to meet that criterion. Accordingly, the test BI proposes does not tighten the confidence interval as suggested by the Mylan position.

4. Drug Content Within 10% of Reference Product

Mylan tries to deflect BI's argument that drug content be within 10% of the labeled amount by stating that it is based on a relatively old FDA statement, yet Mylan can point to no more recent statement contradicting it. FDA should apply the 10% rule to clonidine patches, given the acknowledged narrow therapeutic index for this drug. Even if FDA applied a different standard in the case of other patches, that does not mean that FDA, in its scientific judgment, should not distinguish a potent drug such as clonidine, particularly where it is to be used in a seven-day patch.

Clonidine Patches Raise Issues Different From Those Relating to Estradiol Patches

Mylan in its comment on the Petition for Stay dismisses the safety argument raised by BI as having been addressed and rejected by FDA in its response to the Berlex petition concerning estradiol transdermal products. Mylan fails to recognize critical distinctions between estrogen and other ANDA transdermals on the one hand, and clonidine transdermals on the other. In fact, there are virtually no published data regarding any significant potential short-term side effects of estrogen. Estradiol patches thus present little or no risk of potential short-term therapy complications. By contrast, the Catapres-TTS system incorporates a potent drug which can have potentially significant short-term side effects. Our Supplement details these risks at length.

Mylan's Argument that BI's Labeling Resolves the Safety Problems with Mylan's and Elan's ANDA Products Assumes the Very Therapeutic Equivalence BI Maintains Neither Can Demonstrate.

Mylan argues that any safety risks from the potency of clonidine would also be present with the BI patch, and thus FDA has resolved them in BI's labeling. BI's labeling, like the studies that BI has conducted, concern the BI product which contains a rate-controlling membrane. **It is precisely the point that the BI product, with its rate-limiting membrane, does not present the safety risks to persons with unusually high skin permeability that exist with a patch that relies on the skin as its only rate-controlling mechanism.** BI's labeling is only intended to and does address the

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contraindications and side effects associated with BI's product, a seven-day transdermal clonidine product with a rate-controlling membrane. BI's labeling and the studies supporting it thus offer no protection to or comfort for Mylan or Elan or their potential patients. Obviously, if, as BI believes, the products without this important safety feature pose different safety risks than the Catapres-TTS system, those different safety risks are nowhere mentioned or considered in BI's approved labeling.

The Policy of the Statute Does Not Support Mylan's Position.

Mylan argues, in the face of the legitimate safety concerns raised by BI, that BI's Petition and Supplement should be denied because the Hatch-Waxman Amendments were, it says, enacted to prevent harm to the public associated with the price of innovator drugs. The Amendments were not, however, intended to reduce prices at the expense of public safety. Rather, the Amendments provide FDA with the requisite authority to require that ANDA applicants demonstrate that their products are not designed in such a way as to make them less safe than the reference listed drug.

BI does not, of course, contend that the Mylan or Elan products may not have merit, only that they should be required to demonstrate their safety and efficacy in patients with a variety of skin permeabilities by undergoing additional testing as NDA products.

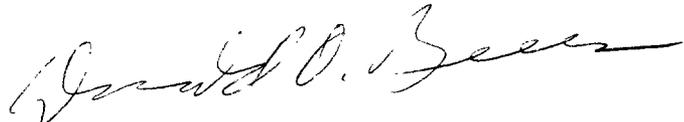
BI submits, therefore, that it is Mylan whose requested relief is contrary to public policy. Indeed, Mylan does not indicate, because it cannot, how addressing the concerns raised by BI would be thought to impose any burden upon Mylan out of proportion to the risk that the failure to test would pose. The legitimate concern raised by BI – that a generic lacking the safeguard of a rate-limiting barrier could endanger patients with high skin permeability – is capable of resolution by scientific testing. Persons with high skin permeability can be identified. The generic applicants, unlike BI, have their proposed products available and can compare them to the Catapres-TTS system in patients with high skin permeability in a controlled test. If FDA requires the generic applicants to perform the testing that would resolve the issue, either it will be demonstrated that the generic products should not be marketed or it will be demonstrated that BI is mistaken. If, on the other hand, FDA fails to require the testing, and BI's concerns are valid, FDA will have permitted one or more potentially dangerous products to enter into the stream of commerce. BI urges FDA not to abdicate its responsibilities to public health and safety on this important issue.

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CONCLUSION

For the reasons discussed in the Petition, the February 20, 2002 Supplement to the Petition, and this Response, BI submits that FDA should not approve generic clonidine patches not including rate-limiting barriers and should otherwise grant the BI Petition in all aspects.

Sincerely,



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