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PHARMACEUTICALS, INC.

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.

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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.

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[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

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[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.

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[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,

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[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. <u>ALZA's Comparison to OxyContin® is Disingenuous and Inappropriate.</u>

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

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[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.

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[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]

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[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' 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

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[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]

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[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.

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[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

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[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

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[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 200as 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

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& 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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