DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 202144

ANDA APPROVAL

Actavis Laboratories FL, Inc.
2945 West Corporate Lakes Blvd.
Suite B
Weston, FL 33331

Attention: Janet Vaughn
Director Regulatory Affairs

Dear Ms. Vaughn:

This is in reference to your Abbreviated New Drug Application (ANDA) received on August 2, 2010, and submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Hydromorphone Hydrochloride Extended-release Tablets, 8 mg, 12 mg, and 16 mg.[1]

Reference is also made to your amendments dated September 2 and December 14, 2010; April 6, September 19, October 25, and November 7, 2011; January 27, February 7, March 6 (2 submissions), April 6, June 14, June 18, July 9, July 23, July 25, September 10, October 12, October 17, and November 1, 2012; February 8, April 2, and April 26, 2013; and April 22, April 30, and May 2, 2014.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Hydromorphone Hydrochloride Extended-release Tablets, 8 mg, 12 mg, and 16 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Exalgo Extended-release Tablets, 8 mg, 12 mg, and16 mg of Mallinckrodt Inc.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

Apparatus:	USP Apparatus II (Paddle)
Speed:	50 rpm
Medium:	0.05M Phosphate Buffer, pH 6.8
Volume:	900 mL
Temperature:	37°C ± 0.5°C

[1] ANDA 202144 received on August 2, 2010, was for the 16 mg strength only. An amendment for the 8 mg and 12 mg strengths was received on September 2, 2010.

Specifications:

2 hr:	(b) (4)
4 hr:	
8 hr:	
16 hr:	
30 hr:	

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement – Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Exalgo Extended-release Tablets, 8 mg, 12 mg, and 16 mg, of Mallinckrodt, Inc., is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patents No. 5,702,725 (the '725 patent) and 5,914,131 (the '131 patent), are scheduled to expire on July 7, 2014.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '725 and '131 patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Hydromorphone Hydrochloride Extended-release Tablets, 8 mg, 12 mg, and 16 mg, under this ANDA. You notified the agency that Watson Laboratories, Inc.-Florida (Watson) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '725 and '131 patents was brought against Watson within the statutory 45-day period in the United States District Court for the District of New Jersey [Mallinckrodt Inc., v. Watson Laboratories Inc.-Florida v. Alza Corporation and Mallinckrodt Inc., Civil Action No. 10-06424-FSH-PS]. You have also notified the agency that the litigation was dismissed.

With respect to 180-day generic drug exclusivity, we note that Watson was the first ANDA applicant for Hydromorphone Hydrochloride Extended-release Tablets, 8 mg, 12 mg, and 16 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Watson may be eligible for 180 days of generic drug exclusivity for Hydromorphone Hydrochloride Extended-release Tablets, 8 mg, 12 mg, and 16 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The agency notes that Watson failed to obtain tentative approval of this ANDA within 40 months[2] after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) (forfeiture of exclusivity for failure to obtain tentative approval). The agency is not, however, making a formal determination at this time of Watson's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after Watson

[2] For applications submitted between January 9, 2010, and July 9, 2012, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-114) extends the 30-month period to 40 months.

begins commercial marketing of Hydromorphone Hydrochloride Extended-release Tablets, 8 mg, 12 mg, and 16 mg, or (b) at any time prior to the expiration of the last listed patent if Watson has not begun commercial marketing. Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In accordance with section 505-1 of the FDCA, an ANDA is required to have a REMS if the applicable listed drug has an approved REMS.

Section 505-1 of the Act 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 the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated April 19, 2011. In that letter, you were also notified that in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for applicants of Extended-release and Long-Acting (ER/LA) opioid analgesics.

Your proposed REMS, submitted October 25, 2011 and amended on June 14, June 18 and October 17, 2012; and April 2, 2014, and appended to this letter, is approved.

The REMS consists of a Medication Guide and elements to assure safe use.

This REMS will use a single, shared system for the elements to assure safe use and the REMS assessments. This single, shared system is known as the ER/LA Opioid Analgesic REMS. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C), FDA can require the submission of a REMS assessment if FDA determines that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits outweigh the risks of the drug or to minimize burden on the healthcare system of complying with the REMS.

We remind you that section 505-1(f)(8) of the Act 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 the submission containing a proposed modification of the REMS or any REMS assessments with the following wording in bold capital letters at the top of the first page of the submission:

ANDA 202144
REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 202144
PROPOSED REMS MODIFICATION

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. You should advise the Office of Generic Drugs of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA)(Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). 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" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachments: Package Insert
REMS

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

/s/

ROBERT L WEST

05/12/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.