noven
PHARMACEUTICALS, INC.

December 10, 2004

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

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/CP1 (submitted to FDA on November 12, 2004) ("ALZA Petition").

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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,

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[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.

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[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

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[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.

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[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

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[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 bioavailability[31] 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

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[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; 3275-3278; 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; *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

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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 Program[40] 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.

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[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; 3275-3278; 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.

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[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

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[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

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[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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