DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403 **TENTATIVE APPROVAL**

Hospira, Inc.
275 North Fields Dr.
Dept. 0389, Bldg H2-2
Lake Forest, IL 60045

Attention: Jennifer Hefele, Ph.D.
Manager, Regulatory Affairs

Dear Dr. Hefele:

Please refer to your New Drug Application (NDA) dated April 29, 2010, received April 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Injection, 1, 2, and 4 mg/mL.

We acknowledge receipt of your amendments dated June 25, August 27, September 20, October 8, 11 and 28, November 22 and 23, and December 13 and 23, 2010 and January 5 and 27, and February 3, 16, 22, 24 and 25, 2011.

This NDA provides for the use of Hydromorphone Hydrochloride Injection for the management of pain in patients where an opioid analgesic is appropriate.

We have completed our review of this application, as amended, and it is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the package insert, carton and immediate container labels**)** and submitted labeling (text for the package insert submitted February 24, 2011, carton and immediate container labels submitted February 25, 2011). This determination is based upon information available to the Agency at this time, i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product. This determination is subject to change on the basis of any new information that may come to our attention.

Your application contains certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications").

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV

certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patent 6,589,960 in the United States District Court for the Northern District of Illinois. Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
   b. the date the court decides that the patent is invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,
   c. the listed patent has expired, and

2. we are assured there is no new information that would affect whether final approval should be granted.

Two or six months prior to the expiration of the patent, as appropriate, submit an amendment to this application identifying changes, if any, in the conditions under which your product was tentatively approved. Any changes to in the conditions outlined in this NDA require our review before final approval and the goal date for our review will be set accordingly. Your amendment should include updated labeling, chemistry, manufacturing and controls data, and a safety update.

Before we issue a final approval letter, this NDA is not deemed approved. If you believe that there are grounds for issuing the final approval letter before the expiration of the patent, you should amend your application accordingly.

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing

studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

There is an impurity [redacted] (b) (4) that has not been qualified for safety at the proposed levels. There is a risk that this impurty could be associated with genotoxicity or adverse events, although we note that this drug [redacted] (b) (4) has been approved for use in marketed products.

Based on the above, FDA has determined that if NDA 200403 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risk of genotoxicity or histopathological changes associated with exposure to the drug [redacted] (b) (4) at the proposed levels.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 200403 is approved, you will be required to conduct the following:

1. Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug [redacted] (b) (4) tested up to the limit dose for the assay.

2. Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug [redacted] (b) (4) tested up to the limit dose for the assay.

3. Conduct a 3-month repeat-dose toxicology study in a single species with the isolated drug [redacted] (b) (4)

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Division Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

SHARON H HERTZ
02/25/2011