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SUBJECT: Forwards rept of inconsistent blind performance test results involving HHS-certified labs on 910403.Possibly caused by inadequate mixing of specimen pool prior to aliquoting.Samples maintained at MetPath Lab.

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WASHINGTON PUBLIC POWER SUPPLY SYSTEM

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Docket No. 50-397
January 6, 1992
G02-92-003

U.S. Nuclear Regulatory Commission
Attn: Document Control Desk
Washington, D.C. 20555

Gentlemen:

Subject: Fitness for Duty Program, Unsatisfactory HHS-Certified Laboratory Performance, Report No. 92-001

Transmitted herewith is a report of inconsistent blind performance test results involving the HHS-certified laboratories that provide drug testing services for the Supply System Fitness for Duty Program. This report is submitted per the requirements of 10CFR26, Appendix A, Subpart B, 2.8, e.4, and includes a record of investigative findings signed and dated by the individual responsible for the day-to-day management and operation of the HHS-certified laboratory in question.

The Supply System feels this matter should be referred to the U.S. Department of Health and Human Services (DHHS) for investigation. All applicable documentation is maintained either by the Supply System or the HHS-certified laboratories. Additional information will be provided upon request and full Supply System cooperation will be extended during any NRC/DHHS investigation.

Very truly yours,

G.C. Sorensen
Manager, Regulatory Programs

Encl.: Unsatisfactory HHS-Certified Laboratory Performance, Report No. 92-001 (with Attachments A-C)

cc: J.B. Martin/NRC Region V
P.L. Eng/NRC
N.S. Reynolds/W&S
D.L. Williams/BPA/399
NRC Site Inspector/901A
Dr. V. Yates/Northwest Health Services
P.E. Grady/BPA/399

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WASHINGTON PUBLIC POWER SUPPLY SYSTEM
NUCLEAR PLANT NO. 2

FITNESS FOR DUTY PROGRAM
UNSATISFACTORY HHS-CERTIFIED LABORATORY PERFORMANCE
REPORT NO. 92-001
JANUARY 2, 1992

BACKGROUND

The Supply System Fitness for Duty (FFD) Program currently utilizes onsite initial screening by EMIT testing followed by confirmation testing conducted by two HHS-certified laboratories. Before the Medical Review Officer can determine that a test is confirmed positive, all test results from onsite screening and both HHS-certified laboratories must be positive. The certified laboratories currently in use are:

Laboratory of Pathology P.O. Box 14950 Seattle, WA 98114-0950 (206)386-2672	MedTox Laboratories 402 West County Road D St. Paul, MN 55112 (612)636-7466

At the FFD Program inception, the Supply System utilized the services of two HHS laboratories: Laboratory of Pathology (LOP) and MetPath of Teterboro, New Jersey. The services of MetPath were terminated in August 1991, and a contract with a new HHS laboratory, MedTox, was executed at that time.

DESCRIPTION OF UNSATISFACTORY PERFORMANCE TEST RESULT

On April 3, 1991, the Supply System's Medical Review Officer (MRO) notified the FFD Office that she had received inconsistent laboratory analyses results for 27 blind samples. The MRO noted that the LOP results were negative for all 27 blind samples; however, MetPath found all samples positive for opiate metabolites, specifically codeine. The MRO did not have an explanation for the inconsistent results.

Subsequent conversations between the Supply System FFD staff and LOP disclosed that LOP's EMIT screening of the 27 samples in question was positive for opiate metabolites, specifically codeine; but, confirmation testing by Gas Chromatography/Mass Spectometry (GC/MS) found codeine below the 300 ng/ml cut-off level with no morphine detected. In contrast, the MetPath GC/MS results were above the 300 ng/ml cut-off level and morphine was detected.

At the Supply System's request, both LOP and MetPath re-analyzed five samples. The re-analysis results were the same as the initial results: LOP negative for opiates/codeine and MetPath positive with morphine detected.

During the April-May 1991 time period, the Supply System was in the process of initiating onsite screening by EMIT testing. Therefore, a specimen from the same batch of pooled urine that involved the inconsistent test results was tested by EMIT screening. Results of this onsite EMIT screening were positive for opiates.

Litigation/legal packages for the five re-analyzed specimens were obtained by the Supply System from LOP and MetPath and were provided to a Supply System consultant for review. Dr. Larry B. Howard, Ph.D. DABFT, Associate Bensinger-Dupont and Associates, reviewed the information in both litigation packages. In his first report (Attachment A), Dr. Howard noted "the explanation for the difference in results between LOP and MetPath is not apparent from the data submitted." In Dr. Howard's second report (Attachment B), he concludes "the MetPath results are correct and the Laboratory of Pathology results are low - (negative) secondary to loss of drug during analysis."

Upon receipt of Dr. Howard's evaluation, the Supply System requested on November 18, 1991, that LOP investigate the situation and submit a report to the Supply System by December 20, 1991. Both of Dr. Howard's reports were provided to LOP for information. On December 16, 1991, the Supply System FFD Office received the results of the LOP investigation (Attachment C).

CAUSE OF THE UNSATISFACTORY PERFORMANCE TEST

The LOP report states: "...there is no definitive conclusion as to the cause of the discrepant results." The report offers three possible explanations:

1) Inadequate mixing of the specimen pool prior to aliquoting;

2) Problem in hydrolysis with a lack of conversion of codeine glucuronide to free codeine;

3) Problem in extraction that was not corrected by the internal standard.

The second and third explanations, however, were discounted by LOP in their report (Attachment C). The first explanation, inadequate mixing of the pool, has been determined by further Supply System investigation to not have occurred. The procedures for preparing and submitting blind performance specimens preclude inadequate mixing. For each blind specimen sent to the HHS laboratory, one 100 ml container is filled from the thoroughly mixed pool at the

EMIT laboratory and transported to the collection facility where it is split into two aliquots, one for each laboratory. Therefore, each laboratory receives an identical, thoroughly mixed specimen. Discussions with EMIT laboratory and collection site personnel disclosed that special emphasis is placed on adequate mixing of the pooled urine and the split specimens.

CORRECTIVE ACTIONS TAKEN BY THE LABORATORY

Since the results of the LOP investigation are inconclusive and the cause of the inconsistent results has not been determined, corrective actions have not been initiated.

It should be noted that since the problem was initially identified in April 1991, three similar inconsistent test results involving opiate metabolites, specifically codeine, have been obtained. These tests, however, involved specimens obtained during random testing and were not blind samples. Prior to termination of the contract with MetPath, a random specimen was analyzed as positive for opiates by Supply System EMIT screening, and analyzed by MetPath as positive for opiate metabolites, specifically codeine. The LOP analysis for the same specimen was negative. After termination of the MetPath contract and execution of the new MedTox contract, two more random specimens were analyzed positive for opiates by Supply System EMIT screening and Medtox. Again, LOP results were negative.

Even though there have been three inconsistencies that involved individuals rather than blind performance specimens, the Supply System has elected to continue using LOP as one of the two HHS-certified laboratories required by the program. This decision was based on:

- To date, results of investigations involving the inconsistencies are inconclusive.
- LOP performance for the analysis of the other four NIDA panel of drugs has been acceptable.
- LOP analysis of blind specimens for opiates has been satisfactory since the April 1991 inconsistencies.
- The three inconsistencies involving individuals did not have a material effect on the program because the MRO was able to verify legal prescriptions in all cases.

MetPath Laboratory of Teterboro, New Jersey, is currently maintaining approximately 10 ml of the original blind specimens that were tested positive by MetPath and negative by LOP. In the

attached LOP report, a request was made to allow LOP to re-analyze the remaining 10 ml specimens. However, it is the Supply System's position that the specimens should remain at MetPath in long-term storage until DHHS/NIDA determines the most appropriate disposition.

Attachments (A-C)

ATTACHMENT A

WASHINGTON PUBLIC POWER SUPPLY SYSTEM

Urine Collection and Drug Test Program

Supplemental Report

Date: June 26, 1991

Subject: Toxicological evaluation of Laboratory of Pathology Litigation Package on WPPSS controls collected 4/3/91 and analyzed 4/4/91.

Specimens:

Donor Number	Accession Number
680-55-6433	0403:1587
680-55-6435	0403:1592
680-55-6450	0403:1604
680-55-6449	0403:1617
680-55-6434	0403:1619

Summary:

1. Specimen chain of custody easy to follow and well documented. There is no question as to the identity of the samples.
2. EMIT results on all specimens show reasonably consistent values and indicate positive for opiates. All EMIT values fall much closer to the high positive control than to the low positive control. (Table II).
3. GC/MS chain of custody form contains both laboratory accession number and donor identification number. These also check.
4. There is considerable apparent variation in the amount of codeine and codeine internal standard extracted, as shown in the variation in areas in Tables IIIB and IIIC.
5. Standard quantitative data expressed as the ratio of codeine to constant internal standard shows acceptable ratios and the quantitative data from the WPPSS controls is consistant with this data. (Tables IV A & IV B)
6. Actual MS analytical sample data on the five control samples, reportedly of the same sample origin, shows excessive variation in quantitative values. The rising values with sample sequence may or may not be due to chance. (Table V)

Conclusion: Laboratory of Pathology data is acceptable except in the apparent recovery of codeine from urine. This could originate either in the hydrolysis or possibly extraction steps. There are wide swings in the amount of codeine and codeine internal standards recovered, although the ratios are consistent.

Results

I EMIT Report

Table I

Donor I.D.	Laboratory Accession No.	
680-55-6433	0403:1587	positive for opiates
680-55-6435	0403:1592	positive for opiates
680-55-6450	0403:1604	positive for opiates
680-55-6449	0403:1617	positive for opiates
680-55-6434	0403:1619	positive for opiates

11 EMIT Results

Table 11

Controls (prior to sample run)	Description	Opiate Reading
403-1295C	Low positive control	+4.6
403-1296C	Neg. for all drugs	-526
403-1297C	High positive control	+385
403-1808R	Blind (Neg.) control	-531
Samples:		
403-1587	Donor Specimen	+290
403-1592	Donor Specimen	+300
403-1604	Donor Specimen	+290
403-1617	Donor Specimen	+290
403-1619	Donor Specimen	+270
Controls (after sample run)		
403-1299	Low positive control	+29
403-1300	Negative control	-581
403-1296	Negative control	-526
403-1301	High positive control	+376

These adjusted optical density readings indicate a considerable amount of opiate is present near the high positive control level. Results are very acceptable.

111 GC/MS Results

Table 111A Tune Data

Drug	Ion	Concentration	Area (Instrument Response)
Codeine	282	500 ng/ml	1,379,967
Codeine (deuterated) Internal Standard	285	833 ng/ml	1,356,738

Table 111B Codeine Quantitative Control Values

(c) Codeine, Subthreshold Control	206.29 ng/ml	*523,275
(b) Codeine, Threshold Control	306. ng/ml	*302,451
(a) Codeine, High Control	1655.48ng/ml	4991,349

Instrument response is not proportional to concentration.

Table IIIC

(a)	Codeine Internal Standard	833 ng/ml	1,482,150
(b)	Codeine Internal Standard	833 ng/ml *	485,155
(c)	Codeine Internal Standard	833 ng/ml *	1,246,945
(d)	Deuterated Codeine in Opiate Negative Control	833 ng/ml	1,268,707
(e)	Deuterated Codeine in Blind	833 ng/ml *	618,916

Instrument response to 833 ng/ml of deuterated codeine varies from 485,155 to 1,482,150. This appears to be due to variations in recovery of codeine. This is, however, compensated for by apparent similar failure to recover the internal standard.

Table IV A

Drug	Concentration	Area	Ratio
High Control			
Codeine I.S.	833ng/ml	1,482,150	3.36
Codeine	1655ng/ml	4,991,349	
Treshold Control			
Codeine I.S.	833ng/ml	485,155	.62
Codeine	300ng/ml	302,451	
Subthreshold Control			
Codeine I.S.	833ng/ml	1,246,949	
Codeine	206ng/ml	523,275	.42
Negative Control			
Codeine I.S.	833ng/ml	1,268,707	
Codeine	negative		----
Blind Control			
Codeine I.S.	833ng/ml	618,916	
Codeine	negative		

Table IV B

Cases			
403-1587			
Codeine I.S.	833ng/ml	709,409	.39
Codeine	193.51ng/ml	279,252	
403-1592			
Codeine I.S.	833ng/ml	1,255,934	.43
Codeine	214ng/ml	548,723	
403-1604			
Codeine I.S.	833ng/ml	1,048,810	.52
Codeine	259ng/ml	554,637	
403-1617			
Codeine I.S.	833ng/ml	1,132,807	.59
Codeine	293.88ng/ml	677,221	
403-1619			
Codeine I.S.	833ng/ml	959,297	.58
Codeine	288.61ng/ml	563,209	

Table V

Sample Results

Sample#	Drug	Reported Concentration	Area
403-1587	Codeine	193.51 ng/ml	279,252
	Codeine I.S.	(833) ng/ml	709,409
403-1592	Codeine	214.77 ng/ml	548,723
	Codeine I.S.	(833) ng/ml	1,255,934
403-1604	Codeine	259.9 ng/ml	554.637
	Codeine I.S.	(833) ng/ml	1,048,810
403-1617	Codeine	293. ng/ml	667,221
	Codeine I.S.	(833) ng/ml	1,132,807
403-1619	Codeine	288.ng/ml	563,209
	Codeine I.S.	(833) ng/ml	959,297

All of the results in Table V reportedly came from the same sample and show an unusually wide variation in value.

The explanation for the difference in results is not apparent from the data submitted. It would be interesting and/or informative to compare hydrolysis and extraction procedures between the two laboratories. It would also be usefull to look at a similar litigation package from the other laboratory.

Respectfully submitted,

Larry B. Howard Ph.D
Toxicologist, Associate
Bensinger, Dupont & Associates

ATTACHMENT B

WASHINGTON PUBLIC POWER SUPPLY SYSTEM

FEC 10/31/91 PS.

Urine Collection and Drug Test Program

Supplemental Report

Date: 13 October 1991

Subject: Toxicological evaluation of WPPSS controls analyzed 4/5/91 and 4/10/91 as reflected by MetPath Litigation Package.

Specimens: Original invoice-bar code numbers are used throughout the MetPath chain of custody analysis procedure. Specimens sent to MetPath cannot be connected directly to specimens sent to Laboratory of Pathology by information contained in the litigation packages.

MetPath Specimen Numbers:

TO 8337 78
TO 8214 78
TO 8215 78
TO 8233 78
TO 8238 78

Summary:

1. Chain of custody documentation follows specimens from receipt to report using bar code numbers. There is no doubt as to specimen or analyte identity. (Tables I&II)
2. MetPath used a different EMIT coding system than Laboratory of Pathology. No meaningfull quantitative figure is reported for EMIT specimens. However, MetPath diluted their WPPSS specimens 1-2 for confirmation of opiates suggesting the opiate screening values, like Laboratory of Pathology screening values, were high. (Table II)
3. MetPath ran the same specimens for confirmation on the 5th and 10th of April at two different concentrations. Results were positive for codeine at levels considerably above the cut-off. Morphine (codeine metabolite) was also identified. (Table III)
4. Codeine values reported by MetPath are well within the quantitative variation allowed for GC/MS quantitation. (TableIII)
5. Opiate hydrolysis and recovery procedures can be checked by proficiency testing through submission of equivalent amounts of codeine present as codeine salt and codeine glucuronide in alternate control samples. WPPSS is in a unique position to implement this because they use two laboratories showing markedly different quantitative opiate results.

Conclusion:

The main difference in the results of the two laboratories is quantitative. Unfortunately the use of cut-off values to differentiate positives from negatives carries quantitative differences over into the qualitative area. (positive vs negative) The discrepancy in results between the two laboratories illustrates the difficulty in drawing positive conclusions based on this type of data.

MetPath could hardley have accidently added more codeine and morphine to 5 specimens. If codeine and morphine are not in the urine, they can not be extracted from it.

Additionally, toxicologists historically have had trouble in extracting significant amounts of analytes from biological matrices.

Based on the above, it is the opinion of the undersigned that the MetPath results are correct and the Laboratory of Pathology results are low-(negative) secondary to loss of drug during analysis. Data submitted in the litigation packages does not directly reflect error with either laboratory, although MetPath data is more consistent. Qualitative interpretation, not quantitative consistancy is the forte of GC/MS. Unfortunately, NIDA regulations discourage laboratories from checking questioned results by other methods. Selective proficiency testing or submission of questioned specimens to a third laboratory seem the best alternatives.

Respectfully submitted,

Larry B. Howard PH.D DABFT
Forensic Toxicologist
Associate, Bensinger-DuPont
and Associates

Table I

Specimen Date and Number Summary

Specimen Number	Date Collected	Date Received	Date Screened	Dates Confirmed	Result
8337	4/03/91	4/04/91	4/04/91	4/05/91 4/10/91	+ codeine
8214	4/03/91	4/04/91	4/04/91	4/05/91 4/10/91	+ codeine
8215	4/03/91	4/04/91	4/04/91	4/05/91 4/10/91	+ codeine
8233	4/03/91	4/04/91	4/04/91	4/05/91 4/10/91	+ codeine
8238	4/03/91	4/04/91	4/04/91	4/05/91 4/10/91	+ codeine

Table II

EMIT Confirmation--Chain of Custody

Specimen #	Train Map# Screening	EMIT Opiate Results	Train Map# Confirmation
8337	040410	-T05 (+)	040501
8214	040411	-T05 (+)	040501
8215	040411	-T05 (+)	040501
8223	040411	-T05 (+)	040501
8238	040411	-T05 (+)	040501

Negative value (Opiate)--190
Positive value (Opiate)--T05
EMIT control values were not included in MetPath litigation package. Laboratory of Pathology package was more inclusive in this respect.

Table III A

Confirmation Results MetPath

Specimen #	I.S.Ratio Codeine	Urine Diluted 4/5/91 codeine conc.ng/ml	morphine conc.ng/ml	I.S Ratio Codeine	Undiluted Urine 4/10/91 codeine conc.ng/ml	morphine conc.ng/ml
8337	1.29	375.1	136.3	1.32	549.7	43.9
8214	1.25	361.8	107.5	1.37	573.7	63.0
8215	1.14	332.8	93.5	1.36	566.0	81.0
8233	1.23	356.4	131.7	1.37	572.	67.0
8238	1.11	322.4	89.5	1.38	574.	152.
Threshold :						
Control	1.0	300.		.74	300.	
2xTreshhold						
Control	1.56	600		1.44	600.	

Table III B

Confirmation Results Laboratory of Pathology

Specimen#	I.S.Ratio codeine	Urine Diluted 4/5/91 codeine conc.ng/ml	morphine conc.ng/ml	I.S.Ratio codeine	Undiluted Urine 4/10/91 codeine conc.ng/ml	morphine conc.ng/ml
1604		NA	NA	.52	259.	N.D.
1617		NA	NA	.59	293.9	N.D.
1619		NA	NA	.58	288.6	N.D.
1592		NA	NA	.43	214.0	N.D.
1587		NA	NA	.39	193.5	N.D.
Threshold Control				.62	300.0	

NA =Not Applicable
N.D.=Not Detected

ATTACHMENT C

Rec'd 12/16/91
D. Coody

Laboratory of Pathology
SEATTLE

Nordstrom Medical Tower
P.O. Box 14950
Seattle, WA 98114-0950
206/386-2672, 800/458-6836
FAX: 206/386-6009

December 4, 1991

Donald Coody
Supervisor, Fitness for Duty
Washington Public Power Supply System
P.O. Box 968
3000 George Washington Parkway
Richland, WA 99352

Dear Mr. Coody:

This report is submitted in response to your letter of November 18, 1991, regarding the discrepant results obtained on blind specimens sent to both this laboratory and MetPath in April of this year. Thank you for enclosing Dr. Howard's reports for use in preparing this response.

We must agree with Dr. Howard that "the explanation for the difference in results between LOP and MetPath is not apparent from the data submitted." After review of the analytical data and Dr. Howard's reports there is no definitive conclusion as to the cause of the discrepant results.

There are some possible explanations that could be proposed as to what might have contributed to this problem:

Since the codeine present in the pool from which these specimens were obtained was an accidental contaminant, inadequate mixing of the pool prior to aliquoting could have resulted in specimens of differing concentration.

As Dr. Howard points out, there could have been a problem in hydrolysis of the specimens with a lack of conversion of codeine glucuronide to free codeine in the LOP specimens.

There could have been a problem in extraction of the specimens that was not corrected for by the internal standard.

The problem was likely not due to the extraction, since all of the specimens behaved similarly and the internal standard in each extract appears to have successfully corrected for any difference in extractiodn efficiency or injection volume. In addition, proficiency survey data show that this laboratory can accurately and consistently identify and quantitate codeine in proficiency specimens. A summary of recent survey results in the range of these samples follows:

Codeine Proficiency Survey	Target Value (ng/mL)	LOP Value (ng/mL)
CAP, FUDT	390	405
DHHS/NIDA	508	516
DHHS/NIDA	384	319
DHHS/NIDA	384	378

Proficiency survey specimens do not generally contain codeine glucuronide since this codeine metabolite is not commercially available. As a result, the efficiency of the hydrolysis of codeine glucuronide to codeine is not tested by survey specimens. Morphine glucuronide, however, is found in the DHHS/NIDA survey and does test the laboratory's ability to hydrolyze this metabolite, and our results have been acceptable. It is our understanding that MetPath uses an acid hydrolysis similar to the one used in this laboratory, so it is difficult to point to a concrete problem with hydrolysis.

As Dr. Howard suggested, it would be informative to compare the results and procedures of both laboratories. Since he feels that the MetPath specimens are correctly quantitated, it might be very useful for WPPSS to direct MetPath to send one of the specimens in question to us to verify whether or not we can recover the same amount of codeine from the same sample. Due to the length of time since analysis, it may be necessary for MetPath to re-analyze the specimen as well.

In summary, the discrepant results are not easily explained and may be due to either a true difference in the specimens received by each laboratory or there may have been a problem in the hydrolysis of these specimens; although we have not been able to demonstrate such a problem. It is unlikely that the problem was due to an extraction problem. Further study of this problem could be undertaken by an exchange of a specimen as described above.

If there are further questions regarding this issue please call me at (206) 386-2438.

Sincerely,

Arthur M. Zebelman, Ph.D.
Scientific Director