DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021338/S-005

SUPPLEMENT APPROVAL

The Medicines Company
900 Saginaw Dr., Suite 200
Redwood City, CA 94063

Attention: Deborah Ware
Senior Director, Regulatory Affairs

Dear Ms. Ware:

Please refer to your Supplemental New Drug Application (sNDA) dated June 30, 2014, received June 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for IONSYS (fentanyl iontophoretic transdermal system.)

We acknowledge receipt of your amendments dated July 24, September 8, October 2, and 29, November 12, and December 12, and 17, 2014, and January 9, 23, 28, and 30, February 5, and 27, March 6, and 12, and April 21, 28, and 29, 2015.

This "Prior Approval" supplemental new drug application provides for conversion of the approved package insert to the Physicians Labeling Rule (PLR) format, a reformulation of the device into two separate components, and a proposed risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled, *SPL Standard for Content of Labeling Technical Qs and As,* available at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021338/S-005**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

However, we remind you of your previous PREA postmarketing requirement (PMR), specified in our May 22, 2006, original NDA approval letter:

1191-1 Deferred pediatric study under PREA for the treatment of short-term management of acute post-operative pain in patients requiring opioid analgesia during hospitalization in pediatric patients ages 6 to less than 17 years of age.

As noted in the deferral extension granted letter dated December 13, 2013, you will conduct this study according to the following schedule:

Final Report Submission: 03/2017

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2905-1 Continue to use microscopy techniques to monitor for corrosion during the stability studies. If any discoloration of the circuitry is observed, an analytical technique such as XPS or SEM should be used to characterize the discoloration. If corrosion is observed, evaluate the potential impact on device performance. Monitoring of corrosion must continue for a minimum of 3 years from the date of commercial launch of the product. Submit a Field Alert if corrosion is observed. If no corrosion is observed, this result can be submitted in the annual report.

The timetable you submitted on April 21, 2015, states that you will submit the results of this monitoring according to the following schedule:

Final Report Submission: 12/2018

Note that for PMR 2905-1, when you submit your final report, you may also submit a Prior Approval Supplement with supportive data to the NDA to request reduced monitoring, which will be reviewed by the Agency.

2905-2 Due to the complexity of the product and the continued concern for malfunction and safety of the system, provide quarterly reports of any device malfunctions, any adverse events or medication errors associated with or suspected to be associated with device malfunction, and any patient or provider complaints regarding device malfunction. After three years of submitting quarterly reports, submit a comprehensive discussion of the reports of any device malfunctions, any adverse events or medication errors associated with or suspected to be associated with device malfunction, and any patient or provider complaints regarding device malfunction, and provide an explanation of how you addressed those adverse events.

The timetable you submitted on April 21, 2015, states that you will conduct this reporting

according to the following schedule:

First quarterly report – Year 1: 10/2015
Second quarterly report – Year 1: 1/2016
Third quarterly report – Year 1: 4/2016
Fourth quarterly report – Year 1: 7/2016

First quarterly report – Year 2: 10/2016
Second quarterly report – Year 2: 1/2017
Third quarterly report – Year 2: 4/2017
Fourth quarterly report – Year 2: 7/2017

First quarterly report – Year 3: 10/2017
Second quarterly report – Year 3: 1/2018
Third quarterly report – Year 3: 4/2018
Final Report Submission – Year 3: 7/2018

Submit clinical protocols to your IND 041574 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of an approved drug outweigh the risks.

Since IONSYS was approved on May 22, 2006, based in part on data included in your supplemental NDA submission, including information regarding the nature and functioning of the new delivery device, we have become aware of the risk of respiratory depression resulting from accidental exposure to persons for whom it is not prescribed. Accidental exposure to a person for whom IONSYS is not prescribed may occur either in the hospital when a health care provider or another person interacts with a patient wearing an IONSYS device or if the device were not removed from the patient before he/she was discharged from the hospital. We consider this information to be "new safety information" as defined in section 505-1(b) of the FDCA.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for IONSYS to ensure the benefits of the drug outweigh the risk of respiratory depression resulting from accidental exposure to persons for whom it is not prescribed.

Pursuant to 505-1(f)(1), we have determined that elements necessary to assure safe use are necessary to mitigate the risk of respiratory depression resulting from accidental exposure to persons for whom IONSYS is not prescribed.

Your REMS includes the following elements to mitigate these risks:

- Health care settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain health care settings

Your proposed REMS, submitted on April 28, 2015, and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan must include, but is not limited to, the following:

The following metrics should be reported for every reporting period, unless specified otherwise, to assess the effectiveness of the IONSYS REMS program:

a) IONSYS REMS Program Implementation Metrics

1. Dates of IONSYS REMS program launch, to be completed for the first six month assessment only, should include the following:
    a. REMS website goes live
    b. REMS Call Center is operational
    c. Hospitals are able to complete the REMS certification process
    d. First notification of hospital certification is sent

b) IONSYS REMS Program Utilization Metrics (Provide data for each reporting period and cumulatively)

1. Hospital enrollment and education statistics
    a. Number of Hospitals enrolled stratified by:
        i. State
        ii. Method of enrollment (i.e., online or fax or mail or e-mailed)
    b. Number of incomplete enrollments, and the number of these that subsequently became enrolled
    c. Number of sent certification notification letters and returned mailings for each reporting period
    d. Number of Hospital Authorized Representatives who successfully completed the IONSYS REMS Knowledge Assessment for each reporting period and cumulatively
        i. Descriptive statistics (mean, median, and range) of the number of attempts associated with completion of IONSYS REMS Knowledge Assessment
        ii. Correct answer rates for each question in the IONSYS REMS Knowledge Assessment

e. Number of Hospitals de-certified for non-compliance with the IONSYS REMS Program requirements and reasons for decertification for each reporting period and cumulatively in tabular format

2. Compliance with the IONSYS REMS-required distribution statistics
   a. Number of wholesalers/distributors enrolled
   b. The number of orders received and shipped for IONSYS
   c. Number of certified hospitals that have received at least one shipment of Ionsys
   d. Number of orders shipped to non-certified or decertified hospital locations and corrective actions taken for each non-compliance instance

3. Compliance with the IONSYS REMS-required dispensing statistics
   a. Number of accidental exposures to IONSYS in the inpatient setting, stratified by the following:
      i. Healthcare providers
      ii. Patients for whom IONSYS is not prescribed
      iii. Pediatric non-patients
      iv. Other non-patients
   b. A root cause analysis for accidental exposures

c) Periodic Surveys of healthcare providers
A random sample of healthcare providers who prescribe, dispense, or administer IONSYS will be selected to assess their understanding regarding the key risk messages, appropriate use of IONSYS, and IONSYS REMS program requirements through periodic knowledge, attitude, and behavior (KAB) surveys. Survey results will be reported annually after the initial IONSYS REMS approval.

d) Non-compliance and other issues
1. Frequently asked questions and problems identified by the IONSYS REMS Call Center.
2. Description of any incidents of prescribing/dispensing from non-IONSYS REMS certified hospitals and any incidents of dispensing of IONSYS for outpatient use.
3. The number of inpatient prescriptions of IONSYS dispensed on the same day as discharge
4. Corrective actions for non-compliance with REMS requirements, if identified, as well as the outcomes of the corrective actions will be specified for the reporting period.

e) Adverse Events
1. Number and descriptions of post-marketing reports of the following adverse events received by the Sponsor during the reporting period, and cumulatively
   a. Reports of abuse, overdose, accidental exposure, respiratory depression, or other serious complications associated with IONSYS
   b. Any serious adverse events associated with a dispensed and unused IONSYS
   c. Any adverse events reported from a non-IONSYS REMS certified hospital
   d. Any medication errors associated with IONSYS

f) Audit Results for each reporting period and cumulatively, including but not limited to:
1. Number of audited hospitals.

2. Summarize all instances of non-compliance and resulting improvement plans. Group these observations into critical, major, or minor. Provide a definition for each category (critical, major, minor)
3. Identify the REMS Improvement Plans (RIPs) from the current reporting period and from previous reporting periods that were implemented during the current reporting period
4. For any Continuous Improvement Plans (CIPs) not completely implemented, explain why they are not complete and provide an expected completion date

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If*

you are not proposing a REMS modification, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021338 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021338 REMS ASSESSMENT
NEW SUPPLEMENT FOR NDA 021338
CHANGES BEING EFFECTED IN 30 DAYS
< other supplement identification >
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021338
PRIOR APPROVAL SUPPLEMENT
< other supplement identification >
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021338
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021338 REMS ASSESSMENT
< other supplement identification >
PROPOSED REMS MODIFICATION (if included)

If you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 021338

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

ADDITIONAL COMMENTS

You revised your labeling to include the MR UNSAFE symbol in the Prescribing Information and you wish to retain the previously approved labeling on the product including the text "WARNING: REMOVE BEFORE MRI." We remind you that for future production of the product, you have agreed to add the MR Unsafe icon symbol to the product together with the current text "WARNING: REMOVE BEFORE MRI."

Section 7.2.1 of IEC 60601-1 (3rd Edition) requires certain symbols and explanations to be permanently labeled on the housing. We remind you that for future production of the product, you have agreed to add the Applied Parts symbol to the product together with the explanatory text.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Sr. Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS
REMS Materials

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON
04/30/2015

SHARON H HERTZ
04/30/2015