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Comparison of Positive Screening and Confimatory Results From Federally Mandated Drug Testing of Urine

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COMPARISON OF POSITIVE SCREENING AND CONFIRMATORY RESULTS FROM FEDERALLY MANDATED DRUG TESTING OF URINE

by

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ABSTRACT

COMPARISON OF POSITIVE SCREENING AND CONFIRMATORY RESULTS FROM FEDERALLY MANDATED DRUG TESTING OF URINE.

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The purpose of this study was to analyze the accuracy of FDA approved immunoassays for the detection of drug positive urine samples.

Federal civilian employees are tested under the strict protocol of the Department of Health and Human Services mandatory guidelines for federal workplace drug testing programs. The guidelines provide for a two instrument testing protocol for the analysis of urine samples. The first is an FDA approved immunoassay. Samples which test positive on this screening immunoassay are then submitted for confirmatory testing with the "gold standard" gas chromatography/mass spectrometry.

Agency monthly drug testing summaries, required under the DHHS guidelines were sought from the six largest federal agencies which performed drug testing on its civilian employees in 1993 and 1994. These agencies were: Department of Air Force, Army, Justice, Navy, Transportation and Veterans Affairs. This study covered more than half of the federal civilians tested during 1993 and 1994.

Calculations were made of the positive predictive value (PPV) of the screening test, false presumptive positives and confirmed positive rates for each agency and immunoassay. Positive predictive values are defined as the probability that the specific immunoassay screen accurately predicts true lab positive urine samples.

The study concluded that GC/MS confirmation is scientifically necessary to ensure accurate results. Failure to submit samples for GC/MS testing would result in 200-370 false positives annually among federal civilian employees. Those employees would then be subject to disciplinary actions, including removal.

There were differences among immunoassays tested. The screening tests accurately identified positive marijuana samples in 98.7% of the cases. Similarly opiates testing was the most problematic, positive predictive values approached 72%. Amphetamine/methamphetamines immunoassays detected a weak 77% of lab positive urine samples. Comparisons among immunoassays utilized by federal agencies drug testing laboratories found the best overall positive predictive values for radioimmunoassay (RIA) at 90.8%, followed by Enzyme Multiplied Immunoassay EMIT (88.8%), and lastly KIMs at 82.0%. Surprisingly KIMs showed weaknesses for the detection of phencyclidine (PCP).

The study concluded that while there are areas where federal drug testing costs may be reduced (such as limiting the testing of phencyclidine and choosing the most accurate immunoassays), confirmation of positive screens by GC/MS is critical to ensure the integrity of federal drugtesting programs and should be used by private industry.

ACKNOWLEDGEMENTS

Nearly ten years ago, I was tasked by the President of a large federal labor union to "learn as much as you can about drug testing." Even though I had years experience as an analytical chemist, I did not expect to become so enthralled with this subject, nor to continue to learn about drug testing into the next decade.

From an Occupational Health standpoint, most employees in the workplace will be subject to drug testing throughout their careers. Employers have instituted a wide variety of testing protocols. My goal in this study was to see how effective the very best programs actually are (i.e. those of the federal government).

I would like to acknowledge and thank for their assistance the Freedom of Information Divisions of several federal agencies, this includes: the Departments of Agriculture, Air Force, Army, Commerce (Treasury), Energy, Interior, Justice, Health and Human Services, Labor, Navy, Transportation and Veterans Affairs. Without their assistance and data this study would have been impossible. Secondly I would like to thank for their assistance and cooperation those contract laboratories which performed drug testing services for the federal agencies in this study, they are: Northwest Toxicology, Pharmchem, Department of the Navy Drug Screening Labs, and Laboratory Corporation of America.

Special thanks go to my insightful thesis advisors, Professor Jim English, Drs. W. Smith Chandler, Rod Handy and Colin Box. Most of all, I wish to thank my family, my husband Brian, son Mikey, and parents Jack and Nancy McLaughlin..

Mary M. Stuck

TABLE OF CONTENTS

LIST OF TABLES

LIST OF TABLES (CONTINUED)

Chapter I

INTRODUCTION

In 1986 President Reagan signed Executive Order 12564 which established a federal drug free workplace program. It required the head of each executive branch agency to establish a random testing program of civilian employees in sensitive positions and a voluntary drug testing program. The order also authorized agency urine testing when there is a reasonable suspicion that an employee uses illegal drugs; in an examination authorized by the agency following an unsafe practice or accident; as part of or to follow up counseling or rehabilitation for illegal drug use; and when an individual applies for employment with the agency. The Executive Order required the Department of Health and Human Services (DHHS) to promulgate standards on how drug testing would be conducted.

Legal scholars such as Schroeder (1990), contend that federal initiatives such as President Reagan's Executive Order and Public Law 100-71 which govern the scope of federal drug testing, (and by extension the mandatory guidelines promulgated by DHHS) have been the driving force for employment drug testing in this country. There is also little doubt that drug testing methodology and drug testing itself have undergone a major metamorphosis since its infancy with the military in the 1970's (MacDonald, Wells and Fry, 1993).

With the advent of E.O.12564, a remarkable decade ensued- numerous lawsuits were filed which not only challenged the Constitutionality of drug testing under the 4th and 14th Amendments (see NTEU v VonRaab, 109 S.Ct.1384, and Skinner v Railway Labor Executives Assn 109 S.Ct. 1402), but also posed serious allegations of inaccurate and imprecise drug testing, citing the 5th Amendment right to due process.

Those concerns were particularly well founded. In the year preceding the issuance of EO 12564 the Center for Disease Control (CDC) published the results of a blind study it had conducted with the National Institute of Drug Abuse (NIDA).

The CDC reported that each of the 13 drug screening laboratories it tested had reported multiple false positive and false negative results on blind samples, although they performed well on open proficiency samples. The labs reported unacceptable results for amphetamines in 100% of the cases, 91% were unacceptable for cocaine, etc. (Hansen, Caudill and Boone, 1985).

In light of studies such as those conducted by the CDC, professional organizations were very concerned about early drug testing practices. Accurate and reliable test results were needed to forestall potential legal liability. The American Society of Clinical Chemistry spearheaded a consensus that the "gold standard" of testing required both a screening test and a gas chromatography/mass spectrometry confirmation (Substance Abuse testing committee [SATC], 1988).

Mandatory guidelines for federal testing

NIDA scientists and forensic toxicologists worked intensely to fulfill Reagan's mandate under EO 12564 and to define a practical laboratory program that would permit testing of urine for the five commonly used illicit drugs and their metabolites (marijuana, cocaine, amphetamines, opiates and phencyclidine) with a minimum of error and maximum of protection for employees (Under the Influence, 1994).

The result of their work was first published as the "mandatory guidelines for federal workplace drug testing programs" in April 1988 (DHHS, 1988). Just three months later a national certification program was implemented by NIDA.

The guidelines contain a number of safeguards, not the least of which is a mandatory certification program for all laboratories conducting urine testing of federal civilian employees. The guidelines include urine collection procedures, chain of custody provisions, strict quality control requirements, use of blind performance test specimens, a two step testing procedure and verification of all samples by a medical review officer. Specifically, the testing protocol includes screening by a FDA approved immunoassay and confirmation of all specimens which screen positive by gas chromatography/mass spectrometry (GC/MS).

In the nearly ten years which have elapsed since the issuance of the federal drug free workplace program drug testing has improved dramatically. Recent proficiency results are a far cry from the "Crisis in drug testing" which the CDC reported in 1985 (Hansen et al, 1985).

In fact with the possible exception of the 1990 study conducted by Knight, Freedman, Puskas, Martel and O'Donnell, where they found 2% false positives and 20% false negatives among certified laboratories, NIDA certified laboratories have consistently scored above 95% on blind studies. (Frings, 1987; Dyszel,1993; Drug testing methods, 1990).

Laboratories certified by DHHS (or more specifically the National Institute of Drug Abuse branch of DHHS which was renamed SAMHAS in 1994), have had remarkable success.

Fay points out in his 1991 book on drug testing, certification by HHS "has come to be regarded by the courts as a standard for judging the accuracy and reliability of employer drug-testing activities." It was not until 1990 that a laboratory certified under the guidelines had their certification revoked or suspended, when NIDA decertified three laboratories for false positive results for methamphetamines.

Although notified by the Assistant Surgeon General at the Bureau of Prisons (BP) in July 1989 that BP had erroneously disciplined an employee for using an illegal methamphetamine caused by the legal form of methampetamine found in an over-the counter drug, (GAO, GAO/GGD-91-25, 1991), DHHS failed to alert federal agencies and laboratories of the problem. It resurfaced in 1990 when three laboratories certifications were suspended because of a similar problem excessive ephedrine or pseudo ephedrine in over the counter medications gave false positives. This led to procedural changes implemented by DHHS. (Under the Influence, 1994).

Regulation of private industry drug testing labs

While it was estimated in 1992 that over 7 million Americans were subject to federal government drug testing requirements (The medical review, 1992), in the past decade private industry has also increased the use of drug testing.

More than 90% of the Fortune 500 companies report drug testing their employees (DeCew, 1994). Drug testing laboratories compete for the estimated $500 million dollar annual drug testing market (Newman, 1994).

Both the Senate and House considered legislation every year from 1988-1991 which would require that **all** laboratories which analyze urine samples for drugs for U.S.A. companies be certified and meet DHHS requirements. The most aggressive plan was presented by a House Subcommittee in 1991. Entitled the "Drug Testing Quality Act," (HR33) the legislation would not only have required that all drug testing in the US be conducted in accordance with or exceed the guidelines set forth by HHS, but also that laboratories and lab personnel who "knowingly" violate the standards would be liable for substantial civil and criminal penalties (US House, 1991). HR33 was never passed nor even brought before the entire House. Drug testing for private industry remains in 1996 largely unregulated.

Too Costly

After 1991 drug testing standards for federal employees may have if anything, loosened. In November 1992, the General Accounting Office (GAO) published a report entitled "Employee Drug Testing: Opportunities Exist to Lower Drug Testing Program Costs."

Utilizing the agency reports to DHHS and the DHHS semi-annual survey, GAO found that direct costs of federal civilian drug testing were $7.6 million for the period from October 1990-September 1991.

The direct costs in dollars were broken down as: 3.4 million for laboratory analyses, 3 million for sample collection, 1 million for medical review of test results and 0.2 million for purchase of blind performance test samples (GAO, November 1992). These exorbitant costs existed despite only about 0.5% of the samples tested were verified as positive.

To reduce costs GAO recommended eliminating the Medical Review Officer's (MRO) review of negative samples, reducing quality assurance programs, reducing frequency of sampling and collecting samples in house. HHS decreased the number of blind samples required and decreased the frequency of blind challenges (from 6 to 4 per year) when it revised the guidelines in 1994. (DHHS, June 1994).

The semi-annual survey published by DHHS which covers the period from October 1992-March 1993 listed 2.0 million dollars in direct costs for the 6-month period (DHHS, June 1995). The most recent semi-annual survey covering October 1993- March 1994 still lists 1.6 million direct testing costs, while testing 30% fewer employees than the Oct 1992-March 1993 period. (DHHS, February 1996).

Although laboratory testing represented the largest percentage of direct costs, GAO did not propose to alter the immunoassay screening and GC/MS confirmation. Rather in the updated guidelines, DHHS authorizes the use of an additional immunoassay to "minimize possible presumptive positives due to the presence of structural analogues in the specimen." (DHHS, 1994, section 2.4 (e)(4)).

The guidelines continue to mandate the confirmation of positive samples by GC/MS. Such testing is extremely costly; expenses average $58 per person tested (DHHS, February 1996).

The costs of laboratory testing is indeed a critical factor for many companies. Typically a screening tests runs $15-25, with the confirmation rising to $75 (Drug testing methods, 1990).

A GAO investigation on testing in the private sector found numerous companies completely omitted confirmatory testing. Some private industry companies report retesting positive samples with the same test (i.e. usually an immunoassay screen). (GAO, 1988). McMillan (1989) citing both this report and a study conducted by Thomas-Holladay (1989) wrote "it is most unfortunate that with the widespread proliferation of drug testing programs many companies do not perform any confirmatory testing."

On-Site Testing

Recently numerous companies have opted for less expensive alternatives to the immunoassay screen/GC-MS confirmation. Confirmation by GC/MS not only involves labor consuming and time consuming preparations and separations, but also highly trained personnel.

Syva the manufacturer of enzyme multiplied immunoassay (EMIT), in its 1990 pamphlet entitled "Emit Drug Abuse Assays: How Accurate Are They?," does not stress the need to confirm the screening results by GC/MS. While GC/MS is mentioned as a reference method, Syva recommends confirmation by a method with comparable sensitivity (GC/MS is significantly more sensitive), but which differs chemically.

Syva also contends that "repeating the test or obtaining verbal corroboration from the suspected user may be adequate confirmation." (Syva, 1990)

In contrast, one of the manufacturers of radioimmunoassay, Roche, includes a warning with each of its procedures to confirm positive results by GC/MS.

On site testing is the latest tool used by some private companies. David Evans an attorney specializing in drug testing, has written a series of articles on the use of non-instrument, on-site testing. Evans contends that on-site testing may actually be superior in court since there will not be a question of loss of chain of custody (i.e. the employee is assured that it is actually his sample). (Evans, April, 1992). Evans further contends that while non-instrument on-site tests are not as accurate as GC/MS, they are as accurate as many laboratory tests, and on-site testing does not require the use of trained laboratory technicians to perform the testing. (An Interview with David Evans, December 1992), (Evans, January/February 1992).

Towt and his Roche Diagnostic Systems colleagues (1995) reviewed the performance of the onsite ONTRAK TESTCUP which contained immunochromatographic reagents. The TESTCUP system was found to be similar to other immunoassays in reactivity and accuracy for the analyses of benzoylecgonine, morphine and marijuana (THC).

Similarly a study by Jenkins, Darwin, Huestis, Cone, and Mitchell (1995) reinforces the need to confirm the onsite AccuPINCH THC test (a competitive enzyme immunoassay), with GC/MS.

DuPont, Saylor and Shiraki (1993), reviewed a number of immunoassay on-site drug testing products. These products which are about the size of a standard playing card included immunoassays from Roche, Abuscreen & On-Trak, Hycor's accuPINCH, EZ Screen manufactured by Editek, Drug Screening System Triage of Biosite Diagnostics, and ASCEND Multiimmunoassay.

While the authors recommend on-site testing for cost effectiveness and speed of analyses, they also note that questionable or challenged results of on-site testing should always be retested with the currently accepted "gold standard," gas chromatography/ mass spectroscopy at a reference laboratory. (DuPont, Saylor and Shiraki, 1993).

Statement of Problem

In an era when the U.S. government is combating unprecedented financial deficit is it only a matter of time until the extensive requirements DHHS promulgated for federal drug testing are revised? Costs exceed more than $23,000 per positive test result. (DHHS, 6/95). Utilizing SAMHSA (Substance Abuse and Mental Health Services Administration) surveys covering October 1992-March 1994, that federal civilian drug testing costs were approximately 12 million dollars per year for 1993 and 1994. The testing covered approximately 70,000 employees per year. (DHHS, 6/95, 10/95, 2/96).

Specifically the laboratory analysis is the most costly aspect of the entire testing process and government regulations for laboratory analysis exceed those used in most of private industry. GAO has already recommended a number of changes which DHHS has implemented.

Methodology of the screening immunoassay has improved dramatically in the past decade. Detection limits have decreased, problems such as ibuprofen interference on the EMIT marijuana screen have long since been resolved (Mac Donald, 1990). Some manufacturers contend that immunoassays may be adequately confirmed by repeating the test and even contend that some alleged "false positives" are caused by a failure in the confirmatory testing procedures (Syva, 1990).

Gas chromatography/mass spectrometry is clearly the "gold standard" of drug testing, its use helped to eliminate and resolve a number of erroneous results in the 1980's. However GC/MS is also riddled with time consuming preparations and separations, expensive equipment and the necessity to have highly trained personnel. With the large body of knowledge that exists regarding the immunoassay screens and potential interferences, is it necessary to continue the use of GC/MS as the "gold standard" of confirmatory testing?

Research Questions

Have immunoassays used for drug testing improved to such an extent that confirmation by GC/MS is no longer necessary? Is there a difference between the results obtained by the immunoassay and GC/MS for each of the five major drugs and metabolites tested in the federal civilian workforce?

Purpose of the study

The purpose of this study is to determine, under the same analytical conditions (i.e. federal agencies which follow DHHS guidelines and utilize DHHS certified labs), whether a difference exists between the number of positive test results from the screening test and number of positive confirmatory tests.

Which of the five major drugs or metabolites marijuana (THC), cocaine (benzoylecgonine), amphetamines/ methamphetamines, opiates,phencyclidine has the lowest positive predictive value(PPV) - and thus least likely that the positive screening test is indicative of a true positive? Which has the highest PPV?

Assumptions

1. All collection and testing was done in accordance with DHHS guidelines.

2. The laboratory utilized a FDA approved immunoassay and GC/MS confirmation.

3. Only samples which tested positive on the immunoassay screen were submitted for confirmatory testing.

4. All lab personnel were trained in accordance with HHS and agency requirements.

5. Contract laboratories accurately submitted to each agency a synopsis of agency samples tested, number screened positive for each drug or metabolite, and number confirmed positive for each drug or metabolite.

6. Blind Performance Test Specimens (BPTS's) were included in the monthly statistical summaries.

Limitations

1. Some laboratories (e.g. Navy labs) perform two radioimmunoassay (RIA) screens prior to confirmatory testing. Would expect therefore a higher percentage of samples to be confirmed, since second screen would help eliminate "random" errors of carryover, cross contamination.

2. Since only samples which screen positive are submitted for confirmatory testing, this study will not generate "false negative" rates.

3.Statistical differences between results obtained from immunoassay and confirmatory testing will be underestimated for the above reason.

4. There are differences in interferences **between** immunoassays. Thus comparisons should identify which immunoassay method was used.

5. Differences exist between threshold limits of screen (immunassay) and confirmation Gas Chromatography/ Mass Spectrometry test. GC/MS is better able to quantitate and is more sensitive than any of the initial immunoassay screens.

6. The screening cutoff limit for marijuana was lowered from 100 ng/ml to 50 ng/ml in June 1994

7. Some data was obtained from contract labs via agencies as a direct response to FOIA request, nearly two years after it was initially derived.

8. Any missing months of agency data will necessitate insertion of data by the researcher, using agency monthly averages.

Definition of terms

Amphetamines- general term to describe synthetic ephedrine derivatives. Structurally the compound contains a phenyl group with an amino group on the side chain.

Analyte- substance being measured (e.g. codeine, phencyclidine).

Blind Performance Test Specimens (BPTS's)- prepared urine samples (blind samples) spiked with known levels of drugs or drug metabolites, used to monitor the performance of the drug screening laboratory. BPTS's appear to the laboratory analyst as routine urine samples.

Cannabinoids- cannabis sativa is an Indian hemp plant that contains a psychoactive component identified as delta-9-tetrahydrocannabinol (Δ 9-THC). "Marijuana" is the common term for the leaves and flowers.

Chain of custody- procedures to account for the integrity of each urine sample by tracking its handling and storage from the point of specimen collection to final disposition of the sample.

Cocaine- an alkaloid of the plant Erthroxylon coca, a central nervous system stimulant. Chemically the structure is benzoylmethylecgonine. The two main metabolites are benzoylecognine (35-45%), and ecgonine methyl ester (32-49%).

Confirmatory test- a second analytical procedure to identify the presence of a specific drug or metabolite, which is independent of the initial test and which uses a different technique and chemical principles from that of the initial test in order to ensure reliability and accuracy. Currently gas chromatography/ mass spectrometry is the only confirmatory approved by DHHS for the analysis of urine samples for drugs of abuse.

Cross reactivity- In immunoassays, interaction of antibodies with substances similar to drug that assay was designed to measure.

Cutoff limit- (or threshold limit), established by DHHS for each instrument, drug /metabolite, level at or above which the sample will be classified as positive.

Detection limit- lowest analyte concentration that can be reliably measured. Detection limits are always lower than cutoff limits. (I.e. detection limit of a THC RIA 1-5 ng/ml.)

False negative- apparent absence of a drug or drug class which is in fact present in the sample at or above the pre-established cutoff limit.

False positive- apparent presence of a drug or drug category which is not in fact present.

False presumptive positive- positive test result on the initial immunoassay screen, which is not confirmed to be positive by the second GC/MS confirmatory test

FOIA- Freedom of Information Act

Immunoassay- screening test based on the principle of competition between (added) labeled and unlabeled antigen (drug) for binding site on a specific antibody. There are three basic immunoassays Radioimmunoassy (RIA), Enzyme Multiplied Immunoassy (EMIT or EIA), and Fluorescence Polarization Immunoassay (FPIA).

Interference- a part of the sample other than the target analyte under investigation which can or did cause a response in the analysis. Interferences may contribute to either false positive or false negative results.

Matrix effects- interferences caused by physiological sample constituents (e.g. proteins, electrolytes), rather than the target analyte, may results in enhancement, suppression or other alteration of results.

Metabolite- compound produced from chemical changes of a drug in the body.

Medical Review Officer (MRO)- a licensed physician responsible for receiving laboratory results who has knowledge of substance abuse disorders and has appropriate medical training to interpret and evaluate an individual's positive test result together with his or her medical history and other relevant biomedical information.

Opiates- a class of narcotic drugs manifesting sedative, mood-altering and analgesic properties. They include the naturally occurring alkaloids from opium- morphine and codeine, semisynthetic opiates such as heroin, oxycodone and hydromorphon. Morphine and codeine are derived from unripe seed capsules of the poppy plant.

Phencyclidine- 1-(1-phenylcyclohexyl)piperidine (PCP) was first used as an experimental general anesthetic under the trade name Sernyl. PCP is synthesized with relative ease and has psychotic side effects.

Positive Predictive Value (PPV)- likelihood that a positive screening test is predictive of actual drug use.

$$PPV = \frac{\text{true positives (or GC/MS positives)}}{\text{Positives on screening test}}$$

Presumptive Positive- sample which has been flagged as positive by a screening test but has not yet been confirmed by an equally sensitive alternative chemical method (GC/MS).

SAMHSA- Substance Abuse and Mental Health Services Administration a subdivision of the Department of Health and Human Services (previously National Institute of Drug Abuse or NIDA). Responsibilities include monthly listing of all laboratories approved by DHHS to perform federal civilian testing, and compilation of semiannual surveys on federal drugfree workplace programs.

Screening tests- used to detect potential drug users and eliminate from further testing specimens that are drug free. Screening tests must have low detection limits, and be relatively specific and sensitive. Only FDA approved immunoassays have been authorized by DHHS for use as screening tests for federal employees urine tests.

Sensitivity- likelihood that a test will give a positive test result when the drug is actually present.

$$\frac{TP}{TP+FN} \times 100 = \text{SENSITIVITY}$$, where TP=true positive, FN= false negative

Alternatively sensitivity has also been defined in drug testing literature as the ability of a particular screening test to differentiate among a class of drugs- e.g. ability to discriminate between morphine and codeine opiates.

Specificity- likelihood that a test will give a negative result when the drug is absent.

$$\frac{TN}{TN+FP} \times 100 = \text{SPECIFICITY}$$, where TN= true negative, FP = false positive

Testing Designated Position (TDP)- Civilian positions which the federal government, Department of Justice and federal courts have determined have met the criteria for random drug testing.

Verified positive test result- a test result that has been screened by a FDA approved immunoassay, confirmed by GC/MS assay to be at or above the cutoff limits established by HHS, and determined by the Medical Review Officer to have no legitimate medical reason for the drugs presence in the employee's system.

CHAPTER II

LITERATURE REVIEW

Scope of the literature

The review of the literature was limited to the period immediately preceding the issuance of EO 12564 (i.e. 1985), until the present. It focused on immunoassays, GC/MS and federal testing programs.

Review of the literature

There is a multitude of literature regarding the efficacy of various immunoassays and GC/MS for the analysis of marijuana (THC-COOH metabolite), cocaine (benzoylecgonine metabolite), opiates, amphetamines/methamphetamines, and phencyclidine.

Most comparisons of immunoassays include a description for a valid screening test and provide an overall explanation of the technique. Screening tests, also called presumptive tests, are in general initial sorting procedures to eliminate from further consideration those samples which are drug free or contain drugs below the established cut-off level. Conversely screening tests also highlight for further consideration (i.e. confirmatory testing), those samples which apparently contain one or more target drugs (or metabolites) at or above their respective threshold or cut-off level (Dubowski, 1990).

As noted by the Council on Scientific Affairs [COSA] (1987), while screening tests strive for maximum sensitivity, some weakly positive samples will be interpreted as negative owing to sensitivity or precision limitations (Blanke, 1987).

It is impossible for any screening test to correctly identify 100% of the positive test results and 100% of the negative test results. This is especially true near the detection limit of the instrument. (Jenny, 1989).

Inherent in the DHHS selection of FDA-approved immunoassays as the screening choice for urine samples, and the DHHS determination of where the cutoff limits should be for particular drugs, is the recognition that immunoassays will results in a certain percentage of false negatives.

Although false negatives are best avoided since a negative test result ends the testing process, while presumptive positives are submitted for confirmatory testing by GC/MS, from the employee/employer standpoint, the negative consequences of a false positive test result (i.e. loss of job, possible criminal charges), many believe it is perhaps best to err on the side of false negatives.

Immunoassays

Immunoassay techniques involve competition between the sample containing the drug to be tested and a labeled (or added) drug, for binding sites on the specific antibody to the drug. As described by Hawks (1986), the antibodies are protein substances with sites on their surfaces to which specific drugs or drug metabolites will bind. These antibodies are formed by inoculating animals with appropriate immunogens (e.g. sheep antibodies are often included in the immunoassay kits).

The differences in methodology between various immunoassays lies in the manner in which the antibody has been produced, incorporated into the system (suspended in media, bound to solid surface), and the actual binding to the antibody (The medical review, 1992).

There are three major categories of FDA-approved immunoassays. Enzyme multiplied immunoassay (EMIT or EIA), is marketed by Syva Corporation; fluorescence polarization immunoassay (FPIA) marketed by Abbott labs under the trade name TDx and ADx, radioimmunoassy (RIA) marketed under the name Abuscreen by Roche Diagnostics; and as Coat-a-Count by Diagnostic Products Corporation. (The medical review, 1992).

Hawks (1986) contends that the differences between immunoassays is mainly in the indicator that is used. Smith and Joseph (1989) explain, by the amount of drug present measured via radioactivity (RIA), fluorescence (FPIA), or enzyme activity (EMIT).

Radioimmunoassay

Radioimmunoassay (RIA) is the oldest immunoassay method. The sample and a known quantity of radiolabeled drug are combined with antibodies and allowed to equilibrate. The excess unlabeled drug must be separated from the drug bound to the antibodies before drug concentrations can be determined by gamma counting equipment. There is an inverse relationship between the gamma count and drug concentration. (Montagne, Pugh, and Fink, 1988). A positive test specimen is identified when the radioactive counts are equal to or lower than those of a positive control prepared in the same manner as the unknown urine (Hawks, 1986).

Schwartz (1988) identifies the advantages of RIA as: low limit of detection, small sample volume required, automation of pipetting and counting, and reasonable cost of testing. Disadvantages include use of radioactive substances, obligatory separation of free and bound fractions, high equipment costs and relatively slow turnaround times.

[COSA] (1987) lists several other problems with RIA: needs special training in use of radioactive substances, and expensive gamma counter, discrete tests (only one drug may be tested at a time), adulterants may cause false presumptive positives, linearity of response and cross reactivity with other drugs may produce both false negatives and false positive results. Others list the handling, storage and disposal of radioactive wastes as a liability ([SATC], 1988; Mandel, 1992).

Armbruster, Schwarzhoff, Hubster and Liserio (1993), have used RIA successfully for years, but note the methodology suffers from short reagent shelf life, lack of automated analysis and waste disposal requirements.

Enzyme Multiplied Immunoassay

Concerns with the handling of radioactive material, licensing, etc. do not arise with enzyme multiplied immunoassay (EMIT or EIA). Introduced in 1972 by Syva, urine is mixed with a specific antibody and enzyme substrate. The enzyme activity of the drug is measured. (Smith & Joseph, 1989).

EMIT is based on the immunochemical recognition of the three dimensional molecular structure of the drug (Schwartz, 1988). There is an inverse relationship between the extent of enzyme indicator reaction and the drug concentration in the sample (Montagne et al, 1988). Most clinical labs currently use EMIT, it has the advantage of a nonisotopic endpoint that can be measured photometrically. In contrast with RIA, analysis time is short and it is a homogeneous assay requiring no separation step for free and bound fractions ([SATC],1988).

Mandel (1992) contends that EMIT is less sensitive than FPIA or RIA and less precise at low drug concentrations. EMIT is prone to cross reactivity (Cone, Dickerson, Paul and Mitchell, 1993). False or unconfirmed positives may result from temperature changes in the sample (DeCew, 1994); (Smith and Joseph, 1989).

Armbruster et al discussed the potential for carryover using EMIT technology following the analysis of samples with high drug content, particularly cocaine. Schwartz (1988), contends that the ease of adulteration is another disadvantage.

Fluorescence polarization immunoassay

Fluorescence polarization immunoassay (FPIA) is a competition between drugs in the urine and fluorescent drug analogue for limited sites on the antibody. (Schwartz, 1988).

If large amounts of drugs are present, less fluorescent drugs will bind to the antibody. The reaction mixture is exposed to plane polarized light of a wavelength that will excite the fluorescent label.

Among the advantages of FPIA is the lack of radioactivity, its ease of operation, speed and ability to yield quantitative results automatically. It is highly sensitive but susceptible to sample adulteration ([COSA], 1987).

At least two other studies confirm the proclivity for FPIA results to be adulterated. Schwarzhoff and Cody (1993), studied various potential adulterants and concluded that a number are capable of causing false negative results. Baiker, Serrano and Lindner (1994) also found that adding bleach created some false negatives for FPIA results.

Kinetic Interaction of Microparticles in Solution (KIMS)

In 1992, a new immunoassay methodology was introduced by Roche called kinetic interaction of microparticles in solution to be used with Roche ONLINE assays. (Armbruster et al,1993). KIMS is an extension of Roche's ONTRAK assays which utilize latex immunoassay techniques.

As described by Armbruster et al (1993), with typical immunoassay technology the drug of interest is conjugated to a "tag" or analytical signal, such as a radioisotope, enzyme or fluorescent molecule. With KIMS, the analytical signal is produced by microparticles. Just as with the other immunoassay technology, when a urine sample containing the drug of interest is mixed with reagents, unconjugated drug in the sample will "compete" for antibody binding sites, the amount of lattice formation "is inhibited proportional to the concentration of the drug in urine." (Armbruster et al, 1993). The absorbance difference between the first and final readings decrease with higher drug concentrations.

Recently both ONTRAK (latex) and ONLINE (KIMS) have been increasingly utilized by DHHS accredited laboratories. In fact the Laboratory Corporation of America which performs testing for the Department of Transportation, reports that it utilizes KIMS on approximately 90% of the screening samples. (Personal communication, May, 1996).

Gas chromatography/ mass spectrometry confirmation

Gas chromatography/mass spectrometry (GC/MS) combines the chemical separating power of the gas chromatograph "fingerprinting", with the molecular identifying power of the mass spectrometer ([COSA], 1987). Drugs are identified with GC/MS by their gas chromatographic retention time and by ions that form in the mass spectrometer (Schwartz, 1988).

GC/MS can be operated in several modes. As pointed out by the Clinical Chemistry substance abuse testing committee (1988), with high drug concentration the mass spectrometer can be operated in the "full scan" mode.

In this mode the complete mass spectrum of the analyte is presented, from its molecular ion to the fragments formed by the ionization process. This "fingerprint" provides the most conclusive identification of the compound. This identification can be based on matching of the mass spectrum with those contained in the MS library.

Alternatively the mass spectrometer can be operated in the selected ion monitoring mode. In this mode only the currents of a few fragments characteristic of the analyte are monitored.

Preparation of samples for GC/MS is often labor and time consuming. Extraction techniques are utilized in which the drug or analyte is separated by a procedure designed specifically for that analyte. Most GC/MS procedures chemically change the analyte to form a derivative (The medical review, 1992).

Urine testing of drugs of abuse

Opiates

Morphine, codeine and semisynthetic derivatives of morphine (i.e. heroin) belong to the class of drugs called opiates. Heroin (diacetylmorphine) is strictly a drug of abuse, whereas morphine and codeine are commonly used in analgesics and cough medicines and are often prescribed. (Hawks and Chiang, 1986).

The Department of Health and Human Services guidelines require the analysis of codeine and/or morphine above the cutoff limits and clinical evidence by the Medical Review Officer to verify illegal use of opiates. Heroin may only be verified with clinical evidence (heroin tracks) or by a confirmation of the presence of 6-monoacetylmorphine with GC/MS. (DHHS, 1994).

Part of the exceptional provisions that DHHS put in place to verify opiates are due to the extended use of opiates in nonprescription drugs, prescription drugs, their crossreactivity, and availability in everyday foods (like poppy seeds).

There have been a series of studies conducted on poppy seed cakes, muffins, rolls, etc., which point to positive morphine results caused by the poppy (opiate) seeds. Positive results may occur approximately 3 hours after ingestion of one to two rolls or muffins. ([SATC], 1988). McCutcheon and Wood (1995), recently conducted a study on Nabisco Sociables crackers, and affirmed a positive test result (both screening and confirmatory testing) approximately 2 hours after ingestion of a half-box.

Metabolically codeine and morphine often coexist in urine samples. Cone et al in 1993 noted that heroin is rapidly metabolized by hydrolysis to morphine; morphine and codeine are metabolized by oxidation and coupling mechanisms.

Heroin use may be distinguished from morphine or codeine intake by the detection of 6-monoacetylmorphine, a specific marker for heroin use (Tai, Christensen, Paule, Sanders and Welch, 1994).

Lin, Lafolie, and Beck (1994) conducted a study assessing the measurement of urinary opiates, and noted that due to heroin's rapid metabolisis, it is not reliably detected. The analytical target, 6-acetylmorphine may be detected only for a relatively short time (less than 8 hours), after intake. Lin and the others note that the hydrolysis step in the confirmation process of opiates is critical. A failure to do so properly may result in erroneous conclusions.

Another study conducted by Fuller and Anderson (1992) reached a similar conclusion. They found that the failure to analyze samples promptly and/or refrigerate them led to the loss of significant amounts of 6-acetylmorphine by hydrolysis.

Smith and his colleagues (1995) reviewed the effect of various prescription opiates often given as analgesics or antitussives on various opiate immunoassays. Oxycodone (Percodan®) is one of the most commonly prescribed drugs in the opiate series (classified as 6-keto-opiods). The researchers concluded that nearly all of the semisynthetic drugs, specifically hydrocodone, hydromorphone and oxycodone could crossreact and cause false presumptive positive test results for TDx, Abuscreen or EMIT.

Cone et al (1993) conducted another comprehensive study of the four commercial opiate screening immunoassays. They administered known amounts of codeine, morphine and heroin to healthy male volunteers. Cone and his colleagues concluded that less than 5% of heroin and morphine specimens tested as false negatives by each of the immunoassays.

Some codeine specimens were identified as false positives by TDx, Abuscreen and EMIT as a result of multiple codeine metabolites.(Cone et al, 1993). EMIT demonstrates significant cross reactivity. The CAC test was specific for free morphine and thus gave numerous false presumptive positives for codeine.

A unique 1990 Rockwell International blind study which included known interferences of the EMIT screening tests, found that opiates have the highest false positive rate of any of the drugs of abuse. The study reports more than 5% false presumptive positives for opiates. (Knight et al, 1990).

Ferrara and his colleagues (1994) conducted an intensive study comparing nine different screening techniques for various drugs of abuse. The Italian forensic toxicologists reported high false positive and false negative rates (7.9% and 8.0%, respectively) for opiates by Coat-a Count RIA. The FPIA ADx assay was slightly better (6.3% false presumptive positives and 6.5% false negatives).

EMIT I showed the lowest false positive rate (2.8%) but still had a high false negative (6.9%). All test results (positive and negative) were confirmed with another analytical technique and GC/MS. (Ferrara et al., 1994).

Cannabinoids/ Marijuana

Delta-9-tetra hydrocannabinol (THC) is the primary psychoactive ingredient present in the leaves and flowering tops of cannabis plants. THC is rapidly transformed by the liver enzymes to several metabolites- the primary one is 11-nor-delta-9-tetra hydrocannobinol-9-carboxylic acid (9-carboxy-THC). (Hawks and Chiang, 1986).

THC is approved by the Food and Drug Administration and marketed under the trade name Marinol®, for two purposes as an antiemetic for cancer patients utilizing chemotherapy and as an appetite stimulant for AIDs patients. (ElSohly and Jones, 1995).

Cannabinoids are hydrophilic molecules subject to adsorption to solid surfaces from aqueous solutions, such as urine. (Blanc et al, 1993).

Haver, Romson and Sadrazadeh (1991) also point out the tendency for THC to adhere to a variety of surfaces. In their study, Haver and the others found numerous instances of false positive EMIT results due to carryover from previous high drug samples. The study lists carryover as a known problem with high volume analyzers especially if there is inadequate washing of the probe between analyses.

In the late 1980's Ibuprofen (Advil™, Motrin™) was reported to cross react and produce presumptive false positives with several immunoassys for THC. (U.S. House, 1987). The manufacturer however, took steps to rectify the problem; ibuprofen is no longer an interferent in the analysis of cannabinoids. (McBay, 1989). Despite anecdotal stories to the contrary, melanin metabolite from dark skinned persons also does not interfere with the EMIT screen (Schwartz, 1988).

Perhaps more than any other drug-of-abuse, cannabinoid immunoassys are prone to successful adulteration and subsequent false negative results (Schwarzhoff and Cody, 1993). Baiker et al (1994) reported the addition of bleach causes decreased THC concentrations and potential false negatives for each immunoassay.

Altunkaya and Smith (1990) cite several instances of aberrant RIA cannabinoid results (both false positive and false negative). The researchers believe the erroneous results were caused by proteinaceous interfering materials; high blood proteins in urine produced erroneously low radioimmunoassay results.

There have been a series of studies dealing with the stability of THC, and THC derivatives. Paul, McKinley, Walsh, Jamir and Past (1993) found due to its lipophilic nature and low solubility, freezing samples led to a decrease in THC concentration. However, another study by Dugan, Bogema, Schwartz and Lappas (1994) disputed this.

It is clear whether due to lipophilic action, adherence to walls, cross reactivity of immunoassays with other cannabinoid metabolites, or some other reason, that GC/MS results which are specific for the THC-COOH metabolite are often lower than expected from the initial immunoassay screen.

Blanc et al (1993) found that Δ 9-THC concentrations in calibrators and controls have been observed to decline in normal use. This makes quantitation more difficult.

Nonetheless most toxicologists report that cannabinoid immunoassays have consistently given reliable assessments of illegal drug use with few false presumptive positives and with the lowering of the cutoff for cannabinoids from 100ng/ml to 50 ng/ml has resulted in few false negatives (Huestis, Mitchell and Cone, 1994).

The study conducted by Ferrara and his colleagues (1994) found higher false positive (FP) and false negative (FN) rates than previously reported. Ferrara reported for ADx (FPIA) a false presumptive rate of 6.0%, 2.7% false negative. RIA (CAC)- 4.7% FP, 2.4% FN, and EMIT-1 2.5%FP, 10.4%FN.

Armbruster and his associates (1993), compared immunoassay techniques for the analysis of several drugs including marijuana. They found RIA and ONLINE (KIMS) detected 99% of the confirmed positive samples. TDx detected 95% of confirmed positives and EMIT 88%. The researchers concluded the performance of EMIT was comparable to previous studies.

Cocaine

Cocaine (benzoylmethylecgonine $C_{17}H_{21}NO_4$) is mostly excreted in metabolized form. The two major metabolites in urine are benzoylecgonine and ecgonine methyl ester. It has been estimated that total dose eliminated is approximately 46% benzoylecgonine (BE) and 41% ecgonine methyl ester (EME) ([SATC], 1988).

A number of studies document the major metabolites of cocaine and their usefulness as an indicator of illegal drug use. (Hippensteil and Gerson, 1994). The benzoylecgonine metabolite can be detected for a longer period than either the nonmetabolized cocaine or ecgonine methyl ester (48-72 hours by EMIT, 96-144 hrs. by RIA).

Hornbeck, Barton and Czarny (1995) note that cocaine has the shortest detection time in urine of any of the five major drugs monitored by DHHS.

Several studies evaluate the effectiveness of different immunoassays in the analysis of urine samples for cocaine metabolite(s). Armbruster and his colleagues (1993) have experienced an occasional carryover problem following the analysis of a high cocaine sample in their Air Force laboratory. They found a carryover problem occured with RIA, KIMS and EMIT. Yet Armbruster et al document excellent results for screening of cocaine as well as an excellent correlation between screening and confirmatory results. RIA detected 99.6% of confirmed positive samples, EMIT-99.3%, and TDx-98.9%.

Another study by Hailer, Glienke, Schwab and von Meyer (1995), compared the analyses of EMIT d.a.u. and modified ONLINE KIMS method. The researchers found both systems effectively identified positive cocaine samples.

While the results obtained by Armbruster were not completely corroborated by Italian toxicologists Ferrara et al's 1994 study, the second study did find that cocaine immunoassays gave the best overall results/correlation of any of the drugs of abuse. Ferrara and the others found EMIT-1 gave a false presumptive positive rate of 0.9%, a 5.6% false negative (FN) rate. FPIA results were: 0.5% FP and 8.8% FN. RIA: 0.7% FP, 1.7% FN.

Phencyclidine

Phencyclidine (PCP) is one of a series of arylcyclohexylamines that produce similar psychotic effects. PCP undergoes oxidation and conjugation in the body. Unchanged PCP is excreted in the urine in moderate amounts (10% of the dose). (Hawks and Chiang, 1986).

The nonmetabolized PCP which is excreted in the urine is actually what is measured in the laboratory. Immunochemical methods are relatively specific for PCP.

Immunoassay false positives have been reported with the administration of thoridazine (Mellaril™), dextromethorphan (found in prescription cough medicines) and chlorpromazine (Thorazine™) (Smith and Joseph, 1989). Other RIA interferences include diazepam (found in valium) and imipramene (tricyclic antidepressant) (U.S. House, 1987).

Additional potential cross reactive prescription and nonprescription medications reported for RIA and EMIT include: diphendramine, doxylamine, and meperidine ([COSA], 1987).

When threshold limits were first established for phencyclidine by HHS in 1988 at 25 ng/ml for the screening immunoassay, only RIA had a significantly low detection limit to accurately assess urine samples for PCP. Since that time the Syva corporation has developed a new immunoassay (EMIT 700) with acceptable accuracy and detection limits, the previous EMIT assay had a detection limit of 75 ng/ml. Syva also developed a procedure to adapt its previous unit with a 25 ng/ml calibrator. Cary, Johnson, Folsom and Bales's 1992 study reported that the Emit d.a.u could be successfully adapted.

In 1993 Schwarzhoff and Cody found PCP assays remarkably insensitive to adulterations.

Neither Armbruster (1993) nor Ferrara (1994) whose comprehensive immunoassay comparisons discussed most of the drugs of abuse covered phencyclidine. According to Armbruster "too few positive samples were found to allow a method comparison."

Ferrara's study excluded phencyclidine since Italian epidemiological data did not show it to be among the major abused drugs.

One of the few comparisons of immunoassays for the detection of PCP in urine was conducted by Caplan and Levine. (1989). Caplan and Levine compared the TDx, ADx and EMIT d.a.u. assays for phencyclidine. All immunoassays tested correctly identified 50 urine samples which contained phencyclidine.

Amphetamines/ Methamphetamines

The term amphetamines encompasses not only amphetamines and methamphetamines (N-methyl derivatives of amphetamine), but also several other chemically related phenethylamines that are easily available in "over-the-counter" preparations. These substances usually are phenylpropanol amine, pseudoephedrine, and phenylephrine-each of which has the potential to interfere with the screening immunoassay. ([SATC], 1988).

There exists a special need to confirm amphetamines so that the specific substance is accurately identified. While the developers of the DHHS guidelines were aware of the difficulty evaluating amphetamines and methamphetamines due to numerous interferences with the screening immunoassays, they were perhaps unaware of the problem with confirmatory testing until the late 1980's and early 1990's.

As previously discussed in the introduction of this thesis, there were a series of notices in the federal register regarding the suspension and subsequent reinstatement of NIDA certified laboratories which had misidentified methamphetamines. (ElSohly, 1992). The problem arose when most GC/MS confirmation tests were not able to differentiate between d-methamphetamine and legal over-the-counter l-methamphetamine. (The d and l designations refer to the dextro-rotary and levo-rotary optical isomers which are mirror images of each other).

The inability of many GC/MS procedures to distinguish between the two isomers is compounded when taken in combination with the use of legal Vicks inhalers which also contain l-methamphetamine. Many labs were unable to perform a chiral GC/MS assay to separate the two isomers (d and l isomers). (Hornbeck and Czarny, 1993).

The action of certified labs (Roche Biomedical) to misidentify methamphetamines resulted in the firing of some employees for illegal drug use, and subsequent expensive litigation. (Murphy, Barlow, and Hatch, 1994).

Poklis and Moore (1995) examined the response of EMIT immunoassays following use of Vicks inhalers by several volunteers. They concluded that EMIT did produce false positives following use of Vicks inhalers in specified situations.

An extensive two-year study conducted by Hornbeck and Czarny at the San Diego Navy drug screening laboratory, concludes that over-the-counter, prescription medications and inhalers can cause false positive results for the illegal d-methamphetamine. They recommend a chiral separation.

ElSohly and his associates (1992) recommend treating samples with sodium periodate to eliminate over-the-counter interferences.

D' Nicoula, Jones, Levine and Smith (1992) also reference the false positives at several certified testing labs. They assert that amphetamine-like compounds phenylpropanolamine, pseudoephedrine, and ephedrine which appear in over-the-counter cold, stimulant and diet medications, when present in very high concentrations absent amphetamines may produce false positives for methamphetamines.

One hypothesis for false confirmatory tests is that thermal dehydration of ephedrine or pseudoephedrine in the injection port or other heated zone on the GC/MS caused products of methamphetamine. (The medical review,1992).

DHHS took steps to alleviate the problem by requiring quantification of a certain level of amphetamines (≥ 200 ng/ml) in addition to greater than 500 ng/ml methamphetamines, in order to confirm the presence of methamphetamines. (DHHS, 1994).

Methamphetamine is slowly metabolized to amphetamine, therefore urine containing the illegal form of methamphetamine should also contain some amphetamines.

A study by Valentine (1995) and his colleagues utilizing ten volunteers administered d-methamphetamine, concludes that the new DHHS requirements result in numerous false negatives.

Beyond the concerns with the confirmatory testing, the immunoassay screening of amphetamines and methamphetamines is riddled with complications. Armbruster et al (1993) wrote that "amphetamine screening is traditionally a problematic activity and our data underscores the variability that can be expected for immunoassays."

Armbruster and the others conducted a very large study (> 50,000 samples), comparing immunoassays. They found that agreement for the four immunoassays is not as good for amphetamines and methamphetamines as it is for the other four major drugs of abuse, further Armbruster and his colleagues found a number of unconfirmed presumptive positives being reported by several of the immunoassays.

Cody and Schwarzhoff (1993) further assert that "the analysis of samples for the presence of amphetamines and amphetamine analogues is a difficult process and no single immunoassy holds a clear advantage over the other commercially available reagents."

Several over-the-counter preparations used as decongestants and diet aids containing ephedrine and phenylpropanolamine (amphetamine-like compounds) are capable of producing false EMIT and RIA tests if present in significant concentrations.

Hawks and Chiang (1986), list several prescription drugs- benzophetamine, fenfluramine, mephentermine, phenmetrazine and phentermine which can also produce false positive immunoassay results.

There have been several studies comparing the efficacy of each immunoassay test for the presence of amphetamines and methamphetamines. According to a study conducted by D'Nicoula and his colleagues, EMIT showed the greatest tendency to produce false presumptive positives.

Roche's RIA was reported to produce false presumptive positives with l-ephedrine, norephedrine, d-pseudoephedrine, l-pseudoephedrine, d,l-norephedrine, etc.

Each of the immunoassays exhibits strong reactivity to the d versus l drugs for which they are designed. Other reported false presumptive positives were caused by chlorpromazine and fluspirilene for EMIT. (Crane, Dawson and Tickner, 1993). Rantidine used in the treatment of gastric and peptic ulcers also caused presumptive false positives.

It is perhaps to be expected with the large body of interferences, inability to distinguish between legal and illegal optical isomers, that the screening of amphetamines are the least accurate of any of the major drugs of abuse.

Knight and her colleagues (1990) in their blind study of certified labs found not false positives for amphetamines and methamphetamines, but rather the largest percentage of false negatives (37%). Ferrara et al (1994) also found a surprisingly low false positive rate for the immunoassays but high false negative rates. (i.e. 38% for EMIT, 44.9% for RIA).

Baker et al (1995) conducted a study comparing EMIT and ONLINE (KIMS) for the analysis of amphetamines. They found both immunoassays produced false positives. Of 110 positive amphetamine samples, 201 tested positive by EMIT, 137 by ONLINE. This correlates to a positive predictive value (or agreement between the immunoassay and GC/MS), of 55% for EMIT and 80% for ONLINE.

Previous Studies of Drug Testing Programs

Previous studies including the most recent SAMHSA semiannual survey which covered October 1993-March 1994, report verified positive test results for all federal civilian employees of approximately 0.6% of those tested (DHHS, February 1996). The report lists cocaine tested as the most commonly abused drug of the civilian workforce (51%), followed by marijuana at 42%.

A thesis written by Doster and Ross (1993), describes the Air Force military drug testing program in 1992. The Air Force reports 0.35% of their military samples were laboratory confirmed positive during that year. Following review by the Medical Review Officer, 0.10% of Air Force military personnel samples were verified positive for illegal drug use. The 1992 positive results for the Air Force military may be broken down as: 0.32% opiates, 0.17% marijuana, 0.13% cocaine, 0.06% amphetamines, and < 0.01% PCP.

Smith Kline Beecham clinical laboratories have provided one of the few analyses of laboratory positive test results, in contrast to those verified test results which are reported after review by the MRO. They reported that positive confirmatory laboratory tests had declined from 18.1% in 1987 to 8.8% of the more than 2 million samples which they tested in 1991. Smith Kline reported that 34.6% of the 1991 positive test results were for marijuana followed by 29% for cocaine. (The medical review, 1992)

A more recent report from Smith Kline Beecham (1996) asserts that true positive test results have now declined for the eighth straight year and lists laboratory positive rates of 8.4%, 7.5%, and 6.7% for 1993, 1994, and 1995 respectively.

Additionally the prevalence rates were lowest for safety sensitive transportation workforce as compared to the general workforce (3.4% vs 7.5%) for 1995. (Smith Kline Beecham, 1996).

Summary of the Literature

It appears from the array of previous studies which assessed the ability of screening tests to accurately identify positive urine samples, that EMIT is the most widely studied. There have been differences found between the three immunoassays, however generally all are most accurate for the detection of the metabolites of cocaine and marijuana and PCP. More difficulty exists in the analysis of amphetamines, methamphetamines and opiates.

The most recent semi-annual survey of federal drugfree workplace programs (DHHS, 2/96) reports that 54 agencies conducted drug testing from October 1, 1993-March 31, 1994. These agencies average slightly above 0.6% verified positive test results. (Verified test results include a determination by the MRO whether there is a legitimate reason for a drugs presence, and/ or review of data/ chain of custody documents for scientific sufficiency). However the report did not provide information or rates on the samples that were confirmed positive for each of the five drugs/ metabolites, nor did it address screening results whatsoever. (DHHS, Feb. 1996)

Other studies such as those reported by Smith Kline Beecham (The medical review, 1992; Smith Kline Beecham, 1996), and Doster and Ross (1993) while providing data on confirmed positive rates, do not address differences between the results from screening or confirmation nor deal with federal civilans or employees tested under the same stringent DHHS guidelines.

In the ten years that have elapsed since the issuance of President Reagan's Federal drug free workplace program immunoassay technology has improved dramatically. There have been many studies comparing the efficacy of the immunoassy for each of the five major drugs of abuse, but most studies have been conducted in a controlled laboratory environment. Previous studies such as those of Ferrara, Knight, and the others while establishing an impressive array of data concerning the effects of adulteration, interferences, temperature variations etc. dealt almost exclusively with BPTS's, controlled samples and standards which they had prepared or purchased.

Conversely several studies involved administering quantities of drugs to volunteers and monitoring drug levels over a period of time. Armbruster's study may be an exception in that he utilized Air Force military data from his own laboratory, but again military personnel were not subject to the same stringent DHHS requirements as their civilian federal employee counterparts.

This study deals with how the drug free workplace and drug testing actually works in the real world, it involves a large period of time covering many civilian employees tested under a variety of circumstances The existing literature does not address these issues.

Chapter III

METHODS

This chapter is a summary of the methods to be used in conducting this study. The following topics will be reviewed: research questions, hypothesis testing, positive predictive values, false positive rates, population, sampling selection, data acquisition and analysis.

Research Questions

The purpose of this study was to analyze the accuracy of immunoassays for the detection of positive urine samples. This was determined by comparing positive immunoassays with the results of the GC/MS confirmatory testing. Secondly the need for continued confirmatory testing was assessed based on those comparisons.

The following research quesions were constructed from the statement of purpose:

1. Is there a difference in the number of positive immunoassay screens and the number of samples which are ultimately confirmed by GC/MS? From this an even more basic question may be derived- has immunoassay technology improved to such an extent that GC/MS confirmation is no longer necessary, and false presumptive positives no longer occur?

2. For which drugs/metabolites is the difference between the positive rates from the immunoassay and positive GC/MS results most significant? Simply put, which has the lowest positive predictive value?

Hypothesis testing

The use of hypothesis testing in the present study is ill advised. This thesis deals with drug testing as it is actually performed at federal agencies. DHHS protocol requires that all samples be submitted for screening immunoassays but only those which test positive are subsequently submitted for confirmatory testing. (DHHS, 1994). The study is derived not from two independent samples, but rather one very large sample.

Generally hypothesis testing with a z-test would be the statistical treatment of choice given the size of the sample (> 100), although it typically involves two independent samples (Glaser, 1995).

McNemars test for correlated proportions is useful when the same subjects are measured or observed twice. (Dawson-Saunders and Trapp, 1990). It is often utilized when comparing subjects who have received two different medical treatments. Determinations are made of both false positives and false negatives by each technique. In this study false negatives were unable to be derived since the majority of the samples (all which tested negative on the initial inmmunoassay), were not submitted for confirmatory testing.

Dunn (1977) described the usage of hypothesis testing, and z scores coupled with McNemars test when comparing a single sample vaccination study of rubella and measles. Nonetheless, the lack of available information on how the negative immunoassays would have tested by GC/MS, and the dependency of the two tests upon each other is why the z-test, McNemars test and hypothesis testing is inappropriate here.

Positive Predictive Values and False Presumptive Positive Rates

Dawson-Saunders and Trapp (1990) note that studies which compare two methods, where one is considered a "gold standard," often measure the accuracy of the diagnostic procedure by calculating sensitivity (or positive predictive value) and specificity. Specificity or ability to detect negative samples correctly has been determined in previous studies to be well above 99% for the immunoassays tested. (Hansen, Caudill and Boone, 1985; Dawson-Saunders and Trapp ,1990).

In this study, the accuracy of the screening test is determined through the tests ability to correctly identify positive samples or positive predictive value (PPV). This measures the sensitivity of the test. Secondly while unable to directly measure specificity since negative sample are not submitted for confirmatory testing, false presumptive positive rates will help to assess the "specificity" of the test (false positive rates are inversely related to specificity).

In lieu of hypothesis testing many scientific journals recommend the use of confidence intervals while expressing data. This includes Lancet and the American Journal of Epidemiology among others. Confidence levels help assess the precision of the effect estimate.

Dawson-Saunders and Trapp explain the current emphasis on confidence intervals on three factors. Initially readers are reminded that estimates in the study have variability and the same results may possibly not be replicated in another study. Secondly confidence intervals provide the same information that a statistical test provides and more; the 95% interval provides a summary of several statistical tests. Finally, confidence intervals are appropriate in some studies (like this one) when hypothesis testing is not.

Confidence intervals (95%) for a proportion in single groups are calculated in the following manner: observed proportion(p) +/- 1.96 x Standard error of proportion = p +/-1.96 x (p (1-p)/n) to the 1/2 power.

Confidence intervals were computed throughout this study for positive predictive values and for false presumptive positive rates using 95% confidence intervals. This means that in only 5% or less cases the "true" parameter is not within the interval listed.

For instance if a false positive rate of 0.50% is derived from a sample (n) of 1000, the confidence interval is 0.5%+/-1.96 x ((0.5)(0.5)/1000) to the 1/2 power or 0.47-0.53%.

Population

The population of a study is defined by Babbie (1995) as that group about whom we want to be able to draw conclusions, very rarely however are we able to study all the members of the population.

For this study the population of interest is federal civilian employees.

Sampling Selection

The federal drug free workplace semi-annual survey compiled by the Substance Abuse and Mental Health Services Administation (DHHS, 1995), for the period of October 1, 1992- through March 31, 1993 (corresponding to the beginning of this study), lists the six federal agencies which tested the largest number of federal civilians. These are, respectively: Department of Transportation, Department of Navy, Department of Army, Department of Justice, Department of Air Force and Department of Veterans Affairs.

The six federal agencies listed above were utilized for this study since they performed the greatest amount of drug testing. Secondly these agencies test for all five of the major drugs of abuse (some agencies only test for marijuana and cocaine).

More than one agency was chosen to generate a larger sample, to make comparisons between immunoassays (impossible if only one agency were utilized), and to avoid reliance upon a single agency.

Laboratories which provide drug testing services for federal agencies are required under the Department of Health and Human mandatory guidelines for federal workplace drug testing programs (section 2.4 (g)(6)) to provide monthly statistical summaries to the agency of the number of specimens received, reported, screened positive and confirmed positive for each of the five major drugs/ metabolites.(DHHS, 1994).

Each of the six agencies identified above tested under the same DHHS requirements, during the same period and utilized FDA approved immunoassays and GC/MS confirmatory testing.

Data Acquisition

1. A FOIA (Freedom of Information Act) request was made to each of the six federal agencies identified above, requesting monthly statistical summaries for January 1993-December 1994.

2. In the event a response was not received within a two month period, a second certified FOIA request was sent.

3. Additional requests were initiated if information received was incomplete (i.e. missing months) or only confirmatory results submitted.

4. If information was still incomplete after step 3, this was noted. Missing data was asterixed, explained, and results inserted based on the monthly average of that agency for that year. If only confirmatory results were received, the agency was eliminated from the study.

5. Data submitted on an annual summary basis, rather than a monthly summary was accepted and compiled in a yearly format. All data was compiled in a yearly format.

6. Agency drug testing totals were computed for 1993 and 1994. Calculations of false presumptive positives, confirmed positive rates and positive predictive value for each drug/metabolite were computed. Confidence intervals were also determined at the 95% confidence level.

7. Contract laboratories identified as providing drug testing services for federal agencies above were contacted in writing. The lab was asked to indicate which immunoassay screening method used and if multiple screens were performed.

8. Laboratories which did not respond to #7, were contacted by phone, and sent a second certified letter.

9. If more than one immunoassay method was used by the six federal agencies (i.e. some agencies use EMIT and others RIA), comparisons were made between immunoassays.

Data Analysis

Calculations were made regarding the false presumptive positive rates for each drug of abuse. Comparisons were also made for each immunoassay. Calculations were made of false positive rates and confirmed rates for each drug/metabolite and for each agency. Calculations of PPV and false positive rates included confidence intervals set at 95%.

Glaser contends that to assess the quality of a diagnostic test it is critical to know its validity and reliabilty; so also may the quality of a study be gauged on the reliability and validity of both methodology and results. In this study,. the validity (or accuracy) of the screening test is determined by a comparison with the accepted "gold standard" gas chromatography/ mass spectrometry.

The validity of the results are further supported by the stringent DHHS requirements to which the laboratory is required to adhere, agency use of blind proficiency test samples, and laboratory accreditation procedures.

Reliabilty is defined as the reproducibility, repeatibility, precision. It is inappropriate to assess reliability with consistent confirmed positive rates, positive predictive values etc., because the results are dependent upon a multitude of different civilian samples.

Rather, reliabilty is strengthened by agency use of the same DHHS guidelines, covering the same period of time (1993 and 1994). The reliability of a study using a survey or questionnaire is often evaluated using a pretest or test-retest (Babbie, 1995: Doster and Ross, 1993). Clearly this evaluation method is inapplicable in this study.

Glaser (1995) believes that neither reliabilty nor validity is in question in routine lab testing. Laboratory use of quality control samples is indeed crucial however in the determination of reliability. Health and Human Services guidelines mandate the use of quality control samples, and blind proficiency samples.

Chapter IV

ANALYSIS OF RESULTS

This study deals with six federal agencies which conducted the largest amount of drug testing on their civilian employees during 1993 and 1994. Freedom of Information Act (FOIA) requests were submitted to the Departments of the Air Force, Army, Justice, Navy, Transportation and Veterans Affairs, seeking copies of 1993 and 1994 drug testing statistical summaries referenced in DHHS mandatory guidelines for federal workplace drugtesting programs (section 2.4 g(6), (DHHS, 1994)). Specifically this section required DHHS certified laboratories to supply the federal agencies for which it performs drug testing services, monthly statistical summaries of the number of agency samples analyzed, the number which screen positive and are confirmed positive for each drug or metabolite.

This information was in fact obtained from the FOIA offices of each agency identified above. All data was complete with the exception of the Department of the Navy. Navy was missing data from January, February 1993 and June 1994. Data was inserted for the missing months, based on the Navy's monthly average for 1993 and 1994 respectively.

While each of the six federal agencies utilized in this study conducted testing of its civilian employees for each of the five major drugs of abuse (or metabolites), some of the agencies required testing of all urine samples for the five drugs while others authorized the testing for some testing categories of marijuana (THC) and cocaine (benzoylecgonine), only.

As a result, the sample size used in this study range from 65,601 urine samples for phencyclidine, to 94,336 urine samples for benzoylecgonine.

The most recent SAMHSA semi-annual survey discussed earlier, lists 28,199 civilian drug tests performed in the 6 months from October 1, 1993- March 31, 1994. (DHHS, February 1996). It is estimated that this study covers more than one-half of the civilian federal employees tested during 1993 and 1994.

These agencies either performed drug testing through its own DHHS certified laboratory (Navy), or contracted drug testing services from another DHHS certified laboratory. The laboratories which conducted drug testing for the six agencies were contacted during this study and asked which immunassay(s) it utilized, and if it performed multiple screens. Only the Navy which performs drug testing services for itself and Veterans Affairs routinely uses more than one screen on individual specimens. The Laboratory Corporation of America which performs drug testing services for DOT performs an additional TDx screen, following a positive KIMS ONLINE screen and prior to confirmatory GC/MS testing for presumptive positive amphetamines.

The Navy performs two RIA screens using both Roche ABUSCREEN and Coat -a-Count, if the sample is still positive after the completion of both immunoassays then a GC/MS confirmatory test is performed. The Navy Drug Screening Lab at Great Lakes, Illinois wrote "all military labs are required to perform two screening assays"(Personal communication, 4/96).

Table 1 lists the six federal agencies, their contract laboratories and immunoassy utilized in the analysis of agency samples.

Table 1 Agencies and their Drug Testing Laboratories

Agency	Laboratory	Immunoassay
Department of the Air Force	Northwest Toxicology	Emit
Department of the Army	Northwest Toxicology	Abuscreen RIA
Department of Justice	PharmChem	Emit
Department of the Navy	Navy	Abuscreen RIA & Coat-a-Count RIA
Department of Transportation	Laboratory Corporation of America (previously. CompuChem)	90% KIMS, 10% EMIT Additional TDx amphetamines screen.
Department of Veterans Affairs	Navy	Abuscreen RIA & Coat-A-Count RIA

Cummulative screening data from six federal agencies for 1993 and 1994 is included in Table 2. The table lists the total number of federal civilian urine samples tested for illegal drugs under HHS guidelines in 1993 and 1994, at the selected agencies. The civilians were employed by the Departments of Air Force, Army, Justice, Navy, Transportation and Veterans Affairs. Table 2 also includes the number of samples which tested positive by the FDA approved screening immunoassay. Each of those samples were submitted for confirmatory testing. The table also reflects the number of samples which were then confirmed positive by GC/MS.

For example, during 1993 in the six agencies studied, 37,414 urine samples were tested for amphetamines, 184 were screened positive by an FDA approved immunoassay and submitted for confirmatory testing. One hundred forty three samples were ultimately confirmed positive by GC/MS.

Table 2 Departments of Air Force, Army, Justice, Navy, Transportation, and Veterans Affairs Cummulative Screening Results •

Positive Screened/ Positive Confirmations/ Total Screened

Date	Amph	Benzoyl.	Opiates	PCP	THC
TOTALS 93	184/143/ 37414	436/415/ 48813	338/252/ 34029	97/81/ 33159	442/432/ 48813
TOTALS 94	220/169/ 37173	380/377/ 45523	293/205/ 33426	96/83/ 32442	462/452/ 45493

• All screening summaries include blind quality control/ proficiency samples.

Calculations were made of the overall confirmed positive rates for each of the five major drugs of abuse (or metabolites) for 1993 and 1994, using the cummulative data from Air Force, Army, Justice, Navy, Transportation and Veterans Affairs. (Table 2A). This was calculated by dividing the number of confirmed positive samples by the total number of urine samples tested. In 1994 for instance, 1286 samples were confirmed positive from the 45,523 urine samples tested- this generates a confirmed positive rate of 2.82%.

Table 2A
Cummulative federal agency laboratory confirmed positive rates (Departments of Air Force, Army, Justice, Navy, Transportation, VA)

Date	Positive rate
1993 overall	2.71%
Amphetamines	0.38%
Benzoylecgonine	0.85%
Opiates	0.74%
Phencyclidine	0.24%
Marijuana (THC)	0.89%
1994 overall	2.82%
Amphetamines	0.45%
Benzoylecgonine	0.83%
Opiates	0.61%
Phencyclidine	0.26%
Marijuana (THC)	0.99%

Table 2B compiles cummulative false positive rates for the six agencies, they are 0.356% and 0.362% for 1993 and 1994 respectively. It is calculated by subtracting the number of samples confirmed positive from the number screened positive and dividing this by the total number of samples screened. In 1993, there were 1497 positive screens, 1323 confirmed positive in a total of 48813 urine tests (more samples were tested for THC and benzoylecgonine than any other drug, thus the denominator will be that number). This equates to a false positive rate of (1497-1323) / 48813 or 0.356%.

Table 2B
Cummulative federal agency false presumptive positive rates (Departments of Air Force, Army, Justice, Navy, Transportation,and Veterans Affairs)

Date	False Presumptive Positive Rate	95% Confidence Intervals
1993 overall	0.356%	0.352-0.360%
Amphetamines	0.110%	0.107-0.113%
Benzoylecgonine	0.043%	0.041-0.045%
Opiates	0.253%	0.248-0.258%
Phencyclidine	0.043%	0.041-0.045%
Marijuana (THC)	0.020%	0.019-0.021%
1994 overall	0.362%	0.358-0.366%
Amphetamines	0.137%	0.133-0.141%
Benzoylecgonine	0.007%	0.006-0.008%
Opiates	0.263%	0.258-0.268%
Phencyclidine	0.040%	0.038-0.042%
Marijuana (THC)	0.022%	0.021-0.023%

Table 2C lists the cummulative Positive Predictive Value (or PPV) for the six agencies. Positive Predictive Values are an important index in this study. It may be defined as the likelihood that a positive test result from a screening test is indicative of a true positive. (Glaser, 1995). Due to the variation between immunoassays many labs utilize data on positive predictive values data when they select and purchase particular commercial immunoassays. In this study true positives are assumed to be those samples which test positive (at or above the threshold level) on the GC/MS confirmatory test. Marijuana and Benzoylecgonine consistently showed the best PPV in the study.

Table 2C
Cummulative Positive Predictive Value (PPV), (Departments Air Force, Army, Justice, Navy, Transportation, Veterans Affairs)

Date	Positive Predictive Value	95% Confidence Intervals
1993 overall	88.4%	88.1-88.7%
Amphetamines	77.7%	77.3-78.1%
Benzoylecgonine	95.2%	95.0-95.4%
Opiates	74.6%	74.1-75.1%
Phencyclidine	83.5%	83.1-83.9%
Marijuana (THC)	97.7%	97.6-97.8%
1994 overall	88.6%	88.3-88.9%
Amphetamines	76.8%	76.4-77.2%
Benzoylecgonine	99.2%	99.1-99.3%
Opiates	70.0%	69.5-70.5%
Phencyclidine	86.5%	86.1-86.9%
Marijuana (THC)	97.8%	97.7-97.9%

Tables 3, 4, 5, 6, 7, and 8 compiles the data submitted by each agency, they are: Air Force (table 3), Army (table 4), Justice (table 5), Navy (table 6), Transportation (table 7), and Veterans Affairs (table 8). The tables show the number of agency urine samples tested, the number screened positive for each drug and metabolite, and the corresponding number confirmed positive.

In 1994 Northwest Toxicology which performed drug testing services for the Department of the Air Force (table 3), confirmed all 96 THC samples which screened positive by EMIT immunoassay (see also Table 1).

Table 3 Department of Air Force Screening Results •

Pos. Screened/ Pos. Confirmations/ Total Screened

Date	Amph	Benzoyl.	Opiates	PCP	THC
TOTALS 93	11/07/973	81/81/5553	07/05/351	03/03/344	96/96/5553
TOTALS 94	13/11/954	40/40/6098	03/03/303	02/02/303	93/93/6068

• All screening summaries include blind quality control/ proficiency samples.

Confirmed positive rates were determined for each agency , and categorized for each drug/metabolite tested by that agency during 1993 and 1994. This data is contained in table 3A (Air Force), 4A (Army), 5A (Justice), 6A (Navy), 7A (Transportation) and 8A (Veterans Affairs). Tables 4A- 8A are included on later pages following the applicable agency screening results. Confirmed positive rates are defined as the number of positive samples analyzed by GC/MS to be at or above the threshold level, in the total number screened. The threshold level is a predetermined cutoff level established by DHHS below which samples are classified as negative. For example the threshold for marijuana confirmation is 15ng/ml.

Table 3A for instance lists marijuana as having the highest confirmed rate of any of the drugs of abuse at the Department of the Air Force (1.73% and 1.53% for 1993 and 1994).

Table 3A
Air Force laboratory confirmed positive rates

Date	Confirmed Positive rate
1993 overall	3.46%
Amphetamines	0.72%
Benzoylecgonine	1.46%
Opiates	1.42%
Phencyclidine	0.85%
Marijuana (THC)	1.73%
1994 overall	2.44%
Amphetamines	1.15%
Benzoylecgonine	0.66%
Opiates	0.99%
Phencyclidine	0.66%
Marijuana (THC)	1.53%

Tables 3B -8B describe the false presumptive positive rates for the Departments of Air Force (3B),Army (4B), Justice (5B), Navy (6B), Transportation (7B) and Veterans Affairs (8B). Typically false positive rates (or false presumptive positives) are used to assess the number of samples which are identified as positive with the immunoassay screen but are not positive with the GC/MS confirmatory test. This is one of the most commonly used indexes in drug testing literature. Due the low prevalence of drug abuse among federal civilian employees, false presumptive positive rates are quite low. The Department of Air Force false presumptive positive rate (table 3B) of 0.03% for 1994 was the lowest in the study.

Table 3B
Air Force false presumptive positive rates

Date	False Presumptive Positive rate	95% Confidence Intervals *
1993 overall	0.108%	0.100-0.116%
Amphetamines	0.411%	0.408-0.414%
Benzoylecgonine	0%	N/A
Opiates	0.570%	0.520-0.620%
Phencyclidine	0%	N/A
Marijuana (THC)	0%	N/A
1994 overall	0.033%	0.028-0.038%
Amphetamines	0.210%	0.184-0.236%
Benzoylecgonine	0%	N/A
Opiates	0%	N/A
Phencyclidine	0%	N/A
Marijuana (THC)	0%	N/A

* Confidence intervals can not be derived with rates of either 0 or 100%.

As described earlier, the Positive Predictive Value indexes are perhaps the most important statistic in this study. In addition to the cummulative PPV's presented in Table 2C, Positive Predictive Values were determined for each agency for 1993 and 1994 and were determined for each drug/metabolite tested by that agency during the same time frame. As evidenced by Air Force data in Table 3C below, PPV's were excellent for both marijuana (100%) and benzoylecgonine (100%). This was also true of the other agencies.

Table 3C
Air Force Positive Predictive Value
PPV

Date	Positive Predictive Value	95% Confidence Intervals *
1993 overall	97.0%	96.6-97.4%
Amphetamines	63.6%	60.6-66.6%
Benzoylecgonine	100%	N/A
Opiates	71.4%	66.7-76.1%
Phencyclidine	100%	N/A
Marijuana (THC)	100%	N/A
1994 overall	98.7%	98.4-99.0%
Amphetamines	84.6%	82.3-86.9%
Benzoylecgonine	100%	N/A
Opiates	100%	N/A
Phencyclidine	100%	N/A
Marijuana (THC)	100%	N/A

* Confidence intervals can not be derived from rates of either 0 or 100%.

Department of the Army screening results are tabulated in table 4. It is notable that all THC and benzoylecgonine screens were confirmed. Army submitted all of its sample for testing for THC and benzoylecgonine. Some categories (those other than random, it appears) were tested also for amphetamines, phencyclidine and opiates. Drug testing services were supplied for the Army by Northwest Toxicology using RIA. (see Table 1).

Table 4 Department of Army Screening Results •

Pos. Screened/ Pos. Confirmations/ Total Screened

Date	Amph	Benzoyl.	Opiates	PCP	THC
TOTALS 93	19/19/6611	133/133/ 13430	38/29/3848	12/10/2985	119/119/ 13430
TOTALS 94	27/24/5194	139/139/ 8400	28/18/2098	5/5/1114	116/116/ 8400

• All screening summaries include blind quality control/ proficiency samples.

The Department of Army confirmed positive rates are presented in table 4A. As might be expected from the literature review, opiates closely follow cocaine and marijuana with the third highest confirmed positive rates.

Table 4A
Army laboratory confirmed positive rates

Date	Positive rate
1993 overall	2.31%
Amphetamines	0.29%
Benzoylecgonine	1.00%
Opiates	0.75%
Phencyclidine	0.34%
Marijuana (THC)	0.89%
1994 overall	3.61%
Amphetamines	0.46%
Benzoylecgonine	1.65%
Opiates	0.86%
Phencyclidine	0.45%
Marijuana (THC)	1.38%

Table 4B provides data on false presumptive positive rates for the Department of Army. To reiterate the rates are derived from subtracting the number of positive confirmatory tests from the number of positive screens divided by the total number screened. Army and Air Force had the lowest false presumptive positive rates in the study.

Table 4B
Army false presumptive positive rates

Date	False Presumptive Positive rate	95% Confidence Intervals *
1993 overall	0.082%	0.078-0.086%
Amphetamines	0%	N/A
Benzoylecgonine	0%	N/A
Opiates	0.233%	0.223-0.243%
Phencyclidine	0.067%	0.058-0.076%
Marijuana (THC)	0%	N/A
1994 overall	0.155%	0.147-0.163%
Amphetamines	0.058%	0.052-0.064%
Benzoylecgonine	0%	N/A
Opiates	0.48%	0.46-0.50%
Phencyclidine	0%	N/A
Marijuana (THC)	0%	N/A

* Confidence intervals can not be derived from rates of either 0 or 100%.

Table 4C lists Army positive predictive values for each drug/metabolite and overall Army rates for 1993 and 1994. Marijuana had the highest PPV at 100%, opiates had the lowest at 76.3% and 64.3%.

Table 4C
Army Positive Predictive Value
PPV

Date	Positive Predictive Value	95% Confidece Intervals *
1993 overall	96.6%	96.3-96.9%
Amphetamines	100%	N/A
Benzoylecgonine	100%	N/A
Opiates	76.3%	74.9-77.7%
Phencyclidine	83.3%	82.0-84.6%
Marijuana (THC)	100%	N/A
1994 overall	95.9%	95.5-96.3%
Amphetamines	88.8%	87.9-89.7%
Benzoylecgonine	100%	N/A
Opiates	64.3%	62.3-66.3%
Phencyclidine	100%	N/A
Marijuana (THC)	100%	N/A

* Confidence intervals can not be derived from rates of either 0 or 100%.

Department of Justice (DOJ) screening results are listed below in table 5. Justice submitted all urine samples for the battery of analyses including amphetamines, benzoylecgonine, opiates, PCP, and THC (unlike the Army and Air Force, which authorized testing of some categories for only marijuana and cocaine). Testing for the Justice Department was performed by PharmChem using an EMIT immunoassay screen.

In 1994, 2619 urine samples obtained from DOJ employees were tested. Of these 15 were screened positive by the EMIT immunoassay for amphetamines, 5 were later confirmed positive by the GC/MS confirmatory test.

Table 5 Department of Justice Screening Results •

Pos. Screened/ Pos. Confirmations/ Total Screened

Date	Amph	Benzoyl.	Opiates	PCP	THC
TOTALS 93	21/7/2067	11/10/2067	27/16/2067	08/07/2067	08/07/2067
TOTALS 94	15/05/2619	04/04/2619	23/15/2619	04/04/2619	12/12/2619

• All screening summaries include blind quality control/ proficiency samples.

Department of Justice confirmed positive rates are found in table 5A. This table is of special interest because opiates had the highest confirmed positive rates of any of the drugs of abuse at DOJ in both 1993 and 1994.

Table 5A
DOJ laboratory confirmed positive rates

Date	Positive rate
1993 overall	2.3%
Amphetamines	0.34%
Benzoylecgonine	0.48%
Opiates	0.77%
Phencyclidine	0.34%
Marijuana (THC)	0.34%
1994 overall	1.5%
Amphetamines	0.19%
Benzoylecgonine	0.15%
Opiates	0.56%
Phencyclidine	0.15%
Marijuana (THC)	0.46%

Department of Justice false presumptive positive rates are found in table 5B. Amphetamines and opiates had the highest false presumptive positive rates of any of the Department of Justice's tested drugs of abuse.

Table 5B
DOJ false presumptive positive rates

Date	False Presumptive Positive rate	95% Confidence Intervals *
1993 overall	1.25%	1.11-1.39%
Amphetamines	0.68%	0.66-0.70%
Benzoylecgonine	0.048%	0.039-0.057%
Opiates	0.435%	0.415-0.455%
Phencyclidine	0.048%	0.039-0.057%
Marijuana (THC)	0.048%	0.039-0.057%
1994 overall	0.687%	0.667-0.707%
Amphetamines	0.38%	0.36-0.40%
Benzoylecgonine	0.%	N/A
Opiates	0.31%	0.29-0.33%
Phencyclidine	0%	N/A
Marijuana (THC)	0%	N/A

* Confidence intervals can not be derived from rates of 0% or 100%.

Positive Predictive Values for DOJ are contained in table 5C. Amphetamines had a PPV of 33 1/3% for both 1993 and 1994. PharmChem which performed contract drug testing services for the Department of Justice reported use of EMIT as its immunoassay screen.

Table 5C
DOJ Positive Predictive Value
PPV

Date	Positive Predictive Value	95% Confidence Intervals *
1993 overall	66.2%	64.2-68.2%
Amphetamines	33.3%	31.3-35.3%
Benzoylecgonine	90.9%	89.7-92.1%
Opiates	59.3%	57.2-61.4%
Phencyclidine	87.5%	86.1-88.9%
Marijuana (THC)	92.3%	91.2-93.4%
1994 overall	69.0%	67.2-70.8%
Amphetamines	33.3%	31.5-35.1%
Benzoylecgonine	100%	N/A
Opiates	65.2%	63.4-67.0%
Phencyclidine	100%	N/A
Marijuana (THC)	100%	N/A

* Confidence intervals can not be derived from rates of either 0 or 100%.

Table 6 lists screening data for the Department of the Navy. Navy civilian and military analysts performed its own drugtesting services at its accredited labs in Norfolk, Va. and Great Lakes, Illinois. Navy is unique among the drug testing laboratories in that it routinely performs two RIA immunoassay screens. Table 6 is notable in the comparatively large number of phencyclidine samples which screened and were ultimately confirmed positive. For instance Navy labs found about 48 lab positive PCP samples in the two year period.

Table 6 Department of Navy Screening Results •

Pos. Screened/ Pos. Confirmations/ Total Screened

Date	Amph	Benzoyl.	Opiates	PCP	THC
TOTALS 93**	30/26/ 11612	92/82/ 11612	101/85/ 11612	24/20/ 11612	84/80/ 11612
TOTALS 94**	58/51/ 13334	81/81/ 13334	105/60/ 13334	29/28/ 13334	120/115/ 13334

• All screening summaries include blind quality control/ proficiency samples.

** Navy data was missing for January, February, 1993 and June 1994. Data was inserted based on Navy monthly averages for 1993 and 1994 respectively.

Table 6A found below, lists confirmed positive rates for the Department of the Navy in 1993 and 1994. Overall confirmed positive rates were consistent throughout the Navy in 1993 and 1994 at about 2.5%.

Table 6A
Navy laboratory confirmed positive rates

Date	Positive rate
1993 overall	2.52%
Amphetamines	0.22%
Benzoylecgonine	0.71%
Opiates	0.73%
Phencyclidine	0.17%
Marijuana (THC)	0.67%
1994 overall	2.51%
Amphetamines	0.38%
Benzoylecgonine	0.61%
Opiates	0.45%
Phencyclidine	0.21%
Marijuana (THC)	0.86%

False presumptive positive rates for the Navy are contained in table 6B. Navy rates (along with all the agencies in this study), are very low- and this in part may be attributed to the low prevalence of drug abuse among civilians.

Table 6B
Navy false presumptive positive rates

Date	False Presumptive Positive rate	95% Confidence Intervals *
1993 overall	0.327%	0.319-0.335%
Amphetamines	0.034%	0.031-0.037%
Benzoylecgonine	0.086%	0.081-0.091%
Opiates	0.138%	0.132-0.144%
Phencyclidine	0.034%	0.032-0.36%
Marijuana (THC)	0.034%	0.032-0.036%
1994 overall	0.435%	0.427-0.443%
Amphetamines	0.052%	0.049-0.055%
Benzoylecgonine	0%	N/A
Opiates	0.337%	0.329-0.345%
Phencyclidine	0.007%	0.006-0.008%
Marijuana (THC)	0.038%	0.035-0.041%

* Confidence intervals can not be derived from rates of either 0 or 100%.

Table 6C lists Positive Predictive Values for the Navy. For instance the 1993 overall statistics indicate that 88.5% of the Navy results obtained by the RIA screening immunoassay were ultimately confirmed by GC/MS.

Table 6C
Navy Positive Predictive Value
PPV

Date	Positive Predictive Value	95% Confidence Intervals
1993 overall	88.5%	87.9-89.1%
Amphetamines	86.7%	86.1-87.3%
Benzoylecgonine	89.1%	88.5-89.7%
Opiates	84.2%	83.5-84.9%
Phencyclidine	83.3%	82.7-84.0%
Marijuana (THC)	95.2%	94.8-95.6%
1994 overall	85.2%	84.6-85.8%
Amphetamines	87.9%	87.3-88.5%
Benzoylecgonine	100%	N/A
Opiates	57.1%	56.2-58.0%
Phencyclidine	96.6%	96.3-96.9%
Marijuana (THC)	95.8%	95.5-96.1%

* Confidence intervals can not be derived from rates of either 0 or 100%.

The most interesting agency results obtained in this study came from the Department of Transportation. Efforts were made by the researcher to ascertain the validity of the data supplied by Transportation (from Laboratory Corporation of America), including seeking clarification from DOT on at least three separate occasions. Below in Table 7 is a synopsis of the data supplied by DOT regarding drug testing of Transportation civilian employees in 1993 and 1994.

Table 7 Department of Transportation Screening Results •

Pos. Screened/ Pos. Confirmations/ Total Screened

Date	Amph	Benzoyl.	Opiates	PCP	THC
TOTALS 93	75/58/ 11196	91/83/ 11196	99/71/ 11196	13/12/ 11196	72/70/ 11196
TOTALS 94	76/49/ 10954	66/64/ 10954	76/59/ 10954	21/09/ 10954	65/61/ 10954

- All screening summaries include blind quality control/proficiency samples.

Doctor Wingert of the Laboratory Corporation of America reports that his lab

Doctor Wingert of the Laboratory Corporation of America reports that his lab utilized KIMs in approximately 90% of the cases while EMIT was used in about 10%, for the analysis of DOT samples in 1993 and 1994. The Laboratory Corporation of America also used a second immunoassay screen for positive amphetamine samples by TDx. Table 2A lists the confirmed positive rates by the lab for DOT samples.

Table 7A
DOT laboratory confirmed positive rates

Date	Positive rate
1993 overall	0.82%
Amphetamines	0.01%
Benzoylecgonine	0.15%
Opiates	0.59%
Phencyclidine	0%
Marijuana (THC)	0.07%
1994 overall	0.72%
Amphetamines	0.02%
Benzoylecgonine	0.11%
Opiates	0.50%
Phencyclidine	0%
Marijuana (THC)	0.11%

Table 7B lists the false presumptive positive rates for the Department of Transportation in 1993 and 1994. False presumptive positives (or positive tests on the screening immunoassay which subsequently test negative and beneath the threshold level on the GC/MS confirmatory test) ranged from overall rates of 0.500% in 1993 to 0.566% in 1994.

Table 7B
DOT false presumptive positive rates

Date	False Presumptive Positive rate	95% Confidence Intervals
1993 overall	0.500%	0.491-0.509%
Amphetamines	0.152%	0.145-0.159%
Benzoylecgonine	0.071%	0.066- 0.076%-
Opiates	0.250%	0.242-0.258%
Phencyclidine	0.009%	0.007-0.011%
Marijuana (THC)	0.018%	0.015-0.021%
1994 overall	0.566%	0.557-0.575%
Amphetamines	0.246%	0.238-0.254%
Benzoylecgonine	0.018%	0.016-0.020%
Opiates	0.156%	0.149-0.163%
Phencyclidine	0.110%	0.104-0.116%
Marijuana (THC)	0.037%	0.033-0.041%

The Positive Predictive Values for screening immunoassays used in the analysis of DOT employees are listed in Table 7C. To reiterate Positive Predictive Value is defined as the ability of the screening test to accurately assess positive samples. The PCP results with a PPV for 1994 at 42.9% (and a combined rate of 61.8% for both years) may cause concern to the laboratory and agency alike.

Table 7C
DOT Positive Predictive Value
PPV

Date	Positive Predictive Value	95% Confidence Intervals *
1993 overall	84.0%	83.3-84.7%
Amphetamines	77.3%	76.5-78.1%
Benzoylecgonine	91.2%	90.7-91.7%
Opiates	71.7%	70.9-72.5%
Phencyclidine	92.3%	91.8-92.8%
Marijuana (THC)	97.2%	96.9-97.5%
1994 overall	79.6%	78.8-80.4%
Amphetamines	64.5%	63.6-65.4%
Benzoylecgonine	97.0%	96.7-97.3%
Opiates	77.6%	76.8-78.4%
Phencyclidine	42.9%	42.0-43.8%
Marijuana (THC)	93.8%	93.3-94.3%

* Confidence intervals can not be derived from rates of either 0 or 100%.

The Department of Veterans Affairs also utilized the Department of the Navy drug screening laboratories during 1993 and 1994. A summary of the data obtained from Veterans Affairs is contained below in table 8. For instance in 1994, 31 samples were screened positive by the RIA immunoassays for amphetamines and 29 of those were subsequently confirmed. This data is found below in table 8.

Table 8 Department of Veterans Affairs Screening Results •

Pos. Screened/ Pos. Confirmations/ Total Screened

Date	Amph	Benzoyl.	Opiates	PCP	THC
TOTALS 93	28/26/4955	50/46/4955	66/46/4955	37/29/4955	63/60/4955
TOTALS 94	31/29/4118	50/49/4118	58/50/4118	35/35/4118	56/55/4118

- All screening summaries include blind quality control/ proficiency samples.

Table 8A lists the confirmed positive rates for the Department of Veterans Affairs during 1993 and 1994. Veterans Affairs had the highest confirmed positive rates in the study. In 1993, 4.2% of the samples tested were confirmed positive, and in 1994 -5.3%.

Table 8A
Veterans Affairs laboratory confirmed positive rates

Date	Confirmed Positive rate
1993 overall	4.18%
Amphetamines	0.52%
Benzoylecgonine	0.93%
Opiates	0.93%
Phencyclidine	0.59%
Marijuana (THC)	1.21%
1994 overall	5.3%
Amphetamines	0.70%
Benzoylecgonine	1.19%
Opiates	1.21%
Phencyclidine	0.85%
Marijuana (THC)	1.34%

False positives (or false presumptive positives) are contained in table 8B for Veterans Affairs. As with most of the other agencies the false presumptive positive rates are quite low.

Table 8B
Veterans Affairs false presumptive positive rates

Date	False Presumptive Positive rate	95% Confidence Interval *
1993 overall	0.747%	0.735-0.759%
Amphetamines	0.040%	0.035-0.045%
Benzoylecgonine	0.081%	0.073-0.089%
Opiates	0.403%	0.389-0.417%
Phencyclidine	0.161%	0.151-0.171%
Marijuana (THC)	0.061%	0.054-0.068%
1994 overall	0.291%	0.277-0.305%
Amphetamines	0.049%	0.042-0.056%
Benzoylecgonine	0.024%	0.019-0.029
Opiates	0.191%	0.179-0.203%
Phencyclidine	0.%	N/A
Maijuana (THC)	0.024%	0.019-0.029%

* Confidence intervals can not be derived from 0 or 100% rates.

Table 8C contains data on Positive Predictive Values for Veterans Affairs in 1993 and 1994. In 1993 for example, Veterans Affairs RIA immunoassay screens predicted actual laboratory positive test results in 84.8% of the cases.

Table 8C
Veterans Affairs Positive Predictive Value
PPV

Date	Positive Predictive Value	95% Confidence Intervals*
1993 overall	84.8%	83.8-85.8%
Amphetamines	92.9%	92.2-93.6%
Benzoylecgonine	92.0%	91.2-92.8%
Opiates	69.7%	68.4-71.0%
Phencyclidine	78.4%	77.3-79.5%
Marijuana (THC)	95.2%	94.6-95.8%
1994 overall	94.8%	94.1-95.5%
Amphetamines	93.5%	92.7-94.3%
Benzoylecgonine	98.0%	97.6-98.4%
Opiates	86.2%	85.1-87.3%
Phencyclidine	100%	N/A
Marijuana (THC)	98.2%	97.8-98.6%

* Confidence intervals can not be derived fron rates of either 0 or 100%.

Comparison of positive immunoassays and positive GC/MS confirmatory tests.

Research Question #1

Research question #1 asks if there is a difference in the number of positive immunoassay screens and the number of samples which tested positive on the GC/MS confirmatory test. As evidenced by the screened positive rates and confirmed positive rates found in table 9 below, there is in fact a difference between the number and the rate for the two testing categories. This difference exists for all 5 categories overall, and for each individual category of drug/metabolite. Further information on the differences which exist between the initial and confirmatory tests may be found in both the positive predictive value and false presumptive positive rates of the screening test.

Table 9 Comparison of Screening positives and GC/MS positives (95% Confidence Intervals), 1993 and 1994 combined results •

Drug/ Metabolites	n- Number of samples	Screened positive rate	Confirm. positive rate	PPV of screening test	False Presumptive Positive Rate
Amphet.	74587	0.0054	0.0042	77.2% (76.9-77.5%)	0.123% (0.121-0.125%)
Benzoylec.	94336	0.0086	0.0084	97.4% (97.1-97.5%)	0.022% (0.021-0.23%)
Opiates	67455	0.0094	0.0068	72.4% (72.1%-72.7%)	0.258% 0.255-0.261%
PCP	65601	0.0029	0.0025	85.0% (84.7-85.3%)	0.044% (0.042 -0.046%)
THC	94306	0.0096	0.0094	97.8% (97.7-97.9%)	0.021% 0.020 -0.022%)
All 5 Drugs Cummul.	94336	0.03125	0.0277	88.5% (88.3-88.7%)	0.359% (0.356%-0.362%)

- All screening summaries include blind quality control/proficiency samples.

Research Question #2

The second research question dealt with which drug/ metabolite showed the greatest difference between the positive test results of the immunoassay and the positive GC/MS results. The best method of evaluation for this second research question is the positive predictive value. Positive predictive values measure the likelihood that the positive screening test is accurate- and the identified illegal drug is in fact present in the urine sample.

Table 2C (pg. 53) and Table 9 (pg. 78) lists the positive predictive value for opiates (74.6% and 70.0% for 1993 and 1994, the combined rate for both years is 72.4%). The next largest difference was found for amphetamines (77.7% and 76.8% for 1993 and 1994 respectively). Marijuana (THC) had the highest overall positive predictive value of any of the drugs of abuse (97.8%), followed closely by cocaine metabolite (97.4%).

Comparisons were also made between immunoassays. Which immunoassays had the highest PPV for each drug? Which had the highest overall PPV for all five drugs combined? Which was the lowest? Table 10, below lists the screening results by immunoassay- it provides information on the number of samples tested, the number screened positive, and confirmed positive. Both the positive predictive values and false presumptive positive rates were derived from those results. EMIT screening data was used by the Departments of Air Force and Justice. RIA data was used by Army, Navy and Veterans Affairs. The Department of Transportation lab used KIMs as the major immunoassay.

KIMS was reportedly used by Laboratory Corporation of America for DOT samples (for the purpose of this comparison all DOT samples are attributed to KIMs, even though the lab said it used EMIT 10% of the time). (Personal communication, 5/96). It is also important to recognize that Navy labs utilized two screening RIA's for the testing of its own Navy and Veterans Affairs samples.

Table 10 Comparison of Screening Results by Immunoassay, 1993 and 1994 •

Number of Positive samples Screened/Pos. Confirmed/ Total Screened

Immuno	Amphet.	Benzoylec.	Opiates	PCP	THC	All 5 Drugs
EMIT	60/30/6613	136/135/ 16337	60/39/5340	17/16/5333	209/208/ 16307	482/428/ 16337
RIA	193/175/ 45824	545/530/ 55849	396/288/ 39965	142/127/ 38118	558/545/ 55849	1834/1665/ 55849
KIMS	151/107/ 22150	157/147/ 22150	175/130/ 22150	34/21/ 22150	137/131/ 22150	654/536/ 22150

- All screening summaries include blind quality control/ proficiency samples.

Table 10A below lists positive predictive values for each of the three immunoassays studied. Calculations were made for each drug/metabolite tested and data accumulated for all five drugs. While Table 9 presented earlier (pg. 78) showed that amphetamines had the second lowest positive predictive value found in this study at 77.2%, as indicated here radioimmunoassay is by far the most accurate immunoassay for the detection of amphetamines. In fact even assuming the low end of the 95% confidence interval, RIA successfully identified more than 90% of amphetamine samples. While KIMs detected 70.9% of positive amphetamine samples correctly, it is important to consider the second immunoassay screen used by Lab Corp. of America by FPIA.

RIA had higher overall positive predictive values and detected slightly more positive samples than EMIT. However it is inappropriate to use this study as a validation of RIA over EMIT since the data supplied by Navy labs showed use of two RIA screens, while all data supplied by labs which used EMIT, indicated the use of the lone immunoassay.

Data for KIMs shows lower positive predictive values than either other FDA approved immunoassay. Particularly for phencyclidine samples, these results may indicate laboratory problems, questionable lab quality control, and are inconsistent with results for KIMs published in the literature. There was evidence in the literature however that KIMs experienced problems early in it use, and these results were obtained for 1993 and 1994, only a year after the technology was introduced.

Table 10A Comparison of Positive Predictive Values for Different Immunoassays •

Positive Predictive Value (95% Confidence Intervals), 1993 and 1994 Combined

Immuno	Amphet.	Benzoyle.	Opiates	PCP	THC	All 5 Drugs
EMIT	50.0% (48.8-51.2%)	99.3% (99.2-99.4%)	65.0% (63.7-66.3%)	94.1% (93.5-94.7%)	99.5% (99.4-99.6%)	88.8% (88.3-89.3%)
RIA	90.7% (90.4-91.0%)	97.2% (97.1-97.3%)	72.7% (72.3-73.1%)	89.4% (89.1-89.7%)	97.6% (97.5-97.7%)	90.7% (90.5-91.1%)
KIMS	70.9% (70.3-71.5%)	93.6% (93.3-93.9%)	74.3% (73.7-74.9%)	61.8% (61.2-62.4%)	95.6% (95.3-95.9%)	82.0% (81.5-82.5%)

• All screening summaries include blind quality control/ proficiency samples.

For the average employee, false positive rates may be the most important statistic in any study dealing with drug testing methodology. Similarly they help us to at least estimate the specificity of a specific technique as it compares to another technique or instrument.

Table 10B lists false presumptive positive rates for each of the immunoassays. In the event that the guidelines were revised and labs were authorized to use only an immunoassay screen to detect illegal drug use, the 0.532% false presumptive positive rate found by KIMs immunoassay would result in more than 370 false positive federal civilian test results per year. (*This estimate assumes that labs only use KIMs, results of this study are accurate, and that testing continues at the current rate of approximately 70,000 employees per year). Even if other FDA approved immunoassay technology is utilized however, failure to confirm positive test results with the "gold standard" GC/MS would result in false positive test results for at best 209 employees per year (using low confidence interval for RIA).

Table 10B Comparison of False Presumptive Positive Rates by Immunoassay •

Immunoassay False Presumptive Positive Rates (95% Confidence Intervals)

Immuno.	Amphet.	Benzoyle.	Opiates	PCP	THC	All 5 Drugs
EMIT	0.454% (0.452-0.456%)	0.006% (0.005-0.007%)	0.39% (0.38-0.40%)	0.019% (0.018-0.020%)	0.006% (0.005-0.007%)	0.331% (0.324-0.338%)
RIA	0.039% (0.037-0.041%)	0.027% (0.026-0.028%)	0.271% (0.268-0.274%)	0.039% (0.037-0.041%)	0.023% (0.022-0.024%)	0.303% (0.299-0.307%)
KIMS	0.199% (0.194-0.204%)	0.045% (0.042-0.048%)	0.203% (0.198-0.208%)	0.059% (0.056-0.062%)	0.027% (0.025-0.029%	0.532% (0.525-0.539%)

- All screening summaries include blind quality control/ proficiency samples.

Chapter V

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

The following chapter summarizes the findings and recommendations from this study. The chapter covers the following areas in order: summary, interpretation and implications, conclusions and recommendations.

Summary

The purpose of this study was to find under the same analytical conditions whether a difference exists between the number of positive test results from the screening immunoassay and positive GC/MS confirmatory results of urine samples tested for drugs of abuse.

Analytical conditions were fixed, thus eliminating several potential confounding variables. Only federal agencies following DHHS mandatory drugtesting guidelines were utilized. These agencies used the same DHHS approved collection procedures, as well as accredited laboratories. The study covered the time period from January 1993- December 1994.

Whether differences existed between positive screening and confirmatory tests was measured by comparing positive predictive values and false presumptive positive rates for each of the five drugs/ metabolites.

Confidence intervals were established at 95% for each estimate/calculation performed. This means that the researcher is confident to within 95% that the true estimate lies within the range listed. There is only a 5% possibility that the true estimate lies outside the range listed.

The six federal agencies performing the largest amount of drug testing during 1993 and 1994 were chosen to participate in this study. It is estimated that the study results utilizing data from the Departments of Transportation, Navy, Army, Air Force, Justice and Veterans Affairs, covered more than 50% of the federal civilian employees tested in 1993 and 1994.

Interpretation and Implication

The study shows that indeed a difference does exist between the results of the screening and confirmatory tests. This answers the underlying question of the study- immunoassay technology has not improved to such an extent that GC/MS confirmation is unneccessary- quite the contrary.

It was expected due to previous studies/ literature that the analyses of amphetamines and perhaps opiates would show significant differences between the results of the screening and confirmatory tests. (Although much of literature regarding opiates was more relevant to verification of illicit use of opiates by the MRO rather than erroneous screening results). A significant difference was not expected for each drug/ metabolite, nor as evidenced by the data in table 9 (pg. 78) did this occur. Clearly the major problems arise from opiates, amphetamines and PCP. Screening immunoassays for benzoylecgonine and THC are quite accurate- yet none of the immunoassays detected 100% of either metabolite.

As the study progressed many additional questions arose - such as what effect did the Navy' s use of a second RIA immunoassay have on their results? Was the positive predictive value of their screening dramatically improved by the use of this second RIA prior to confirmatory testing?

It may be assumed the second RIA test would have an impact by eliminating from confirmatory testing those samples which may have been contaminated, had carryover problem following a positive cocaine result, or encountered some sort of other random error. The Navy's use of a second RIA appeared quite logical, and cost effective by eliminating further expensive confirmatory testing- those samples which tested negative on the second RIA. Yet, when compared to the Army's results which according to Northwest Toxicology uses a lone RIA prior to confirmatory testing, Navy had a lower positive predictive value for nearly every drug (Tables 4C, 6C).

The Role of the Medical Review Officer

The SAMHSA semiannual surveys covering October 1, 1992 through March 31, 1994 reported the total number of federal civilian employees with urine samples which were verified positive for phencyclidine as 8. This study which covered approximately the same time period, and examined about half of the federal employees tested found more than 82 PCP laboratory confirmed positives per year (table 2, page 50). This is a substantial difference, PCP unlike the other drugs of abuse is not prescribed as a medication, nor contained in over the counter medications or foods. Simply, PCP's presence in urine has no medical justification (MacDonald, 1990).

One assumes PCP laboratory confirmed positives were not verified by Medical Review Officers because of chain of custody, laboratory quality control or other procedural problems.

The last three SAMHSA surveys indicate verified positive test rates of about 0.6%, this study found laboratory confirmed rates of 2.7-2.8%. While it is important to recognize that the laboratory confirmed positive rates derived from this study are inflated because it includes mandatory proficiency samples, there exists nonetheless a substantial difference between laboratory confirmed positive rates and verified positive rates. Clearly the Medical Review Officers are playing a critical role in agency drug free workplace programs, as evidenced by overall statistics and those regarding PCP.

Conclusions and Recommendations

It is perhaps even incumbent upon employees and employers alike to recognize that yes poppy seeds may cause positive opiate results and not just the screening tests. Federal agencies have not been immune to significant breaches from DHHS requirements, particularly Departments of Interior, Transportation, and Navy. (Department of Interior, Inspector General, (1992); U.S. General Accounting Office, 1989, GAO/GGD-89-80; DeRochi, 1995).

For agency officials (or for private industry personnel) who direct drug testing programs, the immunoassay utilized by the laboratory may affect the number and type of samples submitted for confirmatory testing- and the employers ultimate cost.

In only a very few instances did it appear that the monthly statistical summaries had not been faxed or transmitted from the lab to the agency solely as a result of the FOIA request. Agencies need to review these monthly summaries, not just because someone initiated a FOIA request to access them but because they provide valuable information on the state of drug testing at the agency.

One of the purposes of this thesis was to look at how drug testing actually works in the government and overall it appears to be working well. Clearly the confirmatory test continues to play an important role and to be necessary to obtain accurate laboratory results. GAO has not recommended eliminating confirmatory tests for civilian employees, nor based on the results of this study would such a recommendation be merited.

Practical Implications From This Study

1. The Health and Human Services mandate to perform confirmatory testing on all positive urine samples is an appropriate one. Any efforts to reduce costs of federal testing programs should not be directed at limiting the use of GC/MS confirmatory testing.

2. Private companies who fail to use GC/MS confirmatory testing are liable for significant legal consequences. This study shows that failure to use confirmatory testing by GC/MS cannot be scientifically supported.

3. Both federal and private industry might well opt to use the immunoassays found in this study and other studies cited earlier, which provide the best positive predictive value. Utilization of appropriate immunoassays could reduce federal drug testing costs.

4. Federal agencies should utilize data provided by their contract laboratories and

SAMHSA to make decisions on their drug free workplace programs. Agencies need to take an active role in assuring that state of the art technology and knowledge is utilized in the analysis of agency drug testing samples.

5. Due to the limited number of phencyclidine samples which have been verified by MRO's (<0.01%), federal agencies may wish to emulate Departments of Air Force and Army and test for phencyclidine in only rare instances. This should also reduce costs. This topic and why PCP was verified in such a small percentage of cases is recommended for further study.

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