



August 29, 1997

Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863WARNING LETTER
CHI-44-97CERTIFIED MAIL
RETURN RECEIPT REQUESTEDDr. Baldev Raj Bhutani, President
Alra Laboratories, Inc.
3850 Clearview Court
Gurnee, IL 60031

Dear Dr. Bhutani:

During an inspection of your manufacturing facility located in Gurnee, IL, conducted from February 1997 to May 1997, FDA investigators Joyce E. Bloomfield, Steven B. Barber, and Mark I. Kasper documented serious deviations from the Current Good Manufacturing Practice Regulations (CGMP) (Title 21, Code of Federal Regulations, Parts 210 & 211). These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

1. The stability of reworked/reprocessed K+8 and K+10 tablets has not been evaluated and is not being monitored.
2. Production procedures are not always followed and deviations justified (e.g., K+ tablet coating solution is prepared and held under conditions different than the batch record specifies, oven drying times/temperatures are not always recorded, and granulation and tablets have been dried longer than the batch record specifies).
3. Manufacturing processes have not been validated (e.g., K+8 and K+10 granulation drying, compression, coating, and tablet heating; and Eryzole granulation drying and filling), and there is extensive reprocessing of batches failing one or more in-process control tests. Testing composite samples to measure batch uniformity is inappropriate.
4. Test methods are not always followed as written (e.g., the loss on drying test for Eryzole granulation used an open sample container although the method specifies the use of a capillary-stoppered sample container).

5. Out-of-specification (OOS) results are dismissed without adequate justification (e.g., Eryzole lot 83768P assay for Sulfisoxazole was OOS and the results dismissed for purely hypothetical reasons -- low powder fill or incorrect sample preparation).
6. Cleaning procedures have not been demonstrated to be adequate on multi-use equipment, and methods for verification of equipment cleanliness have not been validated. For example, the cleaning procedure should demonstrate that Digoxin residues are removed to below an appropriately specified level by a validated method capable of quantifying at the specified limit. The sampling method recovery rate should be demonstrated for each objectionable contaminant.
7. Equipment is not well-maintained (e.g., rusty ovens and leaking pump and transfer lines, thermocouples are not calibrated).
8. Maximum time limits on the holding of intermediates have not been established.
9. The purified water system was observed to have sagging lines and dead legs, is inadequately maintained, and use points are insufficiently tested and controlled.
10. Periodic reviews of batch records are not performed.

Furthermore, observations concerning Digoxin support the conclusion that batches of this product manufactured by Alra are adulterated within the meaning of the Act. Specifically, your firm has failed to establish a valid dissolution method, failed to validate the manufacturing process to ensure consistent and acceptable performance, failed to investigate OOS results adequately, failed to consistently follow or justify deviations from established manufacturing procedures, failed to determine stability of the product and investigate failures of dissolution and hardness, failed to test loss on drying according to established procedures, and failed to formulate to 100% of label strength, among other deficiencies.

We are particularly concerned about some previously distributed batches which were either reprocessed/reworked or were processed under conditions different than those specified in the batch record: five batches of K+8 tablets (lot nos. 76664P, 76665P, 78706P, 81722P, and 81723P) and ten batches of K+10 tablets (85797P, 71593P, 74624P, 74628P, 77692P, 66461P, 66464P, 66465P, 67484P, and 67487P). You have not kept your ANDA commitment to

place all reprocessed batches on stability. All the lot numbers cited here represent batches currently within labeled expiry. Any response to this letter should address your remedial action plan for these batches.

We have carefully reviewed Alra's written response dated May 21, 1997. Your response indicates that you have corrected or are effecting corrections to several deficiencies: equipment maintenance; purified water system maintenance and controls; validation of the K+8 and K+10 coating and heating steps; review of retesting practices; addition of "check by" date for raw materials; and the establishment of maximum hold times for intermediates. However, your response either offers no comment or inadequate comment on other significant deficiencies observed and noted during the inspection: stability of reprocessed K+8/10 batches; validation of cleaning methods; periodic review of batch records; Eryzole process validation issues (i.e., granulation drying and filling process); and adherence to established manufacturing procedures and testing methods. Your response also states that at least two laboratory analysts employed by Alra were permitted to independently perform laboratory analyses without adequate training or supervision, and that their work is now being questioned. Your response, if submitted, should address actions you have taken or will take to review the accuracy and completeness of their work, as well as describe any changes to your training program intended to prevent such occurrences in the future.

Your response to Digoxin deficiencies also indicates that you are effecting corrections to the deficiencies specified herein; however, as with your other responses, there is insufficient documentation to confirm that corrective actions are adequate or are being effected in a timely manner.

The above identification of violations are not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Current Good Manufacturing Practice regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending Antibiotic Form 6, NDA, ANDA, or export approval requests may not be approved until the above violations are corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

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You should notify this office in writing with 15 working days of receipt of this letter of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Your reply should be directed to the attention of George Bailey, Compliance Officer.

Sincerely,

RSJ
Raymond V. Mlecko
District Director