## Inspections, Compliance, Enforcement, and Criminal Investigations

# Acorda Therapeutics Inc. 5/10/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New York District
158-15 Liberty Avenue
Jamaica, NY 11433

May 10, 2012

**WARNING LETTER NYK-2012-18**

**VIA UNITED PARCEL SERVICE**

Ron Cohen, M.D., CEO
Acorda Therapeutics Inc.
15 Skyline Drive
Hawthorne, New York 10532-2152

Dear Dr. Cohen:

Between August 15, 2011 and September 9, 2011, the U.S. Food and Drug Administration (FDA) inspected your firm, Acorda Therapeutics Inc., located at 15 Skyline Drive, Hawthorne, New York, and identified significant violations of Section 505(k) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 355(k)] and Title 21, Code of Federal Regulations (21 CFR) § 314.80.

Section 505(k)(1) of the Act [21 U.S.C. § 355(k)(1)] and 21 CFR §§ 314.80 and 314.81 require an applicant to establish and maintain records, and to report data relating to clinical experience, along with other data or information, for drugs with an approved application is in effect. Failure to comply with Section 505(k) is a prohibited act under Section 301(e) of the Act [21 U.S.C. § 331(e)].

We acknowledge receipt of your written response dated October 3, 2011, to Form FDA-483 issued to your firm on September 9, 2011, but note that your response was received more than 15 working days from the close of the inspection. Thus, while we have reviewed the response, we have not included a discussion of the response in this letter, as per the Commissioner's Enforcement Initiative announced August 11, 2009.

The first postmarketing adverse drug experience (ADE) reporting compliance inspection of Acorda Therapeutics was conducted in 2006. Observations from the 2006 inspection included late submission of 15-day Alert reports, failure to develop written procedures, and failure to submit follow-up reports. A second postmarketing ADE reporting compliance inspection of Acorda Therapeutics was conducted in 2009. Observations from the 2009 inspection included late submission of Field Alert Reports and the repeat findings of late submission of 15-day Alert reports and failure to develop written procedures. Additionally, during the 2009 inspection, the FDA

Investigator noted that your firm did not complete corrective actions until 2007, even though your response to FDA, dated January 19, 2006, stated that all corrections had been made.

Specific violations observed during the August 15, 2011 through September 9, 2011, inspection include but are not limited to the following:

**1. Failure to submit all adverse drug experiences (ADEs) that are both serious and unexpected to FDA within 15 calendar days of initial receipt of the information as required by 21 CFR 314.80(c)(1)(i).**

From January 22, 2010 through August 15, 2011, you submitted approximately **(b)(4)** late ADE reports to the Agency. These **(b)(4)** reports contained both serious and unexpected adverse drug experiences, including but not limited to, deaths, irregular heartbeats, arrhythmia, acute fulminant hepatitis, hypersensitivity, and memory impairment that should have been submitted to the New Drug Application (NDA) within 15 days of initial receipt of the information. Among the approximately **(b)(4)** reports that were submitted late, **(b)(4)** reports were submitted more than 10 days late, including five reports that were submitted more than 100 days late. For example, report **(b)(4)**, which described a patient who expired, was due to the Agency on August 28, 2010, but not received until January 10, 2011, approximately 136 days late. Please note, these are repeat observations from the January 5-19, 2006 and February 18-26, 2009 inspections at your firm.

As part of your firm's corrective action plan for late reporting, in October 2010, your firm voluntarily terminated its relationship with the contractor processing individual case safety reports (ICSRs) for Acorda and entered into an agreement with a different contractor for adverse event report processing. However, of the **(b)(4)** late reports noted above, **(b)(4)** occurred after you implemented your corrective action plan. Additionally, you promised the Agency in a letter dated October 7, 2010, to conduct training and auditing of your specialty pharmacy distributors. As of September 9, 2011, there was no documentation that training was provided and all specialty pharmacies had not been audited.

As the holder of approved applications, Acorda has the obligation to report serious and unexpected adverse drug experiences to FDA within 15 calendar days of initial receipt of the information, as required by 21 CFR 314.80(c)(1)(i). A root cause analysis should be conducted to determine all causes for late reporting at your firm, and appropriate corrective actions taken. If Acorda, as the application holder, elects to out-source drug safety, Acorda retains the responsibility to ensure that it is done in a manner consistent with FDA regulations.

**2. Failure to develop adequate written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences (ADEs) from all sources as required by 21 CFR 314.80(b).**

Your firm does not have adequate written procedures to ensure that adverse drug experiences are detected, correctly identified, assessed, and reported to FDA in accordance with postmarketing regulations. As explained further below, the lack of adequate procedures appears to have contributed to your failure to timely report to FDA adverse event information.

Up to the time of the most recent inspection, your firm also failed to establish standard operating procedures (SOPs) to ensure that (1) all ADE information obtained from all sources is promptly conveyed to the appropriate Acorda personnel and reviewed; (2) all ADEs are evaluated against the U.S. package insert for seriousness and expectedness; (3) all ADEs are reported accurately from source documentation to the FDA Form 3500A, and (4) all ADEs that are the subject of 15-day Alert reports are promptly investigated and all attempts to obtain additional information about the adverse experiences are recorded, as required by 21 CFR 314.80(c)(1)(ii).

As an example of your failure to develop adequate written procedures for surveillance, receipt,

evaluation, and reporting of postmarketing adverse drug experiences, it was noted during the most recent inspection that **(b)(4)** adverse events associated with patients taking Ampyra were not reported by one of your specialty pharmacies to you or to FDA. Your firm failed to conduct an investigation and implement adequate written procedures to correct this problem and prevent recurrence. Subsequent to this failure, another specialty pharmacy failed to report **(b)(4)** adverse events to you or to FDA.

Please note, this is a repeat observation from the January 19, 2006 FDA inspection at which time Form FDA 483 "Inspectional Observations" was issued to your firm for failure to have written procedures for reporting postmarketing adverse drug experiences for your products. Acorda Drug Safety staff should have SOPs, work instructions, database access, and training sufficient to ensure adequate surveillance, receipt, evaluation, follow-up, and reporting of adverse event information for all of the firm's products.

**3. Failure to maintain records of all adverse drug experiences known to you, including raw data and any correspondence relating to adverse drug experiences, for a period of 10 years as required by 21 CFR 314.80(i).**

Your firm failed to maintain source documents as required by 21 CFR 314.80(i). During this inspection, your firm did not have source documents for approximately **(b)(4)** adverse event reports that were transferred from your first pharmacovigilance contractor to your second pharmacovigilance contractor for processing. This became an issue when the Investigator requested documentation as to why cases that had initially been reported as adverse events were later downgraded to "non-cases." In response, management repeatedly stated that source documents were not available. Acorda's Director of Drug Safety, whose responsibility includes reviewing cases, could not find the source documentation for some cases. Examples of cases for which source documents could not be found are **(b)(4)** and **(b)(4)**. Both are reports of seizures. Another example is report **(b)(4)**, which contained instructions to amend the verbatim from "*hospitalized for UTI"* to just "*UTI*" without rationale or justification for downgrading this report from serious (due to the event resulting in hospitalization) to non-serious.

**4. Failure to report each adverse drug experience not reported under 21 CFR 314.80 (c)(1)(i) at quarterly intervals as required by 21 CFR 314.80(c)(2)(i).**

There were approximately **(b)(4)** complaint reports for a lack of efficacy for Ampyra between January 22, 2010 and January 22, 2011. However, not all reports were reported as adverse events or included in Periodic Adverse Drug Experience Reports. Some of the following terms were used in the complaint reports: no drug effect, no change, no improvement, decrease in drug effect, and conditions worsening.

We note the Ampyra Annual Product Review for 2010 states that Ampyra has been demonstrated to be effective in approximately **(b)(4)**% of the population; therefore, a lack of product effectiveness is expected. However, there has been no investigation of these events and they have not all been reported in Periodic Adverse Drug Experience Reports as required by 21 CFR 314.80(c)(2)(i).

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. It is your responsibility to ensure compliance with all requirements of federal law and FDA regulations. You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action, including injunction, without further notice. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when awarding contracts. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step taken to

prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. You may wish to include dates for when each corrective action will be fully implemented.

Your written response should be sent to Dean R. Rugnetta, Compliance Officer, U.S. Food and Drug Administration, 300 Pearl Street, Suite 100, Buffalo, NY 14202. If you have any questions about this letter, please contact Compliance Officer Dean Rugnetta at (716) 541-0324 or via e-mail at Dean.Rugnetta@fda.hhs.gov.

Sincerely,
/S/
Ronald M. Pace
District Director
New York District

Page Last Updated: 05/16/2012
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.