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December 30, 2004

**SUBMITTED ELECTRONICALLY AND BY HAND DELIVERY**

Dockets Management Branch (HFA-305)  
U.S. Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, Maryland 20852

Re: Docket No. 2004P-0540: Comments of Noven Pharmaceutical, Inc. on London & Mead  
Citizen Petition Requesting Action Regarding Generic Fentanyl Transdermal Products

These Comments are submitted by Noven Pharmaceuticals, Inc. ("Noven") in opposition to the above Citizen Petition (the "Petition"). The Petition was filed by London & Mead ("L&M"), a Washington, D.C. law firm.

In what is now the fourth Citizen Petition submitted regarding the approval of ANDAs for generic formulations of fentanyl transdermal products, L&M requests that the Agency take more extreme action than any prior petitioner. L&M asks FDA to ignore the language and underlying purpose of the Hatch-Waxman Amendments to the Food, Drug and Cosmetic Act ("FDCA" or "the Act") and hold ANDAs for generic fentanyl transdermal products to a higher approval standard than other generic products and even than other transdermal products.

L&M bases its overreaching request on (1) the immaterial fact that fentanyl is a controlled substance and (2) the differences in the designs of the delivery mechanisms of the generic formulations and the reference drug, Duragesic®, which L&M postulates present hypothetical safety and efficacy risks. Based on these concerns, and without citing a shred of

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scientific evidence, L&M boldly demands that FDA (1) require clinical data from applicants that utilize a delivery mechanism that is not the same as that used in Duragesic® to establish safety and efficacy and (2) increase the range necessary to prove bioequivalence for applicants that use the same delivery mechanism as the one used in the Duragesic® patch.

## **SUMMARY**

L&M's approach is irreconcilable with the Act and with FDA's own policies concerning review and approval of ANDAs. It is also irreconcilable with basic scientific principles. As set forth more fully herein, L&M's Petition should be denied on the following grounds:

- The fact that fentanyl is a Schedule II controlled substance is irrelevant to FDA's consideration of ANDAs for generic formulations. ANDA approval depends on the generic applicant meeting specific criteria set out in the Act. Neither the Act nor FDA's regulations provide for consideration of whether or not the drug is a controlled substance, and L&M presents no basis for making that distinction here.
- "Sameness" in design of the delivery mechanism is not required for approval of an ANDA. The Act only requires that an applicant show "sameness" with the innovator product in conditions of use, active ingredients, route of administration, dosage form, strength, labeling and bioavailability. In addition, FDA has previously ruled, based on its review of the Act's legislative history and sound policy concerns, that it will not require that the release mechanism of an ANDA product be the same as that of the reference drug product in order to find that the dosage form is the same. FDA's ruling was upheld by the court.
- The Act does not authorize FDA to require clinical testing of an ANDA product solely because the design of its release mechanism is different from that of the reference listed drug product. Instead, the Act requires that the ANDA product be bioequivalent which, FDA has stated forcefully in detailed analysis upheld judicially, addresses concerns about any difference in the design of release mechanisms.
- L&M's demand that FDA increase the bioequivalence range for generic formulations of fentanyl is based on improper supposition about the risk of potential lethal dosing. Noven's patch has a rate-limiting mechanism that protects against overdosing. Moreover, variations in absorption of fentanyl from transdermal patches based on skin permeability are no different from variations in absorption of any drug product based on physiology of individual users. Because these variations are measured on a normative curve, FDA's current measures for bioequivalence address whether generic formulations of fentanyl transdermal are within an acceptable range of absorption across user populations.

- The relatively broad therapeutic index of fentanyl further protects against the risks L&M hypothesizes based on skin permeability and distinguishes fentanyl matrix patches from patches delivering drugs with narrow therapeutic indices. While L&M's request in its Petition is premised in part on the same skin permeability issue raised in the pending docket regarding clonidine transdermal products, the potential risks raised regarding generic formulations of clonidine are not analogous to fentanyl transdermal products.

L&M's Citizen Petition is the fourth attempt to erect a roadblock to approval of generic formulations of Duragesic® that have met the requirements of both the Act and FDA's standards for safety and efficacy. These petitions have been orchestrated to appear shortly before the branded manufacturer's period of exclusivity ends. The pendency of ANDAs referencing Duragesic® has not been a secret. At the very least, it has been public information since January 25, 2002, the date on which ALZA sued Mylan for patent infringement as a result of Mylan's Paragraph IV ANDA filing.

The congruity of these petitions, all being filed just before exclusivity expires, is more than suspicious; it is conclusive of a blatant attempt to thwart the will of Congress and the public's interest in lower cost medications by, at the very least, delaying FDA approval of generic transdermal fentanyl products. This is done simply by piling onto FDA reviewers more and more last minute petitions to which the Agency understandably desires to respond, if possible, prior to approval of the ANDAs. This spate of unmeritorious petitions is particularly troubling at a time when the Agency is under fire because its resources to review applications in the time required by law are already stretched intolerably thin in the public's view. The arguments in these petitions are, for the most part repetitive, speculative and devoid of scientific support. The petitioners blithely dish up arguments that FDA has previously disposed of or that run counter to basic scientific principles. They show no shame in mischaracterizing the nature of the Noven fentanyl patch and then build on that mischaracterization to construct arguments that cannot withstand scrutiny.

Put simply, the various petitioners are abusing FDA's processes by this strategy. At some point, FDA must say "enough"! In our view, that point was passed some time ago. It has certainly been reached now. FDA must move forward to approve the generic fentanyl formulations both because the science and law support them and to end this assault on, and abuse of, the integrity of FDA's processes.

**I. INTEREST OF NOVEN PHARMACEUTICALS, INC.**

Noven is a leading U.S. manufacturer of prescription transdermal patches. Noven has partnered with Endo Pharmaceuticals Inc. to bring to market a generic controlled-release fentanyl transdermal patch using Noven's matrix transdermal system, of the type described in the L&M Petition. Noven filed an ANDA for fentanyl transdermal system on July 30, 2003.<sup>1</sup> FDA accepted the ANDA for filing on October 1, 2003. L&M's Citizen Petition seeks improperly to delay FDA approval of Noven's ANDA and to place burdens on Noven's and Endo's ability to market their generic transdermal product on a level playing field in competition with the innovator product, Duragesic®. L&M's characterizations of the risk posed by the differences in the delivery systems used in generic fentanyl transdermal products like Noven's and that used in Duragesic® are overstated and unsupported by any scientific evidence. For these reasons, Noven has an interest in the subject matter of the Petition within the meaning of 21 CFR §10.30(d), and thus respectfully submits this response. Noven requests that the Agency deny the action requested by L&M.

On December 10, 2004 and December 23, 2004, respectively, Noven submitted comments on two earlier petitions, in Docket 2004P-0472 ("the Brookoff Petition") and Docket 2004P-0506 ("the ALZA Petition"). These petitions also involved FDA approval of generic

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<sup>1</sup> ANDA 76-804.

transdermal formulations of fentanyl. Copies of Noven's comments on the two petitions are appended hereto as Attachments 1 and 2, respectively. Several of the arguments made in the Brookoff and ALZA Petitions are echoed in the L&M Petition that is the subject of the instant Comments. Noven's Comments on the Brookoff and ALZA Petitions address fallacies in the scientific and legal contentions that purport to support the overlapping arguments in these petitions.

We will not expand the Agency's burden by repeating here the points we made in detail in our comments on the earlier petitions. Rather, Noven incorporates by reference its Comments on the Brookoff Petition in Docket 2004P-0472 (Attachment 1) and the ALZA Petition in Docket 2004P-0506 (Attachment 2), and will focus here on arguments raised in the L&M Petition that either were not presented in the earlier petitions or were offered with a somewhat different thrust.

**II. FENTANYL'S CLASSIFICATION AS A SCHEDULE II CONTROLLED SUBSTANCE IS IMMATERIAL TO FDA'S DETERMINATION OF WHETHER NOVEN'S ANDA MEETS THE STATUTORY REQUIREMENTS FOR APPROVAL.**

As discussed more fully in our Comments to the Brookoff Petition in Docket 2004P-0472, the FDCA specifies the items to be included in an abbreviated new drug application and mandates that FDA "shall approve" an ANDA application "unless" it fails to provide that information or the information provided fails to satisfy one of the enumerated statutory requirements.<sup>2</sup> Nowhere in this specific list does the Act authorize, or even suggest it is appropriate for, FDA to consider whether or not the reference drug on which the ANDA is based is a controlled substance. Indeed, the Act does not endeavor to require an assessment of the type of drug for which an ANDA is being sought. Instead, the Act focuses on proof by the applicant

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<sup>2</sup> Attachment 1 at 4-5, 21-22.

of equivalence between its product and a previously-approved reference list drug product.<sup>3</sup> In short, there is nothing in the Act that indicates FDA has any power to treat an ANDA differently based on the reference drug being a controlled substance. Accordingly, L&M's suggestion that FDA should use a different standard in reviewing ANDAs for fentanyl transdermal products solely because it is a Schedule II controlled substance lacks any merit.<sup>4</sup>

**III. L&M'S DEMANDS BASED ON "SAMENESS" OF DESIGN LACK ANY LEGAL FOUNDATION.**

Aside from its specious invocation of fentanyl's status as a controlled substance, L&M's Petition is grounded on the differences in the designs of the delivery mechanism between the branded product, Duragesic®, and generic formulations of fentanyl transdermal products. As described more fully in Noven's Comments to the Brookoff Petition, Duragesic® utilizes a reservoir delivery system, which contains a physical membrane intended to limit the rate of release of the fentanyl into the skin.<sup>5</sup> In contrast, the generic formulation proposed by Noven utilizes a drug-in-adhesive delivery system, which utilizes the molecular adhesion of the fentanyl to the chemical adhesive in the patch as the mechanism that limits and controls the rate of the delivery of fentanyl into the skin.<sup>6</sup> L&M claims that this difference in the delivery mechanism between the branded product and generic formulations like Noven's necessitates an amplification

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<sup>3</sup> Similarly, FDA's regulations define the manner in which bioequivalence must be demonstrated. Under FDA's rules, bioequivalence information is required to ensure therapeutic equivalence between a pharmaceutically equivalent test drug product and the corresponding reference listed drug. *See* 21 C.F.R. § 314.94(a)(7)(i); 21 C.F.R. § 320.1(e). When that standard is met, FDA approves the ANDA, irrespective of whether the drug is a controlled substance.

<sup>4</sup> Petition at 3. In fact, as discussed in Noven's Comments to the Brookoff Petition, concerns particular to controlled substances, such as abuse and diversion, are more appropriately addressed through means other than the ANDA approval process. *See* Attachment 1 at 21-24.

<sup>5</sup> Attachment 1 at 10.

<sup>6</sup> Attachment 1 at 6.

of the bioequivalence demonstration for ANDA approval, if not a requirement of independent clinical testing for safety and efficacy of fentanyl matrix systems. However, L&M's argument that the design -- specifically, the release mechanism -- of the innovator product and all generic formulations must be the same as the branded product is simply wrong.

**A. The FDCA Does Not Include “Sameness” of Delivery Mechanisms as a Requirement for ANDA Approval.**

As Noven discussed at length in its Comments to the Brookoff and ALZA Petitions, the FDCA specifically enumerates what FDA must consider in determining whether to approve an ANDA. The Act authorizes FDA to reject an ANDA only if, *inter alia*:<sup>7</sup>

- “information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;”<sup>8</sup>
- “information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;”<sup>9</sup>
- “information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug . . . ;”<sup>10</sup>
- “information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application . . . ;”<sup>11</sup> or
- “information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application . . . .”<sup>12</sup>

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<sup>7</sup> Other bases for rejecting ANDAs, such as inappropriate manufacturing controls or the making of a material misstatement, are not at issue here.

<sup>8</sup> 21 U.S.C. § 355(j)(4)(B) (emphasis added).

<sup>9</sup> 21 U.S.C. § 355(j)(4)(C) (emphasis added).

<sup>10</sup> 21 U.S.C. § 355(j)(4)(D) (emphasis added).

<sup>11</sup> 21 U.S.C. § 355(j)(4)(F) (emphasis added).

<sup>12</sup> 21 U.S.C. § 355(j)(4)(G) (emphasis added).

The Act simply does not state that if the design of the drugs or, more specifically, the delivery mechanism differs FDA can deny the ANDA. Nor does the Act indicate that FDA can demand clinical data on safety and efficacy for an ANDA product that meets the above criteria but uses a different delivery mechanism from the reference drug. Accordingly, L&M's request that FDA deny ANDA approval -- or require clinical testing -- of any fentanyl transdermal product that does not utilize the same delivery mechanism as Duragesic® is a request for action beyond FDA's statutory authority.

**B. FDA Has Already Concluded That a Generic Drug Need Not Have the Same Delivery Mechanism as the Reference Drug.**

Aside from the lack of statutory authority for its position, L&M's insistence that generic formulations of fentanyl transdermal have the same delivery mechanism as Duragesic® is contrary to FDA's prior determination that the release mechanisms utilized in generic equivalents need not be the same as those used in the reference drugs.

In its response to an earlier Citizen Petition requesting that FDA deny ANDA approval based on differences in the release mechanisms in the generic formulation and in the reference drug, FDA has already ruled that "in the 1984 Amendments, Congress specifically did not require generic drug products to be identical in all respects to innovator products."<sup>13</sup> In that proceeding, the innovator sought to have FDA deem the generic formulation a different dosage form due to the differences in release mechanisms. Although L&M does not argue that generic formulations of fentanyl transdermal are different dosage forms from Duragesic®, L&M's demand that delivery systems be the same is a request that FDA apply the requirement of sameness applicable to dosage forms to delivery mechanisms. By holding that the dosage form

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<sup>13</sup> FDA Response to Citizen Petition by Pfizer Inc., Docket No. 93P-0421 at 5 (Aug. 12, 1997). ("Nifedipine Petition Ruling").

of two drugs is not different solely because the delivery mechanisms of those drugs differ -- and by expressly stating that generic products need not be identical to innovator products in every respect-- FDA has, in essence, rejected an argument that delivery mechanisms must be the same for purposes of ANDA approval.<sup>14</sup> And, as noted above, "sameness" in delivery mechanisms is not a basis the statute provides to FDA for rejecting an ANDA. As a result, L&M's argument that "the generic product should have 'sameness' . . . from a design aspect"<sup>15</sup> lacks any legal foundation.

Moreover, in explaining why delivery mechanisms need not be the same for approval of an ANDA, FDA stated that its "bioequivalence standards ensure that an approved generic with the same dosage form as the innovator is therapeutically equivalent to the innovator, even if the generic has a different release mechanism."<sup>16</sup> Indeed, FDA noted that "its bioequivalency standards assure the therapeutic equivalence of any pharmaceutically equivalent extended-release product."<sup>17</sup> In light of the assurance provided by the requirement of showing bioequivalence, FDA has deemed sameness of the delivery mechanism -- as suggested by L&M -- an unnecessary inquiry:

[I]f these variations [in release mechanism] result in a product that is not bioequivalent, the generic drug will not be approved. (21 U.S.C. 355(j)(3)(F).) Indeed, it is precisely to ensure that any formulation differences do not result in bioinequivalence that the Agency established bioequivalence regulations and guidelines and that the Agency reviews bioequivalence data so carefully. The Agency's bioequivalence regulations and guidelines ensure that if

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<sup>14</sup> Indeed, FDA has stated that "it 'does not require that . . . the mechanism by which the release of the active drug substance from the formulation be the same [sic].'" *Id.* at 6 (quoting FDA, *Guidance for Industry: Oral Extended (Controlled) Release Dosage Forms: In Vivo Bioequivalence and In Vitro Dissolution Testing 2* (Sept. 1993)).

<sup>15</sup> Petition at 3.

<sup>16</sup> Nifedipine Petition Response at 11.

<sup>17</sup> *Id.*

a drug is not bioequivalent for any reason, including a change in mechanism of release or other formulation change, the drug will not be approved.<sup>18</sup>

The fact that Noven's fentanyl transdermal matrix patch uses a delivery mechanism that differs from that used in the Duragesic® transdermal fentanyl patch is simply not a valid basis upon which to deny ANDA approval.

For the same reasons, L&M's demand that generic formulations of fentanyl transdermal utilizing a different delivery mechanism than Duragesic® must be supported by clinical safety and efficacy data must be rejected. Simply put, FDA's bioequivalence review addresses differences in delivery systems, making clinical testing based solely on such differences inappropriate and unnecessary. FDA has stated that the purpose of Congress' inclusion of a requirement to show bioequivalence is to avoid the need for the more burdensome requirement of clinical testing.<sup>19</sup> As Noven noted in its Comments on the Brookoff Petition, FDA cannot require more from an ANDA applicant than the statute requires.<sup>20</sup> Thus, L&M's argument that FDA direct generic manufacturers of fentanyl transdermal products to undertake clinical studies is divorced from any legal authority or scientific justification.

**IV. L&M'S RELIANCE ON PURPORTED RISKS RELATED TO SKIN PERMEABILITY IS MISPLACED.**

L&M argues that current standards for bioequivalence are insufficient here because of a hypothetical risk that persons with high skin permeability will have an increased rate of absorption of fentanyl from generic transdermal formulations, like Noven's matrix patch. L&M's speculation, however, fails to provide an adequate justification for demanding that FDA

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<sup>18</sup> *Id.* at 13.

<sup>19</sup> *Id.* at 7.

<sup>20</sup> Attachment 1 at 5, 21-22.

ratchet up the current standard of bioequivalence or require clinical testing of generic fentanyl transdermal products.

**A. The Current Standards for Bioequivalence Are Adequate To Address Concerns About Risks Associated with High Skin Permeability.**

In proposing a heightened bioequivalence standard, L&M incorrectly assumes that the current standards are insufficient. First, contrary to L&M's suggestion, Noven's fentanyl patch has a rate controlling mechanism; there is no need for a heightened standard to address a problem that does not exist. Second, the risk of increased absorption L&M describes is an inherent aspect of all drug products: individual users absorb drugs at different rates regardless of the route of administration, dosage form and delivery mechanism. FDA's examination of pharmacokinetic data under its current standards for bioequivalence review already addresses such variability issues. And Noven's pharmacokinetic data establish that the absorption of fentanyl from its matrix patch is, in fact, bioequivalent to that of Duragesic®, resolving any potential concerns. Thus, if FDA deems Noven's product bioequivalent, there is no need for further inquiry under the terms of the FDCA and FDA's standards for ANDA approval.

**1. The Noven Matrix System Does Utilize a Rate-Controlling Mechanism That Limits Absorption of Fentanyl.**

L&M asserts that the risk posed by variations in skin permeability arises because generic formulations of fentanyl transdermal do not utilize a rate limiting membrane like that found in Duragesic®. However, L&M is incorrect in arguing that a matrix system lacks any mechanism for controlling the rate of delivery of the drug from its high concentration in the patch to the skin solely because such a system does not have a plastic membrane as seen in the Duragesic® reservoir patch. As Noven discussed at length in its Comments to the Brookoff Petition, Noven's matrix system regulates delivery of the drug through the molecular adhesion of the drug

to the adhesives in the patch.<sup>21</sup> This force counterbalances the pressure exerted by diffusion and provides an extremely effective and reliable means to ensure a controlled rate of delivery of the fentanyl.<sup>22</sup> Thus, like Duragesic®, Noven's patch is designed to deliver a controlled dose of fentanyl transdermally over a 72-hour period. L&M's assumption that generic formulations designed with a different delivery system from Duragesic® have no rate-limiting mechanism is simply wrong. Accordingly, there is no basis for imposing a heightened bioequivalence standard for ANDA approval.

2. Potential Variation in the Rate of Absorption through the Skin of Users of Transdermal Products Is No Different from Variations That Are Inherent in the Rates of Absorption of Drugs of All Dosage Forms.

In addition to the fact that Noven's fentanyl transdermal matrix design has a rate controlling mechanism, L&M's concern about skin permeability is overstated. L&M notes that the characteristics of the skin are not uniform from individual to individual as the premise for its argument that generic formulations may have higher absorption rates than Duragesic®, regardless of showings of bioequivalence. Yet, such differences in individual users are well known and do not warrant the additional scrutiny L&M requests.

As a practical matter, all physical parameters -- not just skin permeability -- vary from individual to individual. For example, there is an average absorption rate for orally administered drugs among users, and ever-present variability around that average. The variability is an expression of the range of absorptions for the class of users and is a parameter very closely monitored by FDA. Such variability occurs regardless of which part of the GI tract absorbs the drug, as different parts generally have very different rates of absorption. This situation is no

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<sup>21</sup> Attachment 1 at 6.

<sup>22</sup> This fact is established by the pharmacokinetic data submitted by Noven in support of its ANDA for transdermal fentanyl (ANDA 76-804). See Attachment 1 at 7.

different for agents delivered by any other route, including topical and transdermal medications. Because of this inherent variation of absorption rates, absorption is generally measured by means of a normative curve, reflecting the mean, range and variability of the absorption of the drug. As a result, FDA's current bioequivalence standards, which assess the range of variability of absorption, are sufficient to address the phenomenon described by L&M. Indeed, FDA has specifically stated that its current standards "are the best criteria presently available for the determination of bioequivalence, regardless of release mechanism."<sup>23</sup>

In light of the ubiquity of absorption variability across drug dosage forms, L&M cannot logically single out potential variability between users of fentanyl delivered through a transdermal matrix patch as a legitimate safety concern.

3. Noven's Bioequivalence Data Establish That the Rate Controlling Mechanism Utilized in its Matrix Patch Adequately Addresses Concerns Regarding Users with High Skin Permeability.

As a result of the fact that absorption varies among individuals, the appropriate measure of whether there is any basis for distinguishing between the rate of absorption of Duragesic® and the rate of absorption of Noven's matrix patch is -- as with any other ANDA product -- through analysis of pharmacokinetic data in the bioequivalence review. The standard pharmacokinetic parameters for the establishment of bioequivalence measure the rate and extent to which an active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. As FDA has indicated:

FDA's determination of bioequivalence is based on a demonstration of comparable bioavailability between the test and reference drugs, where bioavailability is defined as the extent and rate of drug absorption. The extent of drug absorption is measured by AUC and  $C_{max}$ . The rate of drug absorption is measured by the

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<sup>23</sup> Nifedipine Petition Response at 13.

$C_{max}$  and, in a qualitative sense, by the time to peak concentration ( $T_{max}$ ). ...

FDA has determined that AUC and  $C_{max}$  are the best criteria presently available for the determination of bioequivalence, regardless of release mechanism.<sup>24</sup>

The measure of exposure and rate used by Noven includes the area under the normative curve from time zero to a determined time (AUC 0-t), the area under the normative curve from time zero to infinity (AUC 0-∞) and the maximum concentration ( $C_{max}$ ). These parameters are the standard measures for bioequivalence studies.<sup>25</sup> Under these measures, Noven has presented data in its ANDA to establish bioequivalence to Duragesic®, thereby addressing any concern raised by L&M.<sup>26</sup>

**B. There is No Scientific Justification for Utilizing a Heightened Standard of Bioequivalence for Generic Fentanyl Transdermal Products.**

Despite the fact that the current standards for bioequivalence are adequate to address the concerns raised by L&M, L&M nonetheless suggests that FDA adopt a more stringent standard “because of the potency of fentanyl, since any significant change in plasma levels may have serious or life-threatening clinical consequences.”<sup>27</sup> L&M has overstated the potential consequences of high skin permeability with respect to fentanyl transdermal products by

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<sup>24</sup> *Id.* at 12-13.

<sup>25</sup> See FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -- General Considerations* 8-9 (March 2003) available at <http://www.fda.gov/cder/guidance/5356fml.pdf>. (“FDA Bioequivalence Guidance”). FDA has explained that this Guidance is also “generally applicable to nonorally administered drug products where reliance on systemic exposure measures is suitable to document BA [bioavailability] and BE [bioequivalence] (e.g., transdermal delivery systems and certain rectal and nasal drug products).” *Id.* at 1.

<sup>26</sup> Such measures as partial AUCs, mean residence time, absorption rate constants, etc., some of which are proposed by L&M as alternative more stringent means for determining bioequivalence for fentanyl transdermal products, have never, so far as the public record shows, been considered by the FDA to be variables for determination of bioequivalence.

<sup>27</sup> Petition at 3-4.

ignoring the wide therapeutic ratio of fentanyl. No doubt L&M is attempting to inject into the fentanyl debate the issues that arose during FDA's consideration of ANDAs for clonidine transdermal products, just as ALZA specifically invoked that proceeding in its Petition in Docket 2004P-0506. However, the clonidine example is simply not analogous because clonidine, unlike fentanyl, has a narrow therapeutic index.

First, regarding fentanyl, L&M's statement that "any significant change in plasma levels [of fentanyl] may have serious or life-threatening clinical consequences" as support for its argument regarding skin permeability reflects a basic misunderstanding of the therapeutic index of fentanyl and the actual risk involved in transdermal fentanyl systems. FDA considers a drug with a two fold or less difference between the median lethal dose and the median effective dose to have a narrow therapeutic index.<sup>28</sup> Examples include digoxin, lithium, phenytoin, theophylline, and warfarin.<sup>29</sup> Even for drugs with a narrow therapeutic index, FDA recommends that the traditional bioequivalence limit of 80 to 125 percent for non-narrow therapeutic range drugs remain unchanged, and has approved drugs with narrow therapeutic indices using standard bioequivalence criteria.<sup>30</sup>

Fentanyl has a therapeutic index of between 117-200 when administered transdermally,<sup>31</sup> it is, quite obviously, not a drug with a narrow therapeutic index. Considering the fact that FDA does not generally apply heightened bioequivalence standards even to those drugs that have a

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<sup>28</sup> 21 C.F.R. § 320.33(c).

<sup>29</sup> See FDA Bioequivalence Guidance at 20.

<sup>30</sup> See Gary J. Buehler, Director, Center for Drug Evaluation & Research, U.S. Food & Drug Administration, *The FDA Process for Approving Generic Drugs*, Presentation at the Blue Cross Blue Shield of Michigan Continuing Medical/Pharmacy Education Program, Slide 41 (Oct. 29, 2002) available at [http://www.fda.gov/cder/ogd/02-10\\_BCBS\\_gjb/index.htm](http://www.fda.gov/cder/ogd/02-10_BCBS_gjb/index.htm); FDA Bioequivalence Guidance at 20.

<sup>31</sup> Summary Basis of Approval. Duragesic. October 1990 (obtained via FOIA).

narrow therapeutic index, there is no basis for increasing the bioequivalence criteria for fentanyl transdermal products. The therapeutic index measurement deals directly with the question of potential overdosing; fentanyl's wide therapeutic range indicates that overdosing does not present a significant risk.

Second, by raising skin permeability, L&M is implicitly trying to place the fentanyl ANDAs in the same situation as the ANDAs regarding generic clonidine transdermal products (Docket 2001P-0470). This is simply another ploy to delay the approval of the fentanyl ANDAs. It fails because fentanyl and clonidine are significantly different in the applicable parameters. As discussed in Noven's Comments to the ALZA Petition, in which ALZA expressly referenced the clonidine matter, clonidine has a narrow therapeutic index,<sup>32</sup> unlike fentanyl. Thus, clonidine may present the potential concerns discussed above that are not an issue for fentanyl. Even accounting for varying ranges of permeable skin in the general population, fentanyl is vastly safer than clonidine throughout those ranges of absorption. Indeed, as discussed in Noven's Comments on the ALZA Petition, a more appropriate analogy can be made to the drugs that FDA has approved in a matrix transdermal form.<sup>33</sup> These products -- nitroglycerin, nicotine and estradiol -- have broader therapeutic indices and are therefore more comparable to fentanyl than is clonidine. For these reasons, a comparison between clonidine and fentanyl transdermal products is inappropriate.

Thus, there is no scientific justification for ratcheting up the bioequivalence standard in this case.

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<sup>32</sup> Attachment 2 at 21; see also FDA, *Guidance for Industry: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation A-1* (Nov. 1995), available at <http://www.fda.gov/cder/guidance/cmc5.pdf> (listing Clonidine Hydrochloride Tablets and Clonidine Transdermal Patches as narrow therapeutic range drugs).

<sup>33</sup> Attachment 2 at 21-22.

V. **CONCLUSION**

L&M has submitted another in a string of Citizen Petitions seeking to delay approval of generic fentanyl transdermal products. Like the other petitions, L&M's arguments lack any valid legal or scientific basis for blocking approval of Noven's fentanyl matrix patch. Indeed, without providing any underlying data or citation to a single reference, L&M has the gall to try to delay the ANDA approval process, frustrating the will of Congress and the public interest in low cost medications. FDA should not countenance this attack on the integrity of its processes.

The relief requested by L&M -- that FDA overhaul its ANDA review to impose draconian and unnecessary requirements upon applicants for approval of generic fentanyl transdermal products -- is inconsistent with FDA's statutory authority and FDA's own prior determinations and procedures; it would completely eviscerate the purpose of the Hatch-Waxman Amendments. For the reasons presented herein, FDA should reject L&M's demands forthwith and proceed to approval of Noven's ANDA in time to permit launch on January 23, 2005, when Duragesic® exclusivity expires.

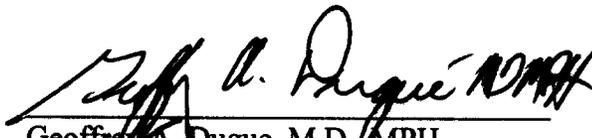
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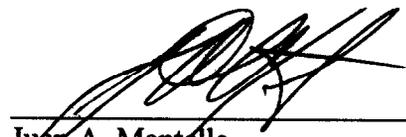
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cc: Gary J. Buehler, Director, Office of Generic Drugs  
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Respectfully submitted,

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