

# Toxicology News

March 2004

An AACC/CAP Educational Newsletter for Toxicology Laboratories

## Postmortem Redistribution of Drugs Must Be Considered

By William H. Anderson

**F**orensic toxicologists involved in death investigations often provide analytical and interpretive support to the medical examiner to determine the role of xenobiotics in a death. Their ability to provide assistance in these cases is determined by the reliability of analytical measurements of drug concentrations in biological fluids and tissues, which in turn depends on the use of accurate, precise, and validated methods; the use of proper controls; and the performance of the assays.

An equally important issue is whether drug concentrations in specimens collected at autopsy accurately reflect the concentrations at the time of death. The evidence is clear that this is not always the case. Substantial changes can occur in blood drug concentrations during the interval between death and autopsy. The term “postmortem redistribution of drugs” is commonly used to describe these changes. This review will describe the historical development of the current concepts of postmortem redistribution and provide recommendations for incorporating the phenomenon into the practice of forensic toxicology.

### Ethanol changes

Forensic toxicologists have recognized the potential for changes in ethanol concentrations after death for many years. Historically, there have been two major concerns about postmortem changes in ethanol concentrations. The first is contamination with microbes, which can result in an increase or decrease in ethanol concentration (1–3). The second concern is the potential for postmortem diffusion from the stomach into the major vessels of the central cavity, resulting in a potential for ethanol concentrations to rise in central cavity blood (4). Recent articles support both of these hypotheses (5, 6).

The general recognition of the potential for mi-

crobial contamination has resulted in the near universal use of preservatives (7) and the collection of alternate specimens such as urine or vitreous humor that are less susceptible to microbial contamination (8). An excellent review of this subject has been published (9). To minimize the potential for contamination by diffusion of the gastric contents or sampling errors due to contamination by trauma, the collection of peripheral specimens and the strict avoidance of collection of central cavity blood via external cardiac blood have been advocated (7, 10).

### Historical background

For a long time, concern about postmortem changes was restricted to ethanol. Prescription drugs or common drugs of abuse were not considered as likely to exhibit postmortem change. The majority of research into the postmortem redistribution of drugs has taken place in the past two decades, although there were earlier indications that it may exist. In 1960, Curry and Sunshine reported large differences in the concentration of barbiturates in blood obtained from vessels of the central cavity and blood from femoral vessels (11). These authors advocated the use of peripheral blood for toxicological analyses and urged research into the relationship of heart and femoral blood drug concentrations. Gee et al. corroborated substantial differences in the concentration of barbiturates in heart and femoral specimens (12). Gee also reported a case in which the heart:femoral ratio for acetaminophen was 2.1:1 and cautioned that the area from which the specimen was collected was an important consideration in the interpretation of toxicological results (13). Vorpahl and Coe reported

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## Antidepressants Require Care In Postmortem Interpretation

By Jeri D. Ropero-Miller

In the United States, antidepressants are not only the eighth leading substance most frequently involved in human exposures (99,800 incidents or 4.2%), they are also the second most common class of drug primarily responsible for death. Moreover, of these antidepressant deaths, 34% (45 of 133) resulted from ingestion of a single antidepressant. Amitriptyline was the sole agent in 12 cases (1).

Because of the prevalence of antidepressant fatalities, toxicologists tend to be familiar with antidepressant therapeutic and toxic reference ranges. Nonetheless, caution is called for in the toxicological interpretation of antidepressant involvement in the cause and manner of death. The phenomenon of postmortem redistribution of drugs must be considered with tricyclic antidepressants and selective serotonin reuptake inhibitors (Case 1) and selective neurotransmitter reuptake inhibitors (Case 2). Other important considerations include drug-drug interactions (particularly drugs affecting protein binding or metabolism by the cytochrome P450 isoenzymes, especially 1A2, 2C19, 2C9, 2D6, and 3A4), and intraindividual differences such as age, organ capacity, disease, and metabolic rate.

In a review of toxicological results, the contribution of antidepressants to the cause and manner of death can be obvious or subtle. Consequently, it is imperative that the decedent's history and autopsy findings are considered in light of the toxicological findings. For example, Case 1 can be easily interpreted as a multidrug suicidal ingestion based on drug concentrations alone; in Case 2, however, the history and autopsy findings in conjunction with the toxicology results indicate an accidental, fatal amitriptyline ingestion probably due to enhanced toxicity by the decedent's diseased state (diabetes mellitus), drug-drug interactions, or a combination of both.

### Case 1

The decedent was a 40-year-old white female of adequate nourishment who had a history of depression and was found in her locked bedroom. At autopsy, the decedent had evidence of minor injuries including a slight abrasion of the chin and several bruises on her extremities. Anatomic findings included focally severe coronary artery disease, enlargement of the heart, and a mild degree of fatty change of the liver. The pathologist ruled this death

a multiple drug overdose including bupropion, diphenhydramine, and sertraline. The toxicological findings were:

|                       | Aortic blood (mg/L) | Iliac vein blood (mg/L) | Liver (mg/Kg) |
|-----------------------|---------------------|-------------------------|---------------|
| Alprazolam            | 0.08                |                         |               |
| Amitriptyline         | 0.26                |                         |               |
| Bupropion             | 5.9                 | 5.2                     | 6.5           |
| Diphenhydramine       | 9.1                 | 5.5                     | 33            |
| Erythro bupropion     | 0.99                | 0.51                    | 5.5           |
| Morpholinol bupropion | 3.9                 | 2.7                     | 6.9           |
| Norsertaline          | 1.5                 | 0.27                    | 18            |
| Nortriptyline         | 1.7                 | 0.64                    | 12            |
| Sertraline            | 7.7                 | 2.0                     | 61            |
| Threo bupropion       | 15                  | 8.3                     | 70            |

In addition, trace amounts of propoxyphene, norpropoxyphene, olanzapine, and oxycodone were present in the aortic blood, but ethanol was not detected.

### Case 2

The decedent was a 26-year-old white female with a history of diabetes mellitus and non-compliance with her medication regimen. The decedent had a history of suicide attempts, but the death investigation indicated that all medication bottles were present and seemingly in order. Autopsy findings included mildly enlarged heart and liver and pulmonary congestion and edema. Autopsy examination revealed a fentanyl patch on the left chest and an insulin pump, which was later revealed to have been activated infrequently. Analysis of the vitreous humor revealed relatively normal electrolyte levels with a glucose of 113, which is inconsistent with either a hypo- or hyperglycemic state. The toxicological findings were:

|                        | Aortic blood (mg/L) | Iliac vein blood (mg/L) | Liver (mg/Kg) |
|------------------------|---------------------|-------------------------|---------------|
| Acetaminophen          | 3.5                 |                         |               |
| Amitriptyline          | 1.1                 | 0.55                    | 9.9           |
| Fentanyl               | 0.002               | 0.002                   | 0.010         |
| Nortriptyline          | 3.8                 | 1.4                     | 31            |
| O-desmethylvenlafaxine | 0.96                | 0.93                    | 2.2           |
| Venlafaxine            | 7.7                 | 2.2                     | <1.6          |

In addition, trace amounts of normeperidine and promethazine were present in the aortic blood, but organic acids and ethanol were not detected.

The presence of a much larger nortriptyline metabolite concentration in the liver and blood compared with the parent drug concentration suggests the possibility of a build-up of medication. Consequently, the cause and manner of death were indicated as accidental amitriptyline poisoning with a

contributing complication of diabetes mellitus.

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1. Watson WA, Litovitz TL, Rodgers GC, et al. 2002 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2003;21(5):353–64.

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## Postmortem Redistribution

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on a series of digoxin cases in which they determined the concentration of digoxin in heart, femoral, and subclavian blood specimens and compared the observed concentrations to the predicted concentration at the time of death (14). The concentration of digoxin differed in each of the postmortem blood specimens and was invariably higher in the heart blood specimens. The concentration in all autopsy specimens was higher than the predicted concentration at the time of death. The results of this study were not extrapolated to other drugs, probably because it was believed that digoxin was highly bound to cardiac tissue and was subsequently released directly into the blood within the heart, which represented a "special case."

Bandt reported on a study of nine cases involving tricyclic antidepressants (15). He analyzed blood specimens from several different sites and collected serial specimens from the same site. In one of his cases, the concentrations of amitriptyline and nortriptyline at the time of death were 0.73 mg/L and 0.70 mg/L, respectively, in blood collected from the external jugular vein. In blood collected five hours later from the right heart, the concentrations were 2.8 mg/L of amitriptyline and 4.4 mg/L of nortriptyline. In another case, serial collections were made from the subclavian vein at postmortem intervals of 16, 24, and 32 hours. The concentrations of amitriptyline were 5.4 mg/L, 8.8 mg/L, and 12.1 mg/L, respectively, and the corresponding concentrations of nortriptyline were 1.1 mg/L, 2.0 mg/L, and 2.5 mg/L. His conclusions from these experiments were that the postmortem concentration of tricyclic antidepressants increases as the postmortem interval increases and the measured concentration depends on the origin of the specimen. Although limited in scope, this research was very important in the history of the study of postmortem redistribution of drugs (16).

## Newer studies

The author and colleagues at the office of the chief medical examiner for the state of Oklahoma became interested in the potential for postmortem redistribution when it became apparent in a variety of cases that pharmacokinetic estimates of dose from measured concentrations of drug in autopsy specimens did not reconcile with known doses nor provide reasonable estimates when the dose was unknown.

These observations led to a series of studies that attempted to gain insight into the problem of postmortem redistribution of drugs. These studies were comprised of: 1) a set of experiments similar to the serial experiments of Bandt (15), with an expanded list of drugs; 2) a comparison of drug concentrations in postmortem heart, femoral, and subclavian blood specimens for a large number of drugs; 3) a comparison of drug concentrations in heart blood specimens collected prior to shipping the body for autopsy with the concentrations determined in heart blood specimens collected at the time of autopsy; and 4) a comparison of heart and femoral blood drug concentrations in a series of cases of parenteral administration of drug.

The data from the serial collection experiments generally agreed with that of Apple and Bandt (16) and has been reported in detail (17, 18). Table 1 summarizes the data from two separate cases involving amitriptyline and propoxyphene, which illustrate a site dependence of drug concentrations in blood collected at autopsy. It is abundantly clear that an exact estimate of dose is impossible because the estimate would greatly depend on which specimen was used for the calculation. The interpretation of the significance of the drugs in these two cases also depends on which blood specimen is collected, especially if blood is the only specimen collected.

The observations and conclusions of the previously mentioned research groups have been corroborated, expanded on, and enhanced by other authors (19–26).

An important publication by Jones and Pounder is especially informative as to the details and intricacies of postmortem redistribution (19). A useful and often cited compilation of drug concentrations in heart and femoral blood has been published by Dalpe-Scott et al. (20). Data has also been presented comparing the concentration of ethanol in heart and femoral blood (27, 28).

Cocaine presents a special set of problems in the interpretation of postmortem results. In addition to temporal and site dependence in concentrations, cocaine undergoes hydrolysis to benzoylecgonine and ecgonine methyl ester (29–31).

## Mechanism unclear

The exact mechanism by which postmortem redistribution occurs is not entirely clear and is most likely a combination of factors. Absorption from the gastrointestinal tract (5, 32), release after death from drug-rich reservoirs and subsequent diffusion into the central vessels (33, 34), direct release of drug from the myocardium into heart blood (14), and redistribution as a result of putrefactive process (35) have all been proposed as contributory mechanisms. It is also possible that drug concentrations in central and peripheral blood specimens may be influenced by incomplete absorption and differential distribution at the time of death (36). It is beyond the scope of this article to discuss in detail all of the research into this area, but a recent publication presents an excellent review (37).

## Areas of agreement

A review of the literature indicates general agreement on many important issues concerning the postmortem redistribution of drugs:

1) The concentration of many drugs in postmortem blood specimens depends on the origin of the specimen. In general, heart blood concentrations are higher than those of peripheral (femoral) specimens. Subclavian specimens are intermediate in concentration, but are often closer to heart blood in concentration than femoral blood.

2) Site dependence may occur with parenteral or oral administration of a drug.

3) The drug concentration tends to change with time and generally increases. Changes can occur rapidly after death. Changes in femoral blood concentrations appear to be of less magnitude than those in central vessel blood.

4) There does not appear to be a way to predict the relationship between drug concentrations in various specimens nor the manner in which the concen-

tration in a specimen may change with time.

5) Site and temporal dependence occurs with metabolites as well as parent drugs.

6) Any or all of the above conclusions may not be relevant for a given case nor for all drugs. Basic drugs with a high volume of distribution are likely candidates for postmortem redistribution, but acidic and neutral drugs with relatively small volumes of distribution have also exhibited redistribution. There may be different mechanisms for redistribution of these disparate chemical classes.

7) The mechanisms for redistribution are complex, may be different in specific circumstances, and may vary from drug to drug. Drugs such as cocaine present special problems. In addition to site and temporal differences, cocaine is subject to postmortem conversion to metabolites.

8) Exact estimates of dose from a single postmortem blood concentration, especially a heart blood specimen, are unreliable and should not be attempted.

9) In most cases, central and peripheral blood specimens along with tissue specimens, a complete autopsy, and competent case investigation are necessary to assess the significance of a drug in the death of an individual.

## Conclusion

Postmortem redistribution is widely recognized and must be considered in most cases involving drug-related deaths. So it is a continuing matter of concern that these considerations are often ignored in death investigations or expert testimony. A relatively recent concern of toxicologists is the interpretation of drugs such as oxycodone and methadone, in which the toxic and therapeutic concentrations may overlap and liver concentrations may or may not resolve the issue. In many of these cases, a proper investigation and thorough autopsy must complement,

**Table 1. Variations in drug concentrations in blood specimens collected simultaneously at autopsy (in mg/L)**

| Site of blood collection | Amitriptyline | Nortriptyline | Propoxyphene | Norpropoxyphene |
|--------------------------|---------------|---------------|--------------|-----------------|
| Case 1                   |               |               |              |                 |
| Left subclavian vein     | 0.94          | 0.45          | 1.8          | 3.8             |
| Right subclavian vein    | 0.77          | 0.35          | 1.6          | 2.9             |
| Left heart               | 2.0           | 1.3           | 5.6          | 8.5             |
| Right heart              | 1.3           | 0.36          | 1.6          | ---             |
| Femoral vessel           | 0.18          | 0.18          | 0.76         | 1.7             |
| Case 2                   |               |               |              |                 |
| Left subclavian vein     | 3.0           | 0.37          | 4.6          | 4.5             |
| Right subclavian vein    | 1.9           | 0.30          | 3.3          | 3.2             |
| Left heart               | 1.3           | -----         | 3.3          | 3.2             |
| Right heart              | 2.2           | 0.08          | 4.2          | 2.1             |
| Femoral vessel           | 0.14          | -----         | 0.46         | ---             |

or in some cases take precedence over, the toxicology report. It is difficult enough to reach sound conclusions when lethality is the matter under consideration, but a non-drug death may present even greater pitfalls. Toxicologists are commonly asked to render an expert opinion as to the significance of drugs detected in postmortem blood specimens in cases involving accidents, especially automobile accidents, and in cases involving the degree of in-

toxication of homicide victims. Testimony on these subjects is often a nebulous exercise when the subject is alive, but is very difficult in postmortem cases and should always be approached with caution. Postmortem redistribution complicates the job of the forensic toxicologist and forensic pathologist, but it does not make it impossible, unless the phenomenon is ignored.

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## Case Studies Show Principles of Pediatric TDM: Part 2

By Holly D. Maples and Henry C. Farrar

*In the December issue, Part 1 of this article presented hypothetical cases based on actual pediatric patient situations to demonstrate important concepts in the proper use of therapeutic drug monitoring (TDM). In that article, Case 1 illustrated the importance of selecting the correct sample collection site. Case 2 focused on clearing the line used for drug delivery before withdrawing blood back through it. In this issue, we present additional examples.*

### Case 3: Reporting times

An adolescent with a perinephric abscess was receiving home intravenous gentamicin therapy with peak and trough concentrations of 4 mg/mL and 0.5 mg/L, respectively (normal therapeutic range of 5–10 mg/L and 1–2 mg/L, respectively). The dose (2.5 mg/kg every 8 hours) appeared appropriate for age and renal function. No sample collection times were listed on the report.

The treating physician requested assistance from the TDM service to adjust the gentamicin dose to achieve a therapeutic peak level concentration. A discussion with the home health nurse revealed that the collection of the peak sample had been delayed by 2 hours because of problems in accessing the line. With this information, the actual peak was estimated to be 8 mg/L, which was appropriate. Thus, no dosing adjustment was needed.

While it is generally assumed that peak and trough concentrations are collected at the correct times, this case demonstrates the importance of knowing the actual timing of drug administration and plasma sampling. If the drug concentrations in this case were assumed to be correct, a dosing adjustment could have resulted in drug toxicity. Because the half-life of an aminoglycoside may be only 1–2 hours in some patients, a delay in the collection of a peak concentration could result in a variation of 50% or more between the reported and actual peak concentrations. Thus, rather than simply reporting a concentration as a peak or trough, the actual time of collection should also be reported.

### Case 4: Defining the therapeutic range

A child was admitted with an infection of his ventriculo-peritoneal shunt, with a positive cerebrospinal fluid (CSF) culture for methicillin-resistant *Staphylococcus aureus* (MRSA). Antibiotic therapy included vancomycin with peak and trough concen-

trations of 25 mg/L and 8 mg/L, respectively, collected at the appropriate sampling times (expected peak and trough concentrations were 20–40 mg/L and 5–10 mg/L, respectively). A repeat culture 3 days after the initiation of therapy was again positive for MRSA. The TDM service was consulted, and the dosing regimen was changed, resulting in peak and trough concentrations of 40 mg/L and 10 mg/L, respectively. Shortly thereafter, the child's CSF cultures cleared.

This case demonstrates that, although a drug concentration may be in the usual therapeutic range, the concentration can still be sub-therapeutic. Because vancomycin penetrates poorly into the CSF, higher serum drug concentrations may be required to achieve adequate tissue concentrations needed for antibacterial effects. Thus, while the therapeutic range of peak concentrations of vancomycin is 20–40 mg/L, concentrations of about 20 mg/L are usually appropriate for bacteremia and line infections, but concentrations of 40 mg/L and higher are often required for central nervous system infections.

The usual therapeutic ranges listed for a drug should reflect this variability. For example, gentamicin is used to treat gram-negative urinary tract infections and may be effective at concentrations as low as 5–6 mg/L. It can be used to treat pulmonary infections in cystic fibrosis patients and patients with gram-negative meningitis at concentrations up to 12 mg/L. Thus, the usual therapeutic range for gentamicin should be 5–12 mg/L.

Some institutions list usual ranges of drug concentrations for specific diagnoses. For example, cyclosporine is used at concentrations of about 100 ng/mL in bone marrow transplant patients, but at concentrations of 200–300 ng/mL in solid organ transplant patients.

Finally, drug concentrations can vary depending on the analytical method. For example, the therapeutic range for cyclosporine can be different when measured by serum radioimmunoassay, whole blood radioimmunoassay, or whole blood high performance liquid chromatography.

Clinical correlation with the patient's condition and diagnosis is critical in interpreting therapeutic drug concentrations and defining therapeutic ranges. Thus, the laboratory must work closely with clinicians to define the therapeutic ranges to be reported.

### Case 5: Timing of sample collection

A 10-year-old with congestive heart failure was started on digoxin. A loading dose of 10 mcg/kg was given intravenously, followed by two doses of 5 mcg/kg given at 6-hour intervals. A digoxin concentration after the third digoxin dose was 4 ng/mL

(usual therapeutic values are 0.8–2.0 ng/mL). The TDM service was contacted to assist with management because a digoxin concentration greater than 2 ng/mL is associated with toxicity. It was discovered that the digoxin concentration had been drawn 1 hour after the dose had been given.

Digoxin has a half-life of approximately 35 hours in children and slowly distributes throughout the body. Therefore, it is generally recommended that trough digoxin serum concentrations be used, typically collected 8–12 hours after a dose. In this case, the patient had no signs of toxicity, and when the digoxin concentration was checked 12 hours post-dose, it was within the usual therapeutic range.

This case demonstrates that the timing of drug concentrations is specific to each drug's pharmacokinetic profile. Concentrations of many antibiotics are obtained within 1–2 hours of infusion because they distribute rapidly and have short half-lives. Drugs such as digoxin distribute much more slowly and therefore are better monitored with trough, or pre-dose, concentrations.

#### Case 6: Choosing the drug to measure

A 2-year-old was diagnosed with a new onset seizure disorder and was started on carbamazepine. Although the child had good seizure control on this drug, the trough serum concentration of carbamazepine was 5 mg/L (the usual therapeutic range is 6–12 mg/L). However, the dose appeared appropriate for the child's weight. The carbamazepine epoxide concentration was 2 mg/L, for a ratio of the epoxide to parent drug of 0.4 (usual ratio of 0.2 in older children and adults). Because the epoxide metabolite has pharmacologic activity equal to that of carbamazepine, no dosing adjustment was needed.

One principle exemplified by this case is that the clinical condition of the patient should always be considered when evaluating a drug concentration. Otherwise there is a great temptation to treat the drug level rather than the patient. Thus, although this carbamazepine concentration of 5 mg/L was somewhat low, it was effective because of the combined effect of the parent drug and its active metabolite.

An active metabolite contributes to both the therapeutic effect and the toxicity of a drug. Carbamazepine epoxide is found in patients with rapid carbamazepine metabolism associated with development (children less than 3 years old metabolize drugs more rapidly than older children); enzyme induction due to other drugs such as phenobarbital and rifampin; or autoinduction (for example, with rapid dosing escalation). Thus, in these situations, measurement of carbamazepine epoxide should be considered when measuring carbamazepine.

With some anticonvulsants, it is also important to consider the free drug concentration. Phenytoin is one such drug. It is typically highly protein bound (>90%). Common settings in which an increased free phenytoin concentration is due to decreased protein binding include patients with renal insufficiency, critically ill patients, and patients with displacement of phenytoin from albumin (for example, in drug interactions with valproic acid). In these situations, the free phenytoin concentration may be in the therapeutic range (typically 1–3 mg/L) although the total phenytoin concentration is suboptimal. Attempts to bring the total concentration into the therapeutic range could result in toxicity from the resulting elevated free drug concentrations. While it is not routinely necessary to measure free drugs or metabolites, such measurements should be considered in patients in whom unusual pharmacokinetic parameters are possible or parent drug concentrations are unexpectedly low for a given dose.

Another problem frequently encountered with anticonvulsant therapy is that a drug concentration is obtained before steady state has been reached, leading to a low result. Because many anticonvulsants have half-lives of greater than 12 hours, 3 to 5 days may be needed to achieve steady state (steady state is achieved after approximately four to five half-lives). In these situations, daily anticonvulsant levels are of limited use because dosing adjustments cannot be made with sufficient accuracy. Aggressive dosing adjustments prior to steady state could lead to drug toxicity secondary to the accumulation of high drug concentrations. Thus, if the patient is not experiencing worsening seizures, measurement of the drug concentration should be delayed until steady state is reached.

#### Table 1. Critical questions for evaluating drug concentrations

- Is the dose appropriate for age, weight, and disease?
- What are the drug concentration goals of therapy?
- What was the timing of the specimen collection?
  - What time was the dose given including flush?
  - What time was the sample collected?
  - Was this an appropriate sampling time for the drug?
- Was the drug concentration drawn at the appropriate site?
- Was the drug concentration drawn using the appropriate technique?
  - Was an adequate flush used in a central line?
- How is the drug concentration reported?
  - Where correct units of concentration used?
  - Is there a therapeutic range available?
- Is the patient's drug concentration at steady state?
- Should an active metabolite or unbound parent drug be considered?

## Conclusion

This review, based on hypothetical cases representative of actual patient situations, demonstrates some key concepts that are needed to effectively evaluate drug concentrations. These concepts are summarized in the accompanying table. Resolution of these key points will promote optimal drug therapy while limiting the risks of concentration-related drug toxicity. Effective communication between clinicians and laboratory personnel is essential to achieve this goal of effective TDM.

## Suggested Reading

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## FDA Issues New Test Guidance

In December, the Food and Drug Administration (FDA) issued new guidance on the data and labeling required of manufacturers to support 510(k) submissions of drug abuse screening tests. The guidance's goal is to gain the safety benefits of drug testing without the costs of an elaborate regulatory approach. One aim of the guidance is to allow manufacturers more flexibility in marketing these tests.

The new guidance defines personnel requirements depending on the end use of the test result. It requires the labeling to state that the tests can produce both false-positive and false-negative results.

The guidance divides the tests into three categories according to intended use (laboratory, home, and workplace/repetitive) and details the submission requirements of each. It addresses specific labeling requirements, including intended use, quality control, limitations, and performance characteristics. The labeling of home-use products is required to aid in the user's understanding of performance and interpretation of results, including addressing the use of professional counseling for positive test results.

The guidance can be viewed at [www.fda.gov/ohrms/dockets/98FR/2003d-0522-gdl0001.doc](http://www.fda.gov/ohrms/dockets/98FR/2003d-0522-gdl0001.doc).

The purpose of *Clinical & Forensic Toxicology News* is to provide practical and timely information on the clinical, forensic, technical, and regulatory issues faced by toxicology laboratories.

*Clinical & Forensic Toxicology News* is an educational service of the forensic urine drug testing (FUDT) program. The FUDT program, cosponsored by the American Association for Clinical Chemistry and the College of American Pathologists, includes three components: FUDT accreditation, the FUDT proficiency testing survey, and this newsletter. The accreditation program is the responsibility of the CAP. The surveys are sponsored jointly by AACC and CAP. The newsletter is published quarterly by the American Association for Clinical Chemistry, Inc., 2101 L St., N.W., Suite 202, Washington, DC 20037, (800) 892-1400 or (202) 857-0717, [cftnews@aacc.org](mailto:cftnews@aacc.org).

*Clinical & Forensic Toxicology News* does not accept advertising and is supported solely by its readers. Annual subscription prices are \$86 (U.S.) and \$96 (international). Subscribers are encouraged to reproduce copy with appropriate acknowledgment of source.

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