DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 29 2010

Rec'd 11/2/2010

John P. O'Donnell, Ph.D.
Chief Scientific Officer
Mylan Laboratories Inc.
1500 Corporate Drive, Suite 400
Canonsburg, PA 15317-8574

Re: Docket No. FDA-2006-P-0329

Dear Dr. O'Donnell:

This letter responds to your citizen petition received on March 17, 2006 (the Petition), your supplements to the Petition dated March 21, 2006 (SUP1); May 25, 2006 (SUP2); August 9, 2006 (SUP3); and November 10, 2006 (SUP4) (collectively, the Supplements), and your petition for stay of action received on July 24, 2007 (PSA).[1] The Petition and the Supplements request that the Agency require all applicants and holders of approved applications for fentanyl transdermal delivery systems (patches) to (1) conduct a study to support the safe use of an overlay with their patches, (2) include information in their labeling regarding the type of overlay(s) that may be used with their respective fentanyl patches, and (3) package their fentanyl patches with a tested and proven overlay system.[2] You also request that FDA publicly address the Petition before granting final approval of any abbreviated new drug applications for fentanyl patches. The PSA requests that FDA stay approval of all applications for fentanyl patches until FDA reaches a decision on Mylan's petition requiring that all such applicants conduct a study to support the safe use of an overlay with their respective patches. The PSA requests that in the alternative, FDA stay approval of all pending applications for fentanyl patches until FDA has concluded the review of Ortho-McNeil's supplemental new drug application (NDA) for labeling information on the use of an overlay system in connection with their fentanyl patch. We have

[1] In addition, you sent Dr. Robert Temple, FDA, a letter dated November 20, 2006, requesting a meeting regarding the use of overlays with fentanyl patches. On March 22, 2007, Mylan and Johnson & Johnson/Ortho-McNeil met with FDA staff. Minutes of this meeting have been placed in this docket.

The Petition, Supplements, and PSA were originally assigned docket numbers 2006P-0123/CP1 and SUP1, SUP2, SUP3, SUP4, and PSA. The number was changed to FDA-2006-P-0329 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] We have also received citizen petitions raising issues related to (1) the safety of reservoir and matrix patches (Docket No. FDA-2005-P-0428, formerly 2005P-0441) and (2) a voluntary risk management plan for both the innovator and generic fentanyl patches (Docket No. FDA-2006-P-0016, formerly 2006P-0290/CP1). This response does not address these citizen petitions, and responses to those petitions will be issued separately. We also received a petition for stay of action raising issues related to fentanyl patches with a substantially higher drug load than those currently on the market (Docket No. FDA-2009-P-0415). We issued a response to that petition on February 22, 2010.

FDA-2006-P-0329

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carefully considered the Petition, its Supplements, the PSA, and the comments filed in the docket.[3] For the reasons stated below, the Petition and its Supplements are granted in part and denied in part, and the PSA is denied.

I. BACKGROUND

A. Fentanyl Patches

Fentanyl is a potent opioid analgesic classified in Schedule II under the Controlled Substances Act.[4] The fentanyl patch is indicated for use in the treatment of chronic pain in patients who require continuous opioid analgesia and is designed to provide continuous delivery of fentanyl through the skin over a period of time.

Ortho McNeil Jannsen Pharmaceuticals Inc. is the sponsor of Duragesic, a fentanyl patch (NDA 019813) approved by FDA in 1990.[5] Duragesic is available in 12.5, 25, 50, 75, and 100 micrograms (mcg)/hour (hr) strengths. The approved labeling states that Duragesic is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time, and
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

The labeling states that Duragesic should only be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to Duragesic 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid. The labeling provides further information regarding usage of Duragesic (see Indications and Usage section of the labeling).

At the time the Petition was submitted, the approved NDA for Duragesic was for a reservoir patch. The design of the Duragesic reservoir patch consisted of four functional layers and a protective liner. The functional layers consisted of:

(1) a backing layer of polyester film;
(2) a drug reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose;
(3) an ethylene-vinyl acetate copolymer membrane that is claimed to control the rate of fentanyl delivery to the skin surface (rate-controlling membrane); and

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[3] One of the commenters is Pri-Cara, Unit of Ortho-McNeil, which markets Duragesic. Pri-Cara submitted comments dated June 29, 2006, supporting the Petition's request that FDA require that applicants for fentanyl patches conduct a study to determine the effect of an overlay with their respective patches.

[4] 21 U.S.C. 812.

[5] Duragesic is manufactured by Alza Corporation and distributed by Janssen Pharmaceutica Products, L.P., both subsidiaries of Johnson & Johnson. As noted above, Pri-Cara markets Duragesic.

(4) a silicone adhesive containing fentanyl.

On July 31, 2009, FDA approved a supplemental NDA for a Duragesic matrix design patch. In the Duragesic matrix patch, the drug is combined with the patch adhesive.[6]

Currently, there are six approved generic fentanyl patches.[7] Four of the generic fentanyl patches have a matrix design (Mylan Technologies Inc. (abbreviated new drug application (ANDA) 076258), Lavipharm Laboratories Inc. (ANDA 077051), Teva Pharmaceuticals (ANDA 077449), and Noven Pharmaceuticals Inc. (ANDA 077775) (ownership of ANDA 077775 was transferred from Hisamitsu Pharmaceutical Co. Inc. to Noven Pharmaceuticals Inc.)). Two of the generic fentanyl patches have a reservoir design (Actavis South Atlantic LLC (ANDA 077062) and Watson Laboratories, Inc. (ANDA 076709)). All of these patches are available in 25, 50, 75, and 100 mcg/hr strengths. The matrix patch from Mylan Technologies Inc. is also available in the 12.5 mcg/hr strength. Duragesic is the reference listed drug (RLD) for all of these generic fentanyl patches.

B. Update to Labeling to Include Information on Use of Overlays

On February 7, 2008, FDA approved the supplemental NDA (S-033) submitted by Johnson & Johnson for Duragesic. The supplemental NDA includes changes to the package insert, carton, information for use, and medication guide, including the addition of information in the labeling regarding the use of an overlay with Duragesic. Specifically, the Duragesic labeling approved on February 7, 2008, included a statement that the kinetics of fentanyl in normal subjects following application of a 100 mcg/hr Duragesic patch were bioequivalent with or without a Bioclusive overlay and that if problems with adhesion persist, patients may overlay the patch with a transparent adhesive film dressing (e.g., Bioclusive or Tegaderm).[8]

As stated, on July 31, 2009, FDA approved a supplemental NDA for a Duragesic matrix design patch. The Duragesic labeling approved on July 31, 2009, continues to include information in the "Dosage and Administration" and "Information for Patients" sections stating that if problems with adhesion persist, patients may overlay the patch with a transparent adhesive film dressing.

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[6] See description of the Duragesic matrix patch on the Duragesic Web site, available at http://www.duragesic.com/duragesic/duragesic_new_look_info.html.

[7] In addition, Sandoz markets an authorized generic version of Duragesic based on the Duragesic NDA.

[8] See "Pharmacokinetics," "Dosage and Administration" and "Information for Patients" sections of Duragesic labeling approved on February 7, 2008.

C. Relevant Law on Generic Drugs and Their Labeling

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) permits a duplicate version of a previously approved innovator drug to be approved without submission of a full NDA. Under section 505(j)(4) of the Act, an ANDA must refer to a previously approved drug product (defined below) and rely on the Agency's prior finding of safety and effectiveness for that drug product. "[T]he listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" is called the reference listed drug (RLD).[9]

The Act generally requires an ANDA applicant to provide, among other things, information to show that the generic drug is bioequivalent[10] to the RLD (see 21 U.S.C. 355(j)(2)(A)(iv)). In addition, under section 505(j)(2)(A)(i) of the Act, a generic drug applicant must include in an ANDA information showing that the proposed conditions of use for the drug have previously been approved for a drug that is listed by FDA as approved for safety and efficacy (the listed drug) (see also 21 CFR 314.94(a)(4)). An ANDA also must contain information showing that the proposed labeling is the same as the labeling approved for the RLD, except for differences related to an approved suitability petition or because the proposed drug product and the reference listed drug are produced by different manufacturers (section 505(j)(2)(A)(v) of the Act; § 314.94(a)(8)). Under 505(j)(4) of the Act, FDA shall approve an ANDA unless it finds that one of the conditions described in the Act exists (21 U.S.C. 355(j)(4)).

After an ANDA has been approved, the ANDA must continue to have the same labeling as the listed drug. As described in the Agency's guidance for industry, *Revising ANDA Labeling Following Revision of the RLD Labeling* (ANDA Labeling Guidance), approved changes in the listed drug's labeling generally necessitate changes in the labeling of the ANDA referring to the listed drug (ANDA Labeling Guidance at 4). ANDA sponsors are responsible for ensuring that the labeling contained in its application is the same as the currently approved labeling of the listed drug (ANDA Labeling Guidance at 5).

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[9] 21 CFR 314.3. RLDs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, 26th Ed., 2006 (commonly referred to as the Orange Book).

[10] Section 505(j)(8)(B) of the Act provides that a generic drug shall be considered to be bioequivalent to the listed drug if:

> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

II. DISCUSSION

A. Studies Regarding the Use of an Overlay with Fentanyl Patches and Labeling Information Regarding the Type of Overlay(s) that May Be Used with Fentanyl Patches

In the Petition, you assert that the innovator of Duragesic has recognized "lack of adhesion" as a problem with fentanyl patches and has offered and is continuing to offer overlays to patients upon request to help the patch adhere to the skin (Petition at 2). You also contend that patients are using various methods such as athletic tape and waterproof band aids to help fentanyl patches adhere to the skin (Petition at 4). In particular, you assert that the application and use of an overlay on a reservoir system such as Duragesic may increase the possibility of fentanyl leakage by causing a stress on the seal of the reservoir (Petition at 5). You also assert that the use of an overlay may cause a patient to receive variable amounts of fentanyl (Petition at 5). You assert that without any studies to support the safe use of a specific overlay, patients using an untested overlay with a fentanyl patch may be more prone to risks associated with variable performance of fentanyl patches (Petition at 5). As a result, you request that FDA require all applicants and holders of approved applications for fentanyl patches to conduct a study to support the safe and appropriate use of an overlay with their respective patch (Petition at 1, 5). We discuss your request below, first as it relates to the innovator and second as it relates to generic sponsors and applicants for fentanyl patches.

1. Overlay studies by the innovator of Duragesic and labeling information regarding the types of overlay(s) that may be used

You request that applicants and holders of approved applications for fentanyl patches be required to conduct a study to support the safe and appropriate use of an overlay with their respective patch. Prior to our February 7, 2008, approval of the supplemental NDA (S-033) for Duragesic, we requested that the sponsor of Duragesic conduct pharmacokinetic characterization studies regarding the effect of an overlay on Duragesic. We therefore grant your request to the extent that it asks FDA to require that the innovator of Duragesic conduct these studies in connection with the labeling change that we describe in further detail below. As also discussed below, however, we disagree with your assertion that an overlay could increase the possibility of leakage of the fentanyl reservoir patch.

FDA has become aware that with most pharmaceutical patches, a proportion of patients will have difficulty maintaining adequate adhesion, and this frequently results in taping of the edges of the patch or the use of an overlay to keep the patch in place. Lack of adhesion has been a well-reported and prevalent problem with both the Duragesic and Mylan fentanyl patches. The lack of adhesion of a fentanyl patch raises the following safety concerns:

- Too little medication may be delivered, causing inadequate pain relief, and possibly leading to withdrawal symptoms;

- Too much medication may be delivered because of the application of multiple patches or reapplication of a new patch prior to 72 hours, leading to toxicity and adverse events; or
- A non-patient may be exposed to the patch if the patch falls off and sticks to another person.

Because there have been numerous reports in FDA's Adverse Events Reporting System (AERS) of patients needing to use an overlay with the Duragesic fentanyl patch, FDA requested that the sponsor of Duragesic perform a pharmacokinetic characterization study with and without an overlay to determine whether the use of an overlay affects the amount of fentanyl absorbed by the patient. The reasons for our request were based on our determination that occlusive overlays may raise safety concerns. We believe that it is possible that occlusive overlays may result in increased skin hydration, increase in the skin temperature or pH, changes in epidermal lipids, or other effects that may compromise the barrier properties of the stratum corneum. The use of the adhesive overlay theoretically could increase the amount of drug absorbed by the patient. For a potent opioid product such as fentanyl, we determined that pharmacokinetic studies using an overlay could assist us in better understanding whether the overlay could make a difference in opioid absorption from transdermal products.

The sponsor of Duragesic submitted the results of its study comparing the pharmacokinetics of Duragesic 100 mcg/hr with and without an overlay in healthy subjects. The study found that a polyurethane semi-occlusive dressing overlay applied over Duragesic did not affect the pharmacokinetic profile for Duragesic. In addition, no deaths or serious adverse events were reported to FDA in connection with this study for which the use of an overlay was cited as the cause of the adverse event. The systemic and topical safety profiles were similar for both treatments, and no new safety issues were identified. As described in section I.B of this response, the labeling for Duragesic was revised to incorporate the results of the overlay study.

We disagree with your assertion that the adhesive overlay could increase the possibility of leakage of the fentanyl reservoir patch by causing stress on the seal (Petition at 5). You are basing your request on speculation that the use of an overlay may cause leakage of the patch, and you have not provided any evidence to support your assertion. The manufacturing controls and specifications provide for adequate seal strength of the fentanyl reservoir patch such that these patches could withstand the usual stress encountered in normal day-to-day activities including the force exerted by the weight of an average person on the patch. Use of an overlay is not expected to result in stress sufficient to rupture the patch. We therefore do not believe that you have demonstrated a need for studies regarding the possibility of leakage of a fentanyl patch because of the use of an overlay.[11]

You request that we require all NDA and ANDA holders and applicants of fentanyl patches to include information in their labeling regarding the type of overlay(s) that may be used with their

[11] As described in section I.A of this response, since the time that the Petition was submitted, FDA has approved a supplemental NDA for Duragesic to change from a reservoir to a matrix design patch.

respective fentanyl patches. We grant your request. As described in section I.B, information regarding the use of an overlay was added to the Duragesic labeling. Because the study conducted using Duragesic and overlays showed no significant increase in the bioavailability associated with the use of an overlay, the product's labeling assures prescribers and patients that it is safe to incorporate the use of an overlay during treatment with the patch. We discuss overlay studies and the labeling of generic fentanyl products in the next section.

2. Overlay studies by ANDA sponsors and applicants and labeling information regarding the types of overlay(s) that may be used

You request that all applicants and holders of approved applications for fentanyl patches be required to conduct a study on the use of an overlay with respect to their respective patches (Petition at 1, 5). You also request that FDA require the labeling for all fentanyl patches to include appropriate information regarding the type of overlay(s) that may be used with the particular fentanyl patch (Petition at 5). You note that under the statutory requirements for ANDA labeling, the holders of approved ANDAs and ANDA applicants for generic fentanyl patches may not include information in their labeling about the use of overlays without the innovator first making the corresponding changes in its product's labeling (SUP4 at 2). You assert that requiring this overlay information in the labeling will ensure that the public has sufficient information to make an informed decision on the appropriate overlay to be used if a patch does not stick to the skin (SUP2 at 2). You also provided suggested labeling revisions in your supplement (SUP2 at Attachment B).

We grant in part and deny in part your request that ANDA applicants and holders of ANDAs for fentanyl patches conduct overlay studies and include information on the use of overlays in their labeling. As explained in the prior section, we determined that occlusive overlays may raise safety concerns. Because of the severity of any adverse events from fentanyl patches and the need for data regarding whether an overlay would affect the safety of the fentanyl patch, we believed that it was appropriate for ANDA applicants and holders of ANDAs for fentanyl patches, in addition to the NDA holder for fentanyl patches, to conduct overlay studies. After we requested that the sponsor of Duragesic conduct studies with and without the overlay for Duragesic, we began requiring that any applicants seeking approval of an ANDA for a fentanyl patch conduct an overlay study prior to approval of its ANDA. We also expected holders of any ANDAs for fentanyl patches approved prior to the change in Duragesic's labeling addressing the use of an overlay to conduct the overlay studies post-approval.

Since that time, the sponsor of Duragesic and multiple ANDA sponsors and applicants have conducted overlay studies and provided the data to FDA. We have reviewed the data and gained further knowledge regarding how the use of an overlay affects the pharmacokinetic profile of fentanyl patches. Based on our review, we have determined that the extent of the occlusive nature of the backing on the currently marketed fentanyl patches affects whether the use of an overlay would alter the pharmacokinetics of the fentanyl patch. We also have determined that the use of an overlay with fentanyl patches that have an occlusive backing does not raise safety concerns.

We therefore have determined that it is appropriate to no longer require that an overlay study be conducted by applicants of fentanyl patches that have an occlusive backing. We also are no longer requesting that sponsors of already approved fentanyl patches conduct overlay studies. Given the need to ensure that fentanyl does not leak from the back of the patch, we expect that all fentanyl patches will be sufficiently occlusive such that an overlay study would not be needed. However, when reviewing proposed fentanyl patches, we will assess the permeability of the backing of the patch, such as the moisture vapor transmission, to determine whether the patch is approvable and whether it raises any safety concerns such that an overlay study would be needed.

As mentioned, the labeling for Duragesic was updated to include information regarding the use of overlays. A generic drug's labeling is required to match the innovator drug's labeling subject to certain exceptions under the statutory and regulatory requirements described in section I.C of this response. Regardless of whether an overlay study is conducted, we expect Mylan and any other generic sponsors to implement the same labeling changes as Duragesic with respect to information regarding the use of an overlay, except for changes necessary because the products have different manufacturers.

B. Co-Packaging Fentanyl Patches with an Overlay

In your fourth supplement, you request that FDA require the sponsor of Duragesic to include in its product packaging one or more overlays that have been demonstrated through an appropriate bioequivalence trial not to alter the rate and extent of absorption of fentanyl or to increase skin irritation (SUP4 at 1). You assert that not every patient who experiences an adhesion problem would know to contact the maker of the product to obtain an overlay (SUP4 at 2). You assert that with a reservoir product like Duragesic prior to its reformulation, a patient who did not appreciate the risks of the drug product and did not know to contact the product's manufacturer to request an overlay could use an untested or inappropriate adhesive such as duct tape in an attempt to salvage an expensive, non-adhering patch (SUP4 at 2). You assert that in so doing, a patient could possibly rupture or tear a reservoir patch, creating a potentially life-threatening situation because of fentanyl leakage onto the skin (SUP4 at 2). You also assert that even if a patient knew to contact the manufacturer to obtain an overlay, it may take several days for the patient to receive it, and in the interim, the patient may have taken inappropriate and potentially dangerous measures to make a non-adhering patch stick (SUP4 at 2). You further request that the same requirements of including appropriate overlays in the product package be applied to holders of approved ANDAs and all pending ANDA applications prior to any further approvals being granted (SUP4 at 2).

We deny your request that we require the co-packaging of overlays with fentanyl patches. Your assertions are based on speculation of possible dangers or patient actions, and you have not provided evidence to demonstrate that co-packaging of overlays with fentanyl packages is necessary for safe use of the product.

We also believe that it is not necessary to co-package overlays with fentanyl patches because the Duragesic label clearly instructs patients to tape the sides of the patch with first aid tape if there is poor adhesion. Co-packaging of overlays with all fentanyl products also would not be appropriate because not all generic patches may require the use of overlays. In reviewing ANDAs for generic patch products, FDA requests comparative studies of adhesive performance of the generic patch and the RLD. The generic patch must perform at least as well as the RLD over the intended duration of patch wear to support approval. If a generic patch demonstrates better adhesion performance, it would not likely have a similar need for patch reinforcement in the form of overlays.

For the reasons described, we do not believe that requiring co-packaging of overlays with fentanyl patches is warranted.

C. Request That FDA Publicly Address the Petition Before Granting Final Approval of Any Abbreviated New Drug Applications for Fentanyl Patches

In your third supplement, you request that FDA publicly address the Petition before deciding to grant final approval of any abbreviated new drug applications for fentanyl patches (SUP3 at 2). We deny your request. As described in section I.B of this response, FDA shall approve an ANDA if the applicable requirements are satisfied (see 21 U.S.C. 355(j)(4)(F)). We are not required to publicly address a related petition prior to approving an ANDA that meets the applicable statutory and regulatory requirements for approval. You also have not provided any justification for our withholding approval of any ANDAs for fentanyl patches prior to addressing the Petition and its Supplements. We therefore did not believe that it was appropriate to withhold approval of any ANDAs for fentanyl patches until we publicly addressed the issues raised in the Petition and its Supplements. Because we are publicly addressing the Petition with this response, we also deny as moot your request with respect to the approval of any future ANDAs.

III. PETITION FOR STAY OF ACTION

In the PSA, you request that FDA stay approval of all applications for fentanyl patches until FDA reaches a decision on Mylan's petition requiring that all such applicants conduct a study to support the safe use of an overlay with their respective patches (PSA at 2). The PSA also requests that in the alternative, FDA stay approval of all pending fentanyl applications until FDA has concluded the review of Ortho-McNeil's labeling supplement for the use of an overlay system in connection with their fentanyl patch (PSA at 2). You assert that you will suffer irreparable harm if a stay is not granted, in that the integrity of the fentanyl patch will be severely compromised regardless of the sponsor marketing this drug product (PSA at 2). You also assert that Mylan would be disadvantaged if FDA approves fentanyl patches without requiring overlay studies and subsequently approves the innovator's labeling supplement, because the applicant would not have conducted the studies but would be permitted in the market with a product that is less safe and could potentially cause more confusion on which products and types of overlays can be used (Petition at 5). You also assert that your position is not frivolous, is being pursued in

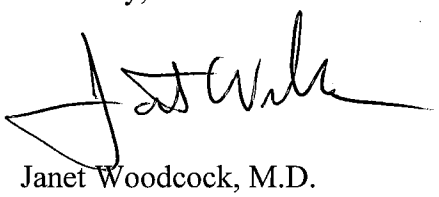
good faith, has demonstrated sound public grounds supporting its requests, and the stay is not outweighed by public health or other public interests (PSA at 2).

We have reached a decision on Mylan's petition, and our decision is described in this response. Therefore, your request that FDA stay approval of all applications for fentanyl patches until FDA reaches a decision on Mylan's petition is now moot. Your alternative request that FDA stay approval of all pending fentanyl applications until FDA has concluded the review of Ortho-McNeil's labeling supplement is also moot. As described in this response, Ortho-McNeil's supplemental NDA was approved on February 7, 2008, and therefore FDA has concluded its review of the supplement. Because the events on which you condition your PSA have occurred, we deny the PSA as moot.

IV. CONCLUSION

For the reasons stated above, the Petition and its Supplements are granted in part and denied in part. We requested that the sponsor of Duragesic conduct a study on the use of an overlay with their fentanyl patches, and the labeling has been revised to include information regarding the use of an overlay with the fentanyl patch. We deny your request that all holders of ANDAs and ANDA applicants conduct a study on the use of an overlay with their patches. We deny your request that we require all applicants to package their fentanyl patches with an overlay and deny your request that FDA publicly address the Petition and its Supplements before granting final approval of any abbreviated new drug applications for fentanyl patches. We also deny the PSA as moot.

Sincerely,



Janet Woodcock, M.D.
Director
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