



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Public Health Service

Food and Drug Administration  
1141 Central Parkway  
Cincinnati, OH 45202

HFI-35  
5/25/97  
5-12-97  
e:lp

May 6, 1997

**WARNING LETTER**  
**CIN-WL-97-323**

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Adam Jerney,  
Chairman of the Board  
ICN Pharmaceuticals, Inc.  
3300 Hyland Avenue  
Costa Mesa, CA 92626

Dear Mr. Jerney:

During a February 19 to March 20, 1997 inspection of your finished dosage drug manufacturing facility, ICN Pharmaceuticals, Inc., located at 705 E. Mulberry St., Bryan, Ohio, our investigator documented deviations from the Current Good Manufacturing Practices Regulations (Title 21 Code of Federal Regulations, Parts 210 & 211). These deviations cause your drug products, Trisoralen® (Trioxsalen, 5 mg.) tablets, to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

1. Failure to adequately validate the formulation and processing of Trisoralen® to assure the tablets meet USP dissolution requirements throughout their labeled expiration date. (FDA-483 Observation #1)
2. Failure to either follow the USP dissolution test method or validate that the method used is equivalent or superior to the USP method. (FDA-483 # 2)
3. Failure to assure lots placed in your stability program are tested at the appropriate intervals. (FDA-483 #6)
4. Failure to conduct adequate investigations and take appropriate remedial action when dissolution failures were identified. (FDA-483 #4)
5. Failure to establish appropriate specifications and controls for active ingredient particle size and for humidity exposure of the active ingredient, inprocess material and bulk tablet storage. (FDA-483 #8 and #9)

The above described violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the 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.

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

We acknowledge receipt of a written response to these observations, dated April 9, 1997, from Joseph Bayman, Plant Manager. However, our review indicates Mr. Bayman's response to be inadequate for the following reasons:

1. In your response to the failure to adequately validate the formulation and processing of Trisoralen® (FDA-483 #1), Mr. Bayman's response basically states that the manufacturing process will undergo validation to ensure that the dosage form has proper dissolution characteristics, and you will not reintroduce the product until such time when you have data to demonstrate that the product will meet dissolution requirements throughout its shelf life.

Your response does not provide a validation protocol nor does it indicate when such a protocol will be developed and provided to the agency. You do not indicate what specific parameters will be examined in relation to the dissolution failures, such as active ingredient particle size or the effect of humidity on the active ingredient, inprocess material and bulk tablets, nor do you provide any timeframes as to when your process validation will start.

2. Regarding the failure to either follow the USP dissolution test method or validate that the method used is equivalent or superior to the USP method (FDA-483 #2), your response discusses the issue as to whether [REDACTED] or [REDACTED] strength [REDACTED] was used to develop the original dissolution methodology, which was later submitted to USP for implementation as the official test method.

Your response states that "Available evidence pointed to the [REDACTED] method having been developed with [REDACTED]". However, you do not provide such evidence in your response. In fact, when such evidence was requested during the inspection, your firm was unable to provide any such evidence to the FDA Investigator. If such evidence is available, please provide this office with a copy of the evidence.

We are also concerned that your firm has been, up to this point, focusing the blame for these dissolution failures almost entirely on the issue of whether the test method was adequate due to the use of [REDACTED] versus [REDACTED] in the simulated intestinal fluid. However, you have provided no evidence to date that the [REDACTED] test method you have been using has actually been validated.

Furthermore, several of the test results obtained during the inspection indicate that your product is failing dissolution even when the current [REDACTED] method is used. Conversely, the lots tested prior to 1994 apparently passed dissolution using the [REDACTED] method. This was the basis for your five year shelf life. In fact, most of the immediate finished product dissolution tests performed using this [REDACTED] method passed USP dissolution requirement. Almost all failures were observed later in stability testing. Your response does not explain why this dissolution method yielded apparently acceptable results for all immediate analyses, and for stability testing from 1984 through 1994, yet is now found to be unacceptable for stability testing.

3. In response to the failure to assure lots placed in the stability program are tested at the appropriate intervals (FDA-483 #4), Mr. Bayman's response states that you hired a Stability Coordinator, in 1995, to manage the stability program more effectively, and you commit to performing all investigations for non-conforming results within 30 days.

This response provides no indication as to exactly what changes have been made to assure your firm meets their obligations for performing timely testing of stability samples. While your response implies that this problem was resolved with the hiring of a Stability Coordinator in 1995, stability documents for lot G0816B/100's indicate testing intervals were not being followed as late as September 1996. The 24 month checkpoint for this lot

was due 9/96; however, the lot was not tested until 2/11/97. Furthermore, numerous instances were observed between July 1992 and September 1996 where dissolution was not carried out to completion. In these instances, testing was halted when the tests did not pass  $S_1$  or  $S_2$  but had not yet failed and the dissolution testing was never carried out to completion at the  $S_3$  test stage.

4. In response to the failure to conduct adequate investigations and take appropriate remedial action when dissolution failures were identified (FDA-483 #4), Mr. Bayman's response states that you disagree with this observation. It says that your records clearly show that there was an investigation but there was no investigation report. The response further states that at the time written, investigations reports were only just becoming a recognized good manufacturing practice.

For your information, 21 CFR Section 211.192 has required written records of failure investigations, since the March 28, 1979. These records are to include conclusions and follow up. While these requirements may have been further clarified in case law, they were in effect at the time in question.

We recognize that the above described observation specifically addressed the failure of four (4) lots of product during development testing of the dissolution methodology conducted in 1984. However, we are still concerned about the adequacy of your current failure investigation procedures. Based on the information provided in this inspection, you did not adequately investigate and resolve stability-dissolution problems with this product, between November 1994 and the time when production was ceased and product recalled in early 1997.

While you have attempted to adjust the analytical method in an effort to obtain passing results, until now you have not adequately investigated the effects of processing variables. Your files contain information which indicates that particle size, humidity and/or some other combination of processing parameters may be a contributing cause to these failures.

In fact, as pointed out in your response, there was some historical evidence as far back as 1984 which attributed dissolution failures to larger particle size of active raw material. None the less, you continued to blame the failures on test methodology, even though these failures continued after changes were made in the test methods.

5. In your response to the failure to establish appropriate specifications and controls for the effects of active ingredient particle size variation (FDA-483 item #8), you indicate that you will perform a microscopic evaluation of historical receipts (presumably raw material retain samples) to evaluate the particle size range of the material and will work with your supplier to establish specifications. Please provide us with your summary of your conclusions in this evaluation, along with an explanation of the protocol followed in conducting the evaluation.

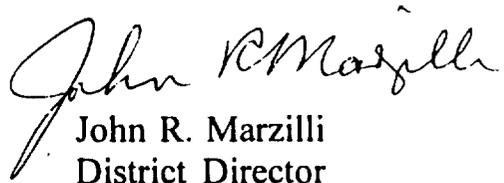
In your response to time, temperature and humidity exposure (FDA-483 item #9) of inprocess materials and bulk tablet storage, you state that you have established that there are no temperature limits beyond what is required in the labeling. The response also states that you are considering humidity limits which, if confirmed as necessary and appropriate, will be incorporated into an SOP for future batches.

We believe your response is inadequate in that it makes no firm commitment that the effect of humidity will be formally studied and incorporated as part of your process validation. The potential adverse effects of humidity over time is discussed in your June 12, 1996 failure investigation memo by John Steichen, Reference: JAS0512. This document points out a direct relationship between percent moisture absorbed and the percentage of the tablets dissolved. The memo suggests both humidity levels and active ingredient particle size are potential causes of the stability-dissolution failures and recommends corrective action include examination and control of these parameters. We believe that any process validation performed for this product without consideration of the variability of these parameters would be inadequate.

You should notify this office in writing within fifteen (15) working days of receipt of this letter of the specific actions you are taking to address these remaining issues, including an explanation of each step being taken to prevent 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 the corrections will be completed. Due to the complexity of these issues, you may also wish to contact this office and make arrangements for your representatives to visit our office to discuss the details of your reply in person.

Your written reply and any supporting documentation should be sent to the U.S. Food and Drug Administration, 1141 Central Parkway, Cincinnati, Ohio 45202-1097, to the attention of Charles S. Price, Compliance Officer. Any questions regarding this letter or other issues may be directed to Mr. Price at telephone (513) 684-3501.

Sincerely,

  
John R. Marzilli  
District Director  
Cincinnati District

cc: Joseph Bayman, Plant Manager  
ICN Pharmaceuticals, Inc.  
705 E. Mulberry Street  
P.O. Box 31  
Bryan, Ohio 43506