Tennessee Valley Authority, 1101 Market Street, Chattanooga, Tennessee 37402

November 30, 1992

U.S. Nuclear Regulatory Commission
ATTENTION: Document Control Desk
Washington, DC 20555

Gentlemen:

In the Matter of	)	Docket Nos.	50-259	50-390
Tennessee Valley Authority	)		50-260	50-391
	)		50-296	50-438
	)		50-327	50-439
	)		50-328	

UNSATISFACTORY LABORATORY RESULT ON PROFICIENCY TEST SPECIMEN

In accordance with 10 CFR 26 Appendix A, 2.8(e) 4, Enclosure 1 is a record of the investigative findings of National Psychopharmacology Laboratory (NPL), which serves as TVA's contract laboratory. The investigation was initiated as a result of a positive result for amphetamine and methamphetamine on a proficiency sample supplied by the Research Triangle Institute (RTI). The positive result for methamphetamine in this sample was incorrect and therefore constituted a false positive.

As delineated in the enclosed report, interim corrective measures have been instituted. Samples from TVA, which screen as positives for amphetamine/methamphetamine on the immunoassay conducted by NPL, are being sent to another National Institute on Drug Abuse (NIDA) certified lab for screening and subsequent confirmation. The backup lab, National Drug Assessment Corporation (NDA), has methodologies which are validated by NIDA. Results of samples sent to the backup lab are reported directly to TVA.

NPL identified 19 specimens for which a positive result was reported to TVA. Of these 19, 11 were identified by TVA as proficiency test specimens. The remaining 8 were the specimens of individuals in TVA's Fitness For Duty program. All 8 of these specimens were determined to be negative results, either as prescribed or noncontrolled substances, by TVA's Medical Review Officer. Therefore, TVA took no action based on these specimen results.

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These 8 specimens will be sent, by NPL, to another NIDA certified laboratory for retesting in accordance with the instructions provided to NPL by RTI in the letter dated October 22, 1992 (Enclosure 2).

A follow up report will be submitted to inform you of the results of the retesting of the 8 specimens.

NPL currently retains its NIDA certification, although the remedial actions discussed in the enclosed letter are required to be completed before confirmatory testing can resume for amphetamines. TVA continues to use NPL as its primary contract laboratory.

Commitments made by TVA are listed in Enclosure 3. If you have any questions concerning this information, please telephone Steve D. Gilley at (615) 751-7667.

Sincerely,

Mark J. Burzynski

Mark J. Burzynski
Manager
Nuclear Licensing and Regulatory Affairs

Enclosures
cc: See page 3

Enclosures
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ENCLOSURE 1

NPL NATIONAL PSYCHOPHARMACOLOGY LABORATORY, INC.

October 30, 1992

Estes Felker, M. D.
Manager, Clinical Services
Tennessee Valley Authority
Chattanooga, TN 37401

Dear Dr. Felker:

As you know our laboratory has come under the scrutiny of the National Institute of Drug Abuse (NIDA) and its contractor, RTI (Research Triangle Institute) because of a false positive methamphetamine report issued by our laboratory for a proficiency test specimen sent through the National Laboratory Certification Program. The purpose of this letter is to report the background of the error, NIDA's response to it, our plans to remediate the problem, and the status of any TVA specimens affected by the situation. At this point I want to stress that thus far there is no indication that there were any false positive methamphetamine results issued for TVA specimens or for any specimens from other clients.

Historically, the problem of false positive methamphetamines began about two years ago when several laboratories reported the drug positive in urine specimens which contained extremely high concentrations of ephedrine. This occurred under the relatively rare circumstance when abusive quantities of over-the-counter medications containing ephedrine were consumed. High concentrations of ephedrine will result in presumptive positives in some immunoassay screening procedures, but the main problem was a conversion of ephedrine to methamphetamine by some GC/MS (gas chromatography/mass spectrometry) confirmation procedures. The reason for this has not been established but appears to be related to the use of relatively high temperatures in the GC (gas chromatograph) and possibly to the condition of the injection port components. As a precaution, NIDA issued a directive mandating that amphetamine (a metabolite of methamphetamine) must be present in suitable quantities before a positive result for methamphetamine could be reported.

During this period our laboratory did not see a similar problem with our procedure. First, we had an opportunity to assay a false positive specimen from one of the accused laboratories and found no trace of methamphetamine. Secondly, we tested our procedure with

high concentrations of ephedrine and saw no significant synthesis of methamphetamine. And third, our immunoassay screening procedure was not sensitive to even massive amounts of ephedrine so it was unlikely that such urines would reach the confirmation stage.

The recent events leading to our false positive methamphetamine result began with a NIDA proficiency test set received on May 7, 1992 which included a specimen containing a high concentration of ephedrine. Our screening process was unaffected by the ephedrine and the specimen was reported negative according to normal protocols. However, RTI instructed the laboratories to perform the amphetamine/methamphetamine confirmation on the specimen under special protocol. Our GC/MS confirmation did detect methamphetamine. This was not considered an official false positive by RTI but did result in substantial communications with them regarding the potential problem. On our part, we replaced all of the injector components in the GC/MS but without effect. We also investigated using lower instrument temperatures but found that the assay would not work at all under these parameters. At this point we began studying other confirmation procedures which did employ lower temperatures, and we were confident that there were sufficient safeguards elsewhere in our protocols to assure that false positive methamphetamine results would not be reported in real specimens.

On September 16, 1992 we received another set of proficiency samples from RTI which contained a specimen especially designed to circumvent the safeguards. In addition to a high concentration of ephedrine the specimen contained amphetamine in sufficient quantity to give a positive result in our immunoassay screening procedure as well as substantiating a methamphetamine positive according to NIDA's directive. Our results for the specimen were positive for amphetamine (correct) and positive for methamphetamine (incorrect) according to our GC/MS confirmation. This was considered an official false positive by NIDA and RTI.

On or about October 1, 1992 RTI notified us to identify all positive methamphetamine results reported since October 1, 1991 and make available all data for a special inspection on October 6, 1992. The inspection team consisted of a representative from RTI and two NIDA inspectors chosen for their expertise with amphetamine analyses. The inspectors closely examined the data for all of the methamphetamine reports and told us that they did not feel that any other false positives had been generated. Approximately fifty data sets were examined which included two TVA results. We were also instructed to discontinue performing amphetamine/methamphetamine GC/MS confirmations on specimens regulated by NIDA until our methodology was approved by RTI and NIDA. As of October 6, 1992 any such specimens which appear as positive by immunoassay are submitted to another certified laboratory for repeat screening and confirmation. The laboratory is the National Drug Assessment Corporation (NDA) in Oklahoma City, OK, and these arrangements have been approved by NIDA. Results are sent directly to TVA by NDA.

I have enclosed a copy of the report for the special inspection. The report basically instructs NPL on how to handle positive amphetamine results generated over the past year and lists minimal requirements for approval of a new amphetamine/methamphetamine confirmation procedure. (Any dates referring to an October 28th deadline have been extended to November 4th.)

Past specimens reported positive will have to be reanalyzed by another laboratory (probably NDA). RTI has expanded this to include any specimens containing amphetamine alone. Prior to reanalysis, an SOP describing the logistical process must be approved by RTI.

We have identified 19 TVA specimens for retesting (see attached list). However, I suspect that a portion of these were proficiency test specimens, and since RTI has specified that known proficiency test samples need not be reanalyzed, I would appreciate your assistance in identifying any such specimens.

NPL is vigorously working to validate a new confirmation assay according to the mandates in the report. We are also investigating two other additional safeguards. The first is a pre-treatment of the specimen prior to GC/MS analysis which will destroy ephedrine and related compounds while not affecting amphetamine and methamphetamine. Second is the incorporation into the assay of a negative urine containing a high concentration of ephedrine to monitor on a daily basis any possible synthesis of methamphetamine by the new confirmation assay. If technically feasible, these will be incorporated into the new procedure.

I deeply regret any inconvenience this problem has caused you and your organization. Please feel free to call me if I have left out any information that you need for your report to the NRC.

Sincerely,

C. Richard Crooks, Ph. D.
Vice President Psychopharmacology

CRC/psk
Enclosures

Enclosure 2

RECEIVED

RESEARCH TRIANGLE INSTITUTE

National Laboratory Certification Program

22 October 1992

0081
Dr. Timothy A. Robert
National Psychopharmacology Laboratory, Inc.
9320 Park West Blvd.
Knoxville, TN 37923

Dear Dr. Robert:

This letter follows our discussions regarding the false positive test result reported by your laboratory, National Psychopharmacology Laboratory (NPL), on PT sample 6862-028-11482-37192 and the recent special inspection of your laboratory. You have informed us that you are developing a new amphetamines confirmatory assay and until the assay is fully validated you are sending specimens found presumptively positive for amphetamines to another NIDA certified laboratory. This procedure of sending out specimens has been adopted for specimens of Federal employees, employees in federally regulated drug testing programs, and clients for whom NPL has agreed to use HHS/NIDA procedures and methods in drug testing. If we have misunderstood this information, please notify us immediately

In light of the false positive test result, the National Laboratory Certification Program (NLCP) is requiring that your laboratory take the following remedial action:

(1) You must submit an updated listing of all specimens subjected to confirmatory testing for amphetamines by your laboratory from 1 October 1991 through the date when your laboratory began to send its presumptively positive for amphetamines specimens to another certified laboratory for testing. This listing must include the accession number for each specimen, the results of screening, confirmatory results obtained including quantitative data for amphetamine and methamphetamine, descriptions of anomalous observations and unknown peaks, and the final reporting status of each specimen. This listing of specimens must be received at RTI on or before 28 October 1992.

(2) NPL must send out for retesting to another certified laboratory aliquots of all of the amphetamine and/or methamphetamine positive specimens previously analyzed by the 1-TPC procedure under the laboratory's HHS/NIDA certification and still in the possession of the laboratory. It is not necessary for NPL to send out any specimens which are known to be performance testing samples. The specimens to be sent out for

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Telephone 919 541-6709 Fax: 919 541-7042

retesting must have 25 mL of urine remaining after preparation of the aliquots for retesting; contact RTI if any specimens would not have 25 mL remaining. An SOP for sending out these aliquots must be sent to RTI for approval by 28 October 1992. The aliquots for retesting may not be prepared and sent out for retesting until the SOP has been approved by the NLCP, and results of these retests must be reported directly to the NLCP staff at RTI. The results of these retests are NOT to be reported as corrected results to any clients unless specifically authorized by NIDA. All costs of these retests are the responsibility of NPL.

(3) NPL must not test employee specimens for amphetamines by use of the new confirmatory assay until the assay is fully validated and you have demonstrated to the satisfaction of the NLCP that this has been done. The validation studies must include:

(a) Interference studies to determine the extent to which compounds of similar chemical structure may interfere with the new assay procedure. In your new assay, the chromatographic peaks for amphetamine and methamphetamine must be completely resolved from those of interfering substances. Compounds to be evaluated should include all amphetamine-like compounds of similar structure and/or chromatographic nature which one could reasonably expect to encounter in large volume forensic urine drug testing. Some examples, but not an all-inclusive list, of such compounds are ephedrine, pseudoephedrine, phenylpropanolamine, and phentermine. Your laboratory must also evaluate whether any non-amphetamine-related components of the urine matrix will interfere with the new assay. As you know, good laboratory practice requires that validation studies include documentation of the method's response to extremely large concentrations of structurally similar compounds (see the attached advisory which was sent to you in February 1991).

(b) Standard statistical evaluations of the new method. These must include, as a minimum, determinations of limit of detection (LOD) and limit of quantitation (LOQ), precision of the assay, coefficient of variance, and range of linearity.

NPL must submit to RTI a summary/synopsis of its assay development and validation data and results. This validation study must be completed to the satisfaction of the NLCP before the new assay may be used to analyze performance test samples or client specimens as provided in item (5) below.

(4) You must FULLY DESCRIBE THE NEW CONFIRMATORY PROCEDURE in your laboratory's Standard Operating Procedures manual. This description must be

submitted to RTI before analysis of performance test samples or client samples as provided in item (5) below can be initiated.

The new confirmatory method must include adequate data reviews by certifying scientists to detect the presence of interferants in large quantities, to effectively compare results of initial and confirmatory tests for consistency of results, and to recognize and initiate appropriate investigations when interferant peaks are present.

(5) You must demonstrate SUCCESSFUL PERFORMANCE OF THE NEW ASSAY. This will be evaluated through the examination of data from the analysis of NLCP Performance Testing (PT) samples containing a variety of amphetamine challenges. The correctness of your laboratory's performance on the PT samples will be determined by application of the normal PT scoring procedures and criteria of the NLCP, and through the examination of data generated in the analysis of these samples. Specifically, the following is required:

(a) NPL must successfully analyze a special set of 40 PT samples. Once your laboratory has completed development and validation studies to your satisfaction, submitted a summary of the studies and the standard operating procedures to RTI, and indicated to RTI that you are ready to analyze performance test (PT) samples, they will be shipped to you. This set of PT samples will focus on amphetamine class challenges. The results of analysis of these samples must be reported to RTI within five working days from the receipt of the samples. Data from the analysis of these PT samples must be available for review during the subsequent on-site inspection.

(b) NPL must retest all of the amphetamine and/or methamphetamine positive specimens previously analyzed by the 1-TPC procedure under the laboratory's HHS/NIDA certification. The specimens for retesting must have 25 mL of urine remaining after preparation of the aliquots for retesting; contact RTI if any specimens would not have 25 mL remaining. You are not authorized to begin retesting of these samples until the laboratory has completed (1) its assay development and validation studies, (2) the SOP for this assay, (3) submitted the information to RTI, (4) completed the analysis of the PT samples and reported the results to RTI, and (5) the NLCP has approved reanalysis of such specimens. Once retesting has been authorized, it must be emphasized that the results of these analyses are NOT to be reported as corrected results to any clients unless specifically authorized by NIDA.

(c) Until NPL has been authorized to resume confirmatory testing and reporting for amphetamines, with each regularly scheduled cycle of NLCP maintenance PT, RTI will direct NPL on how to proceed and which specimens are to be tested.

(6) The laboratory must successfully undergo a special ON-SITE INSPECTION of its amphetamines testing procedures. This inspection is expected to take one day and will be conducted by two NLCP inspectors and one NLCP/RTI staff member. We anticipate that this inspection will take place after the requirements of (1) through (5) above are met. Scheduling of the inspection will depend upon the availability of inspectors at such time as these items have been completed. The inspection will focus on:

(a) The SOP for the amphetamines class assays;

(b) A detailed audit of your laboratory's assay development and validation data. Inspectors will prepare for this audit by reviewing, prior to the inspection, the summary/synopsis of the development and validation data;

(c) Procedural aspects of the assay, such as the isolation, derivatization, GC/MS identification, and quantitation of amphetamines;

(d) Analytical aspects of the assay, to be evaluated through the examination of data from the reanalysis of the amphetamine and/or methamphetamine positive specimens previously analyzed by the laboratory by the 1-TPC procedure;

(e) Performance aspects of the assay, to be evaluated through the examination of data from the analysis of the special set of 40 PT samples and the reanalysis of specimens.

When you have successfully completed the above conditions, RTI will notify you in writing that NPL may resume confirmatory testing and reporting for amphetamines.

The cost of the special PT set and inspection is $16,340. Please send your check for this amount of money, made out to Research Triangle Institute, to the following address before 1 November 1992:

Ms. Sheila Singh
National Laboratory Certification Program
Research Triangle Institute
3040 Cornwallis Road
P.O. Box 12194
Research Triangle Park, NC 27709.

If you have any questions regarding these conditions, please contact me (919-541-6709), Ms. Terrie Baker (919-541-7043), or Dr. Donna Bush (301-443-6014).

Sincerely yours,

Kenneth H. Davis, Jr.
Program Director

cc: Dr. Joseph H. Autry III
Dr. Donna Bush
Ms. Karen Wagner
Ms. Terrie Baker
Ms. Lisa Gilliland
Ms. Sheila Singh
Dr. Edward J. Cone
Dr. Jeffrey A. Gere

Enclosure 3

LIST OF COMMITMENTS

1. TVA will provide NRC with the results of the retest of the 8 specimens originally reported to TVA as positive.