



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

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, 2003.¹ 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

¹ 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.² 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

² Attachment 1 at 4-5, 21-22.

of equivalence between its product and a previously-approved reference list drug product.³ 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.⁴

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.⁵ 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.⁶ L&M claims that this difference in the delivery mechanism between the branded product and generic formulations like Noven's necessitates an amplification

³ 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.

⁴ 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.

⁵ Attachment 1 at 10.

⁶ 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*:⁷

- “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;”⁸
- “information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;”⁹
- “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 . . . ;”¹⁰
- “information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application . . . ;”¹¹ 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”¹²

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

⁸ 21 U.S.C. § 355(j)(4)(B) (emphasis added).

⁹ 21 U.S.C. § 355(j)(4)(C) (emphasis added).

¹⁰ 21 U.S.C. § 355(j)(4)(D) (emphasis added).

¹¹ 21 U.S.C. § 355(j)(4)(F) (emphasis added).

¹² 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."¹³ 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

¹³ 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.¹⁴ 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”¹⁵ 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.”¹⁶ Indeed, FDA noted that “its bioequivalency standards assure the therapeutic equivalence of any pharmaceutically equivalent extended-release product.”¹⁷ 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

¹⁴ 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)).

¹⁵ Petition at 3.

¹⁶ Nifedipine Petition Response at 11.

¹⁷ *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.¹⁸

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.¹⁹ As Noven noted in its Comments on the Brookoff Petition, FDA cannot require more from an ANDA applicant than the statute requires.²⁰ 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

¹⁸ *Id.* at 13.

¹⁹ *Id.* at 7.

²⁰ 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.²¹ 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.²² 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

²¹ Attachment 1 at 6.

²² 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."²³

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

²³ 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.²⁴

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.²⁵ Under these measures, Noven has presented data in its ANDA to establish bioequivalence to Duragesic®, thereby addressing any concern raised by L&M.²⁶

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.”²⁷ L&M has overstated the potential consequences of high skin permeability with respect to fentanyl transdermal products by

²⁴ *Id.* at 12-13.

²⁵ 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/5356fnl.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.

²⁶ 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.

²⁷ 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.²⁸ Examples include digoxin, lithium, phenytoin, theophylline, and warfarin.²⁹ 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.³⁰

Fentanyl has a therapeutic index of between 117-200 when administered transdermally;³¹ 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

²⁸ 21 C.F.R. § 320.33(c).

²⁹ See FDA Bioequivalence Guidance at 20.

³⁰ 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; FDA Bioequivalence Guidance at 20.

³¹ 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,³² 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.³³ 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.

³² 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).

³³ Attachment 2 at 21-22.

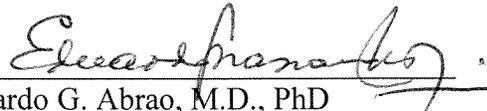
V. CONCLUSION

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.

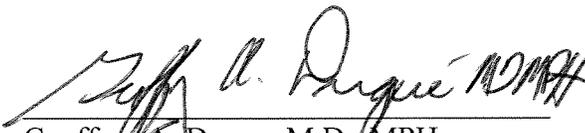
The relief requested by L&M -- that FDA overhaul its ANDA review to impose draconian and unnecessary requirements upon applicants for approval of generic fentanyl transdermal products -- is inconsistent with FDA's statutory authority and FDA's own prior determinations and procedures; it would completely 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.

Respectfully submitted,

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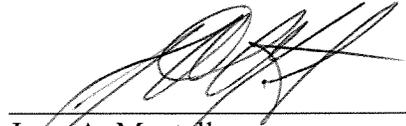
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Attachment 1

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Re: Docket No. 2004P-0472: Comments of Noven Pharmaceuticals, Inc., on Citizen Petition Regarding Approval of ANDA 76-258 for Generic Fentanyl Transdermal System

These comments are submitted by Noven Pharmaceuticals, Inc. ("Noven") in opposition to the above Citizen Petition ("the Petition" or "the instant Petition"). This Petition, by two doctors who have been affiliated with the brand product's manufacturer, Janssen Pharmaceutica Products, L.P. ("Janssen"), was accompanied by another petition, filed shortly thereafter, by ALZA Corporation ("ALZA"),¹ the manufacturer of the patch technology used in the branded product. We will comment on the ALZA petition separately.

However, the congruency of these two petitions, and the timing of their filing less than two months before the expiration of the exclusivity period for the branded drug, strip away the thin veneer of science each strives unsuccessfully to advance and reveal that they are simply further last-ditch efforts to thwart Congress's purpose to provide less costly generic alternatives once a branded product manufacturer has reaped the financial rewards provided by patent protection and, in this case, pediatric exclusivity.

¹ Citizen Petition by ALZA Corporation, Docket No. 04P-0506/CPI (submitted to FDA on November 12, 2004) ("ALZA Petition").

Significantly, the ALZA petition does not ask, as does the instant Petition, that FDA deny generic fentanyl ANDAs based on a finding that the solid state matrix delivery system is not safe under its current proposed labeling. How could it? ALZA's parent corporation, Johnson & Johnson, also markets, through its European subsidiary, the very type of transdermal delivery system the instant Petition seeks to have FDA reject. And, of course, ALZA and Johnson & Johnson would not market a product they believe to be unsafe.

ALZA tries to walk the tightrope it has created, not by asking FDA to deny the ANDAs,² but rather by seeking to delay the ANDA approval. It does this, in part, through the ruse of supporting the instant Petitioners' request that FDA require the generic manufacturer, and all others with similar systems, to "develop and implement comprehensive risk minimization programs" ("RMP"). By taking this tack, however, ALZA severely undercuts the instant Petition; ALZA, in essence, is saying the instant Petition's request for denial of the ANDA on safety grounds lacks validity and, accordingly, should be denied in favor of FDA's requiring instead an RMP.

We agree with ALZA that the instant Petition lacks scientific validity. It also lacks legal validity, for FDA does not have the authority to grant the relief it seeks. FDA cannot lawfully deny the ANDAs for generic transdermal fentanyl based on the Petition, nor can the agency require an RMP as a condition of ANDA approval for the following reasons:

- Petitioners do not even contend that the solid state matrix systems are unsafe under the conditions of use prescribed, recommended, or suggested in the proposed ANDA labeling. As that is the proper legal standard by which FDA must evaluate applications for approval of drugs, the Petition must be denied.
- Petitioners are simply wrong on the science; they misunderstand the nature of the solid state matrix delivery system that they seek to disparage. As a result, they misstate the risk of

² "ALZA supports the approval of generic fentanyl transdermal products, and none of the actions requested in this Petition would prevent FDA from approving such products." ALZA Petition at 9.

abuse and diversion resulting from the use of the solid state matrix system. Put simply, the system does not pose the risk that they misguidedly attribute to it.

- Indeed, the solid state matrix system presents less risk of abuse and diversion than does the reservoir system employed in the branded product, Duragesic®.
- Petitioners' claim that generic formulations using the solid state delivery system are sufficiently different from the branded products' reservoir system to warrant denial of ANDA approval does not withstand scientific or legal scrutiny.
- FDA lacks both the legal authority and, in this case, scientific basis for requiring an RMP as a condition of approval of an ANDA. Congress has expressly listed the items that an ANDA must include. In doing so, Congress also expressly stated that FDA cannot require anything in addition to these enumerated items. An RMP is not among the enumerated items. Accordingly, FDA cannot refuse or delay ANDA approval on the grounds that an RMP is not in place for the product.
- The request that FDA impose an RMP requirement is particularly anomalous and rather remarkable here, where there is no RMP in place for the branded product, Duragesic®.

Thus, on the science and on the law, the Petition is simply wrong and must be denied.

I. INTEREST OF NOVEN PHARMACEUTICALS, INC.

Noven is a leading U.S. manufacturer of prescription transdermal patches, including the type of patch used in Mylan's ANDA and addressed by the Petitioners in their Citizen Petition.³ Noven has partnered with Endo Pharmaceuticals Inc. to bring to market a generic controlled-release fentanyl transdermal system using Noven's solid state matrix system.⁴ Noven filed an ANDA for fentanyl transdermal system on July 30, 2003.⁵ FDA accepted the ANDA for filing on October 1, 2003. Since the Petitioners' characterizations of the delivery systems used in the ANDA submitted by Mylan are inaccurate and misleading, and because Noven's fentanyl transdermal product utilizes a delivery system similar to that of Mylan's product, Noven has an

³ There may be some slight difference between the patches used in Mylan's and Noven's transdermal fentanyl systems of which we are unaware. Our comments here are, however, applicable to all solid state matrix patches.

⁴ While the Petitioners describe these patches as "solid state monolith delivery systems," Noven refers to its transdermal system as a "solid state matrix" system, and uses this term in this response. "Monolith" is a generic term that describes all systems utilizing only one layer. We use "matrix" because the term describes with greater particularity the technology utilized in the ANDAs at issue.

⁵ ANDA 76-804.

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 FDA deny the action requested by the Petitioners.

II. LEGAL FRAMEWORK

Congress enacted the Hatch-Waxman amendments to the FDCA principally to create a more expeditious and less costly regulatory process for FDA pre-market approval of generic versions of previously approved brand-name drugs.⁶ This process enables generic formulations “to be marketed more cheaply and quickly.”⁷ The statute mandates that FDA review the ANDA against specific parameters listed in the statute that provide the criteria Congress stated the agency should use to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in the proposed product labeling.⁸

Section 505(j)(2)(A) of the FDCA specifies the following items that must be included in an abbreviated new drug application:⁹ (i) information indicating the parallels between the new drug and the previously approved listed drug regarding conditions of use, active ingredients, dosage and route of administration, bioequivalency and labeling; (ii) information on components, composition, methods of production; (iii) product samples and specimens of labeling for both the listed and new drugs;¹⁰ and (iv) a certification as to any existing patent rights related to the drug,

⁶ H.R. Rep. No. 98-857, pt. 1, at 14 (1984) *reprinted in* 1984 U.S.C.C.A.N. 2647.

⁷ *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990). Congress recently amended these provisions, in large part to curb abuses by pioneers seeking to extend this monopoly beyond Congress’s intent. *See* Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No.108-173 (117 Stat. 2066) §§ 1101-1103, 1111, 1117 (2003); *see also* 148 Cong. Rec. S7565 (daily ed. July 30, 2002) (statement of Sen. Hatch) (“I must concede, as a drafter of the law, that we came up short in our draftsmanship. We did not wish to encourage situations where payments were made to generic firms not to sell generic drugs and not to allow multi-source generic competition.”).

⁸ 21 U.S.C. § 355(j)(2)(A)(i); 21 U.S.C. § 355(d).

⁹ 21 U.S.C. § 355(j)(2)(A).

¹⁰ 21 U.S.C. §§ 355(j)(2)(A)(i) – (vi); 21 U.S.C. §§ 355(b)(1)(B) – (F).

as well as information regarding any intended use not previously claimed in the application for the listed drug.¹¹ Congress further mandated that FDA “shall approve” an ANDA application “unless” it fails to provide the information required by § 505(j)(2)(A) or if the information so provided indicates that the new drug has failed to satisfy one of the requirements enumerated in that section.¹²

III. THERE IS NO BASIS FOR FINDING THAT A SOLID STATE MATRIX TRANSDERMAL DELIVERY SYSTEM FOR FENTANYL IS UNSAFE.

The only argument advanced by the Petitioners is that generic transdermal fentanyl products using a solid state matrix delivery system are “unsafe” because of differences in the formulation of the solid state matrix delivery system and the reservoir system used in the Duragesic® patch. However, there is no scientific evidence to support this contention.

A. The Solid State Matrix Transdermal Fentanyl System Is Safe For The Uses Prescribed, Recommended Or Suggested In The Product Labeling.

The Act requires parallels in conditions of use, active ingredients, dosage and route of administration, bioequivalency and labeling to ensure that the generic product, like the innovator product, is safe and effective under the conditions of use prescribed, recommended or suggested in the proposed labeling of the drug.¹³ The Petitioners do not even purport to challenge the fact that transdermal fentanyl products utilizing a solid state matrix delivery system are safe under the conditions of use set forth in the product labeling. Accordingly, FDA cannot withhold approval of ANDAs for such transdermal fentanyl products.

¹¹ 21 U.S.C. §§ 355(j)(2)(A)(vii) – (viii).

¹² 21 U.S.C. § 355(j)(4). In addition, section 505(j)(4) contains an additional requirement, not at issue here, that the ANDA not contain an untrue statement of material fact. 21 U.S.C. § 355(j)(4)(K). The requirement in section 505(j)(4)(H) that the ANDA not contain information showing that the inactive ingredients or composition of the generic product are unsafe is addressed in Part III.A.3 of this response.

¹³ 21 U.S.C. § 355(j)(2)(A); 21 U.S.C. § 355(d).

1. The Nature of the Solid State Matrix System.

The simplest way to think of the generic transdermal fentanyl systems at issue is as drug-in-adhesive (“DIA”) systems. For example, whereas Duragesic® uses a delivery system wherein the fentanyl is present in a large physical reservoir from which it is administered through a rate-limiting membrane, in Noven’s DIA system the fentanyl is actually intimately mixed with two different pressure-sensitive adhesives into the layer that is applied to the skin. These two adhesives act as “brakes” on the process of drug delivery. Since the adhesives attract and hold the drug, delivery is controlled at the molecular level.

The DIA, or solid state matrix transdermal system, used by Noven consists of only three layers. Beginning from the side nearest to the skin when the system is applied, the layers are:

1. Release Liner. This is discarded prior to application to the skin, and functions primarily to protect the adhesive from contamination that would prevent it from sticking properly.
2. Drug-Containing Adhesive Layer. In the Noven product, this layer consists of a pressure-sensitive acrylic adhesive mixed with fentanyl and a pressure-sensitive silicone adhesive. In addition, a chemical known as polyvinylpyrrolidone is added to help make the drug more soluble.
3. A drug-impermeable polyester/ethylene vinyl acetate backing.

The affinity of fentanyl for the adhesives utilized in the solid state matrix system not only exists, but is absolutely essential to the creation and functioning of the system. It is this drug-adhesive affinity that allows the fentanyl to be solubilized in the adhesive during creation of the patch. When the system is applied, the thermodynamic driving force from an area of high drug concentration (the drug-bearing adhesive) to an area of low drug concentration (the skin) causes the drug to slowly diffuse out of the adhesive down the concentration gradient into the skin.¹⁴

¹⁴ See, e.g., D.W. Houze, *et al.*, *Transdermal Permeation of Fentanyl from Silicone Pressure Sensitive Adhesive Bands* (July 22, 2003) (Attachment 1).

2. The Design of the Solid State Matrix System Functions to Make the Product Safe under the Conditions of Use Prescribed, Recommended or Suggested in the Proposed Labeling.

The rate of diffusion through a solid state matrix system is very predictable because the degree of affinity of the drug for the adhesive is well known. In fact, dissolution tests are conducted routinely at Noven as part of its acceptance criteria for the various product batches, and the results of these tests, showing release of only 28% of the product in one hour, have been included in the CMC sections of its ANDA. In these tests, the systems are stressed tremendously in an attempt to get them to release the drug at a higher than usual rate, typically by mechanically agitating them and by “pushing” them with diffusion pressure that is never allowed to equilibrate as it would in a biological system. Even under these extreme conditions there is no rapid or immediate release of any significant portion of the drug.

3. Noven’s ANDA for Its Solid State Matrix Transdermal Fentanyl System Satisfies the Statutory Requirements for Safety.

The data Noven has presented in support of its ANDA for generic transdermal fentanyl demonstrates that the product is equivalent to the branded product; it is safe under the conditions of use prescribed, recommended or suggested in the labeling. Despite their claim to the contrary,¹⁵ the Petitioners have neither contended nor presented evidence that a solid state matrix transdermal fentanyl product would be unsafe under the current proposed labeling. Indeed, the labeling is, as the Act requires, identical (in pertinent part) to that for Duragesic®. As in the Duragesic® labeling, Noven’s labeling includes numerous warnings and contraindications regarding the appropriate use of the product, and precautionary information about keeping the product away from children and disposing of used patches properly. As a result, Noven’s proposed labeling meets the requirements of the Act.

¹⁵ Petitioners claim for relief asks that the Commission “refuse to grant final approval to ANDA 76-258 for a generic fentanyl transdermal system under its current proposed labeling.” Petition at 1 (emphasis added).

Nor is there is any evidence that “the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug,”¹⁶ or that “the composition of the drug is unsafe under [the conditions prescribed, recommended, or suggested in the proposed labeling] because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.”¹⁷ If the solid state matrix transdermal fentanyl product is used in accordance with the conditions prescribed in the proposed labeling, it is safe to the individual user. ANDA approval is not based on whether the drug is safe under conditions where it might be intentionally misused; it is based on whether the drug is safe and effective for use by an individual as prescribed, recommended or suggested in the labeling.¹⁸ Indeed, if approval could be denied based on potential safety concerns arising from misuse of a drug, neither aspirin nor ibuprofen would be on the market. Because solid state matrix transdermal fentanyl systems like Noven’s are safe under their proposed labeling, there is no basis for FDA to deny ANDAs for such systems.

The Petitioners also suggest that FDA can deny the ANDAs at issue because the generic transdermal fentanyl patch uses “a delivery or modified release mechanism never before approved for the drug” that adversely affects the drug’s safety or efficacy.¹⁹ This argument is equally unavailing. First, Duragesic® itself is an approved transdermal delivery method for fentanyl; thus, the delivery method proposed in the ANDAs -- a transdermal patch -- has been

¹⁶ 21 U.S.C. § 355(j)(4)(H)(i); *see also* 21 C.F.R. § 314.127(a)(8)(i)(A).

¹⁷ 21 U.S.C. § 355(j)(4)(H)(ii); *see also* 21 C.F.R. § 314.127(a)(8)(i)(B).

¹⁸ 21 U.S.C. § 355(j)(2)(A); *see also Ass’n of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 217-218 (D.D.C. 2002) (noting that FDA “only regulate[s] claimed uses of drugs, not all foreseeable or actual uses,” and agreeing that “the term ‘safe’ was intended to refer to a determination of the inherent safety or lack thereof of the drug under considerations [only] when used for its intended purposes.”) (internal citation omitted); *Am. Pharm. Ass’n v. Mathews*, 530 F.2d 1054, 1055 (D.C. Cir. 1976) (rejecting argument that “where there exists a documented pattern of drug misuse contrary to the intended uses specified in the labeling, the drug is unsafe for approval unless controls ... are imposed.”) (McGowan, J., concurring).

¹⁹ Petition at 3-4 (citing 21 C.F.R. § 314.127(a)(8)(ii)(A)(5)).

approved for fentanyl. Moreover, a difference between the release mechanisms used in solid state matrix patches and Duragesic® does not itself render Noven’s patch or the other generic patches inherently unsafe when used under the conditions prescribed, recommended or suggested in the proposed labeling. As Noven demonstrates in its ANDA and throughout this letter, its solid state matrix delivery system is safe when used in accordance with its labeling.

The fact that the generic transdermal fentanyl products use a release mechanism that differs from that used in Duragesic® does not result in the products having different dosage forms, as defined by FDA.²⁰ Despite the technological differences between the reservoir and solid state matrix systems, both the branded and generic formulations of fentanyl are delivered transdermally through a patch. FDA makes no distinction between patch technologies when considering whether the dosage form of an ANDA product is parallel to that of the innovator product.²¹ In terms of determining equivalency to the branded drug, courts have held that, as long as “a generic drug falls within the same dosage form classification (as defined by the Orange Book) as the pioneer drug, it will meet the threshold dosage form ‘sameness’ requirement” in the Hatch-Waxman amendments.²² Accordingly, there is no principled basis for distinguishing between the dosage forms of the two products.

²⁰ FDA has ruled, and a court upheld, that “a drug’s dosage form is not based on its release mechanism, but on its physical appearance and the way the drug is administered.” See *Pfizer Inc. v. Shalala*, 1 F. Supp. 2d 38, 44 (D.D.C. 1998).

²¹ Food and Drug Administration, Center for Drug Evaluation and Research, Approved Drug Products with Therapeutic Equivalence Evaluations, (“The Orange Book”) 24th Ed., “Appendix: Uniform Terms” (listing dosage forms of drug products).

²² *Pfizer Inc. v. Shalala*, 1 F. Supp. 2d at 46-47 (holding that only the dosage form must be identical to that of the pioneer drug; the release mechanism for the generic product, which is considered to be part of the composition or formulation of a drug, does not need to be the same as that of the pioneer drug in order to satisfy the ANDA requirements.).

4. A Solid State Matrix Transdermal Fentanyl System is Likely Safer Than the Reservoir System Used in the Brand Name Product.

As described above, the solid state matrix design attaches the drug to the product's adhesives on the molecular level. Thus, the rate of diffusion of the fentanyl is highly controlled and predictable. By contrast, the reservoir system currently employed in the brand name product, Duragesic®, presents a danger of over- or under-dosage even when used in a manner consistent with the conditions prescribed, recommended and suggested in the product's labeling.

The Duragesic® fentanyl transdermal system is typically referred to as a reservoir system because the drug is stored at high concentrations in a container that is attached to the delivery system. Reservoir systems consist, essentially, of five "layers." Starting with the side that will end up nearest to the skin, the layers are:²³

1. Release Liner. This is discarded prior to application to the skin, and functions primarily to protect the adhesive from contamination that would prevent it from sticking properly.
2. Skin-Contacting Adhesive. In the case of the Duragesic® system, this is a pressure-sensitive silicone adhesive that also contains fentanyl.
3. An Ethylene-Vinyl Acetate Copolymer Membrane. This thin membrane is meant to control the rate at which the highly concentrated fentanyl in the reservoir diffuses down its gradient into the skin.
4. The drug reservoir of fentanyl and ethanol, gelled in hydroxyethyl cellulose.
5. A drug-impermeable polyester film backing.

Because the entire dosage of the Duragesic® product is contained in a highly concentrated gel that is held behind a rate-controlling membrane, any damage to or defect in this membrane can cause significant problems to the appropriate controlled-release of the drug. For example, earlier this year, the manufacturer of the branded product, Janssen Pharmaceutica, had

²³ See *Physicians' Desk Reference* at 1751-52 (58th Ed. 2004).

to recall five lots of Duragesic® due to a defect in the seal on one edge of the system.²⁴ FDA's published notice of this recall indicated that the breach in the seal created the potential for the product to "release higher or too little medication than [the] intended amount."²⁵ This problem is not presented by the solid state matrix transdermal systems.

B. There Is No Evidence That The Solid State Matrix Transdermal Fentanyl System Poses A Significant Risk For Potential Misuse.

The Petitioners alternately contend that the solid state matrix formulation should be found unsafe based on a flawed hypothesis that this delivery system will lead to greater abuse and diversion by persons attempting to misuse the drug. The likelihood that a drug product will be unsafe under conditions of misuse is not a ground for denying an ANDA application.²⁶ Nonetheless, the Petitioners' contention that the solid state matrix system presents a greater danger of abuse is rebutted by the scientific evidence presented by Noven in connection with its ANDA. In fact, that evidence, when compared with the design of the reservoir system, shows that, if anything, solid state matrix systems like Noven's are less likely to be subject to diversion and abuse than the system utilized in the Duragesic® patch. Thus, even if the Hatch-Waxman amendments permitted FDA to consider the likelihood that a product will be unsafe under

²⁴ FDA Recall # D-134-4 (published in the FDA Enforcement Report on April 28, 2004). In its press release regarding this expansion of an earlier recall, Janssen stated, "DURAGESIC patches contain a strong opiate in the form of a gel. If the gel leaks from the patch, patients can get either too much or too little medication. Exposure to too much medication can occur if the gel leaks directly onto the skin and the body absorbs a higher than intended amount or if any of the medication is swallowed accidentally. This overexposure may cause potentially life-threatening complications. If the drug leaks out, there may not be enough medicine to achieve the desired effect and the patient may experience withdrawal symptoms. The gel should not be touched if it leaks from a DURAGESIC patch. If a patient or caregiver has unintended contact with the gel, they should immediately wash the affected area with large amounts of water only; soap should not be used. Patients should speak with their pharmacist or physician for further instructions." Press Release, Janssen Pharmaceutica Products, L.P., Urgent: Expanded Product Recall: Janssen Pharmaceutica Expands Nationwide Recall of 75 mcg/hour Duragesic® (Fentanyl Transdermal System) CII Patches (Apr. 5, 2004), available at http://www.duragesic.com/html/dur/pd_potential.xml?article=recall.jspf.

²⁵ *Id.*

²⁶ *See supra* note 18.

conditions of misuse, which they do not, there is no scientific justification for such a finding in the case of solid state matrix transdermal fentanyl systems.

1. The Petitioners' Arguments that the Design of the Solid State Matrix Delivery System is Likely to Result in Substantial Diversion and Abuse Lack Any Scientific Basis.

Essentially, the Petition is based on mistakes and misunderstandings of the structure and function of a solid state matrix system. The fact is that, contrary to the Petitioners' contention that the design of the reservoir system will prevent abuse and diversion of fentanyl, the design of the solid state matrix transdermal system is actually more likely to prevent misuse. Instead of confronting this unpleasant fact, the Petitioners prefer to try to debase the generic products utilizing a solid state matrix system as posing a greater risk of abuse and diversion -- and do so based on conjecture and speculation.

- a. Transdermal Fentanyl Products Cannot Adhere to Any Mucous Membrane, Such as the Inside of the Mouth.

The Petitioners first posit that the solid state patch, when applied to the inside of the cheek or other mucous membrane, can be expected to rapidly release its full drug content because there is no rate-limiting membrane. The scientific data refute that argument. The adhesive used to stick the delivery system to the skin in both the Duragesic® reservoir and Noven's solid state matrix systems type is silicone, a pressure-sensitive adhesive. A well-known characteristic of this type of adhesive is that it is rendered completely ineffective by even a small amount of moisture.²⁷ Thus, the solid state system will simply not adhere to a wet mucosal surface, preventing release of the drug.

²⁷ See *Physicians' Desk Reference* at 1754 (58th Ed. 2004).

b. The Solid State Matrix System Additionally Prevents Rapid Release of Fentanyl from the Patch.

Petitioners then speculate that the solid state system might be mechanically held to the oral mucosa. However, even under that scenario, although the rate of drug absorption would be expected to accelerate somewhat,²⁸ the amount of drug released from the solid state matrix patch would be limited by the aforementioned diffusion of the drug from the adhesive polymers.²⁹ Because of this molecularly-limited rate of release, the time required for drug diffusion to take place, even under the improbable constraints imposed by this supposed possibility for use, is still extremely lengthy -- certainly a matter of hours.³⁰ Indeed, due to the length of time that would be needed to accomplish the release of fentanyl using this method, the end result of placing Noven's solid state matrix system on oral mucosa would be absorption predominantly by ingestion through the GI tract of the user. This route further limits the drug's euphoric effects because of fentanyl's lower bioavailability³¹ and slower rate of absorption when absorbed through the GI tract. Thus, contrary to the Petitioners assertions, there is no evidence that oral application of the solid state matrix patch will result in a significant increase in the rate of release of fentanyl. Accordingly, there is little likelihood that the solid state matrix system will be subject to greater abuse and diversion than Duragesic®.

c. Intentionally Cutting a Solid State Matrix System Into Smaller Pieces Will Not Compromise the Controlled Release of Fentanyl.

The Petitioners finally speculate that a generic slow-release system will somehow allow each dosage unit to be easily converted into multiple fast-release dosage forms. However, the

²⁸ Any increase in absorption would be due to a class effect which would equally apply to Duragesic®, and thus does not form a basis for differential treatment of the products.

²⁹ See *supra* Parts III.A.1-2.

³⁰ The evidence for this has been presented in Noven's ANDA (76-804).

³¹ See *Goodman and Gilman's The Pharmacological Basis of Therapeutics* at 1957 (10th Ed. 2001).

structure of the solid state matrix system renders this scenario simply impossible. While either the reservoir system or the solid state matrix can be cut into pieces, such action does not compromise the method of drug delivery or affect the speed of release in any way for the Noven drug-in-adhesive system. As mentioned previously, the release of drug from a DIA system happens through the competing powers of diffusion, acting to push the drug out, and the attraction of the drug for the adhesives, acting to hold it in the system. This process goes on at the molecular level; thus, no amount of cutting can compromise it in any way. The net result from cutting this type of system would be the creation of multiple smaller slow-release units from the larger slow-release unit. As a result, there would be no added benefit to abusers and no increased potential for abuse or diversion.

2. A Comparison with the Design of the Reservoir System Suggests that the Brand Name Drug, Duragesic®, is More Likely to be Subject to Abuse and Diversion.

The scientific evidence not only establishes that the solid state matrix patch is not likely to be subject to significant diversion or abuse, it also leads to the conclusion that the reservoir formulation used in the branded product is actually subject to greater potential for abuse and diversion. Whereas the solid state matrix patch is not susceptible to an increased rate of release from cutting, as described above, there is a very different outcome when incisions are made in the rate-controlling membrane of the Duragesic® system. By merely mechanically puncturing any portion of the Duragesic® delivery system, users can access a large store of fentanyl. Thus, there is the possibility for a completely uncontrolled, rapid release of the gel containing the highly concentrated drug. If one merely holds the gel against a mucosal surface with a gauze pad, the entire drug load of the system may be delivered quite rapidly, especially considering the impact of ethanol in enhancing the drug permeation. The drug can also be injected undiluted or

smoked in some form.³² In truth, since the drug in the Duragesic® system is mixed with ethanol, a well-known skin permeation enhancer, a much higher dose could be administered simply by spreading the gel over a larger surface area of the skin.

In the case of the reservoir system, the uncomplicated mechanical manipulation of the Duragesic® product renders the rate-limiting membrane completely ineffective. The drug is directly available for injection, transmucosal absorption, or even smoking. In the case of the solid state system, the rate-limiting effect of the DIA system cannot be altered by any such treatment. As a result, there is nothing that can be directly injected, transmucosal diffusion is far too slow for drug abuse purposes (in that the ‘high’ is generally associated with rapid flux of the drug concentration upward), and there would seem to be a low likelihood of smoking the acrylic and silicone polymers used in the patch. Thus, for these reasons, it is likely that the solid state matrix system is actually safer with respect to potential abuse and diversion than the Duragesic® system.

3. Experience with the Reservoir System Confirms that it is Subject to Abuse and Diversion in Ways that do not Present Risks for Solid State Matrix Delivery Systems.

Actual reports of the manner in which Duragesic® has been abused and diverted underscore the comparative safety of the solid state matrix delivery system.³³ In suggesting that

³² See Kuhlman JJ Jr., McCaulley R, Valouch TJ, Behonick GS. Fentanyl use, misuse and abuse: a summary of 23 post-mortem cases. *J. Anal. Toxicol.* 2003; 27:499-504; Marquardt KA, Tharrat RS. Inhalational Abuse of the Fentanyl Patch. *J. Toxicol. Clin. Toxicol.* 1994; 32:75-3278; Reeves MD, Giniifer CJ. Fatal Intravenous misuse of Transdermal Fentanyl, *Med. J. Australia* 2002; 177(10): 552-554; Tharp AM, Winecker RE, Winston DC. Fatal Intravenous Fentanyl Abuse: Four Cases Involving Extraction of Fentanyl From Transdermal Patch. *Am. J. Forensic Med. Pathol.* 2004; 25(2): 178-181; Jost U, Wolter E, Borer H. Repeated Improper Intravenous Injection of Fentanyl From a Transdermal System. *Dtsch. Med. Wochenschr.* 2004; 129:313-314; see also *Erowid Experience Vaults*, available at <http://www.erowid.org/experiences/exp.php?ID=16951>; <http://www.erowid.org/experiences/exp.php?ID=20164>; <http://www.erowid.org/experiences/exp.php?ID=37460>.

³³ In fact, the web site *Erowid Experience Vaults*, which is cited by the Petitioners as evidence that “Duragesic has not been a preferred drug among abusers,” is replete with descriptions by actual users of their experience in abusing Duragesic®. Rather than suggesting that these abusers have abandoned their attempts to abuse the product, the site details the abusers’ preferred methods for manipulating Duragesic® in order to effectively utilize the fentanyl

Duragesic® is less likely to be abused and diverted, the Petitioners argue that abuse and diversion of Duragesic® has been limited to several “isolated and self-limited episodes.”³⁴ The Petitioners claim that these events were the result of “certain specific characteristics of the formulation of Duragesic®,” which have served to significantly limit its abuse potential.³⁵ The Petitioners conclusion not only is unsupported by any actual study or rigorous evidence, but their speculation also fails to establish the superiority of the reservoir design of Duragesic®.³⁶ Indeed, the very characteristics of the reservoir design -- characteristics not present in the solid state matrix design -- have led to these instances of abuse and diversion.

For example, the Petitioners describe several “short-lived and disastrous” attempts to directly inject the fentanyl gel from Duragesic® and “self-limited and isolated episodes” of application of a Duragesic® patch or its fentanyl gel contents to mucous membranes.³⁷ While the Petitioners imply that these users were somehow unable to access the fentanyl in

contained in the product. See *Erowid Experience Vaults*, available at <http://www.erowid.org/experiences/>. As described throughout this section, these methods cannot be utilized to compromise the solid state matrix system. Other references to this web site by Petitioners refer to abusers’ experiences with the Actiq® oral transmucosal “lollipop,” and not a transdermal system at all. As explained in Part III.B.5, experiences with the Actiq® product cannot be used to evaluate the likelihood of abuse and diversion of solid state matrix transdermal fentanyl systems.

³⁴ Petition at 3.

³⁵ *Id.* To support this claim, Petitioners cite a *New York Times Magazine* article about OxyContin® abuse wherein it is suggested that some physicians will prescribe Duragesic® rather than OxyContin® when they are concerned about the possibility of OxyContin® abuse. The assertion that the Duragesic® reservoir system is safer than OxyContin® is irrelevant to the relative safety of Duragesic® compared to any solid state matrix fentanyl delivery system, however. Oxycontin® is a tablet that is easily crushed and orally ingested, and there is no debate that fentanyl patches are less likely to be abused or diverted than OxyContin®.

³⁶ Although the Petitioners cite to data from the Drug Abuse Warning Network (“DAWN”) to support their argument that the reservoir design in Duragesic® has resulted in a low incidence of abuse and diversion, DAWN is a national public health surveillance system that monitors drug-related emergency department visits and deaths, and is unreliable as an indicator of actual abuse. In fact, FDA recently issued a warning letter to Janssen Pharmaceutica for claiming in its advertising for Duragesic® that there was a “Low reported rate of mentions in DAWN data” for the product, and for comparing the DAWN data for fentanyl to that for other opioids. FDA found these safety claims to be false and misleading because they suggested without “substantial evidence or substantial clinical experience” that Duragesic® is less abused than other opioid drugs. FDA, *Warning Letter to Ajit Shetty, M.D., Janssen Pharmaceutica, Inc.*, Re: NDA #19-813, MACMIS # 12386 (Sept. 2, 2004).

³⁷ Petition at 7.

Duragesic®, precisely the opposite is actually true.³⁸ Indeed, all the case reports cited by the Petitioners reveal that massive amounts of the opioid were derived from the reservoir system, in some cases causing death.³⁹ As discussed above, the solid state matrix system is not subject to this type of misuse because cutting of the patch does not allow the user to derive a bolus dose.

The Petitioners also cite a published report from the Drug Enforcement Administration’s Diversion Control Program⁴⁰ describing the DEA’s experience with Duragesic® abusers’ practice of freezing the patch, cutting it into pieces and placing it under the tongue or in the cheek cavity for drug absorption through the oral mucosa. While the authors dismiss this unimpeachable information as “rather unlikely,”⁴¹ the fact remains that a solid state matrix delivery system is not subject to this type of abuse because the rate of release is not significantly increased when applied to oral mucosa.

4. The Marketing of a Solid State Matrix Fentanyl Transdermal Product by Janssen Pharmaceutica’s European Affiliate Rebuts the Petitioners’ Assertions Regarding Potential Abuse and Diversion.

The marketing of a solid state matrix fentanyl transdermal system by Janssen Pharmaceutica’s European affiliate substantially undercuts the Petitioners’ safety arguments.

³⁸ The description of these cases as “self-limited” and “short-lived” is inappropriate. While it may be technically true that the death of certain users of Duragesic® makes further abuse by these individuals impossible, that fact cannot be deemed as improving public health, which is the actual goal of drug abuse prevention.

³⁹ Kuhlman JJ Jr., McCaulley R, Valouch TJ, Behonick GS. Fentanyl use, misuse and abuse: a summary of 23 post-mortem cases. *J. Anal. Toxicol.* 2003; 27:499-504; Kramer C, Tawney M. A Fatal Overdose of Transdermally Administered Fentanyl. *J. Am. Osteopath Assoc.* 1998; 32: 98:385-386; Marquardt KA, Tharrat RS. Inhalational Abuse of the Fentanyl Patch. *J. Toxicol. Clin. Toxicol.* 1994; 32:75-3278; Associated Press, April 3, 2002: “Fentanyl Abuse by Health Workers,” available at <http://www.jointogether.org/y/0,2521,549842,00.html>; Liappas IA et. al. Oral Transmucosal Abuse of Transdermal Fentanyl. *Psychopharmacology* 2004; 18:277-280; Reeves MD, Ginifer CJ. Fatal Intravenous misuse of Transdermal Fentanyl, *Med. J. Australia* 2002; 177(10): 552-554; Tharp AM, Winecker RE, Winston DC. Fatal Intravenous Fentanyl Abuse: Four Cases Involving Extraction of Fentanyl From Transdermal Patch. *Am. J. Forensic Med. Pathol.* 2004; 25(2): 178-181; Jost U, Wolter E, Borer H. Repeated Improper Intravenous Injection of Fentanyl From a Transdermal System. *Dtsch. Med. Wochenschr.* 2004; 129:313-314.

⁴⁰ US Department of Justice, Drug Enforcement Administration; Diversion Control Program. Drugs and Chemicals of Concern: Fentanyl, available at http://www.deadiversion.usdoj.gov/drugs_concern/fentanyl.htm.

⁴¹ Petition at 7.

The Petitioners note that in 1998 Janssen considered reformulating Duragesic® in the United States to incorporate a solid state matrix system “that had been approved in Europe.”⁴² In fact, Janssen’s European affiliate, Janssen-Cilag, has recently introduced that reformulated product in some European markets.⁴³ Janssen-Cilag’s marketing presentation for its German fentanyl solid state matrix system compares this new formulation to its existing reservoir system and concludes that the solid state matrix system is “smaller,” “thinner,” has “better adherence properties”, and is “more comfortable.”⁴⁴

It is unlikely that Janssen’s European affiliate would have introduced this “superior” solid matrix product into the European market if Janssen or its parent corporation, Johnson & Johnson, thought it would be subject to substantial diversion and abuse.⁴⁵ Further, as ALZA’s Petition notes, Janssen-Cilag has been removing the reservoir patch from the markets in which it has introduced the matrix patch.⁴⁶ If Janssen-Cilag’s experience in Europe with its fentanyl matrix system had presented additional patterns of fentanyl abuse, there would be no basis for its decision to market the solid state matrix product in place of the reservoir product. Indeed, ALZA concedes in its petition that it has been monitoring the use of fentanyl matrix patches in Europe for any early safety signals, and that none have occurred.⁴⁷ ALZA’s successful transition to a matrix patch in Europe clearly demonstrates these petitions for what they are, naked attempts to game additional exclusivity with no legitimate factual or scientific basis.

⁴² Petition at 9.

⁴³ ALZA Petition at 3.

⁴⁴ The relevant slides of the Janssen presentation, together with an English translation, are attached. (Attachment 2). *See also* ALZA Petition at 3 (noting that “Matrix products do afford some advantages over reservoir products in terms of cosmetics, adhesion, and in the elimination of possible gel leakage.”).

⁴⁵ *See* Attachment 2.

⁴⁶ ALZA Petition at 3.

⁴⁷ ALZA Petition at 7, note 6.

5. The Solid State Matrix Formulation is not Analogous to the Actiq® Fentanyl Oralet.

Lacking evidence to support their hypothesis that solid state matrix systems are subject to greater potential abuse and diversion, the Petitioners attempt to analogize the solid state matrix system to the oral solid state fentanyl delivery system, or oralet, used in the Actiq® “lollipop.” That comparison is specious. Although it is true that neither Actiq® nor solid state matrix transdermal systems have rate-controlling membranes, they can be clearly differentiated in terms of their delivery modality. The fentanyl oralet is designed quite specifically to deliver the medication dose rapidly through transmucosal application. As a part of this design, there is no rate-limiting mechanism to prevent immediate delivery of fentanyl into the blood stream, and the potential for the user to obtain a euphoric dose. As a result, there is concern about the potential for abuse of the Actiq® “lollipop.”

In contrast, the solid state matrix patch is a controlled-release system, which is designed to deliver the active ingredient in a rate-controlled manner over an extended period of time. Unlike the oralet, solid state matrix systems have a built-in rate-control mechanism tied to the molecular affinity of the drug to the adhesive polymers. Thus, while neither product has a rate-controlling membrane like the reservoir system, the solid state matrix does utilize a mechanism to control the delivery of fentanyl into the bloodstream.⁴⁸ As a result of this fundamental design difference, there is no basis for analogizing the solid state matrix patch and the Actiq® “lollipop.” Moreover, as discussed above, the rate-controlling mechanism of the solid state matrix cannot be defeated by placing the patch in the mouth. Therefore, there is no similarity

⁴⁸ On the other hand, the purified drug-gel-ethanol mixture released by even slight damage to the rate-limiting membrane of the Duragesic® system certainly allows delivery of the drug into the bloodstream at least as fast as the oralet, and far faster than the hours required for a solid state system like Noven’s matrix patch.

between the rate of mucosal absorption of fentanyl from the oralet and the solid state matrix systems, and no analogous concern about potential abuse.

In addition, the cited abuse and diversion of Actiq® arises out of use of the drug in the manner prescribed, recommended and suggested in the product labeling, i.e., through oral intake of the “lollipop.” Here, the purported potential for abuse described by the Petitioners would only arise -- if it were even scientifically possible -- from a use inconsistent with the recommendation for use, i.e., mucosal intake as opposed to dermal intake, requiring actual physical alteration of the drug product. There is simply no valid comparison between the fentanyl oralet and the solid state matrix fentanyl transdermal system.

Finally, FDA worked with the manufacturers of Actiq® to develop an RMP prior to the marketing of the product due to FDA’s strong concerns that the nature of delivery of fentanyl in this product -- through a “lollipop” designed for oral use -- could result in accidental use of the product by children.⁴⁹ There is no comparable risk related to the use of transdermal fentanyl patches and the labeling contains numerous cautions regarding use of the product in children and warns adult patients to keep the product out of the reach of children.⁵⁰

In sum, there is no scientific evidence to support the Petitioners’ spurious contention that fentanyl transdermal products using a solid state matrix delivery system are subject to some heightened risk of abuse or diversion. Instead, the solid state matrix design will likely be less attractive to potential abusers than the Duragesic® reservoir patch, and is therefore less likely to

⁴⁹ See FDA Talk Paper, FDA Approves Actiq for Marketing: Drug Offers Cancer Patients Relief From Breakthrough Cancer Pain (Nov. 5, 1998), available at <http://www.fda.gov/bbs/topics/ANSWERS/ANS00921.html> (noting that “Because of the uniqueness of the dosage form and because fentanyl is a potent schedule II narcotic, FDA advisory committee members and the Agency were extremely concerned that this product be packaged and marketed to minimize the opportunity for diversion, abuse, or access by children.”).

⁵⁰ See *Physicians’ Desk Reference* at 1751-55 (58th Ed. 2004).

be abused or diverted. Accordingly, there is no scientific or legal basis for denying approval of generic fentanyl transdermal solid state matrix patches on safety grounds.

IV. FDA CANNOT REQUIRE THE DEVELOPMENT AND IMPLEMENTATION OF AN RMP PRIOR TO APPROVAL OF AN ANDA APPLICATION.

Building on their faulty scientific assumptions and misplaced speculation that the formulation of generic transdermal fentanyl patches is unsafe, the Petitioners request that FDA deny final approval of ANDAs for generic fentanyl transdermal products absent a Risk Management Plan developed and approved by FDA. The Petitioners contend that FDA should require generic fentanyl transdermal products to have RMPs in place prior to approval, in order to “give equal weight to abuse potential, along with efficacy and safety issues, when evaluating a new drug for approval.”⁵¹

However, Congress has clearly defined and limited the criteria that FDA can consider in approving an ANDA. FDA has previously recognized and respected those limitations in connection with establishment and implementation of RMPs for generic products and has never required an RMP as a condition of ANDA approval. Thus, the Petitioners’ efforts to delay the final approval of any ANDA based on their complaints that are nothing more than conjecture about potential abuse and diversion -- especially when there is no existing RMP for the branded product -- would violate the FDCA.

A. The Express Language Of The Hatch-Waxman Amendments Prohibits FDA From Requiring An RMP As A Condition Of ANDA Approval.

While Noven understands the utility of RMPs in certain specific circumstances, it is clear that FDA does not have the authority to require an RMP as a condition for ANDA approval. As discussed above, Congress’s primary purpose in enacting the Hatch-Waxman amendments was

⁵¹ Petition at 14.

to create a more expeditious and less costly regulatory process for FDA pre-market approval of generic versions of previously approved brand-name drugs.⁵² To accomplish its goals in the Hatch-Waxman amendments, Congress set out the exact information it wanted an ANDA to contain. FDA was given the somewhat unusual, sharp and clear directive that the agency could “not require that an abbreviated application contain information in addition to [eight specifically enumerated items listed in the statute].”⁵³ Yet, in demanding an RMP, the Petitioners are asking FDA to do just that -- to require additional information in the ANDAs for generic transdermal fentanyl products. Moreover, as explained in the prior section, the protection gained from what the Petitioners would have FDA require is illusory. Giving in to their demands would thwart the express language in the FDCA and the Congressional policy behind Hatch-Waxman and the ANDA process, without any evidence to support the purported benefits that the Petitioners recite. Without enunciating some basis that is expressed in the statute as grounds for denial -- which the Petitioners have yet to do -- FDA cannot deny approval. The Petitioners’ request that FDA deny approval absent the development and implementation of an RMP is therefore a request for ultra vires action that exceeds FDA’s statutory authority.

B. Requiring An RMP As A Condition Of ANDA Approval Would Be Inconsistent With FDA Policy And Precedent.

Requiring the applicants to provide an RMP prior to approval would also contradict FDA policy. FDA has expressly ruled that:

Compliance by generic manufacturers with the essential elements of [a] risk management program is an issue distinct from approval of general versions of isotretinoin...Action can be taken to address these issues [adverse reactions] should they materialize, but their potential occurrence does not block the ability of duplicate producers to enter the marketplace. Thus, the possibility that one

⁵² H.R. Rep. No. 98-857, pt. 1, at 14 (1984) *reprinted in* 1984 U.S.C.C.A.N. 2647.

⁵³ 21 U.S.C. § 355(j)(2)(A).

or more manufacturers of isotretinoin will fail to fully meet their risk management obligations is *not* an impediment to approval of their applications conditioned on full performance.⁵⁴

Thus, FDA has already rejected the Petitioners' position that approval of fentanyl transdermal ANDAs can be denied absent development and compliance with an RMP.

Moreover, in the agency's recent Draft Guidance on the development of RMPs, FDA has recommended (not ruled, as Petitioners suggest) that manufacturers should consider implementing such programs when "a product may pose an unusual type of risk."⁵⁵ FDA has explained that its Guidance is directed to sponsors of innovator products, acknowledging that "a generic product may have the same or similar benefit-risk balance as the innovator and may, therefore, be an appropriate candidate" for consideration of an RMP when such circumstances are present.⁵⁶ Notably, in this case there is no RMP in place for the innovator product, Duragesic®. That fact alone substantially undercuts the Petitioners' arguments, as Section 355(j) is surely not premised on requiring more of an ANDA applicant than the innovator.

C. Requiring An RMP As A Condition Of ANDA Approval Would Be Illogical In The Case Of Generic Transdermal Fentanyl Products.

Finally, requiring an RMP prior to ANDA approval for generic transdermal fentanyl systems would be inconsistent with the role of RMPs. Development and implementation of RMPs for controlled substances better lend themselves to post-approval commitments. Most often, RMPs for pharmaceuticals are aimed at pharmacological risks -- even when used as indicated. For example, FDA requested an RMP for generic formulations of Accutane® because the drug may cause birth defects in the event of fetal exposure through maternal use during

⁵⁴ See FDA Response to Citizen Petition by Hoffmann-LaRoche Inc., Docket No. 02P-0059/CP1 at 8 (November 8, 2002) (emphasis added).

⁵⁵ FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans* (Draft) (posted May 4, 2004), available at <http://www.fda.gov/cder/guidance/5766dft.htm>.

⁵⁶ *Id.*

pregnancy. With respect to transdermal fentanyl, however, any risk that may exist is not pharmacological but would be behavioral. The risk of diversion and abuse the Petitioners speculate will occur with the solid state patch would be the result of an intervening behavioral pattern: persons seeking to use the drug for illegal recreational purposes rather than for its intended use of pain management. This risk will manifest itself -- if at all -- only after approval. The proper tailoring of a full RMP for transdermal fentanyl will therefore benefit from at least some post-approval experience in how, if at all, the introduction of the generic formulation affects this drug's abuse.

V. CONCLUSION

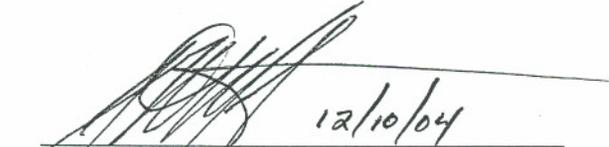
Despite their claims of potential abuse and misuse of generic transdermal fentanyl products, the Petitioners fail to advance any valid scientific or legal basis to support their conjecture. The scientific data submitted by Noven in support of its ANDA, as well as the information and analysis presented in this Response, establish not only that solid state transdermal fentanyl delivery systems are safe for the conditions of use prescribed, recommended and suggested in the proposed labeling, but also that the Petitioners' claims of potential misuse and abuse are scientifically flawed and their demands are contrary to governing law. In these circumstances, by delaying ANDA approvals, FDA would only be playing into the hands of those who seek to game the system and thwart Congress's clear goal of reducing the costs of prescription medicines by the timely introduction of safe and effective generic competition.

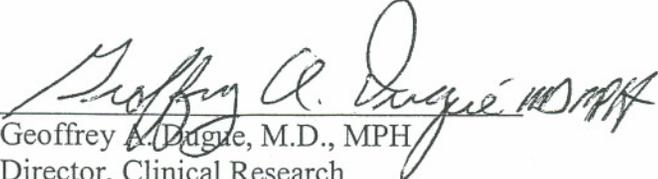
Accordingly, Noven respectfully requests that the instant Petition be denied and that FDA proceed to approval of generic solid state transdermal fentanyl products so that they may be launched to compete with the branded product and with each other on January 23, 2005 -- the date on which the branded product manufacturer's monopoly ends.

Respectfully submitted,

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Attachment 1

ABSTRACT

Amine compatible silicone pressure sensitive adhesives release fentanyl rapidly through human cadaver skin with little control of permeation rate. The addition of standard silicone pressure sensitive adhesive to a simple platform containing 2.5% fentanyl in amine compatible silicone adhesive reduces fentanyl permeation rates and results in the controlled release of fentanyl through human cadaver skin.

INTRODUCTION

Amine compatible silicone pressure sensitive adhesive (PSA) was developed to provide effective adhesion for transdermal delivery devices (TDD) containing base drugs with a pKa >8. Essentially, most of the adhesive's silanol groups (Si-OH) are substituted by methyl groups (Si-CH₃) to yield an adhesive that exhibits sufficient tack for instantaneous skin adhesion¹. Currently, amine compatible silicone PSA is used commercially as an adhesive layer for transdermal delivery of fentanyl. These systems require the use of ethanol containing reservoirs and rate controlling membranes to achieve controlled drug permeation. Here, simplified drug in adhesive (DIA) systems, utilizing amine compatible silicone PSA and standard silicone PSA blends have been evaluated for their ability to control drug permeation rates.

EXPERIMENTAL METHODS

TDDs were prepared from the following materials:

Fentanyl Base – Mallinckrodt Inc.

Silicone BIO-PSA® 7-4202 – Dow Corning Corp.

Silicone BIO-PSA® 7-4502 – Dow Corning Corp.

The following compositions were produced by casting polymer blends on 3M™ Scotchpak™ 1022 release liner, drying for 5 minutes at RT, then 5 minutes at 92° C in a convection oven. Dried matrix was laminated to the polyester side of 3M™ Scotchpak™ 9732 backing and had a coat weight of 10.0 +/- 0.5 mg/cm².

Component	Formula Number				
	1	2	3	4	5
Fentanyl	2.5	2.5	2.5	2.5	2.5
BIO-PSA® 7-4202 (amine comp)	97.5	72.5	47.5	22.5	0
BIO-PSA® 7-4502 (standard)	0	25.0	50.0	75.0	97.5

Solvent components were measured to achieve (%) dry weight listed above.

A permeation study was performed with stratum corneum obtained from split thickness cryopreserved cadaver skin by the heat separation technique. 0.5cm² circular patches (n=3) were cut from adhesive laminate, placed upon stratum corneum and mounted on modified Franz cells that were magnetically stirred at ~300rpm and maintained at 32°C. The receiving solution was 7.5 ml of 0.9% NaCl and 0.01% NaN₃ which was replaced at each sample point. The permeation samples were analyzed by HPLC using a Phenomenex® Columbus C8, 5µm, 10.0 x 0.46cm column with a flow rate of 1.5 ml/min. The detector is set at 210 nm. Mobile phase is: Buffer:acetonitrile:methanol (50:30:20). Buffer is 10mM KH₂PO₄ + 4.5 mM OSA at pH 3.0

RESULTS AND DISCUSSION

Drug became crystallized in formula 1, therefore this matrix was not included in the permeation study. Figure 1 illustrates the results obtained for drug permeation from the 4 remaining formulas. Table 1 presents the permeation rates determined for these 4 formulas over the duration of the three day study.

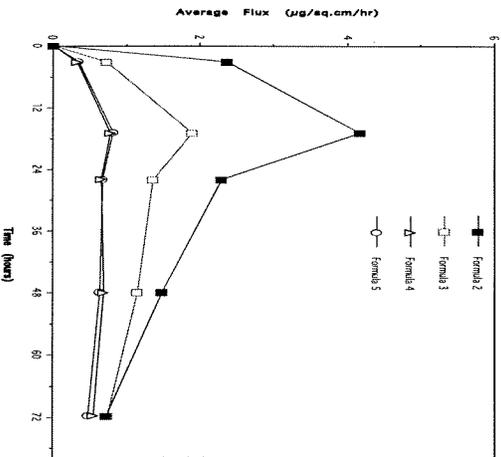


Figure 1

Formula Number	Permeation Rate (µg/cm ²)
2	1.92
3	1.20
4	0.65
5	0.62

The addition of standard silicone PSA provided the solubility in the matrix to mediate release of drug through the skin, similar to results found when blending silicone and acrylic PSAs.² Previously, according to Kanios et al., blends of silicone PSAs have been used for the manipulation of adhesive performance properties (i.e. peel and shear)³. These results indicate that the solubility parameters of silicone adhesives differ substantially enough to permit effective manipulations of drug release rates through human cadaver skin.

CONCLUSION

Simple silicone blend DIA systems have the ability to control fentanyl release rates effectively. Fentanyl permeation is slowed as the silanol content of the matrix increases. Investigation of improving flux rate to reduce patch size while utilizing this controlled release technique could lead to highly efficient systems with very low irritation potential.

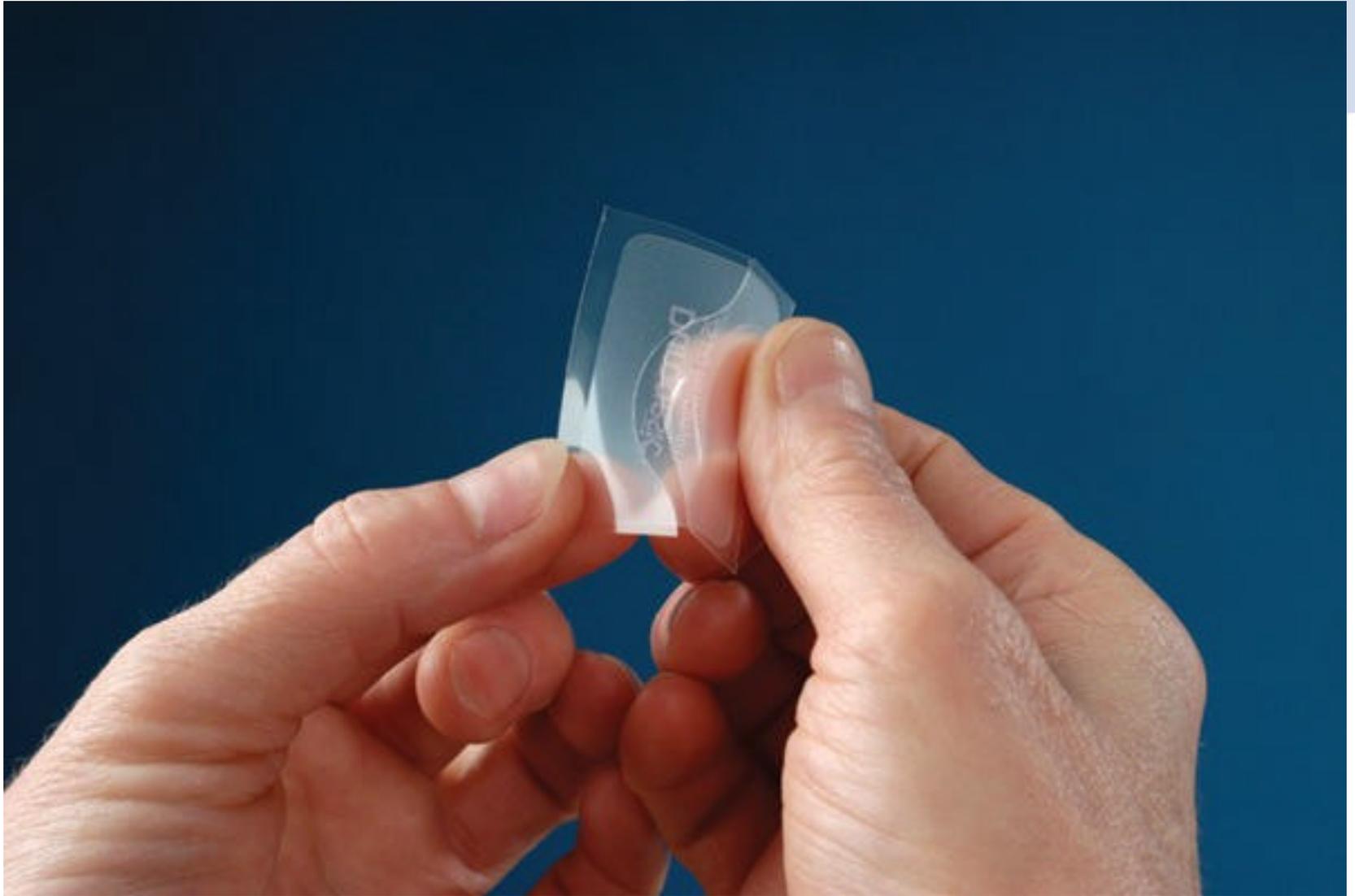
References

- Woodard, J.T., and Metevia, V.L. Transdermal Drug Delivery Devices with Amine-resistant Silicone Adhesives, US Patent 4,655,767 (assigned to Dow Corning Corp.)
- Miranda, J. and Sablotesky, S. Solubility Parameter Based Drug Delivery System and Method for Altering Drug Saturation Concentration. US Patents 5,474,783 and 5,656,286 (assigned to Noven Pharmaceuticals, Inc.)
- Kanios, D.P., Mantelle, J., Nerker, L.S., Raul, V.A., Ullman, K.L. Pressure Sensitive Adhesive Compositions for Transdermal Delivery Devices. US Patent 6,337,086 (assigned to Dow Corning Corp.)

Attachment 2

Durogesic[®] SMAT







Elastischer Matrixaufbau

3 Schichten

Transparente Abdeckfolie	51 µm
Polyacrylat-Klebeschicht mit Fentanyl	48 µm

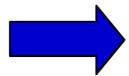
➔ Dicke des Pflasters < 0.1 mm!

➔ Keine Transportvermittler nötig

Eigenschaften des Klebstoffs

Ziel:

Kontrollierte und gleichmäßige Wirkstofffreisetzung mit guten Trageeigenschaften



Besonderer Klebstoff in Fentanyl D-Trans Matrix garantiert eine **gute Haftung** an der Haut und einen **optimalen Wirkstofffluss** durch die Haut.



Vergleich Reservoir/ D-TRANS[®] Matrix



Eigenschaft	Durogesic TM (Reservoir Pflaster)	D-TRANS [®] Fentanyl Matrix
Pflasteraufbau	Reservoirsystem mit gelartigem Inhalt; 5 Schichten	Elastischer Matrixaufbau; 3 Schichten
Pflastergröße	25 µg/h – 18.7 cm ² 50 µg/h – 34 cm ² 75 µg/h – 44.2 cm ² 100 µg/h – 57.0 cm ²	– 10.5 cm ² – 21 cm ² – 31.5 cm ² – 42 cm ²
Klebstoff	Silikon-Klebstoff	Polyacrylat-Klebstoff

Matrix kleiner



Vergleich Reservoir/ D-TRANS[®] Matrix

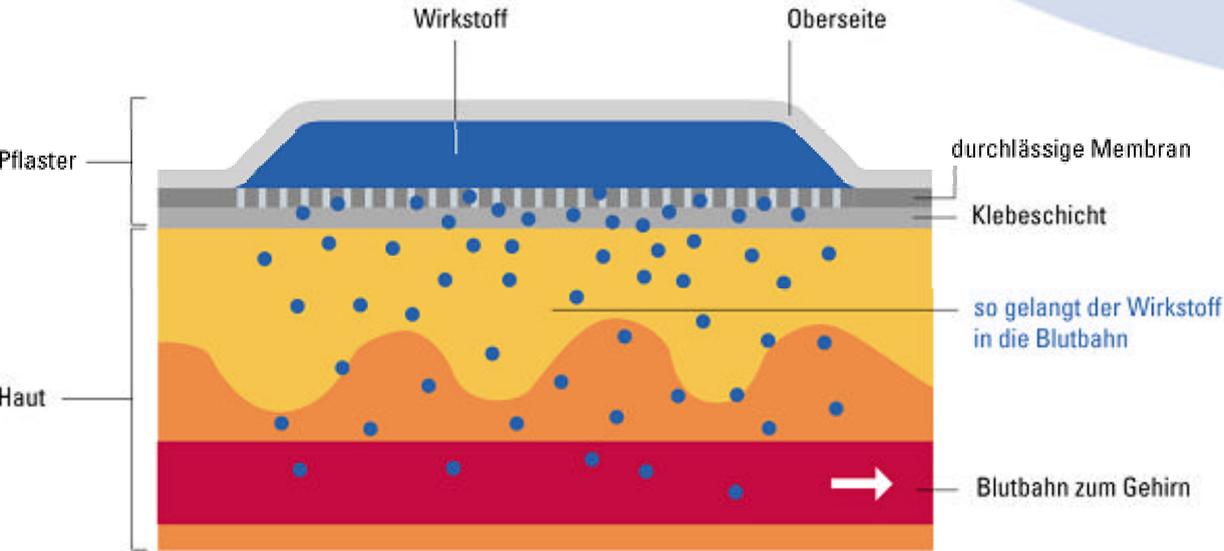


Eigenschaft	Durogesic [™] Reservoir	D-TRANS [®] Matrix
Wirkstoffschicht	Fentanyl suspendiert in Wasser/Ethanol und Hydroxyethylzellulose	Fentanyl direkt gelöst im Klebstoff
Kontrolle der Abgaberate	Durch Membran und Stratum corneum	Durch Matrix-Monomere und Stratum corneum
Transportvermittler	Ethanol	Keiner
Abziehfolie	Polyethylenterephthalat = PET, ohne Schlitzung	PET, geschlitzt, einseitig silikonisiert

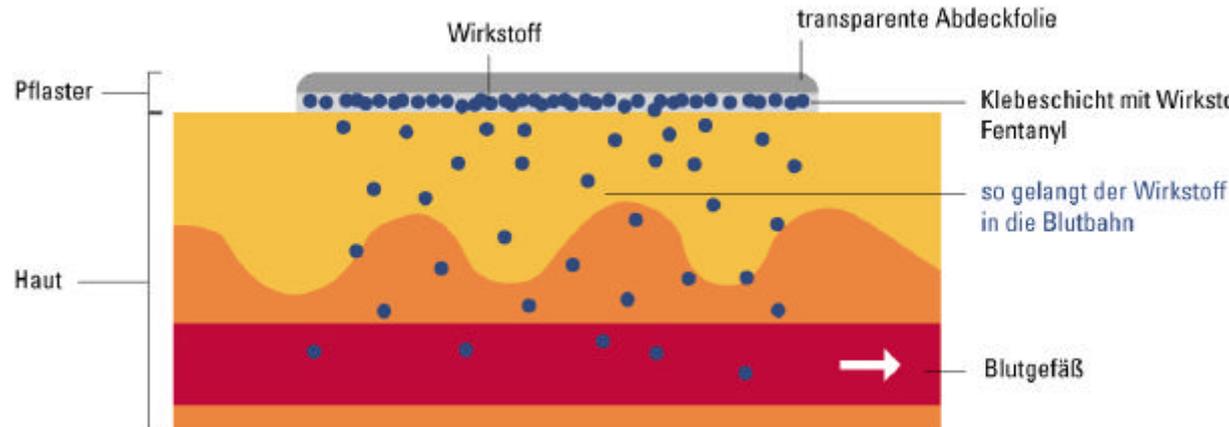
Durogesic SMAT- Pflastereigenschaften auf einen Blick

- **klein:** noch 26 – 44% kleiner als Durogesic
- **dünn:** über 80% dünner als Durogesic
- **flexibel:** elastischer Matrixaufbau
- **transparent:** bessere Trageigenschaften
- **praktisch:** einfachere Handhabung
- **angenehm:** noch höherer Tragekomfort

Schematischer Aufbau



Durogesic-Reservoir



D-TRANS[®] FENTANYL MATRIX

Klinisch-pharmakologische Studien

D-TRANS[®] Fentanyl MATRIX

Bioäquivalenz

Mehrfachdosis

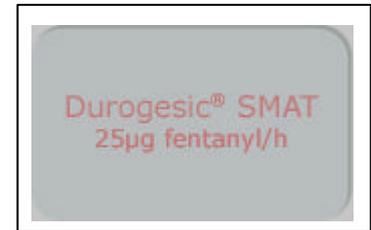
Dosisproportionalität

Demographische Einflüsse

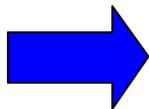
D-TRANS[®] Fentanyl MATRIX



← 25 µg/h →



Gleiche Abgaberraten



Bioäquivalenz



Bioäquivalenz-Studie

Pflastersysteme:

Durogesic-Reservoir; 100 µg/h

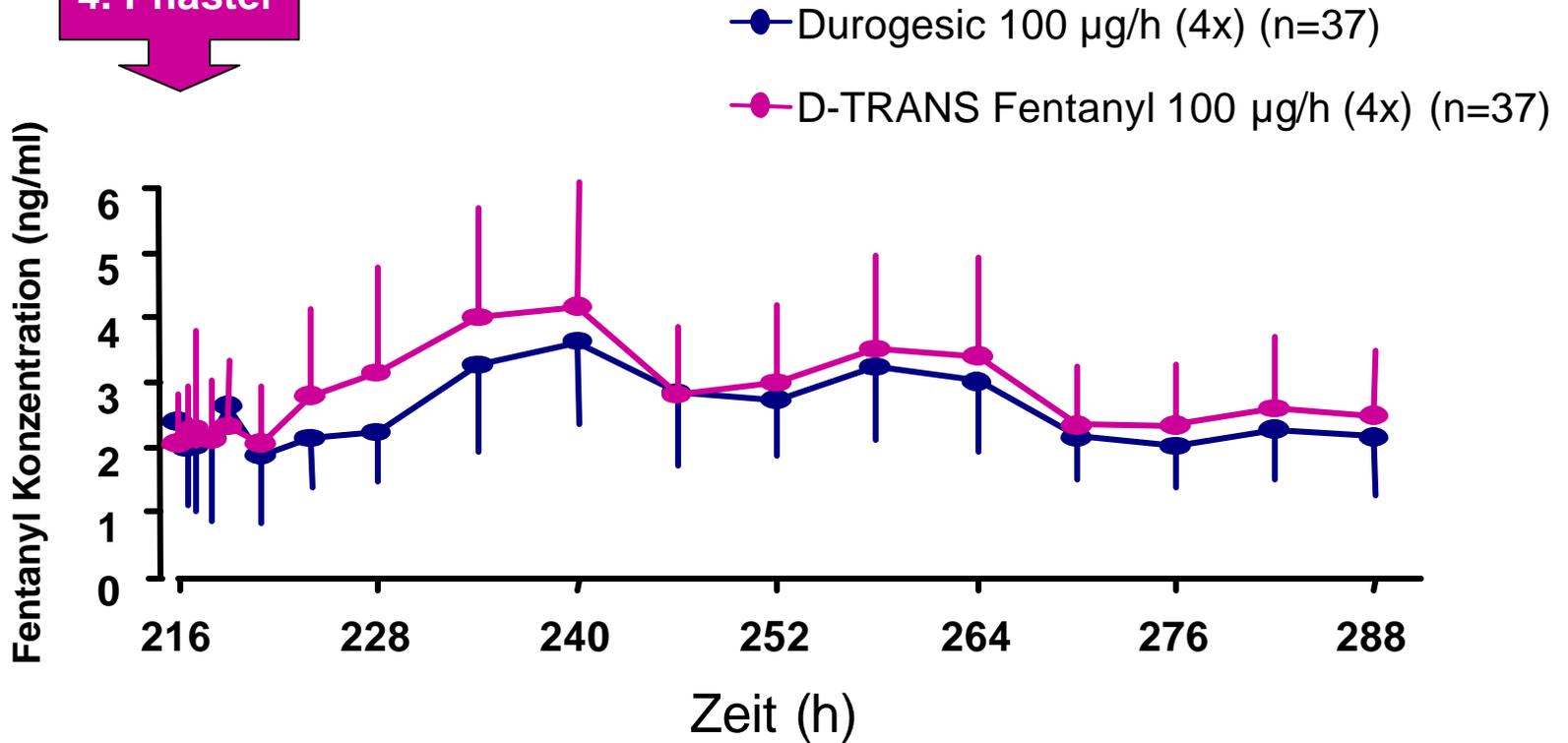
D-TRANS[®] Fentanyl Matrix; 100 µg/h

Studiendesign: Randomisiert, Crossover

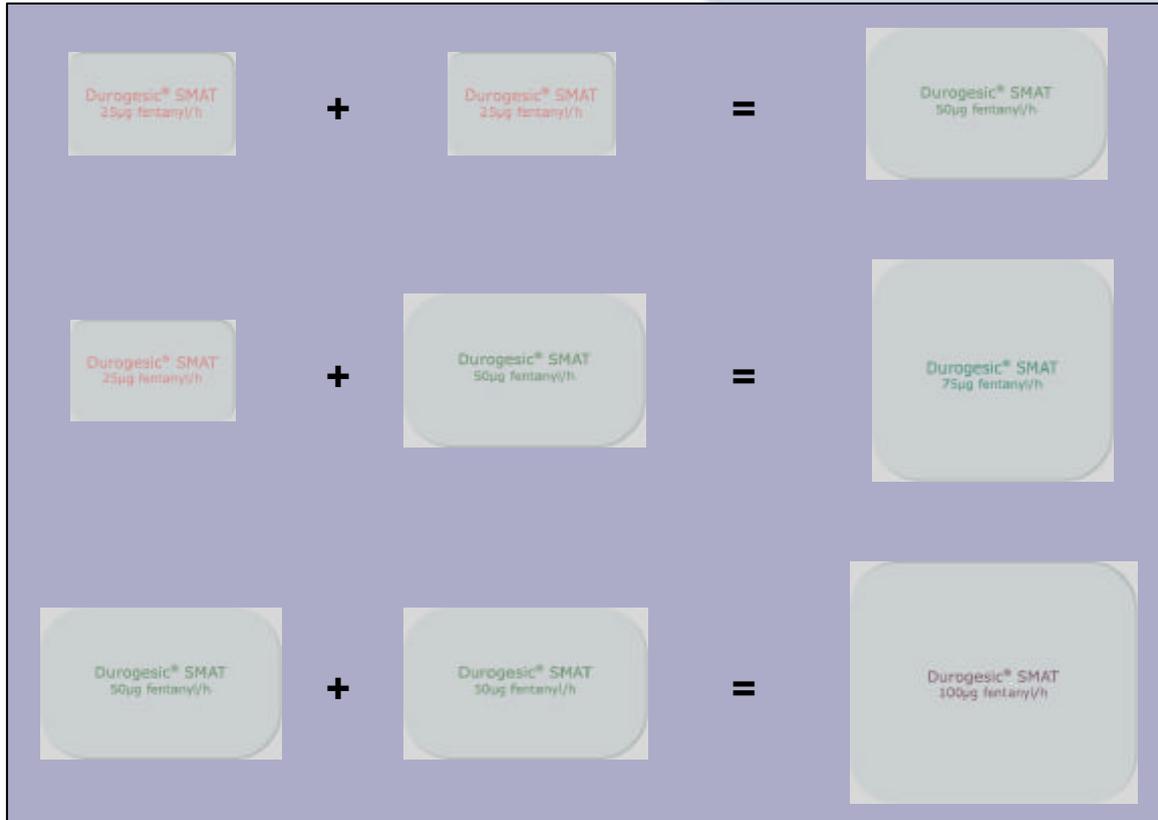
Ergebnis (n=37): Bioäquivalenz ✓

Bioäquivalenz im Steady State - Mehrfachdosierung

4. Pflaster



Dosisproportionalität



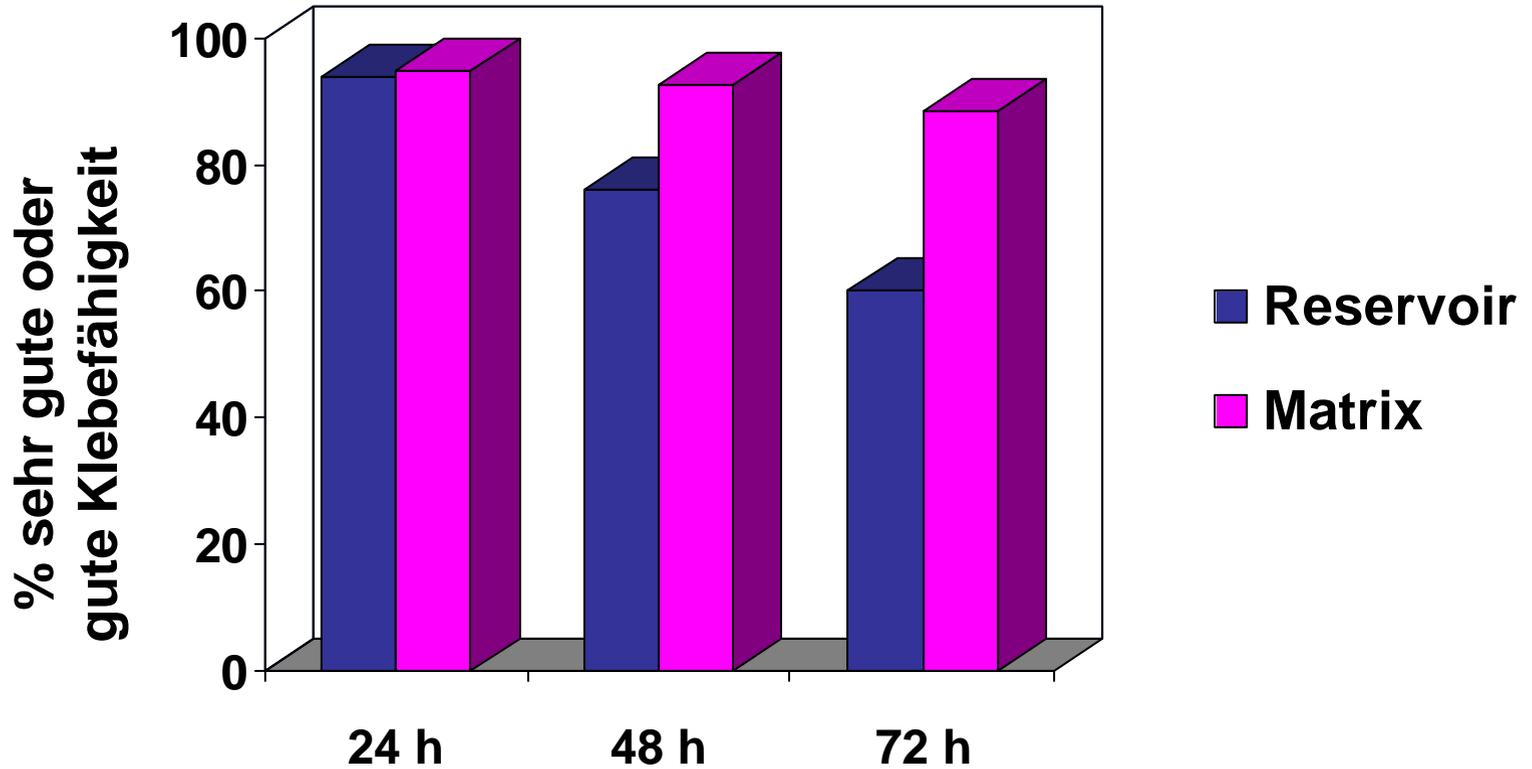
**Alle 4 Pflastergrößen sind
dosisproportional (n=124)**

Demographische Einflüsse

Pharmakokinetik unabhängig vom Hauttyp



D-TRANS: Ausgezeichnete Klebefähigkeit



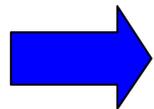
Hautverträglichkeit

Studie Kontakt-Sensibilisierung (D-TRANS Placebo; n=201):

21 Tage Expositionsphase

14 Tage Ruhephase

48 Stunden Re-expositionsphase



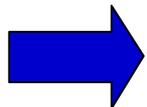
Keine Kontakt-Sensibilisierung

Hautverträglichkeit



Studie Phototoxizität (n=37):

- Zwei 2.4 µg/h D-TRANS Fentanyl Pflaster (1cm²) und 2 D-TRANS Plazebos (1cm²) für 24 h auf dem Rücken appliziert
- 2 beklebte (1x wirkstoffhaltig und 1x Plazebo) and 1 unbeklebte (Kontrolle) Hautstelle/n UV-A Licht ausgesetzt

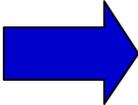


Keine Phototoxizität

Durogesic[®] SMAT

Die Vorteile auf einen Blick:

- bewährte gute Wirksamkeit und Verträglichkeit
- ausgezeichnete Klebeeigenschaften
- hervorragende Hautverträglichkeit
- einfache Handhabung
- hoher Tragekomfort
- unempfindlich gegen Beschädigung

 **Noch sicherer Therapieerfolg durch erhöhte Patientenzufriedenheit**

Durogesic[®] SMAT

**ist das einzigartige 3-Tage-Schmerzpflaster,
das die Verlässlichkeit von Durogesic[®] mit
allen Vorteilen der fortschrittlichsten D-Trans[®]
-Technologie verbindet.**

DUROGESIC® SMAT

Translation Sheet

Page 4:

Elastic Matrix Structure
3 Layers
Transparent cover layer
Adhesive layer of poliacrylate with fentanyl
<0.1 mm! Thick
No carriers needed

Page 5:

Adhesive Properties

Goal:

Ensure the continuous controlled release of the active substance keeping the patch on the skin all the time

- The adhesive/glue guarantees the adherence to the skin and optimal absorption through it

Page 6:

Reservoir Patch vs. D-TRANS® Matrix

Features	Reservoir Patch	D-TRANS®
Patch Structure	Reservoir System with a gelatine substance contained and 5 coats	Matrix structure with 3 coats
Patch Size		
Adhesive	Silicon	Poliacrylate

Page 7:

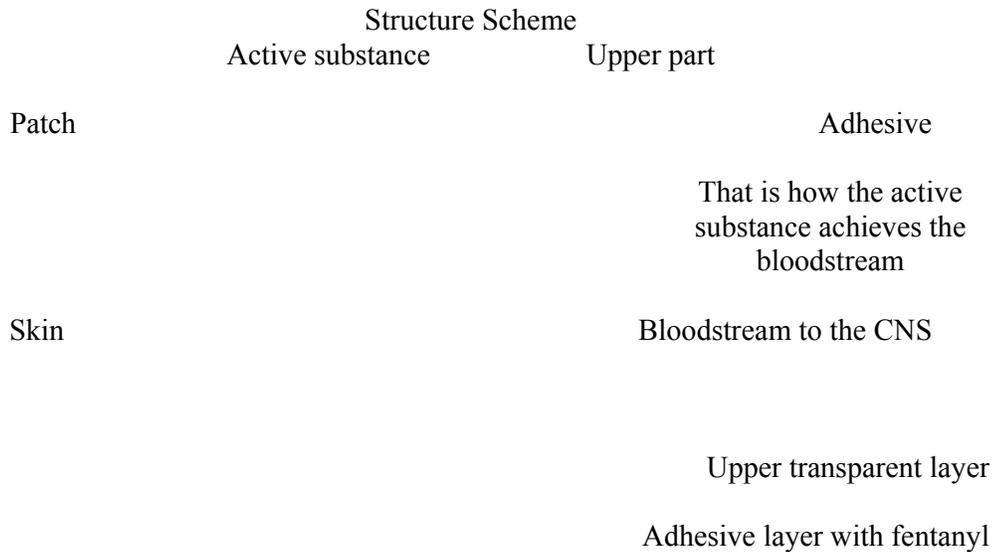
Reservoir Patch vs. D-TRANS® Matrix

Features	Reservoir Patch	D-TRANS®
Active substance layer	Fentanyl suspended in water/Ethanol and Hydroxiethyl-cellulose	Fentanyl dissolved directly in the adhesive
Control of the release rate	Through a membrane and the <i>stratum corneum</i>	Through a matrix monomere and the <i>stratum corneum</i>
Carrier	Ethanol	None
Protective layer	Smooth	One side of silicon the other is rough

Page 8:

Patch Properties “at first sight”
Small: 26-44% smaller than DUROGESIC
Thin: 80% thinner than DUROGESIC
Flexible: Elastic matrix structure
Transparent: Better adherence properties
Functional: Easy to handle (put on/take off)
Comfortable: More comfortable when using it

Page 9:



Page 10:

Clinical-Pharmacological Studies

Page 11:

Bioequivalence
Multiple doses

Dose proportionality

Dermatological influences

Page 12:

Same release rate control
Bioequivalence

Page 13:

Bioequivalence Study
Patch Systems
Design of Studies: Randomised, crossover
Result (n=37): Bioequivalence

Page 14:

Bioequivalence in Steady State
Dose Multiple
4 Patches
time (h)

Page 15:

Dose Proportionality
The four sizes are proportional to the doses

Page 16:

Dermatological Influences
Pharmacokinetic
Not affected by the different types of skin

Page 17:

D-TRANS: Outstanding adhesive properties
% Adhesive Property

Page 18:

Skin Tolerance
Study of skin sensibility
21 days of Exposure Phase
14 Days of non-exposure
48 h of re-exposure phase
Without altering skin sensibility after contact with the patch

Page 19:

Skin Tolerance
Photo-toxicity study (n=37)
2 DTRANS Fentanyl patches and 2DTRANS Placebos around 24h on the back
2 skin areas with patch (one with fentanyl and the other with placebo) and 1 area
without patch (control area) exposed to UVA light.
No photo-toxicity.

Page 20:

- Advantages at first sight:
- Proven good efficacy and tolerance
 - Outstanding Adhesive Properties
 - Outstanding skin tolerance
 - Easy to handle
 - High comfort whilst using it
 - Resistant

The success of the therapies is even more ensured due to the increased patients' satisfaction

Page 21:

Durogesic SMAT is the only 3 days analgesic patch that combines the safety of Durogesic® with all the advantages of the D-Trans Technology®.

Attachment 2



December 23, 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-0506: Comments of Noven Pharmaceutical, Inc. on ALZA Corporation 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 ALZA Corporation ("ALZA"), the manufacturer of the patch technology used in the branded fentanyl transdermal product, Duragesic®.

In filing the Petition, ALZA seeks to have its proverbial cake and eat it, too. ALZA first affirms that it "supports FDA approval of generic fentanyl transdermal products."¹ Scientific integrity requires no less. Yet, in virtually the same breath -- and based on conjecture, incorrect assumptions and flawed studies -- ALZA asks FDA to require manufacturers of generic fentanyl transdermal products "to develop and implement" Risk Minimization Programs ("RMPs") and to classify such products as different dosage forms from the branded product, Duragesic® rather than as pharmaceutical equivalents.

¹ Petition at 1.

At the outset, it is noteworthy that, true to its word, ALZA's "Actions Requested" do not include a request that FDA require that RMPs be in place prior to ANDA approval.² Again, scientific integrity demands no less. Holding ALZA to its word, FDA should proceed to ANDA approval in time for the January 23, 2005 launch of the generic versions, and consider the need for RMPs for Duragesic® and generic fentanyl transdermal products at a later date, if at all.

However, to the extent ALZA is suggesting that FDA should require RMPs as a condition of approval for generic formulations of fentanyl transdermal, there is neither a scientific nor legal basis for such a requirement.³ In fact, it is quite remarkable that ALZA would have the temerity to petition FDA for an RMP for its generic competitors when there is no RMP in place for its branded product Duragesic®, especially in light of the reported cases of abuse of Duragesic® tied to the reservoir design of its delivery system. Requiring RMPs for only generic versions would be unprecedented and quite anomalous.

ALZA also requests that FDA reclassify solid state matrix patches as a different dosage form from the reservoir patch. By this ruse, ALZA seeks to delay approval of the ANDAs and to incapacitate the generic manufacturers from marketing their products and competing on a level playing field with ALZA's branded product, Duragesic®. However, this request, as well, is both scientifically and legally unsustainable.

As discussed herein:

- ALZA does not even contest that solid state matrix fentanyl generic transdermal products are safe under the conditions of use prescribed, recommended and suggested in the proposed labeling, the ultimate legal standard that guides FDA's drug approval process.

² Petition at 1. The requested action is that FDA require RMPs for generic fentanyl transdermal products, but does not specify that those RMPs would need to be developed and implemented prior to ANDA approval.

³ Petitioners may be stating gingerly that RMPs should be a condition of approval in the last sentence of the Petition, where they remark that "Product specific risk minimization programs are needed to support the introduction of products, including fentanyl matrix products that may present a greater potential for diversion and abuse in the US environment." Petition at 9.

- ALZA's position is severely undercut by the facts that (1) it believes ANDAs for fentanyl patches should be approved and (2) ALZA is taking off the market in Europe the fentanyl reservoir design (used in the Duragesic® patch in the U.S.) and replacing it with the solid state matrix design that ALZA attacks in this Petition and that has been approved in European countries.
- The science advanced by the Petitioner cannot withstand scrutiny. Put simply, the solid state matrix system does not pose the risk ALZA purports to attribute to it.
- FDA has already ruled that different mechanisms of delivery do not place products in different dosage form categories. The ruling was based on a detailed analysis of the legislative history of the Food, Drug and Cosmetic Act ("FDCA") and sound policy considerations in light of the Act's purposes. The court upheld FDA's ruling. Thus, this is an unproductive argument for ALZA to rely upon.
- In any event, the design of Noven's generic fentanyl transdermal patch is as safe as is Duragesic's® under the conditions of use recommended in the proposed labeling -- and, indeed, less subject than is Duragesic® to misuse in the form of abuse and diversion.

In sum, ALZA's Petition is nothing more than a thinly-veiled attempt to extend its monopoly power of its Duragesic® product beyond the time Congress allotted to it. ALZA's double standard -- one for its product, another for potential competitors -- is problematic from both legal and scientific perspectives. It also collides with Congress's goal of giving innovators exclusivity to reap the benefits of monopoly pricing for a certain period of time, and then permitting the public to reap the benefits of competition. Since ALZA's naked attempt to extend its monopoly and stifle generic competition can withstand neither scientific nor legal scrutiny, ALZA's Petition should be denied.

I. INTEREST OF NOVEN PHARMACEUTICALS, INC.

Noven is a leading U.S. manufacturer of prescription transdermal patches, including the type of "matrix" patch addressed by ALZA in its Citizen Petition. Noven has partnered with Endo Pharmaceuticals Inc. to bring to market a generic controlled-release fentanyl transdermal patch using Noven's matrix transdermal system. Noven filed an ANDA for fentanyl transdermal

system on July 30, 2003.⁴ FDA accepted the ANDA for filing on October 1, 2003. ALZA'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 ALZA's Duragesic®. ALZA's characterizations of the delivery systems used in generic fentanyl transdermal products like Noven's are inaccurate and misleading. 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 ALZA.

On December 10, 2004, Noven submitted comments on an earlier petition, in Docket 2004P-0472, which also involves FDA approval of generic formulations of fentanyl transdermal ("Brookoff Petition"). A copy of Noven's submission is appended hereto as Attachment 1. Many of the arguments made in the Brookoff Petition are echoed in the ALZA Petition that is the subject of the instant Comments. Thus, Noven's comments on the Brookoff Petition address in detail the numerous fallacies in the scientific and legal contentions that purport to support the overlapping arguments in the two petitions.

We will not expand the Agency's burden by repeating here the points we made in detail in our response to the earlier Petition. Rather, Noven incorporates by reference its Comments on the Brookoff Petition in Docket 2004P-0472 and will focus here on arguments raised in the ALZA Petition that either were not presented in the earlier petition or were offered with a somewhat different thrust.

⁴ ANDA 76-804.

II. FDA CANNOT REQUIRE THE DEVELOPMENT AND IMPLEMENTATION OF AN RMP PRIOR TO APPROVAL OF NOVEN'S ANDA APPLICATION AS A MATTER OF LAW.

Building on faulty scientific assumptions and misplaced speculation that matrix transdermal fentanyl patches are more likely to be abused than is its own product, ALZA requests that FDA require that all applicants for generic transdermal fentanyl products develop and implement RMPs approved by FDA. However, Congress has clearly defined and limited the criteria that FDA can require in an ANDA. FDA has previously recognized and respected those limitations in connection with establishment and implementation of RMPs for generic products and has never required an RMP as a condition of ANDA approval. ALZA does not provide any legal authority for FDA to require an RMP here. Thus, FDA cannot make final approval of any ANDA for a fentanyl transdermal matrix patch contingent upon the submission of an RMP. We have provided in detail the uncontroverted legal authority that supports this position in our Comments on the Brookoff Petition.⁵ We will not repeat that discussion here, but rather incorporate it by reference.

III. ALZA HAS FAILED TO PRESENT ANY COMPETENT SCIENTIFIC EVIDENCE OF A HEIGHTENED RISK FOR POTENTIAL ABUSE OF FENTANYL TRANSDERMAL MATRIX SYSTEMS THAT IS SUFFICIENT TO NECESSITATE RMPs FOR GENERIC FORMULATIONS.

While Noven recognizes the utility of RMPs in certain circumstances, ALZA misstates the potential for abuse of matrix products such as Noven's in suggesting that RMPs for generic fentanyl formulations are necessary. Indeed, the "possible" abuse ALZA suggests is based on mere conjecture and is without any sustainable scientific support, especially considering the nature of the solid state matrix design.⁶ In advancing its hypothesis, ALZA downplays the

⁵ See Attachment 1 at 21-23.

⁶ See *id.* at 6-7, 11-14.

capacity for abuse that has actually been reported with Duragesic® and uses false comparisons to draw improper conclusions about the relative likelihood of diversion of the matrix formulation. As Noven discussed in detail in its Comments on the Brookoff Petition, there is no basis for an argument that Noven's matrix design is subject to greater potential abuse than is Duragesic®; in fact, Noven's product will likely be less attractive to abusers than is Duragesic®.⁷ As a result, there is no need for Noven to implement an RMP for its fentanyl transdermal patch, especially considering the fact that, to our knowledge, ALZA has not implemented, or even proposed, an RMP for Duragesic®.

ALZA postulates two incorrect reasons why fentanyl matrix formulations might be subject to greater abuse than the Duragesic® system: (1) matrix patches can be cut into pieces, creating "unit doses," and (2) when soaked in various solvents, there is a greater percentage yield of fentanyl from matrix systems than from the Duragesic®. ALZA attempts to support its conjecture with a flawed study that it commissioned. Neither the arguments nor the data are persuasive.

A. **ALZA's Claims of Potential Abuse Based on the Design of Matrix Systems are Flawed.**

ALZA first argues that the fentanyl transdermal matrix systems are likely to be abused based on two design elements. Both of ALZA's theories -- that either cutting matrix patches or attempting to extract fentanyl through soaking of matrix patches will facilitate abuse -- are wrong.

⁷ See *id.* at 11-21.

1. Cutting the Solid State Matrix Patch into Smaller Units Does Not Impact the Rate at which Fentanyl is Delivered.

The fact that the matrix patch can be cut into pieces is immaterial. As discussed in great detail in Attachment 1, Noven's submission in Docket 2004P-0472,⁸ the controlled-release of fentanyl from a solid state matrix patch results from the combination on a molecular level of fentanyl with two different pressure-sensitive adhesives. No amount of cutting can compromise the release of drug from such a drug-in-adhesive system, as release occurs through the competing powers of diffusion, acting to push the drug out, and the attraction of the drug for the adhesives, acting to hold it in the system. As a result, cutting the Noven patch into "unit doses" for sublingual or buccal exposure will not result in the user deriving a euphoric dose. Although the rate of drug absorption might be expected to accelerate somewhat when placed in the mouth, the fact is that the amount of drug released from the solid state matrix patch would be limited by the controlled rate of diffusion of the drug from the adhesive polymers. Thus, the net result from cutting Noven's matrix system would be the creation of multiple smaller slow-release units, which would have no added benefit to abusers and no increased potential for abuse or diversion.

2. Usable Doses of Fentanyl Cannot be Easily Extracted From Matrix Patches.

ALZA's suggestion that fentanyl can be more easily extracted from matrix systems for smoking or injection is equally flawed. Soaking the patch in a substance such as methanol, a metabolic poison, for several hours is neither a quick nor easy way for an abuser to gain access to the opioid. In fact, after soaking the patch, the user would need to undertake further steps to extract the drug from the noxious adhesives mixed with it in solution, as well as removing the methanol itself.

⁸ See Attachment 1 at 6-7, 13-14.

ALZA's argument that soaking the Duragesic® patch results in lower yield of fentanyl than soaking a matrix patch is misplaced. ALZA ignores the fact that virtually the entire concentrated dose of fentanyl contained in the reservoir of the Duragesic® patch can be obtained merely by cutting open the reservoir, which can be done quickly and easily. In comparison, any fentanyl obtained from soaking a matrix patch would be mixed with chemicals that would grossly degrade the purity of the drug, as noted above. Thus, in contrast to ALZA's "Room Temperature Soak" chart measuring the yield of fentanyl in solution after several hours of soaking,⁹ a user can obtain a virtually undiluted yield of abusable fentanyl in seconds from the Duragesic® patch.¹⁰ Certainly, the ability to manipulate a concentrated dose of fentanyl from the gel in the Duragesic® reservoir for immediate use (without further need to extract the drug from solution) would be more attractive to an abuser than attempting to extract fentanyl from the matrix patch. The latter, by ALZA's own admission, can only be done after several hours of extraction in chemical solvents, followed by further time and effort to extract the drug from the adhesive mixture for purposes of injection or smoking.¹¹

In sum, there is no reliable evidence that the design characteristics of the Noven matrix patch will lead to the potential abuse that ALZA cites as the basis for its demand for RMPs for generic formulations of fentanyl transdermal products.

⁹ Petition at 5.

¹⁰ This dose, contrary to ALZA's implication, can be split into multiple, usable doses merely by applying the fentanyl gel to gauze. *See* Attachment 1 at 14. Other users have developed more creative ways to portion this otherwise potentially lethal dose in order to abuse the product. *Id.* at 15, n.32.

¹¹ The fact that ALZA also soaked its own matrix patch in non-toxic liquids, such as rum and vodka, and obtained significant yields after several hours is also immaterial. First, as discussed in Noven's Comments on the Brookoff Petition (Attachment 1 at 13), fentanyl has lower bioavailability and a slower rate of absorption when absorbed through the GI tract, limiting the euphoric effect of drinking the fentanyl in solution. Moreover, regardless of the toxicity of the extracting agent itself, ALZA's argument again ignores the fact that the silicone and acrylic adhesives utilized in Noven's patch would be co-extracted and thereafter need to be removed.

B. The Study ALZA Cites in Support of its Argument Regarding Potential Abuse is Unreliable.

In an attachment to its Petition, ALZA presents the results of an unpublished study it commissioned that ALZA improperly contends constitutes scientific support for the notion that a fentanyl transdermal matrix system will be more “attractive” to abusers than the Duragesic® system. While ALZA describes the study as “valid and reliable,” there are substantial questions about the internal and external reliability of both the study and the scale used to measure potential abuse. With respect to the internal reliability of the study, the researchers themselves note that “nearly a quarter of both the developmental and confirmation samples claimed experience with the fentanyl matrix patch, which is not available.”¹² The only explanation provided is the possibility that the study participants did not take the task seriously, were not entirely truthful, had a tendency “towards braggadocio” or misunderstood the research materials.¹³

Frankly, both the problem and the explanation are mind-boggling. First, nearly 25 percent of the study participants claimed experience with a product that does not exist! Then, on top of that, ALZA offers the even more amazing excuse that the study participants did not take the whole thing seriously or were lying. And, this is the data ALZA would have the U.S. Food and Drug Administration rely upon! This is hardly an endorsement of the study’s credibility, or, for that matter, ALZA’s.

The study is also externally unreliable. First, the number of participants in the study -- 40 total, with 5 subjects or fewer listed as casual abusers -- is extremely small. Second, the researchers themselves acknowledge potential bias in the ratings provided by the participants,

¹² Petition Exhibit 2 at 78 (emphasis added).

¹³ *Id.*

because the determinations of attractiveness were based on information provided by the researchers on cards rather than on independent experiences by the participants.¹⁴ The “information” ALZA provided to the participants has not been provided with the Petition. If the information provided to the participants misstated the nature and potential for abuse of Noven’s patch in any way close to ALZA’s mischaracterization of matrix patches in its Petition, the participants’ responses are essentially worthless. Moreover, since the participants had no actual experience with the difficulty of obtaining fentanyl from a matrix system, responses that that system was hypothetically attractive are not accurate indicators of the real potential for abuse of such products. Third, drug abuse researchers have never reached agreement as to a “Gold Standard” for measuring opioid attractiveness and there is no reason to believe that the standard proposed in the study will become such a “Gold Standard.” Absent such a standard, and in light of the fact that this ALZA-commissioned study has not been peer-reviewed, there is nothing to commend the method utilized -- agreement between the participants as to attractiveness -- as a valid measure of potential for abuse.¹⁵ Even the researchers point out that “attractiveness... is only a component of predicting whether an opioid product will be abused.”¹⁶ Thus, the study cited by ALZA provides no reliable support for a claim that RMPs are necessary for generic fentanyl products.

C. ALZA’s Comparison to OxyContin® is Disingenuous and Inappropriate.

ALZA not only relies on this flawed study to suggest that generic fentanyl is subject to heightened abuse, but suggests that in light of the abuse potential, “[t]his situation is somewhat

¹⁴ *Id.* at 79.

¹⁵ The researchers understate this point in noting that “the demarcation between reliability analyses and validity analyses is less clear.” *Id.* at 30.

¹⁶ *Id.* at 79.

similar to FDA's approval of generic versions of OxyContin®."¹⁷ Yet, in another show of trying to walk a tightrope, only two pages earlier ALZA admits that abuse of Duragesic® and fentanyl is significantly lower than reported cases of abuse of OxyContin®. As ALZA's own self-serving statements confirm, the suggestion that fentanyl is subject to the type of abuse that has been reported with OxyContin® is absurd. Moreover, in the OxyContin® situation, the branded manufacturer had begun working with FDA on implementing a substantial RMP almost a year before any generic formulation even obtained tentative approval.¹⁸ The generic oxycodone manufacturers voluntarily agreed to implement RMPs for their generic oxycodone formulations prior to marketing.

Those facts are not similar to the current situation; they are in stark contrast to it. In the situation at issue, the risk of abuse ALZA attributes to solid-state matrix formulations is speculative, there is no evidence that the generic formulation will be abused at either a greater or even equal rate as the branded product, and ALZA has not implemented or proposed -- and FDA has not suggested the need for -- an RMP for its branded product Duragesic®.

D. ALZA's Experience in Europe Suggests that Fentanyl Transdermal Matrix Systems are not More Likely to be Abused.

Finally, ALZA asserts that its experience marketing fentanyl transdermal matrix systems in Europe is irrelevant because opioid abuse essentially is not a problem in Europe as it is in the United States.¹⁹ This contention flies in the face of the European Union's establishment of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in response to an

¹⁷ Petition at 6.

¹⁸ Purdue Pharma L.P. had been working with FDA on a proposed RMP as early as August 2001. See Petition for Stay of Action, Docket No. 04P-0006, PSA-1 at 5 n.9 (filed Jan. 7, 2004). FDA tentatively approved the first ANDA for a generic formulation of extended-release oxycodone hydrochloride (filed by Endo Pharmaceuticals Inc.) on July 31, 2002.

¹⁹ Petition at 3.

increasing prevalence of drug abuse in Europe and Europol's increased focus on drug abuse throughout Europe. Baseline EMCDDA data from 1999 for opioids alone reveal that the potential for abuse in Europe is not as different as ALZA claims. For example, in the United Kingdom, 18% of 15 to 16 year olds surveyed in 1999 perceived heroin as "very or fairly easy" to obtain; that percentage was similar to most other countries in Europe.²⁰ Moreover, under European government-sponsored AIDS prevention programs in which syringes are made available to drug abusers, 27 million syringes were distributed in the United Kingdom in 1997; in 1999 almost three million syringes were distributed in Portugal; and nearly a million syringes were distributed that same year in Austria.²¹

Based on these data, ALZA's bald contention that "the environment regarding prescription drug abuse in Europe differs from that in the US and a significant problem with matrix systems would not be anticipated" is unsupportable. ALZA does not cite to any expert opinion (though it mysteriously mentions such an opinion without any citation) and fails to elaborate on the factors present in Europe that somehow reduce the risk of potential abuse of an opioid. Moreover, one published study has expressly described instances of fentanyl abuse (in non-transdermal formulations) in Europe.²² In light of the fact that abusers in Europe have experience with fentanyl, the lack of reported abuse in Europe of the fentanyl matrix system marketed by ALZA's affiliate argues against ALZA's dire predictions of abuse from the marketing of fentanyl matrix formulations in the United States.

²⁰ EMCDDA & Europol, *European Union Strategy on Drugs 2000-2004* 15, 21, 24, 31, 40, 46, 55 (Draft, Snapshot 1999-2004) (Version 27/07/04), available at <http://snapshot2004.emcdda.eu.int/?nNodeID=5563>.

²¹ *Id.* at 44, 46, 57.

²² Kronstrand R, Druid H, Holmgren P, Rajs J. A cluster of fentanyl-related deaths among drug addicts in Sweden. *Forensic Sci Int* 1997; 88: 185-195.

In sum, there is no scientific basis for ALZA's speculations about abuse of Noven's matrix system or its suggestion that Noven's matrix delivery system is more likely to result in abuse and diversion of fentanyl than the current reservoir system used in Duragesic®.

IV. THERE IS NO BASIS FOR TREATING NOVEN'S FENTANYL TRANSDERMAL MATRIX SYSTEM AS A DIFFERENT DOSAGE FORM FROM DURAGESIC®.

The Federal Food, Drug and Cosmetics Act requires parallels in conditions of use, active ingredients, route of administration, dosage form, strength, bioequivalency and labeling to ensure that the generic product, like the innovator product, is safe and effective under the conditions of use prescribed, recommended or suggested in the proposed labeling of the drug.²³ Under this rubric, FDA has previously determined (i) that a patch is a single dosage form and (ii) that different mechanisms of delivery between a branded and generic drug are not a lawful basis for characterizing the drugs as having different dosage forms. ALZA's suggestion here that FDA should arbitrarily deem the transdermal patch utilized in Noven's product to be a different dosage form from ALZA's transdermal patch is inconsistent with the law, with FDA's prior position and has no valid scientific basis.

A. ALZA's Request that FDA Designate Transdermal Matrix Patches and Transdermal Reservoir Patches as Different Dosage Forms is Inconsistent with Federal Legal Precedent and Policy.

ALZA argues that the lack of a rate-controlling membrane in a matrix product might affect the rate of fentanyl delivery and, as a result, such products should be classified as a different dosage form from reservoir patches.²⁴ Under the Hatch-Waxman amendments to the FDCA, FDA must determine whether certain enumerated characteristics of an ANDA applicant's product are parallel to that of the reference listed drug. In addition to showing sameness in

²³ 21 U.S.C. § 355(j)(2)(A); 21 U.S.C. § 355(d).

²⁴ Petition at 7.

conditions of use, active ingredients, route of administration, dosage form, strength and labeling, the ANDA applicant must demonstrate bioequivalency between its proposed generic product and the branded product.²⁵ As a result, the statute contains a separate mechanism -- bioequivalence - - by which FDA ensures that the rate and amount of drug delivered by a generic applicant's product are equivalent to those provided by the reference listed drug.²⁶ The dosage form requirement does not and need not encompass rate and amount of drug delivered, as an ANDA applicant will be required to demonstrate the equivalent rate and amount of delivery under the bioequivalency provision.

FDA has previously ruled that a drug's dosage form should not be based on the product's release mechanism, since rate of release is already adequately regulated by the bioequivalency requirement. In its response to a Citizen Petition requesting that FDA redefine dosage forms with varying release mechanisms as distinct dosage forms, FDA explained that in implementing the FDCA's provisions through regulations it had found "no scientific basis for distinguishing dosage forms on the basis of release mechanisms," and that the "bioequivalency standards assure the therapeutic equivalence of any pharmaceutically equivalent extended-release product."²⁷ FDA noted that the term "dosage form" is not defined in the Act, and that when Congress amended the FDCA in 1984 to establish the abbreviated approval process for generic drugs it neither required generic drug products to be identical in all respects to innovator products nor overturned FDA's established system of dosage forms, under which no distinction in dosage form was based on the release mechanism of the products.²⁸

²⁵ 21 U.S.C. § 355(j)(2)(A)(i) - (iv).

²⁶ See 21 C.F.R. § 320.1(e) (definition of "bioequivalence" in FDA's regulations).

²⁷ FDA Response to Citizen Petition by Pfizer Inc., Docket No. 93P-0421 at 5, 11 (Aug. 12, 1997). ("Nifedipine Petition Ruling").

²⁸ *Id.* at 3, 5.

In its ruling on the nifedipine Petition, FDA reviewed its current dosage form classifications and specifically pointed to extended-release patches as a type of dosage form that included products with varying release mechanisms.²⁹ FDA explained that, while these products might vary in “the way they ‘house’ the drug, the ‘reservoir’ of drug, and the size of the patches,” they were all the same dosage form.³⁰ Thus, the fact that Noven’s fentanyl transdermal matrix patch uses a delivery mechanism that differs from that used in the Duragesic® transdermal fentanyl patch does not result in the products having different dosage forms under the FDCA. Despite the technological differences between the reservoir and solid state matrix mechanisms, both the branded and generic formulations of fentanyl are delivered transdermally through a patch. FDA makes no distinction between patch technologies when considering whether the dosage form of an ANDA product is parallel to that of the innovator product.³¹

When FDA’s ruling was challenged, the court agreed with FDA’s interpretation and held that, as long as “a generic drug falls within the same dosage form classification (as defined by the Orange Book) as the pioneer drug, it will meet the threshold dosage form ‘sameness’ requirement” in the Hatch-Waxman amendments.³² The court further relied on FDA’s ruling and stated that “a drug’s dosage form is not based on its release mechanism, but on its physical appearance and the way the drug is administered.”³³ For these reasons, there is no principled

²⁹ *Id.* at 5.

³⁰ *Id.*

³¹ Food and Drug Administration, Center for Drug Evaluation and Research, Approved Drug Products with Therapeutic Equivalents, (“The Orange Book”) 24th Ed., “Appendix: Uniform Terms” (listing Dosage forms of drug products).

³² *Pfizer Inc. v. Shalala*, 1 F. Supp. 2d 38, 46 (D.D.C. 1998), *aff’d in part and rev’d in part*, 182 F.3d 975 (D.C. Cir. 1999) (holding that only the dosage form must be identical to that of the pioneer drug; the release mechanism for the generic product, which is considered to be part of the composition or formulation of a drug, does not need to be the same as that of the pioneer drug in order to satisfy the ANDA requirements.).

³³ *Pfizer Inc. v. Shalala*, 1 F. Supp. 2d at 44.

basis for distinguishing between the dosage forms of transdermal matrix patches and reservoir patches.

As discussed in our comments on the Brookoff Petition, Congress enacted the Hatch-Waxman amendments to the FDCA principally to create a more expeditious and less costly regulatory process for FDA pre-market approval of generic versions of previously approved brand-name drugs after the branded manufacturers' generous periods of exclusivity had expired.³⁴ This process enables generic formulations "to be marketed more cheaply and quickly."³⁵

FDA's position on the appropriate basis for distinguishing between dosage forms is consistent not only with the statutory criteria set forth in the FDCA and its legislative history for evaluation of an ANDA, but also with the goal of encouraging generic competition and innovation.³⁶ In its ruling on the nifedipine Petition, FDA explained why its decision constituted good policy, stating that the dosage form categories established in the Orange Book:

have effectively served the public, the Agency, and the industry. The categories are useful in that they are sufficiently differentiated to make a reasonable distinction based on dosage form, which includes the appearance of the drug. However, the categories are also useful in that they are not so narrow as to be virtually product-specific. As a result, these categories have allowed the FDA to make threshold determinations that products have the same dosage form while encouraging manufacturers to develop innovative release technologies and allowing the public the benefit of safe and effective generic drug products."³⁷

³⁴ H.R. Rep. No. 98-857, pt. 1, at 14 (1984) *reprinted in* 1984 U.S.C.C.A.N. 2647.

³⁵ *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990). Congress recently amended these provisions, in large part to curb abuses by pioneers seeking to extend this monopoly beyond Congress's intent. *See* Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173 (117 Stat. 2066) §§ 1101-1103, 1111, 1117 (2003).

³⁶ In its nifedipine Petition ruling, FDA explained that the Petitioner's request that FDA redefine its dosage form classification system based on the release mechanisms of the products would "undermine the purpose of the Act's generic drug provisions." Nifedipine Petition Ruling at 6.

³⁷ Nifedipine Petition Ruling at 6-7; *see also Pfizer Inc. v. Shalala*, 1 F. Supp. 2d at 44 (quoting FDA's decision with approval).

In fact, fentanyl transdermal matrix systems are an example of generic manufacturers developing an innovative release technology that presents numerous improvements over the branded product and may actually result in less abuse and diversion of the drug than is experienced with the reference listed drug product.³⁸ Furthermore, as FDA itself has noted, a dosage form classification system based on release mechanism would severely limit the number of generic drug products that pharmacists and physicians could substitute for reference listed drugs, and this “would undermine Congress’ intent to make low cost generic drugs available to consumers.”³⁹

Thus, FDA should maintain its position regarding the proper means for distinguishing between dosage forms. To do otherwise would result in reevaluation of the limits of a drug’s dosage form each time a branded product’s exclusivity were about to expire and would create substantial impediments to generic competition, as generic manufacturers would have no way to predict whether their products in development would qualify as the same dosage form as the branded product with which they seek to compete.

B. ALZA’s Purported Scientific Grounds for Classifying Matrix and Reservoir Patches as Different Dosage Forms Are Insupportable.

ALZA attempts to side-step the lack of any legal basis for determining that the products are different dosage forms by suggesting that two external conditions might impact the rate of release of fentanyl from a matrix patch and that, as a result, Noven’s generic formulation should be classified as a different dosage form for scientific reasons. None of the arguments ALZA presents, however, is capable of withstanding scientific scrutiny.

³⁸ See Attachment 1 at 14-18. ALZA has recognized the advantages inherent to a fentanyl transdermal matrix system and the removal by ALZA’s European affiliate of its fentanyl transdermal reservoir patch in the markets in which it has introduced a matrix patch leads to the conclusion that ALZA itself believes that matrix systems represent an improvement over a fentanyl transdermal reservoir patch. These advantages include less likelihood of fentanyl leakage. See Petition at 3.

³⁹ Nifedipine Petition Ruling at 7.

1. Noven's Fentanyl Transdermal Matrix System Does Not Present a Heightened Risk For Patients With Stripped Skin.

First, ALZA suggests that the rate of release through a matrix system might be increased when used by patients with compromised skin. ALZA makes no independent argument to support this supposition, instead relying on a separately-filed Citizen Petition (Docket No. 2004P-0340). In its response to that Petition, Mylan Technologies Inc. ("Mylan"), another applicant seeking approval to market a generic fentanyl transdermal patch, decisively rebutted the arguments in the Petition cited by ALZA. That Petition drew incorrect conclusions from the two studies on which it relied, including the study cited in ALZA's petition, and Mylan effectively noted the flaws in the Petitioner's arguments.⁴⁰ For the reasons set forth in Mylan's response in Docket 2004P-0340, ALZA's argument that the rate of fentanyl delivery might be higher in matrix users with compromised skin is incorrect and does not warrant classifying matrix systems as different dosage forms.

As noted by Mylan, use of transdermal fentanyl systems on compromised skin is contraindicated in the product labeling for Duragesic® and in the proposed labeling for the generic transdermal matrix systems. Specifically, the Duragesic® labeling states that the product "should be applied to non-irritated and non-irradiated skin on a flat surface such as chest, back, flank or upper arm. ... Hair at the application site should be clipped (not shaved) prior to system application. If the site of DURAGESIC® application must be cleansed prior to application of the system, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents

⁴⁰ Mylan demonstrated that (1) the observation that stripped skin is more permeable than intact skin is well-known and was no doubt contemplated by FDA in review of ANDAs for matrix systems; (2) the studies cited in the Petition do not contain data supporting the Petitioner's conclusions that application of transdermal matrix systems to stripped skin can result in toxic fentanyl blood levels; (3) the study of the Cygnus patch that was relied upon by the Petitioner involved a product that is not a generic equivalent to Duragesic® and its data are therefore not applicable to generic transdermal fentanyl products; and (4) the use of the patch on stripped skin is contraindicated in the labeling for Duragesic and its generic equivalents.

that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to system application.”⁴¹ In addition, the patient information distributed with Duragesic® instructs patients as follows: “Do not put the DURAGESIC® patch on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.”⁴² The labeling and patient information for Noven’s generic fentanyl transdermal product will contain the same warnings and instructions.

Furthermore, ALZA has presented no data to indicate that mere removal of an adhesive bandage would result in skin so compromised that rapid absorption of fentanyl would result. In fact, the only *in vivo* quantitative study performed to examine this issue showed little change in the amount of drug that was absorbed (penetration of hydrocortisone on the forearm increased from 1% to only 3%), despite the fact that the study involved stripping of the stratum corneum to the glistening layer, where water loss is so high that the skin appears wet.⁴³ Thus, it cannot be assumed, as ALZA would have the Agency do, that routine incidental application of adhesive tape will have a significant effect on the delivery of any transdermal medication.

2. Noven’s Fentanyl Transdermal Matrix System Similarly Does Not Present a Heightened Risk With Respect to Heat.

ALZA then argues that because heat will impact the rate of release of fentanyl from matrix patches, those products should be classified as a different dosage form. This argument fails because, as ALZA acknowledges, “[i]t is well established that the application of heat to a fentanyl transdermal system enhances delivery.”⁴⁴ This statement is true regardless of the design of the delivery system. That is why the labeling for Duragesic® -- and Noven’s proposed

⁴¹ See *Physicians’ Desk Reference* at 1754 (58th Ed. 2004).

⁴² Patient Information, Duragesic (Fentanyl Transdermal System) (May 2003), available at <http://www.fda.gov/cder/pediatric/labels/Fentanyl.pdf> at 28.

⁴³ Kee Chan Moon & Howard I. Maibach, *Percutaneous Absorption in Diseased Skin: Relationship to the Exogenous Dermatoses*, in EXOGENOUS DERMATOSES: ENVIRONMENTAL DERMATITIS 217-226 (Torkil Menne & Howard I. Maibach eds., 1991).

⁴⁴ Petition at 7.

labeling -- warns that “[t]here is a potential for temperature-dependent increases in fentanyl released from the system.”⁴⁵ In fact, both the “Warnings” and the “Precautions” sections of the labeling contain a detailed instruction to clinicians, in capitalized text, stating: “All patients and their caregivers should be advised to avoid exposing the Duragesic® application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system.”⁴⁶ The labeling further advises of the possibility of an increase in serum fentanyl concentrations for patients with a fever and cautions clinicians to monitor any patients with an elevated body temperature.⁴⁷ Finally, the Duragesic® patient information, which is provided directly to patients to whom fentanyl transdermal systems are prescribed, contains the following warning: “**Do not use heat sources such as heating pads, electric blankets, heat lamps, saunas, hot tubs, or heated waterbeds. Do not take long hot baths or sun bathe.** All of these can make your temperature rise and cause too much of the medicine in DURAGESIC® to pass into your body.”⁴⁸ Again, the labeling and patient information for Noven’s generic fentanyl transdermal product will contain identical warnings and instructions.

As this external factor (whether from an external source or from an increase in body heat) impacts the rate of release regardless of the delivery system, there is no reason to classify matrix systems as a different dosage form. Indeed, ALZA determined that the rate of delivery was not any greater for its own matrix system without a rate-controlling membrane when exposed to heat

⁴⁵ See *Physicians’ Desk Reference* at 1753 (58th Ed. 2004).

⁴⁶ *Id.*

⁴⁷ *Id.*

⁴⁸ Patient Information, Duragesic (Fentanyl Transdermal System) (May 2003), available at <http://www.fda.gov/cder/pediatric/labels/Fentanyl.pdf> at 26 (emphasis in original).

than the rate for its Duragesic® reservoir system.⁴⁹ Thus, there is no evidence to suggest that exposure to heat renders the Noven matrix system a different dosage form from the Duragesic® reservoir transdermal system.

3. The Clonidine Citizen Petition Does Not Present a Valid Comparison to the Safety Considerations Relevant to FDA's Review of Fentanyl Transdermal Matrix Systems.

ALZA's reference to the pending Citizen Petition (Docket No. 2001P-0470) regarding transdermal clonidine is also unavailing. Drawing a parallel between the generic clonidine transdermal matrix system and a fentanyl transdermal matrix system is inappropriate for a number of reasons.

Fentanyl and clonidine are very different drugs. Clonidine has a narrow therapeutic index,⁵⁰ defined as a less than 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values,⁵¹ whereas fentanyl has a therapeutic index of at least 117.⁵² Transdermal absorption, like GI absorption or any other physiologic property, demonstrates variability that can be described by a normative plot. Fentanyl's therapeutic index of at least 117 demonstrates that, even accounting for the range of permeability of skin found in the general population, it is vastly safer than clonidine throughout that range of skin absorption, thus making ALZA's comparison of the two drugs misplaced.⁵³ A more appropriate analogy can be made to

⁴⁹ Petition at 8.

⁵⁰ See 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).

⁵¹ 21 C.F.R. § 320.33(c).

⁵² The therapeutic indices for fentanyl are between 117 and 200 as an analgesic. See Summary Basis of Approval. Duragesic. October 1990 (obtained via FOIA request).

⁵³ Subsequent to the submission of the ALZA Petition to FDA, the law firm of London & Mead submitted its own Citizen Petition related to FDA approval of ANDAs for fentanyl transdermal systems. Citizen Petition by London

the drugs for which FDA has approved NDAs in a matrix transdermal form. These products -- nitroglycerin, nicotine and estradiol -- have broader therapeutic indices and are therefore more comparable to fentanyl than is clonidine.

Moreover, unlike fentanyl, clonidine is well known to be irritative to the skin.⁵⁴ Since compromised skin is potentially more likely to have a higher rate of absorption -- leading to contraindication in the labeling of transdermal products -- clonidine has an inherent characteristic that might lead to overdosage when delivered transdermally. This is not true for fentanyl. Thus, any concerns regarding safety of a clonidine patch have little, if any, bearing on the determination of whether a fentanyl matrix system meets the criteria for ANDA approval.

V. CONCLUSION

ALZA has failed to advance any valid scientific evidence to support its speculation that the matrix delivery system utilized in Noven's generic fentanyl product has a greater potential for abuse and misuse than its branded reservoir delivery system. Instead, the scientific data previously submitted by Noven in support of its ANDA, as well as the information and analysis presented herein and in the Comments Noven submitted in response to the Brookoff Petition, establish that Noven's fentanyl transdermal matrix delivery system (i) is not subject to the risk of abuse hypothesized by ALZA and (ii) is, in fact, substantially less likely to be subject to potential abuse than is Duragesic®. The relief ALZA seeks in the form of an RMP for generic -- and only generic -- fentanyl transdermal systems is neither legally permissible nor scientifically justifiable. Similarly, ALZA has failed to provide any valid scientific or legal basis for FDA to

& Mead, Docket No. 04P-0540/CP1 (submitted to FDA on or about December 7, 2004). The London & Mead Petition deals more particularly with the issue of skin permeability, and Noven will be submitting a separate response in that docket that addresses the issue in greater depth.

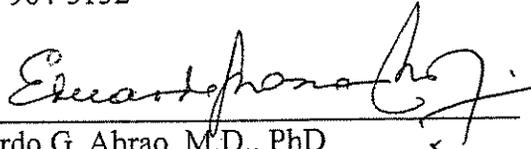
⁵⁴ See *Physicians' Desk Reference* at 1002-03 (58th Ed. 2004).

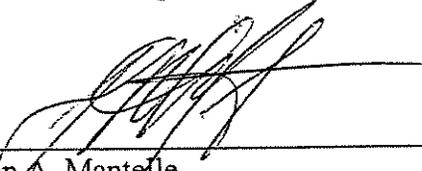
determine that the matrix patch should be classified as a different dosage form from the reservoir patch.

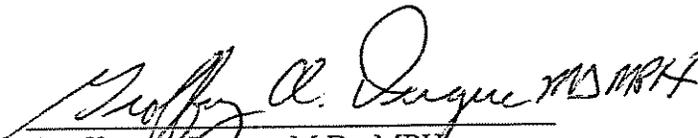
Accordingly, Noven respectfully requests that the Citizen Petition be denied and that FDA proceed to approval of Noven's ANDA for its generic fentanyl transdermal matrix patch so that Noven may compete with the branded product when ALZA's monopoly ends on January 23, 2005.

Respectfully submitted,

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Attachment 1

Attachment 1 to Noven's
Comments in Docket 2004P-
0506 has been omitted, as it
duplicates Attachment 1 to the
instant Comments.