DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 040688

LABELING ORDER

WraSer Pharmaceuticals
Attention: Heath Wray
121 Marketridge Road
Ridgeland, MS 39157

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules, 356.4 mg/30 mg/16 mg.

On August 1, 2013, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules to address the risk of serious skin reactions following exposure to acetaminophen, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, detailing the reasons why.

On August 14, 2013, FDA received your notification detailing the reasons why you believe a labeling change to address the risks listed above is not warranted for Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules; specifically that you plan to withdraw this application in light of the Federal Register notice dated January 14, 2011, because your product has more than the acceptable 325 mg of acetaminophen. However, as explained in the August 1, 2013, safety labeling change notification letter, requirements under section 505(o)(4) of the Act apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your product, because your application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.

The discussion period for this labeling change for your application opened on August 14, 2013 and was extended on September 16, 2013 for an additional 30 days. The discussion period ended October 13, 2013. Under the authority of Section 505(o)(4)(E) of the FDCA, we are ordering you to make all of the changes in the labeling listed in the August 1, 2013 letter (attached), as modified below.

Rarely, acetaminophen may (b) (4) cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious (b) (4) skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pursuant to Section 505(o)(4)(E), a supplement containing all of the changes to the labeling that are listed in the August 1, 2013, letter, as modified in accordance with this letter, must be received by FDA by November 8, 2013, for Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules. A changes being effected (CBE) supplement would be appropriate for this submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by October 29, 2013, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level." The appeal should be submitted as correspondence to your ANDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submissions should be sent to:

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Building 22, Room 6465
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Carrie Lemley
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
7520 Standish Place
Rockville, MD 20855

Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Amy Bertha, CDER Formal Dispute Resolution Project Manager, at (301) 796-1647. Appeals received by the Agency later than October 29, 2013, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your product and injunction.

If you have any questions, call Carrie Lemley, Labeling Project Manager, at (240) 276-8986.

Sincerely,

{See appended electronic signature page}

Lawrence X. Yu, Ph.D.
Acting Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE: Safety Labeling Change Notification Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 040688

SAFETY LABELING CHANGE NOTIFICATION

WraSer Pharmaceuticals
Attention: Heath Wray
121 Marketridge Road
Ridgeland, MS 39157

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules, 356.4 mg/30 mg/16 mg.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules was approved, we have become aware of published cases of serious skin reactions following exposure to acetaminophen, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis. A small number of published cases describe positive rechallenges in which patients had a recurrence of the serious skin reaction when inadvertently exposed to acetaminophen after recovering from the initial episode. There are also several well-documented case reports in the medical literature in which the only drug administered prior to the reaction was acetaminophen, or acetaminophen hypersensitivity was demonstrated by patch testing or other means. Additionally, we have become aware of supportive data in published epidemiological studies and in case reports submitted to FDA's Adverse Event Reporting System (FAERS). We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above we believe that the new safety information should be included in the labeling for all acetaminophen containing products as follows:

Revise the **WARNINGS** section of the package insert as described below (additions are noted by underline and deletions are noted by ~~strikethrough~~). The Serious skin reactions subsection should immediately follow the Hepatotoxicity subsection under the WARNINGS section.

WARNINGS

Serious skin reactions

Rarely, acetaminophen can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of severe skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil monetary penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you have any questions, contact Carrie Lemley, Labeling Project Manager, at (240) 276-8986 or carrie.lemley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

ROBERT L WEST

08/01/2013

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

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/s/

LAWRENCE X YU
10/24/2013