Jazz Pharmaceuticals Issued Warning Letter Over Reporting

SILVER SPRING, Md., Oct. 18, 2011 - The FDA today posted on its website a warning letter sent to Jazz Pharmaceuticals over, among other issues, recording keeping and post marketing reporting. The letter is below.

Public Health Service
Food and Drug Administration
San Francisco District Pacific Region
1431 Harbor Bay Parkway
Alameda, CA 94502-7070
Telephone: 510-337-6700
FAX: 510-337-6701

October 11, 2011

Bruce C. Cozadd, Chairman and Chief Executive Officer
Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304

REF: FEI 3005615655

Dear Mr. Cozadd:

During our April 27, 2011 through May 6, 2011 inspection of your firm, Jazz Pharmaceuticals, Inc., located at 3180 Porter Drive, Palo Alto, California, investigator(s) from the Food and Drug Administration (FDA) 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 C.F.R.) § 314.80.

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

We reviewed your firm's response to the FDA inspectional observations, dated May 20, 2011, and note that it lacks sufficient

corrective actions, as detailed below.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Failure to develop adequate written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA [21 C.F.R § 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 in the possession of , the specialty pharmacy under contract with you as the sole distributor and dispenser of Xyrem, as required by the Risk MAP under which Xyrem was approved.[1] For example, while your contract with refers to SOPs for adverse event reporting, and specifies that no SOPs may be created or modified without Jazz' approval, no such adverse event reporting SOPs were provided during the inspection. You further indicated that prior to the discovery of the unreported deaths in April 2011, you had no procedures for monitoring 's compliance with the terms of your contract as relevant to adverse event reporting.

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

Your response describes the implementation of certain corrective actions, including establishing SOPs and re-training your staff on established ADE related procedures. Your response, however, is inadequate because your firm did not provide an evaluation of the impact of your new SOPs or provide the details for re-training your staff (i.e., an assessment of training effectiveness) and whether there is a need to re-train staff at the call center and pharmacy).

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For example, your firm failed to submit seventy-four (74) serious unexpected ADE reports within 15 calendar days of initial receipt between the time period of January 2003 to December 2010. The following are examples of the serious unexpected ADEs that were not submitted to FDA:

1
JPI-P-014767
Xyrem
Serious outcome: Death/unexpected
10/08/2007

2
JPI-P-014773
Xyrem
Serious outcome: Death/unexpected

03/17/2004

3
JPI-P-014774
Xyrem
Serious outcome: Death/unexpected
05/06/2005

4
JPI-P-014776
Xyrem
Serious outcome: Death/unexpected
12/03/2003

5
JPI-P-014778
Xyrem
Serious outcome: Death/unexpected
10/27/2006

6
JPI-P-014787
Xyrem
Serious outcome: Death/unexpected
11/30/2009

7
JPI-P-014789
Xyrem
Serious outcome: Death/unexpected
01/17/2007

8
JPI-P-014793
Xyrem
Serious outcome: Death/unexpected
11/08/2010

9
JPI-P-014813
Xyrem
Serious outcome: Death/unexpected
01/21/2008

10
JPI-P-014839
Xyrem
Serious outcome: Death/unexpected
12/01/2010

FDA acknowledges your subsequent submission of the completed 74 FDA Forms 3500A on May 5, 2011, and your May 20, 2011 response.

During the course of the inspection, Ms. Wissel, your Senior Vice President and Chief Regulatory Officer, acknowledged the dates above as being the dates of receipt by Jazz. In your May 20, 2011 response, however, your firm states that you did not receive or have knowledge of the ADEs until April 21, 2011, because prior to that date, these reports were received by and in the possession of , the specialty pharmacy that is the exclusive distributor of Xyrem, under contract, to fulfill your obligations under the Xyrem REMS. You therefore now appear to dispute that you were responsible for reporting these events until 15 business days after April 21, 2011. We disagree with this position, given the exclusive and contractually specified role of in performing tasks required for meeting your legal obligations under the Xyrem REMS. For example, under your contract with , with regard to the "Xyrem Success Program," is responsible for "Adverse Event Reporting: Collecting and reporting of all adverse events per standard operating procedures." That contract further specifies that must provide "Reporting as required by federal and state laws, including the Xyrem REMS", and elaborates that must provide data/reports on Adverse Events as follows: "Reporting form collecting adverse event provided to Jazz Pharmaceutical's Medical Information; reports also submitted to Jazz Pharmaceuticals' Quality Assurance if associated Product Adverse Events Quality Complaint (PQC)."[2] Under these circumstances, your firm is responsible for the adverse drug experience information received by , and the ADEs above were not reported within the 15 calendar day requirement.

In addition, your response describes the implementation of certain corrective actions, including auditing and the call center, and reconciling your firm's safety databases with and the call center regarding all ADEs. Your response, however, fails to specify details on the search criteria and method for reconciling the safety databases. Your response also did not state a specific timeframe for completion of corrective actions. The proposed corrective actions did not consider the root cause of the deviation.

Your firm received an FDA Form 483 on September 27, 2007, for similar postmarketing adverse drug experience violations. However, your corrective actions for that observation, including optimizing the receipt, work flow, communication, and submission processes for ADE reporting, were not sufficient to prevent subsequent reporting violations, including several of the examples given in the table above, nor to make you aware of the newly-discovered adverse events reports received by prior to our 2007 inspection. As discussed above, sponsors of new drug applications must establish procedures that will assure that adverse drug experiences looked for, received, and promptly recorded and evaluated to determine whether or not 15-day Alert reports should be submitted to FDA.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, injunction. FDA may re-inspect to verify corrective actions have been completed.

Neither the above list of violations nor the Form FDA 483 "Inspectional Observations" presented to you at the completion of the inspection are intended to be an all-inclusive list of deficiencies at your firm. It is your responsibility to ensure adherence to each requirement of the Act and applicable regulations. FDA requires drug manufacturers to establish written procedures for the surveillance, receipt, evaluation, and reporting of post marketing adverse drug experiences to FDA. These procedures should assure that adverse drug experiences are recorded, evaluated, and submitted to the FDA within established timeframes as required by 21 C.F.R. § 314.80.

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 being 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.

Please send your reply to the following address:

Darlene Almogela
Director, Compliance Branch
U.S. Food and Drug Administration
San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94502

If you have any questions regarding any issue in this letter, please contact Carl Lee, Compliance Officer, at (510) 337-6737 or by fax at (510) 337-6703.

Sincerely,
/S/

Barbara Cassens
District Director

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[1] This Risk MAPP is also referred to in your contract with [] as the “Xyrem REMS”.

[2] The contract also indicates that Adverse Event Reports specified in the contract are “data” under the terms of the contract, and, as such, are the exclusive property of Jazz.